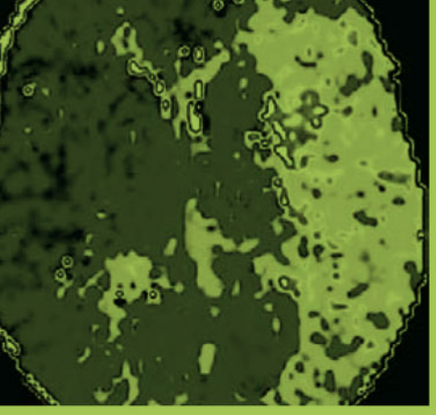

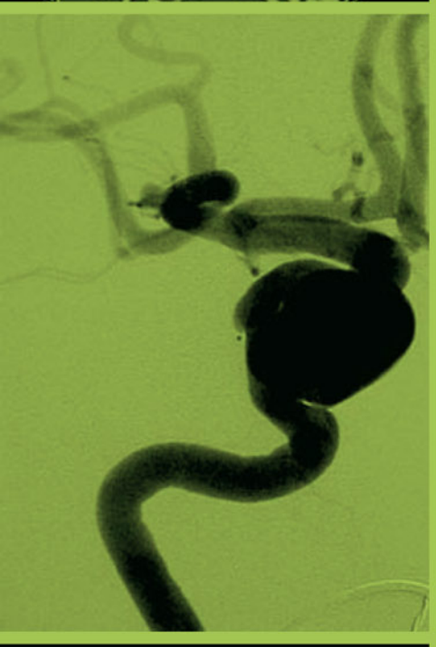

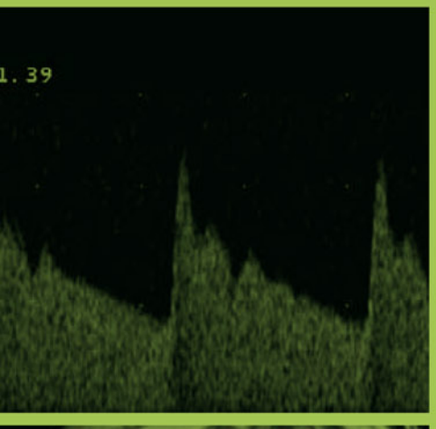

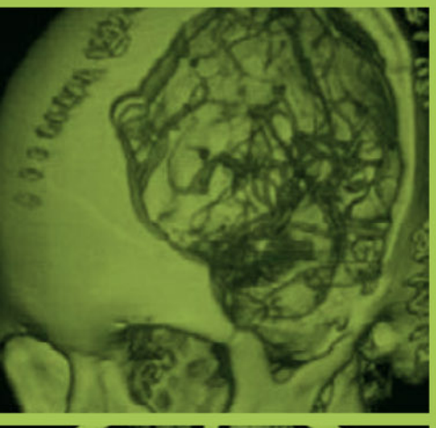

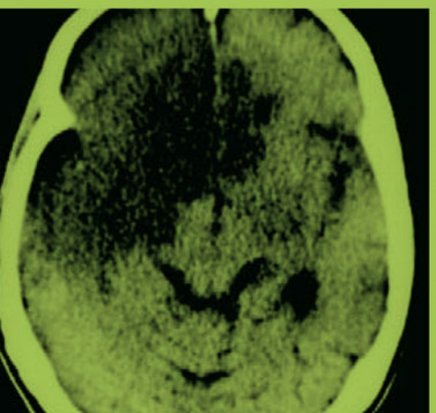

Daniel Agustín Godoy

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To my parents Mirtha and Justino
for giving me the life, education
and the opportunity to study and
acquire this wonderful profession.

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and Alvaro who have suffered my absences
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have shared with me over than 23 years
of hard and tireless work, uncertainties,
anxieties, sorrows and joys in the Intensive
Care Units where I have worked.

To the life...

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Prologue

This book deserves to my gratitude, more than my prologue.
Many years ago, when this project started, its aim was simple: to provide the physician with a quick and practical tool for consultation. However, the enormous generosity, selflessness and spirit of collaboration of great teachers and world opinion leaders in this subspecialty made it possible to transform it in what it is today.
Some time ago (I still remember well his e-mail), Prof. Stephan Mayer of Columbia, New York, in that period President of the Neurocritical Care Society, described the book as "magnum opus". In my humble opinion this definition was very exaggerated, but his words were like a shot of optimism that undoubtedly lead the way. My teachers and friends encouraged me, helped me, I held back, and therefore they all have my eternal gratitude. In particular, I'd like to mention two persons who had a great role in my professional life, with whom I shared most of my professional life, two great friends: Esteban Piacenza, who taught me how to take my first steps in intensive care, and Prof. Walter Nigri, neurosurgeon, who introduced me into the neurocritical care.
Of course it was not so easy. Editing a book of this magnitude is a Herculean task, only understandable by those who have done something similar. In addition, during its preparation I had to overcome a rough and long illness (and this is the reason for its delay). However, like everything one undertakes in life, it has a special flavor when the effort needed has been intense. So I'd like to recommend to potential readers two sentences that accompanied me throughout my life, especially during difficult periods and obviously while editing this book: «Persistence is the key to success» and «What's to come is better».
Simply thanks to all those who made possible to make this dream come true.

Daniel A. Godoy

Preface

«During revolutions scientists see new and different things when looking with familiar instruments in places they have looked before. It is rather as if the professional community had been suddenly transported to another planet where familiar objects are seen in a different light…» [1]
Thomas S. Kuhn

This volume, which we have the honor to introduce, presents the work of a group of international experts in neurocritical care. Dr. Daniel Godoy has completed thedaunting task of introducing the beginner and updating the specialist on current knowledge in brain injury. Anyone who has been involved in editorial projects will have experienced the trials and tribulations of uniting the efforts of many; Dr. Godoy's book is no exception. He has met this challenge patiently and tenaciously. Having known him for many years, we feel he is to be commended for his devotion and drive. His extraordinary interest in science has made him a well-known expert his field bringing about an ever-increasing level of activity in neurointensive care in Argentina.
Many of the contributors to this book are known personally to us, colleagues with different specialties who we also consider friends, having come together through a shared fascination with an undoubtedly complex and heterogeneous medical challenge: neurocritical care.
This book is dedicated to brain-injured and neurocritically ill patients. The management of these patients constitutes a growing subspecialty that remains unrecognized by many international medical associations but has played a prominent role in intensive care over the last two decades.
Neurocritical care as a subspecialty evolved from the need to provide highly specialized care to neurosurgical patients. Later, patients with severe traumatic brain injury (TBI), hemorrhagic stroke, and acute central nervous system disorders were included in this line of care. Each of these patients requires specialists who are knowledgeable of their particular clinical situations in addition to rapid and often complex management of intracranial hypertension, technical equipment, and skilled nurses [2]. Indeed, specialized nursing forms the backbone of modern neurocritical care units.
As with the management of other complex pathologies (e.g. neurovascular disorders, endoscopic surgery, skull base fractures, and pediatric neurology), subspecialization in neurosurgery is essential to improving outcome and reducing complications.
In neurosurgery, outcome is always improved when the patient is in the hands of an expert instead of a general, though versatile, neurosurgeon. However, some sectors of the

international intensive care societies still view neurocritical care subspecialization with skepticism, if not with mistrust. In our opinion, these attitudes reflect irrational fears and are at odds with scientific evidence in support of subspecialization. Several studies have shown that neurocritical care specialization reduces mortality, improves functional outcome in almost all diseases studied, and is cost-effective for the health care system [3]. This has been demonstrated in patients with severe TBI, spontaneous subarachnoid hemorrhage, intracerebral hematoma, and ischemic stroke [3-5]. Admittedly, in some cases it is not easy to discern whether the determinants of improved results are the specialized units themselves or the well-structured clinical management protocols. In patients with severe TBI, the rigorous application of the Brain Trauma Foundation guidelines has been shown to significantly reduce mortality [6]. What should be remembered, however, is that such protocols have been created using procedures designed by neurocritical care specialists. What has brought added value to subspecialization most is the human factor, as noted by Smith: "Members of a multidisciplinary team who care regularly for patients with acute brain injury are more likely to be aware of the adverse impact on the brain of secondary physiological insults and to be more obsessional about their prevention, recognition and treatment" [2].

Despite contradictions, doubts, and disagreements, neurointensive care has reached organizational levels unthinkable just a decade ago and neurointensive care units can now be found in nearly all countries. Nonetheless, the tempo of change varies and the models are diverse. The Neurocritical Care Society in the United States and the Canadian Neurocritical Care Society were founded in 2003 [3]. The European Society of Intensive Care Medicine has also established a neurointensive care section, the Neuro-Intensive Care and Emergency Medicine Section. Access to specialized accreditation is homogeneous, however, following several models and using methods of access, while in other countries no models have been implemented at all.

In our opinion, and contrary to popular belief, a well-planned subspecialization based on competencies as well as generic and specific skills will not restrict but rather widen the viewpoint of the specialist and add value to the care of neurocritically injured patients. This provides a driving force for translational research, an indispensable tool in the 21st century that increases knowledge and improves mid-term therapeutic strategies and prognosis. Translational research, which is promoted by the US National Institutes of Health (http://commonfund.nih.gov), is only feasible with a therapeutic approach using multidisciplinary teams with different perspectives and methodologies to obtain a comprehensive understanding of these patients. This allows new therapeutic strategies to move from bench to bedside and back again. To be successful, this kind of research requires teams to work in an atmosphere that fosters collegial effort among neurointensivists, neurosurgeons, and neurologists with a vocation for research in collaboration with basic researchers. This ideal scenario is only possible within the context of neurocritical care units. Who should lead these units would be a side issue were it not for contentious debate in some countries and in certain scientific societies. We feel that intensive care experts are the most qualified professionals to lead these groups and facilitate the collaboration of different specialists with the common goal of improving prognosis in neurocritically ill patients.

The many research projects carried out during the Decade of the Brain (1990-2000) have produced an enormous wealth of information, and our ability to understand the underlying pathophysiology of many of the conditions affecting TBI patients is challenged, even for our colleagues in neurocritical care. These rapid advances in neuroscience over the past 20 years have led to difficulties in filtering, reading, understanding, and assimilating the latest findings. One of the great advantages of this book is that it may serve both those wishing to enter the field of neurocritical care and specialists seeking a time-

ly update. This volume originated in Latin America, where health systems are heterogeneous and free universal health coverage is not yet a constitutional right in some countries. It is therefore important to underscore that specialization in neurocritical care is only valid in certain socio-economic contexts where health care priorities are well defined. What is desirable in certain circumstances may not be so in others. The adequate context for subspecialization is perhaps more typical in developed countries, with high-tech hospitals or academic organizations that provide incentives for the management and maintenance of high-cost units. In such settings, treatment should be optimal and auditable, and serve as a guide for the design and validation of intervention protocols at other centers with fewer resources.

It is a great honor for us to introduce readers to a work that will leave a significant mark on Latin American and international neurointensive care thanks to Dr. Godoy's commendable effort to make an English version available. It is important that a project of this scale come from Latin America because it serves as a proof t ofthe enthusiasm for this subspecialization, which has been solidly established in that part of the world over the past 15 years.

New generations of intensivists, neurosurgeons, neurologists, and anesthesiologists are facing new challenges. Perhaps the most difficult challenge is to modify the collective consciousness with the idea that the optimal management of brain-injured patients cannot be carried out without a multidisciplinary approach. This is currently not being taught during specialized training, nor is it accepted elsewhere in different scientific fields, where specialists perpetuate a sterile debate about their identities and delineate characteristics that divide rather than unite them.

We believe we are witnessing what Kuhn called a "paradigm shift" or a turning point in neurocritical care. Kuhn also noted that such changes are almost never brought about by new findings but rather by the synthesis and critical review of what is already known. Frequently, it is the observer's point of view, not the observed fact, that changes. Some evident examples in pathophysiology include cortical spreading depression described by Leão in 1944, basic concepts of brain edema first described by Klatzo in 1967, and the pathophysiology of cerebral vasospasm in spontaneous subarachnoid hemorrhage, all of which were far too summarily debated for decades. In the last five years, these three areas, to name just a few, have seen dramatic advancement in terms of knowledge about the mechanisms of brain injury that had long been elusive. Improved understanding has come about by re-examining long-cherished concepts through the use of new monitoring tools and methods in molecular biology. This increased knowledge opens new therapeutic expectations, an idea best summarized by Pang et al: "the application of what we know will have a greater impact on health and illness than any new drug or technology to be introduced in the next decade" [7].

Dr. Godoy has edited a volume that will serve as a starting point rather than a final goal, opening new inroads and stimulating the interest of readers in search of knowledge. We believe that the breadth of the topics covered, the careful selection of the authors, and the quality of each section will meet if not exceed expectations.

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The management of acute cerebral injury has been very limited until the last decades. Before the introduction of the CT scan, there were surgical options for removing expanding hematomas only if suspected studying alterations of the brain vascular tree in angiography. Vascular neurosurgery was at the beginning, possibly not in the acute phase, and it took the microscope to become a viable option. On the medical side, supportive measures, including oxygenation and nutrition, were available, but nothing specific for the brain could be attempted.

When few pioneers started the continuous measurement of intracranial pressure in patients in Scandinavia [1] and France [2], the path toward medical treatment was opened, with a very consistent pattern: the availability of new technology (starting with ventricular catheters, for instance) offered new information. This information was confirmed and clarified in the experimental setting, with the development of animal models. Without this seminal work, summarized in the first ICP meeting in Hannover [3] clinical information (as neurologic symptoms and signs, or the previous neuropathological background) and experimental data could not have reached, and improved, daily clinical practice.

It has been a growing understanding of the pathological changes in the injured brain that has made the modern medical and surgical approach possible.

It took some time to apply the discoveries of the pioneers to the current practice (the artero-venous difference in oxygen content had been published during the second world war [4] and applied in neurointensive care only 30 years later), but the process started, and continues.

The book which I am introducing states this path in its title, and describes a management based on pathophysiology. It is with a mix of pride and anxiety that we may propose, nowadays, such a treatment founded on scientific understanding of what is normal and what is pathologically altered. Pride because the knowledge has advanced so much, and anxiety because our ignorance is still so endless.

The plan of the book is clear: since there is no treatment if the problem, and possibly its causes, are not identified, every therapy should be based on measurements. Neuromonitoring is the tool of trade in intensive care, and should incorporate cutting edge technology with patience, repeated clinical observation, careful identification of neuroworsening. On purpose, the clinical examination belongs to the introductory section, and an abundance of technology, with specific emphasis on the importance of intracranial pressure, comes in the following parts.

A major contribution of intensive care to brain-oriented strategies has been a comprehensive approach to systemic physiology. The patient with an injured brain can have

chances only if other organs and systems (as the lungs, and the acid-base equilibrium, etc.) are preserved. General support, and the interactions between the affected brain and other organs, are covered in a section devoted to "general support".
Further attention to this problems is given in section seven, where the interactions between systemic parameters (as glucose concentration or arterial pressure) and the brain are described.
The way the brain reacts to different insults has common aspects, as inflammatory responses, edema, etc., but also specific features. Sections five to nine summarize the most relevant pathologies, from ischemic to hemorrhagic lesions, trauma, tumors etc. and also mention new-comers, as the specific problems related to the expanding field of neuroradiological interventions.
Finally, there are "milestones that we should not forget". Neurointensive care does not exist without knowledgeable nurses. The intracranial pressure measurement starts (or unfortunately ends) with a catheter well maintained, and that becomes vital when the drainage of hydrocephalus is concerned. Dealing with patients with severe brain damage has plenty of ethical implications, up to the problems related to brain- death and organ donation.
All these aspects in a book. A book which arrives in an era of electronic information sharing, and in the field of neuroscience, one of the fastest moving. If completeness was the aim, the book will look as a library, and would become outdated tomorrow. But the aim is to be of practical use, and to assist the clinical practice of the busy physician. Then clarity and synthesis have been the priority, rather than academic perfection.
The intelligent reader will find what is necessary for starting, rather than finishing, his approach to neurointensive care.
If this book will reinforce interest and curiosity, suggesting further reading and research, it will have accomplished a valuable goal.

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Section 1. Introduction to Neuroinjury

1 Neuroscience Critical Care: Two Experts' Point of View

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1.1 History, Organization, and Vision for the Future: Prof. Mirski's Point of View

1.1.1 Introduction

Neurocritical care, a subspecialty of medicine and neurology, principally deals with life-threatening diseases and trauma of the nervous system, including the brain, spinal cord and peripheral nerves. Its contemporaneous form can be traced back to the formal designation of Intensive Care Units (ICUs) during the 1980s, incorporating for the first time an interdisciplinary group of physicians from neurology, anesthesiology, and neurosurgery whose interests coincided with the management of neuroscience critical care patients. Such patients receive treatment for strokes, ruptured aneurysms, traumatic brain and spinal cord injury, seizures, swelling and infections of the brain, brain tumours, and respiratory muscle weakness. Besides dealing with critical illnesses of the nervous system, neurointensivists also manage co-morbidities and medical complications involving the heart, lung, kidneys or any other body system. Most neuroscience ICUs are a collaborative effort of a larger clinical and academic neuroscience cooperative where neurointensivists, neurosurgeons, neurologists, radiologists, pharmacists, physician extenders (e.g., nurse practitioners or physician assistants), critical care nurses, respiratory therapists, rehabilitation therapists, and social workers all work together to provide coordinated care for the critically ill neurologic patient. The success of a neuroscience ICU can usually be easily measured by how central the clinical domain has become to the management of neuroscience patients. In addition to the efficiency and quality of care brought about by subspecialty expertise, the neuroscience ICU often becomes the epicentre of interdisciplinary consultation, patient triage, consensus of care, and departmental administrative overlap. Furthering this process, the Neurocritical Care Society was founded in 2004 by a host of clinical neuroscience experts to promote quality care, professional collaboration, research, training, education and advocacy.

1.1.2 Brief History of Brain Injury, Neurologic Disease, and Neuroscience Critical Care

The origins of acute, "intensive" medical attention to the nervous system derive from physical evidence. Far before the earliest written records of medical practice, the first case of brain injury to the humanoid species dates to almost 1 million years ago in a

specimen of the semi-erect hominid *Australopithecus africanus* which had sustained a blow to the occiput, leaving behind a defect the size of an antelope humerus bone found near the skull – indicating that death had occurred by clubbing (the first evidence of a homicide). Pre-historic examples of trephination abound, many datable from 10,000 BC to 3000 BC, as the earliest physical documentation of medical therapeutics [1].

Although the Kahun Gynecological Papyrus (1800 BC) is recognized as the oldest record in the medical literature, the Edwin Smith Papyrus (1600 BC) [2], a copy of part of an ancient Egyptian textbook on trauma surgery, appears to have drawn on material at least 1000 years earlier [3]. Of the seven Egyptian papyri on the art of medicine (Edwin Smith, Hearst, Ebers, London, Berlin 3038, Carlsberg VIII, Chester Beatty VI), the Edwin Papyrus may be the sole recovered text to describe the management of neurological disease. Within its evocative analysis, the text contains the first descriptions of cranial sutures, the meninges – the brain's protective structures –, features of the cortical surface, and a narrative on cerebrospinal fluid, along with its intracranial pulsations. Skull fractures are classified as fissures, smashes, (comminuted), compound comminuted, and comminuted and depressed. Also described are basilar skull fractures with bleeding from the ears, and an account of a head injury resulting in aphasia, the first such neurological diagnosis, which was considered as an ominous sign. It is plainly evident from the text that the ancient Egyptians held a rational view of functional anatomy emanating from common practices based on mysticism found in many other contemporary sources of that period.

Records from other ancient civilizations, particularly those of the Greek and Roman Empires, reveal much about the characterization of neurological disease. Famous for his formal oath of medical practice, Hippocrates, himself the son of a physician (Heraclides), stressed the importance of the medical history, wound inspection and palpation [4]. Focusing on head trauma, Hippocrates described three mechanisms of primary injury: 1) attack by another; 2) extracranial or intracranial injury sustained in a fall; and 3) an injury from a projectile. Hippocrates categorized such injuries so that he could infer from his observations the mechanism of the trauma. He classified weapons as being "rounded, smooth surfaced, blunt, heavy and hard" which produce depressed fractures and contused brain tissue, "and are more disposed to suppurate, and to have a discharge, and take longer to become clean." Other weapons may be more "elongated, slender, sharp, and light," typically yielding superficial lacerated bleeding wounds "when they take place in the bone without fissure, contusion, or depression." [4].

Hippocrates offers a detailed description of the signs and symptoms of a victim befallen a mortal head wound but surviving initial injury. "Fever will generally come on if in winter, and in summer the fever usually seizes after seven days. And when this happens, the wound loses its colour, and the inflammation dies in it; and it becomes glutinous, and appears like a pickle." He goes on to mention that "convulsions seize the other side of the body; for, if the wound be situated on the left side, the convulsions will seize the right side of the body; or if the wound be on the right side of the head, the convulsion attacks the left." Finally, "blisters form on the tongue and he dies delirious."

Hippocrates even makes the first suggestion of therapeutic hypothermia, as he states that death from head trauma: "for the most part, some become apoplectic and die before the end of seven days, if in summer; and before fourteen, if in winter." [4].

Wound inspection and palpation, including head trauma, was also key to overall assessment. The finding of hair in a wound demonstrated that the underlying skull may have been damaged. Hippocrates also experimented with probing techniques to ascertain the significance of injury. There is evidence that he also recommended trephination for the management of skull fissures or fractures, with the intent to create a passage for draining excess blood or cerebrospinal fluid. Along such lines of practice, some historians even credit Hippocrates with being the first to treat hydrocephalus.

Aristotle described the brain meninges and the supratentorial versus the subtentorial compartments of the brain, although he did not understand the importance of the brain for neurological function. Celsus, in ancient Roman times, wrote on brain trauma and suggested that brain stem injuries were graver than those more cephalad. He recognized that intracranial hemorrhage could occur without frank trauma to the skull. Galen (Galen of Pergamum) gave a detailed account of medical anatomy (based on monkeys) that remained unsurpassed until the publication of the anatomic descriptions and illustrations of human dissections by Andreas Vesalius in 1543. In the context of neurophysiology and critical care, Galen perhaps made one of the first inferences to neurogenic asphyxia by defining the importance of the recurrent laryngeal nerves for vocal cord function [5].

Arabic culture made major contributions to medical practice. Influential practitioners such as Rhazes and Abul-Qasim Al-Zahran described neurological injuries, including intracranial bleeding, concussions, and skull fractures. Ominous signs and symptoms following traumatic brain injury included vomiting, convulsions, encephalopathy, and fever [1].

During the Medieval Period, Roger of Salerno (c. 1170) reported on trephination for head trauma but also described in detail the procedure and benefits of head wound debridement and cleansing [1]. Lanfrancus (1296) correctly assigned reversible neurological injury to mild trauma to the brain, and equated a grim prognosis of traumatic brain injury to the constellation of fever and seizures. Guy de Chauliac (1290) is credited with having successfully performed a limited brain resection following head trauma.

It was not until the Renaissance, however, that anatomic structures were brought into association with disease states and therapeutics were improved. With the advent of the printing press, concepts and material could be widely disseminated, fostering rapid advancement in all fields, including medicine and neurology. Although Vesalius's seminal work on anatomy was revolutionary for medicine, he is believed to have rarely performed formal dissection of the cerebrum removed from the cranium during his course of describing the neuroanatomic elements of the brain.

Much work was left to anatomists such as Thomas Willis who published his "Anatomy of the Brain" in 1664 followed by "Cerebral Pathology" in 1676. He coined the term "neurology", and his concepts continued to refine contemporary understanding of epilepsy and stroke/paralysis.

Jean Louis Petit (1674-1750) was perhaps the first to correlate increased intracranial pressure with hemorrhage, and that delayed loss of consciousness was pressure related as opposed to the initial unconscious state following impact to the head. Unfortunately, the causes of morbidity and mortality secondary to elevated intracranial pressure were not universally appreciated; throughout most of the 18th century, serious injury was correlated only with the presence of a skull fracture. It was therefore inconceivable to convict a criminal of murder if the victim had been killed by blows to the head but there was no evidence of skull fracture [1].

Coincident with investigations into reviving the head trauma victim, resuscitation of the medically dying patient was promulgated during the 16th century by Paracelsus and later by Vesalius. Although Galen had described long before that introducing air into the oropharynx could serve to inflate the lungs, the latter described a method for artificial ventilation by inserting a reed into the tracheal lumen [6]. By the 18th century, upon the discovery of oxygen (1774) and carbon dioxide (1754), the concept of respiration and ventilation was set on a new scientific foundation. Techniques in both positive and negative pressure ventilation were introduced during the early 19th century and were later refined during the poliomyelitis epidemic between 1918 and the 1950s. The famed negative pressure "iron lungs" from the 1920s onward were remarkable devices that saved

uncountable lives. Developed by Sir Henry Gauvain, an iron lung machine was first used at Boston Children's Hospital in 1928.

The management of respiratory failure in poliomyelitis was probably the first medical example of neurological critical care. Ironically, during the early decades of the 20th century, it was those physicians who were interested and trained in neurological disease who were usually the primary caregivers of such patients and so could be defined as being the first "neurointensivists". Some neurologists provided invasive therapeutics such as tracheostomy, bronchoscopy and even abdominal surgical procedures [7].

While neurosurgical procedures were slowly refined during the 19th century, a landmark contribution to the ability to visualize, and hence resect lesions within the brain, was Dr. Walter Dandy's innovation of air ventriculography, which he described in 1918, and the less invasive technique of pneumoencephalography, which he developed and published in 1919. For this achievement he was nominated for the Nobel Prize in 1933. These two diagnostic techniques spurred advances in neurosurgery, as Dr. Dandy became increasingly skilled in operating on the brain and spinal cord. In 1921 he described an operation for the removal of pineal region tumours, in 1922 the complete removal of tumours of the cerebellopontine angle, and in 1922 the use of endoscopy in the treatment of hydrocephalus ("cerebral ventriculoscopy"). In parallel to his operative skills, Dandy also devoted considerable attention to perioperative care and operative efficiency. With the creation of his famous "brain team" at Johns Hopkins, which would dominate clinical neurosurgery between the 1920s and the 1940s, his recognition of the need to provide subspecialty support for his post-operative patients led to the establishment of the first acknowledged surgical, as well as the first neurosurgical, intensive care unit (3 beds) in 1923.

Thereafter, post-operative neurosurgical wards became commonplace, although they functioned separately from the parallel development of post-trauma "shock units" during World War II and high acuity medicine of the 1930s and 1940s. The 1950s brought together the increased utility of mechanical ventilation and landmark innovations in cardiac resuscitation. In 1958, Baltimore City Hospital (Maryland, USA), now the Johns Hopkins Bayview Medical Center, opened the first integrated, fully staffed ICU in the U.S. under the direction of Dr. Peter Safar. At the time, only about 25% of hospitals (>300 beds) had an ICU care model, but by the late1960s nearly 95% of hospitals had one in place [8].

With further advances in neurosurgery, and the ability to manage critical illness, neurology and post-operative neurosurgery became increasingly commonplace and more neuroscience patients were being admitted to the ICU. By the early to mid 1980s there was recognition among some neurologists that once again there was a need for physicians within their specialty to assist in the management of such a hospital population. But since medical and surgical-anesthesiologist intensivists were often not savvy to the critical care needs of neuroscience patients, a niche opened for a new neurologist/neurosurgeon/anesthesiologist: the neurointensivist.

Through the 1980s and 1990s, four major centres of neuroscience ICU training emerged: Dr. Allan Ropper at Massachusetts General Hospital; Dr. Thomas Bleck at the University of Virginia at Charlottesville; Dr. Matthew Fink at Columbia University; and Dr. Daniel Hanley at Johns Hopkins. These four neurologists were instrumental in defining the subspecialty of neurocritical care in the U.S. Meanwhile, in Europe, Dr. Werner Hacke pioneered efforts to unite acute stroke management and neuroscience ICU care.

1.1.3 Organization to Accommodate Practice

Today, neurocritical care has become an established subspecialty: the NeuroCritical Care Society was founded in 2003 and publishes its own journal – *The Journal of Neurocriti-*

cal Care (PubMed); fellowship and specialty received accreditation by the United Council for Neurologic Subspecialties (UCNS); and a formal match fellowship selection process came into being in 2009.

The position of neurological intensive care can be viewed as a gradual coalition between three patient populations and their respective venues of management: the post-operative neurosurgical patient – the neurosurgical ward/ICU; the stroke population – the neurology ward/stroke unit; and the neurological patient – the ward and medical ICUs. The advancement of medical therapeutics in neurological care, especially in the treatment of seizures, ventilatory support for neuromuscular disease, and thrombolysis and interventional neuroradiological intervention in cerebrovascular disease have enabled the neurocritical care concept to gain ground as a subspecialty ICU arena. That stated, the overlap in care within each of these unit environments and the limited availability of trained neurointensivists have each contributed to the number of currently applied neuroscience ICU practice models.

The simplest provision of a neurointensivist is as a consultant physician to an ICU practice. Such physicians provide valuable input into the management of critically ill patients, but their focus of attention and authority is typically limited. In such a model of care, comprehensive ICU management remains the responsibility of a critical care team not under the control of the consultant. Yet, as more and more neurointensivists are trained and populate hospital domains previously without any neuroscience ICU support at all, this model is often the initial step to be taken.

In medical centres that tap into resources of neurosurgery and anesthesiology, it is more likely that neuroscience ICU care can be offered in a more comprehensive fashion, whether delivered in an open, semiclosed, or closed ICU model. Although the last clearly offers the most unified approach to patient management, it requires a very collegial relationship between the neuroscience departments, as well as hospital support for highly trained nursing staff and additional resources. The specific type of the incorporated model also has much to do with a medical centre's emphasis of care. In neurosurgically dominant facilities, attention must be directed to afford maximal efficiency to perioperative management and to facilitate bed availability and care protocols. Where neurological admissions are common, having efficient links between the Emergency Department and the ICU is paramount, and the integration of a stroke centre matrix is also vital. In larger settings, both neurosurgical and neurological needs are met. In the framework of acute neurosciences, the neuroscience ICU acts as a "hub" of clinical activity, with neurosurgery, acute neurology, stroke team, and interventional neuroradiol-

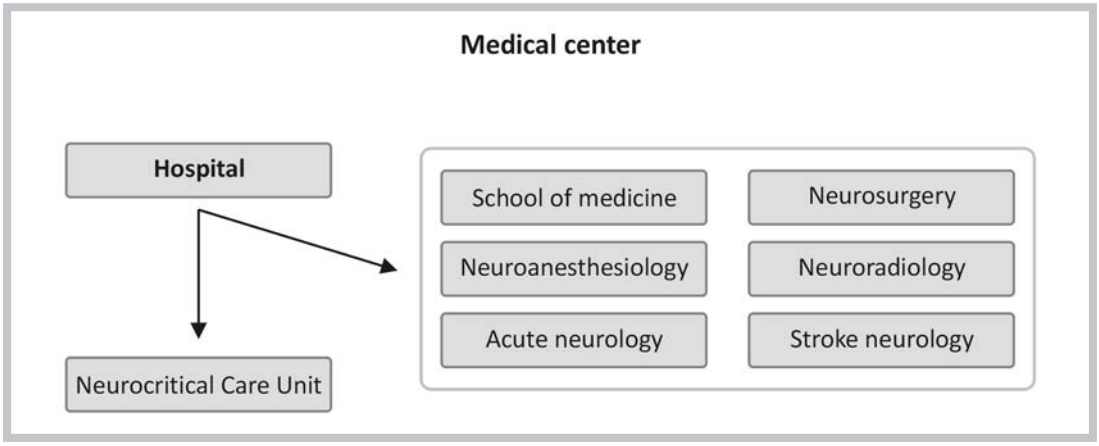

Figure 1.1. Acute interdisciplinary ICU program.

- Consultative vs. comprehensive
- Internal construct (closed vs. open)
- Protocols (or not)
- Staffing model: intensivists, nurse practitioner (NP), fellow, resident
- Educational and training role: fellow, resident, NP
- Billing format: admitting MD, consultative
- Breaking out: lofty goals, academics

Table 1.1. **Neuroscience Intensive Care Unit: organizational perspective.**

ogy as the key spokes in the comprehensive acute neuroscience program (Figure 1.1).

As the neuroscience ICU becomes established and clinical activity increases, the staffing model becomes key to continued growth and success. Comprehensive care, the goal of any ICU team, is possible only with the provision of ample physician level coverage – attendings, nurse practitioners, fellows and residents – for 24/7 patient oversight. A variety of staffing models exists in U.S. neuroscience ICUs and is an important element in the organizational perspective and intent of the ICU (Table 1.1).

1.1.4 The Standalone Neuroscience ICU: The Hospital Versus the Physician Argument

As medical centres strive to grow their acute neuroscience programs, the debate of creating a subspecialty neuroscience ICU versus managing patients in a more generic model of critical care (general medical or surgical ICU) is often entertained. Arguments for both clinical domains can be made. The hospital argument against a subspecialty ICU is mainly justified by the increased inefficiency of the ICU system. Limited bed flexibility, staffing with ICU specific nurses, and increased physician coverage all increase the overall cost of ICU management (Table 1.2).

On the physician side, there are numerous overt and potential patient outcome benefits and financial remuneration to the medical centre that should offset the inefficiencies inherent to a subspecialty ICU system. These advantages can be summarized as 1) direct patient benefit in outcome measures as supported by published data; and 2) strengthening hospital neuroscience initiatives and efficiencies of care (Table 1.3). With regard to improved outcomes, there are several published comparative series that review patient care in both neurological and neurosurgical disease. In neurology, intracranial hemorrhage is the most common diagnosis as it accounts for the highest incidence of a homogeneous group of neurological admissions to a neuroscience ICU. Reports by Diringer et al. and Mirski et al. both support the benefit of a neurological subspecialty ICU in terms of decreased mortality, from an estimated 40-50% in a general ICU to a mean of about 20-25% [9,10]. Others groups have also reported the benefits of a subspecialty neuroscience ICU, with lower

- Administrative and political goals/conflicts
- Other ICUs – Patients selection
- Territorial issues
- Increases cost/patient
- Sacrifice bed efficiency
- Dilutes Intesivist coverage pool

Table 1.2. **Impediments towards a subspecialty neuroscience ICU.**

- Improvement in patient outcome
- Sensitive neurological evaluations
- Precise match therapeutics to neuropathophysiology
- Neurocritical trained nursing
- Cohesive and comprehensive rounds
- Neurological monitoring – capable and savy
- Hub of clinical neuroscience communication
- Neurological and neurosurgical priority
- Academic concentration
- Centrepiece – Acute Neuroscience Center of Excellence

Table 1.3. **Standalone Neuroscience ICU: the physician argument.**

mortality and improve ICU management [11-13].

Furthering the argument, the U.S. business community led an initiative to provide improved ICU care to their insured employees as a means to enhance quality of care and reduce spending. The Leapfrog Initiative http://www.leapfroggroup.org) lists ICU care metrics presumed to achieve these goals. Among them are several pertinent to the presence of an ICU intensivist: 1) intensivist(s) present in the ICU during daytime hours, days per week, with no other clinical duties during this time; 2) return rates of over 95% of pages within 5 minutes; and 3) reliance on a physician (e.g., fellow or resident) or a non-physician extender in the hospital and able to reach ICU patients in less than 5 minutes during non-daytime hours. In an environment clamouring for more physicians to specialize in critical care, the arrival of neurointensivists to direct and manage existing neuroscience ICUs (or neurosurgical units which are commonplace) makes good business sense. Modelling out such intensivist-driven care, Pronovost and colleagues at Johns Hopkins estimated a cost savings to a medical centre, beyond the additional expense of financing a subspecialty intensivist-driven ICU, of between $ 800,000 and $ 3,000,000. Even in a worst case scenario, the savings would exceed $ 1 million on average [14] (Table 1.4).

Revenues	• Clinical ICU professional fee • Other clinical revenue (e.g. consults, etc.) • Extramural salary support (e.g. research grants, etc.) • Neurophysiology laboratory (e.g. transcranial doppler, ultrasound) • Joint agreement (Medical Center and ICU) • Clinical trials, ICU courses
Expenses	• Salary and benefits • Additional (Faculty/fellow educational allotment) • Faculty direct overhead (physical plant) • Departmental overhead (administration) • Supplies and equipment

Table 1.4. **Potential areas of revenue and expense for a neuroscience ICU. Specific to this issue, comparison of the function and cost of care of a newly formed neuroscience ICU as compared with the same patient population cared for in a mixed medical-surgical ICU set up just 2 years earlier yielded substantial cost savings in length of stay and cost reduction in expenditures for radiology, pharmacy and laboratory testing services [10].**

1.1.5 Conclusions

Looking toward the future, the reality is that even if all the current academic fellowship training sites for neurocritical care continue to graduate several dozen subspecialty intensivists, their number will be too few to meet the demand within the acute neurosciences. In large, medium, and even smaller community hospitals, there will be a greater need for neurological expertise in the critical care environment as we promote newer therapies for acute stroke, head injury, and perioperative care. In general, much of this domain is beyond the usual training of a medical or surgical intensivist. That may indeed have to change. But currently neurological disease is not well addressed in ICU programs in the U.S., and too few neurologists seek engagement in a hospital critical care setting. The likely answer lies in the realm of the expanding demand and supply of telehealth solutions that can provide virtual bedside consultation directly between an intensivist or a surgeon and a neurointensivist. In the U.S. alone there is a disproportionate situation of a mere 50 well-staffed neuroscience ICUs amongst 6000 hospitals and their corresponding medical and surgical critical care areas. As a sudden genesis of first tier comprehensive neurological centres is unlikely, it appears reasonable to expect that the care provided in such domains must be directed outwards. That will very likely be the second evolution of neurological critical care.

1.2 NICU Organization: Past, Present and Future: Prof. Robertson's Point of View

I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least part of the work.
Harvey Cushing

Neurocritical patient care draws a parallel line with the principles of general intensive care which requires a thorough understanding of the pathophysiology and focuses initially on the resuscitation of patients in extreme physiological deterioration. The focus of the initial approach is usually on the acute condition without considering in detail the patient's medical chronic condition. Then, the intensivist should gather the patient's medical history, essential to complement the assessment of his/her current physiological condition. General intensive medical care has been predicated on the ability to give time for a specific therapy to work or for restoring tissue to promote the recovery of organ function. However, there are few available effective therapies for brain injury (trauma, vascular, etc.): the limited plasticity of the fully mature brain should also be considered.

1.2.1 Past

The history of neurosurgery and the management of traumatic brain injury (TBI) are inextricably linked. Trepanation was sometimes named the "first surgical procedure", with the first reported trepanations found in Northern Africa and dating back to around 10000 BC [1]. There is abundant archeological evidence for the success of trepanation worldwide, with the Peruvian Pre-Columbian collection being perhaps the most noted [2]. Identifying the purpose of this practice isn't easy, but some answers include both medical reasons and mystical practices: treatment for headache after TBI [3], treatment for epilepsy, migraine or psychiatric disorders, and even "letting out the evil spirit."
It is prudent to mention that there is ample room for speculation in this area, and that the "after surgery" care provided by the "first neurosurgeons" also gives rise to controversy. Very likely, trepanation developed in different regions of the world independently. A precise starting point of the history of neurosurgery and neurocritical care surgery is a topic of discussion, and some medical historians have preferred to establish arbitrary phases in the history of neurosurgery [4] or characters or regions, without any current convention universally accepted.
To mention some from the ancient world: the Edwin Smith Surgical Papyrus is about 3700 years old and an alleged copy of a 5000-year-old manuscript (during Egypt's Old Kingdom [5]) describes injuries in the head, spine and/or spinal cord, as well as other neurological conditions. Of course, the father of modern medicine is the Greek Hippocrates of Cos who, in his treatise "On Injuries of the Head" written around 400 BC, described six specific types of TBI, treatments and even prognosis [6]. Six centuries later, Galen (129-200 AD), a Greek physician working in Rome, improved the trepanation technique based on the foundations of the Hippocratic body of works and collected, developed, and expanded all previous medical knowledge. His works became the basis of knowledge of the nervous system taught up until the Renaissance and into the late sixteenth century [7]. In the Middle Ages, neurosurgical developments, like all other scientific knowledge, were obscured by medical scholasticism, where metaphysical

explanations became prominent in medical schools and "Hippocratic/Galenic orthodoxy" prevailed. The subsequent translation of Greek and Latin writings into Arabic and back into Latin led to many misunderstandings, particularly in the anatomical works, and those new findings that differed from the ancient texts were unfortunately ignored. The lack of anatomical knowledge and poor surgical outcomes led physicians to recommend against brain surgery.

With the Scientific Revolution of the sixteenth to the nineteenth century, neuroanatomy based on direct observation returned, allowing new detailed descriptions of anatomy and physiology, including other vital organs such as the heart and vessels, as well as innovative approaches. The first published attempt (failed) to resurrect a dead patient, with the implicit hope that the brain would recover, can be attributed to Paracelsus in 1530. Jackson, in 1746, described the insertion of a tube into the airway to provide artificial respiration. He proposed the possibility that "it may be necessary to make an opening in the windpipe for this purpose."

Joseph Black discovered carbon dioxide in 1754, and Joseph Priestley discovered oxygen in 1774. Chaussier developed a device that administered oxygen to humans in 1780, which closely resembled the mask with reservoir bag in use today (but without a valve). Concern about possible adverse consequences of positive pressure ventilation and excessive oxygen administration began soon after its appearance, and still continues today. Negative pressure ventilation started with the first tank respirator invented in 1832 by Dalziel, and pursued by von Hauke 40 years later.

In 1880, Waldenburg invented the cuirass respirator which covers only the chest instead of the entire body below the neck. Bowditch invented the first mechanical ventilator in 1879, with several of his contemporaries making significant contributions [8].

Little progress was made during this period of almost 400 years owing to the lack of the concept of brain mapping, availability of anesthesia, and understanding of infections. The immediate need for trepanising after TBI was not appreciated and less importance was given to the neurological damage until the last decades of the nineteenth century. Hutchinson in 1867 published a series of works that introduced a new diagnostic sign for brain injury: third cranial nerve palsy. In that year, Lister published his first works on antisepsis.

1.2.2 Present

Modern neurosurgery can trace its origins back to the late nineteenth century. By 1880 a surgical environment free of infection was established, laying the scientific basis for deliberate surgical invasion of the central nervous system as we know it today. Results of surgical interventions, though imperfect, were significantly improved over previous useless treatments. The most important contributions to our understanding of the microscopic anatomy of the nervous system were made by Santiago Ramón y Cajal in a series of works that began in 1892. Neurologists fostered neurosurgical interventions by diagnosis and locating lesions. Since most of the surgeons lacked any neurological skill, they also helped the neurosurgeons in the operating room and postoperative care.

In 1920, Cushing talked about neurosurgery as a "new specialty", creating a separate entity, the American Association of Neurological Surgeons. He reported a 7.4% operative mortality in his series in Boston. At that time, European centres reported mortality rates between 40% and 50% [9], emphasizing the need for special training beyond general surgery, turning it into a national American model, with a subsequent demonstration of its success in training, treatment outcomes, and research productivity: Cushing's model became the global model.

The poliomyelitis epidemic with subsequent respiratory failure revived the development of negative pressure ventilators. Stewart and Rogoff improved the original concept of the tank in 1918. In 1929, Drinker and McKhann described further refinements, and Drinker's "iron lung" saved countless lives. The subsequent use of endotracheal tubes allowed wider use mechanical ventilators. In the polio epidemic of the 1950s, medical students frequently used the reservoir bag system to ventilate patients for weeks. The mechanical ventilator was first introduced by the Bennett Corporation in 1948. The ability to maintain the breathing of polio patients with any of these mechanical ventilation systems defined the start of modern neurocritical care.

Many neurologists became the family doctors for these patients. A battle began between neurologists and infectivologists over who should take care of patients with other forms of neurogenic respiratory failure, such as tetanus, botulism, Guillain-Barré syndrome, and myasthenia gravis. Fortunately, in the early 1950s, Salk developed the polio vaccine which, with the Sabin vaccine, led to the near eradication of this scourge from the face of the earth.

Again, medical historians face the question of the first general intensive care unit with three reasonable candidates: Johns Hopkins Hospital in Baltimore, Maryland, in 1928 [10], with a three-bed unit specialized in post-surgical care; Bjørn Ibsen, in Copenhagen, Denmark, in 1952 [11]; and Peter Safar in 1961 in Baltimore City Hospital, whose interest focused on cerebral protection and resuscitation. Therefore, the early generation of intensivists viewed neurological function as a major part of their responsibility [8]. At the University of Colorado, Earnest established a neurological ICU in 1969. Jackson led a course in intensive care for neurologists in Cleveland in the 1970s.

The Baylor College of Medicine opened its neurosurgical ICU in 1982 at Ben Taub General Hospital in the Texas Medical Center in Houston, and it is still one of the largest units specialized in neurotrauma critical care and research. Ropper, Kennedy, and Zervas opened a neurological/neurosurgical ICU at Massachusetts General Hospital and wrote the first textbook on neurocritical care in 1983 [12]. Hanley and Borel opened a neurocritical care unit with a training program at Johns Hopkins Hospital, Fink at Columbia, and Haley and Bleck at the University of Virginia in 1989. Although the first contemporary neurosurgical ICUs date back about 40 years, neurocritical care is a recently recognized specialty: in 2007, the United Council for Neurological Subspecialties approved neurocritical care as a subspecialty and the first certification exam was also featured that year.

Evolution of Technology in Neurocritical Care

Neurocritical care is an important and ongoing topic in research, education and medical practice. After brain injury, a key principle is that the primary lesion helps to determine the prognosis, but secondary injury (inflammation, edema, free radicals, etc.) also plays an important role in the outcome. Of paramount importance in neurointensive care is the close monitoring of the factors that usually ensue and contribute to the worsening of secondary injury, i.e., hypoxemia, hypotension, seizures, fever, and intracranial hypertension.

Initially, neurological ICUs (NICUs) between the 1960s and 1980s focused almost exclusively on the postoperative care of neurosurgical patients, and neuromonitoring was restricted mainly to serial neurologic examination and, in some units, monitoring of intracranial pressure (ICP). Often, these neurological examinations did not reveal changes in brain function until they were irreversible. The idea was to detect clinical deterioration as soon as possible, allowing early efforts to reverse or correct any damaging process. This era can be considered as the age of "clinical neuromonitoring" [13]. A brief description of the evolution of the technology typically used in modern neuromonitoring and management is provided here.

Intracranial Pressure Monitoring

The first published reports of left ventricular puncture date back to 1850. Over the next 100 years, the procedure was refined; with the addition of a manometer in 1948, the modern system of external ventricular drainage (ventriculostomy) was introduced, but its routine use began only in the early 1970s for treating Reye's syndrome and subarachnoid hemorrhage. In the early 1980s, several reports appeared showing better results in severe TBI with the use of ICP monitoring. In 1995, ICP monitoring was officially recommended for trauma victims with a Glasgow Coma Scale (GCS) score of 3-8 [14]. Typically, ventriculostomy is one of the first procedures taught to neurosurgery residents and it is still the most complex procedure carried out without supervision. Technology has now provided several new strategies to measure ICP non-invasively, but the need to place a ventriculostomy will continue.

Temperature and Brain Tissue Oxygen Monitoring

Clark introduced his semipermeable probe of polarographic cells in the 1960s. In the 1980s, Fleckenstein developed the $PbtO_2$ system used in LICOX systems. Since the temperature coefficient is required to calculate the value of oxygen, researchers assumed that rectal temperature reflected brain temperature. Studies carried out by the Baylor College of Medicine at Ben Taub General Hospital later found that brain temperature was consistently and significantly higher than core temperature after brain trauma [15]. The advent of new combined monitors has helped to underscore the importance of controlling fever in patients with severe TBI and to monitor the effectiveness of therapeutic hypothermia. Another new method uses fibre-optic technology and measures $PbtO_2$, $PbtCO_2$ and pH.

Monitoring of Jugular Venous Oxygen Saturation ($SjvO_2$)

Cerebral venous oxygenation was investigated as part of neuromonitoring for 70 years by Gibbs who started in 1935. Use of the fibre-optic catheter in TBI introduced in 1983 by Cruz in Brazil and Philadelphia led to the wider acceptance of $SvjO_2$ monitoring supported by validation studies which showed its usefulness in neurotrauma at the Baylor College of Medicine in Houston, Texas, in the 1990s.

Microdialysis

Devised in 1974 by Ungerstedt in Stockholm, Sweden, human brain microdialysis in neurointensive care has become by far the most widely used application of this minimally invasive technique. Since 1984, bedside analyzers have been used more in Europe than in the United States in patients with severe TBI and subarachnoid hemorrhage. The substances that can be potentially measured are innumerable: neurotransmitters/metabolites related to energy (the most common current application), markers of tissue damage and inflammation, drugs administered, etc. The first effort to reach consensus on the indications for microdialysis in neurointensive care was undertaken in Cambridge in 2000, with a follow-up meeting held at the Karolinska Institute in Stockholm in 2002.

Therapeutic Hypothermia

The first modern scientific report describing the clinical application of therapeutic hypothermia in a case series of patients with severe TBI was published by Fay in 1945. In the 1960s, Rosomoff and Safar carried out studies that discouraged its use because of the adverse effects with profound hypothermia (<30° C). But in the 1980s interest was revived using mild hypothermia with few and minor severe adverse effects thanks to improvements in the capabilities of ICUs to control and prevent side effects. Therapeutic

hypothermia is now used for neuroprotection and management of ICP, one of its most studied uses, and always deserves close neurointensive care. Theoretically, local hypothermia may have certain advantages over the adverse effects of systemic hypothermia, and this matter is still under development.

Electroencephalographic Monitoring (EEG)

Far from being unique to neurocritical care, EEG monitoring has become a common tool in NICUs. The first physiological studies were presented by Berger in 1920 in Germany. Gibbs published his first works in clinical EEG in 1935 in Boston at Massachusetts General Hospital, and Jennett in 1974 wrote his work on epilepsy after TBI. In the neurointensive care setting, continuous EEG (cEEG), short-term EEG, and new variants such as the compressed spectral array (CSA) and bispectral index (BIS) help in the diagnosis, prognosis and assessment of targeted therapy.

Neuroimaging

It would be hard to imagine modern neuroscience without the currently available neuroimaging techniques. Since its emergence in 1972 and thanks to the availability of computers, computed axial tomography (CT) easily replaced the archaic use of the angiogram to diagnose epidural hematoma, improving mortality and disability rates [16], transforming all the neurosciences, initially with a special clinical impact on neurotrauma. Neuroimaging is constantly evolving: mastering all new techniques seems impossible, but their usefulness in research and clinical practice remains undeniable. Radiology is one of the best examples of the impact of technology in today's medicine.

Neurocritical care shares with general critical care several important systemic monitoring tools, as well as therapies essential to closely monitor and improve the chances of survival and recovery during the acute phase of illness, and they have become the standard care recommended by management guidelines. Management includes invasive blood pressure (arterial line), CO_2 at the end of expiration ($ETCO_2$), pulse oximetry, mechanical ventilation, continuous electrocardiography, central venous catheter, vasoactive drugs, sedation, nutrition, prophylaxis for gastrointestinal hemorrhage, thrombosis, seizures, pressure ulcers, and infections among others, which are typically provided in conjunction with neuromonitoring, not to mention the irreplaceable role of the clinical laboratory.

Assessment Scales

Because critical care is focused on severely ill patients, where "severe" is not always easy to define, several sets of scales have been developed to help establish specifically how severe ill a patient is, thus facilitating the selection and evaluation of therapy, fulfilling criteria for entry into a research study, and to establish prognosis. Jennett and Teasdale published the Glasgow Coma Scale (GCS) in 1974, and Jennett the Glasgow Outcome Scale (GOS) in 1975 [17], both designed to clinically evaluate the central nervous system status in patients with neurotrauma. The APACHE scale (Acute Physiology and Chronic Health Evaluation) issued in 1981, replaced by APACHE II in 1985 by Knaus, was calculated from 12 routine physiological measurements (blood pressure, arterial pH, etc.) during the first 24 hours after admission. A refined scale known as APACHE III was published in 1992. SAPS II (Simplified Acute Physiology Score), devised by Le Gall in 1993, describes patient morbidity when comparing the results with other patients.

SAPS III is a system to predict a specific definition of mortality (e.g., 30-day mortality) when comparing groups of patients, but it requires computer calibration to achieve its functionality. The SOFA scale (Sequential Organ Failure Assessment Score) devised by

Vincent in 1996 [18] is used to track patients' status daily during their stay and to predict outcome and mortality; it evaluates the degree of failure of 6 organ systems (respiratory, cardiovascular, neurological, hepatic, renal and coagulation). The MPM scale (Mortality Probability Models), introduced by Lemeshow in 1988, predicts mortality at ICU admission, and an updated version (which requires no calibration) was introduced in 2005 [19]. The logistic model published by Narayan in 1988 uses multivariate analysis to predict the probability of positive or negative outcome in coma patients after severe TBI.

These are some of the most commonly used scales. There is still interest in developing new systems of scales or improving the existing ones in order to make them more accurate and specific. No scale is perfect or unlimited, and no scale is generally superior to good clinical judgment. Therefore, decisions in individual patients should never be taken based solely on a statistically derived scale of severity of injury. Where scale systems can be used is to estimate quantitatively the degree of acuteness in severe patients and to adjust the outcome assessments of hospitals [20].

The socioeconomic impact of general or specialized critical care undeniably derives from the fact that nearly 6 million adults are admitted to intensive care each year and that one out of 5 Americans dies in intensive care [21,22]. About 2% of the U.S. population are admitted to an intensive care unit each year, occupying 5-10% of all hospital beds but accounting for 20-35% of total hospital costs [23]. Despite its size, there is no formal standardization or federal monitoring of intensive care.

ICUs continue to have a significant local *colour*, with wide variation in staffing patterns. There is poor consensus on who should be admitted to an ICU, who should provide intensive care, and how much intensive the care should be delivered [24-28]. One third to one half of the U.S. population will enter an ICU during their last year of life [29,30], and a fifth will die there [31]. One aspect of the ICU on which there is little debate is that it is costly, absorbing about 1% of the U.S. gross domestic product [21,32]. There is also growing concern about the possible long-term sequelae of surviving critical illness [33,34].

Hence, it is essential to understand that intensive care is a significant part of a health care system, which is extremely large, extremely expensive, but not necessarily optimal. This is not always the case, as the U.S. health system is by far the most expensive in the world [35] but ranks 37th in overall performance and 72nd in population coverage [36]. ICUs are a smaller portion of health systems in other industrialized countries but still represent a significant and disproportionate segment of care and medical costs [37-39]. Even changes in how intensive care is proportionate may have public health ramifications that can affect an entire nation [40].

Together with the projection of the World Health Organization (WHO) that by 2020 road accidents, a major cause of TBI, will be the third leading cause of global burden of disease and injury, after ischemic heart disease and unipolar major depression [41], also the COMPACCS (Committee on Manpower for Pulmonary and Critical Care Societies) estimated that by 2020 the supply of pulmonologists will meet only 35% of the demand. By 2030, the gap will widen to 46% of demand. The shortage calculated for intensivists is 22% and 35% for 2020 and 2030, respectively [27].

This has placed the inevitable task on neurocritical care of proving its importance and, above all, its effectiveness. In 1989 and 1991, two studies conducted in England and the United States, respectively, documented considerable variability in the management of patients with severe TBI [42]: this led to the creation of TARN (Trauma Audit & Research Network) in Europe and the Guidelines for the Management of Severe Traumatic Brain Injury in the United States [14]. Subsequent publications comparing mortality before and after guidelines implementation showed a marked reduction in mortality [43-45],

with subsequent evaluations in 2000 and 2006 showing marked adherence to guidelines since 1991 [46].

In 1997, members of the Task Force of the European Society of Intensive Care Medicine published recommendations for the minimum requirements for intensive care in ICUs [43], emphasizing the fact that intensive care medicine depends on the tight interaction between human, technological and space resources. Since the creation of NICUs, data on long-term outcome and quality of life of survivors of NICUs have been limited. A recent study in Austria found, however, that TISS-28 (Therapeutic Intervention Scoring System) scores on admission and at discharge and age were independent predictors of poor outcome in this unselected representative population of neurocritical care [47].

Outcome measurement is a suitable tool to reflect the daily work of intensivists and to legitimize its important implications for the allocation of hospital resources. Given the association between mortality and the economic impact of such patients, a more detailed understanding of this patient population may facilitate care and management decisions [48]. The purpose of any recommendation is to provide guidance for those planning a new department or adapting an existing one. However, it should be clarified that most recommendations are not always based on well-documented scientific evidence, but rather express the view of experts involved in intensive care medicine and may require adjustment to local situations. Many existing intensive care departments may be unable to comply with some recommendations due to human and financial resource issues.

As an emerging subspecialty, neurocritical care is a highly specialized field which demands specialized staff. There is growing concern about the need for trained personnel in neurocritical care, emphasizing the trend toward more efficient and accurate practice patterns designed for neurocritically ill patients. Modern NICUs are not only a place for neurocritical patients but also a place where advanced medical technology is coupled with the understanding of organ dysfunction resulting from nervous system failure. Several different types of institution-dependent practices of NICUs have emerged, in part because of competition between neurointensivists, neurosurgeons, neurologists, and other intensive care physicians, resulting in three different models of NICU organization: open, closed and closed-cooperative (hybrid). The selection of “best practice” is still under discussion and under scrutiny.

The open NICU is probably the most common model, especially in private practice. It involves a neurointensivist with privileges to admit patients to a NICU but not responsible for all patients of a NICU. The neurosurgeon can admit patients directly to a NICU and consult other intensivists to manage ventilated patients. The open model may decline in tertiary centres but it may persist in smaller NICUs where there are fewer resources for *in situ* 24-hour supervision of an intensivist [49].

In addition, other factors driving these changes include reductions in salary [50], loss of the physician’s individual autonomy, sharper distinction between hospital-based and consulting-based practice, and the increasing emphasis on patient outcomes. Some authors have demonstrated shorter duration of ICU stay, improved mortality rates and greater team satisfaction with the closed model.

The closed NICU is the model where all neurological ICU patients are managed primarily by the neurointensivist. After discharge from a NICU, patients are attended by the neurologist or the neurosurgeon team. Some units also take care of non-neurological patients. Most procedures are carried out by the NICU team.

The hybrid NICU is where neurology/neurosurgery continues to have an active role in managing NICU patients (mainly with regard to informing the family and taking long-term management decisions). The NICU team handles routine situations and is re-

sponsible for most procedures [51]. This model is generally adopted in teaching hospitals.

TBI cases are medically complex, involving the physical, cognitive, behavioural, social and emotional aspects of survivors. Often catastrophic, these cases require substantial financial resources not only for the patient's survival but also to achieve optimum results in productive life, with a return to family responsibilities and work. TBI cases involve the injured person, his/her family, medical professionals including the attending physician and therapist, the attorney, the employer, the community resources, the source of resources, and usually the insurance company. The case management department facilitates the achievement of optimum results by engaging the collaboration of all parties involved, assessing priorities and options, coordinating services, and educating and communicating with all that concerns [52].

At the Ben Taub General Hospital (a Trauma Level 1 teaching hospital), our NICU has 16 beds managed by the Baylor College of Medicine and the staff of the Harris County Hospital District. It may be defined as a closed model, with a neurointensivist as medical director attending patients on the daily rounds, undertaken by the chief neurosurgeon of neurosurgery and neurosurgical residents (grades II, III, IV and chief resident), one or more temporary rotators (from general surgery, maxillofacial surgery, otolaryngology, plastic surgery, undergraduate medical students), a research team member, a physician assistant, the head nurse, the nursing administrator, and usually both a nurse from the previous shift and one from the following shift, joined once a week by the case manager, and the nutrition and rehabilitation staff.

The neurosurgery team performs the physical examination, writes progress notes and medical prescriptions, checks lab results and images, decides on admissions and discharges, performs most procedures and asks for consultations from other services when necessary. The medical director is available within the hospital 7 days a week during working hours and is reachable 24/7 by phone. The neurosurgery team is available within the hospital 24/7. The research team is available within the hospital during working hours and 24/7 by phone.

The nurse/patient ratio is 1:2, in a distribution of 13 contiguous beds arranged in a C shape, with a sink/bed ratio of 1:2, and a group of three additional isolation rooms that close the ring where the nurses' station and administrative assistant occupy the centre, with an additional team for the telemetry monitoring system. Other routine staff that is usually not present during the daily rounds consists of inhalation therapy staff, radiology technicians who operate a portable CT scanner (exclusive of the NICU) for simple skull CT in addition to xenon-CT in coordination with the research team, the team of nuclear medicine for blood cerebral flow scanning with radionuclide, bioengineering technicians, social workers, pharmacy staff, and cleaning staff familiar with the NICU environment.

Medical Staff

The appointment of a neurointensivist as medical director and the availability 24/7 within the hospital of a neurosurgeon for trauma patients have been shown to improve survival, mortality and outcome, increase efficiency, reduce the length of stay, reduce the use of resources, facilitate the implementation of protocols (drugs, ventilation weaning, etc.) and daily formal visits to the patients, lower the level of frustration for nurses, improve the layout and clinical record documentation [45,47,53-56]. In contrast, there are also data demonstrating that academic institutions in the United States that offer 24/7 coverage by staff within the hospital and other medical extensions as critical care support, either by pager or cell phone, do not offer any temporary change in mortality, length of NICU or hospital stay [57].

Non-medical Staff

The collaboration between the NICU physician and the nurse has been promoted as a way to improve care. Theoretically, this allows the contribution of both professionals and should produce decisions that lead to better outcomes because the decisions are based on more complete information. Collaboration is defined as physicians and nurses working together, sharing responsibility for solving problems and making decisions to formulate and carry out plans for patient care [58].

This can be conceptualized and measured at either the individual patient or the organizational level of the NICU, and both types of collaboration have been positively associated with patient's outcome in the neurocritical care setting [59]. The value of having nurses specialized in different ICUs has also been emphasized [58,60-62].

The importance of the nurse/patient ratio was highlighted in the European Prevalence of Infection in Intensive Care (EPIC) study conducted by the European Society of Critical Care Medicine, which suggested that minimizing the nurse/patient ratio reduced the spread of infections acquired in the ICU [63]. However, ICUs throughout the country are struggling to recruit and retain nurses. The projected growth rate of 6% in the supply of nurses will not match the 40% increase in demand by 2020 [64], and physician assistants (PAs) have been proposed as a partial solution to predicted shortages of doctors and nurses [65]. Although only about 6% of graduate PAs take advantage of advanced training programs [66], the example of effective functioning of PAs in surgical ICUs has been explored [67].

Research Team

Besides the undeniable importance of research to expand knowledge and enhance the practice of evidence-based medicine, placebo groups have demonstrated significantly improved outcomes when comparing data from the late 1980s: as we have seen, this course may be related to adherence to management guidelines, neuromonitoring and the presence of a specialized intensive care team; in theory, however, patients could benefit from having only closer monitoring as when they are enrolled in a research study. In fact, it has become a common joke among investigators when asked about their availability to be study subjects, expressing their enthusiasm to participate and, if possible, to choose to belong to the placebo group. Awareness of the society about the importance of research lies primarily with the research teams: the errors committed by this particular workforce can negatively impact on the desire of society to participate in the future.

Rehabilitation and Physical Therapy

The early rehabilitation program in the acute phase has been associated with improved cognitive functioning levels, shorter duration of coma, and shorter hospital stay of patients with severe TBI [68]. However, some authors have found no benefit gained from early rehabilitation in elderly patients or patients with pre-existing morbidity after TBI [68]. Additional work is needed to determine how physical rehabilitation impacts on specific medical issues, long-term outcome and cost of health care.

Case Management

Severe TBI is often considered catastrophic in terms of cost, recovery time, consequences and burden on society. The case manager's work in the long-term recovery after a disaster is to identify the needs of the survivor and connect him/her with resources, working with the committee for long-term recovery to do what is necessary to put patients back on their feet. The case manager works over the long term with the survivor to make

a thorough assessment of his/her needs to determine which ones are related to the disaster and then help the survivor to develop a recovery plan.
The relationship between the manager and the survivor is to advocate; in doing so, the development of the relationship is as important as the patient's needs. Because staff have experienced the largest growth compared with other hospital personnel, they also face the need to demonstrate their effectiveness. While this has also been explored [69], evidence for case management effectiveness is mixed. Some studies show a positive relationship [70,71], whereas there are conflicting results concerning the effects of case management on functional status, quality of life, family impact and other aspects of recovery. Further research is needed to resolve the doubts of the effectiveness of case management among TBI survivors and their families [69]. The value of the case management department at the patient's level is irrefutable, even though the evidence for its effectiveness on a large scale remains unclear.

Transport of Critically Ill Patients

Despite the enormous sophistication of NICUs, sometimes not all patient care can be carried out there. Patients may need to be transferred to the radiology department, operating room, or more importantly, to other medical centres with ICU facilities for specialized care. These situations can jeopardize patient safety, as demonstrated in several studies [72-74], where increased adverse events during transport between facilities were rare, although analysis of the data in greater detail revealed a number of preventable events.
Patients transferred over greater distances or receiving vasopressor drugs may be at increased risk for minor adverse events during flight. Improvement could be achieved through better communication between the referring and the receiving hospital, and through strict adherence to and the use of a checklist of published protocols. Patients transported between ICUs are still critically ill and should be handled as such. A transport environment presents challenges not faced in an ICU, and care provider capabilities are limited once outside the unit. The transport of critically ill patients should be avoided at all cost, and it is advisable to plan to have portable diagnostic equipment for radiology procedures or make transports shorter (e.g., having the operating room nearby on the same floor).

Trauma Centres

NICUs must have well-defined communication channels in order to work closely with emergency rooms and rescue services, especially in the care of neurotrauma patients. This has led to the creation of regional trauma care services, with a positive impact on survival, mortality, length of stay, outcome, and resource utilization. A Level 1 trauma centre requires the immediate availability of trauma surgeons, anesthesiologists, specialized doctors, nurses, and a resuscitation team. Its goals include providing complete trauma care, serving as a regional resource, and providing education and research. The positive relationship between trauma systems and neurosurgeons has also been documented [75].

1.2.3 Future

The future of NICUs and other specialized ICUs seems to be both amazing and disturbing. Neurointensive care is expanding, with much work still to be done and countless questions to solve, while facing shortages in financial and human resources, along with the rest of the health system: physicians should participate as active players by explor-

ing different solutions to the economical issues, while improving care in terms of outcome and cost-effectiveness. Having an *ideal* NICU is by definition impossible not only because of financial cuts but because patients, families, nurses and physicians have different perspectives on what an ideal ICU would be and what kind of culture would exist in an ideal ICU [76].

In the future, inputs from all these stakeholders will be required to help create an ideal ICU and the environment around the bed [77]. The NICU at Emory Hospital, Georgia, has explored a more patient/family-targeted approach, with rooms designed with enough space to perform complicated procedures at the bedside, eliminating the need to transport fragile patients elsewhere in the hospital. For the patient's family there are rooms equipped with a folding sofa, wireless Internet access, and TV adjacent to the patient's room. Separated by a glass wall, the rooms foster the family's role in the healing process. Amenities within the unit, such as showers, kitchen and laundry facilities, alleviate many of the daily pressures on families.

The future often depends on technological advances and the NICU is no exception: cECG with improved diagnostic accuracy, as in arrhythmia, reduced autonomic activity, accurate non-invasive continuous blood pressure monitoring, systemic arterial blood gas monitoring, venous blood gas monitoring in the superior sagittal sinus (SSS), monitoring of cerebral tissue oxygenation, online indirect calorimetry. In 30 to 100 years, nanotechnology will provide us with new tools able to monitor cell and tissue function with unparalleled detail [78], perform quantitative pupillometry [79], diagnose diffuse axonal injury (DAI), and predict the outcome with magnetic resonance imaging-diffusion tensor imaging (MRI-DTI) [80].

Two recently published studies examining the feasibility of telemedicine in the ICU and the associated outcome of patients [81,82] proposed telemedicine as a way to relieve the predicted shortage of neurointensivists. New biomarkers of damage in brain injury have been documented, such as the breakdown products of αII-spectrin (spectrin breakdown products [SBDP]) after severe TBI [83] and subarachnoid hemorrhage [84], along with the neuron-specific enolase, S100B, and myelin basic protein in ischemic and traumatic injury [85]. Advances in technological and neuroprotective agents have attracted the attention of researchers, but much clinical work remains to be done in trying to answer physiological questions in TBI patients, such as individualization of treatment and prognosis based on the stratification of the pathophysiology of injury, early intubation at the emergency scene, and hyperoxia as neuroprotective treatment, adequate hemoglobin concentration, appropriate prophylaxis for venous thromboembolism, detection and treatment of adrenal insufficiency that probably contributes to the outcome [86]. Also, health care will continue to feel the pervasive influence of computers (electronic medical records, lab results and electronic images). Developing countries where resources are even more limited should recognize the fact that simple data collection can help to improve the outcome despite low budgets [87], for example, detailing the incidence, the causes, the approaches and the results, while keeping in mind the guidelines for improving data quality in a database of brain injury [88].

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2 Basic Anatomy Applied to the Interpretation of Axial Tomography of the Brain in Emergency Medicine

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2.1 Introduction

At the time of acute brain injury, intracranial structures (meninges, brain, brain stem and cerebellum), the circulating blood volume and cerebrospinal fluid lose their "harmony" within the common area of the cranial vault, affecting its structures and vital areas, thus impairing mental functioning and then the autonomous system, rapidly leading to brain death and ultimately to the cessation of the body's vital functions. These structures bear a special relationship from the point of view of development, configuration, anatomy and localization. Therefore, it is essential that the health personnel in charge of the initial management of these patients possess a basic knowledge of brain anatomy for an adequate understanding of the process underlying neurological impairment after acute brain injury.

2.2 Development

2.2.1 Cranium

The cranium develops from day 22 of gestational age. The "cranial membrane" chondrifies (day 38) and by day 54 begins to ossify from 110 bone centres, generating 45 bones in the newborn, with subsequent fusion for the development of the 32 bones composing the adult cranium. Cranial growth is determined by the growth of brain tissue, which "pushes forward" ossification of the structures. Around the first year, 90% is completed and adult size may be reached at an age of about 6 to 7 years. The initial bone structure is a single-sheet structure. But after 4 years of age it is divided by the diploë, thus setting the basis for the so-called inner and outer cortical plates. The cranial "sutures" (remnants of the cranial growth centres) are active during labour. Afterwards, they follow cranial growth, which occurs especially during the first 3 years of life and permanently closes at about 6 years of age. They are divided into major (metopic, lambdoid, sagittal and coronal) and minor (squamous) plates located between the temporal bones. Between the sutures are the fontanels (spaces between the sutures) where ossification completes. Among these are the anterior or bregmatic one (diameter about 4 cm x 2.5 cm, closes around at 2 ½ years of age), and in the rear the lambdoid one (triangular, closes at around 3 months of age). In the lateral region, the anterolateral or sphenoi-

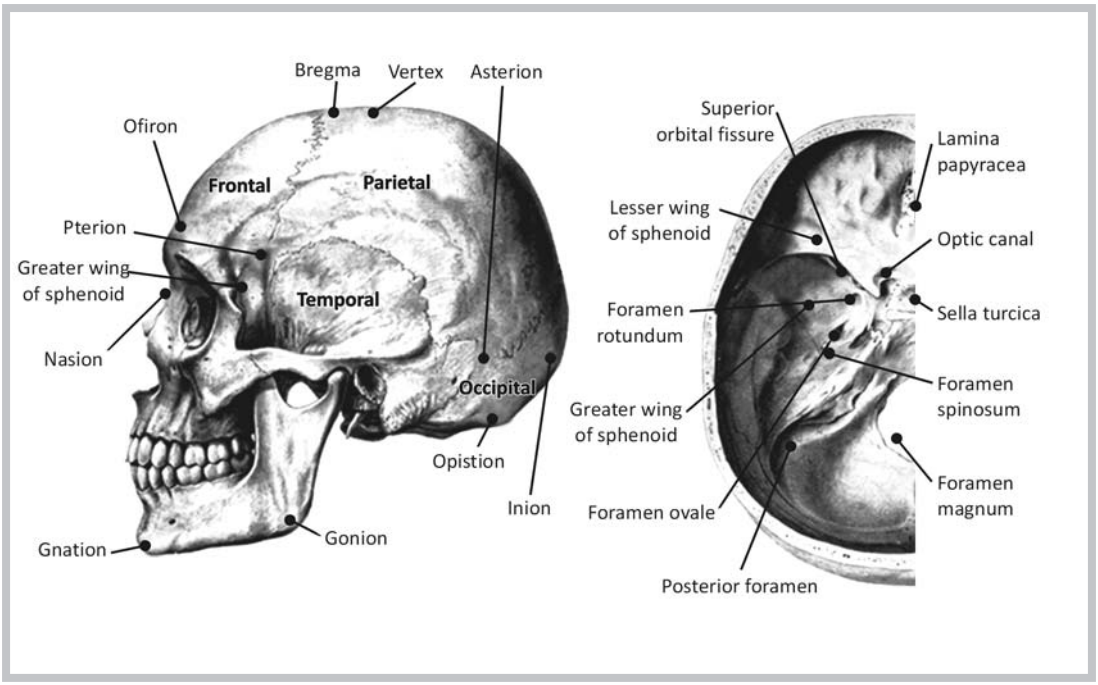

Figure 2.1. **Adult skull bones (side view), including anatomic landmarks for skull procedures. Internal axial view of the base of the skull (anterior, middle and posterior cranial fossa) with major holes of the base [1].**

dal fontanel and posterolateral or mastoid fontanels form. Once chronological maturity is reached, the cranial vault is divided into a group of four unpaired bones (frontal, ethmoid, sphenoid, and occipital) and two groups of paired bones (temporal and parietal). Each of these bones has, in turn, subdivisions (parts, faces, sheets, etc.) that are important as surgical reference points or "corridors" [1,2]. Within these anatomical structures we will detail foramina or holes that lead to vascular and neural key structures.

In the sphenoid bone is the **foramen rotundum**, from which the second portion of the V2 trigeminal nerve or superior maxillary nerve emerges from the cranium. The **foramen ovale**, through which the lesser petrosal nerve, the third portion of the trigeminal nerve, V3 or lower mandibular nerve emerge and the accessory meningeal artery enters and the **foramen spinosum**, through which the meningeal nerve (branch of V3) emerges and the middle meningeal artery enters (very important in trauma, as it is one of the most common causes of epidural bleeding).

If bleeding is out of control, this orifice usually has to be plugged with hemostatics to isolate the extracranial portion and stop the bleeding. In the occipital bone is the **jugular foramen**, where the inferior petrosal sinus emerges and the sigmoid sinus converges to become extracranially the jugular vein (jugular bulb) where the jugular oximetry catheter is placed, along with cranial nerves IX (glossopharyngeal), X (vagus or pneumogastric) and XI (spinal accessory). The posterior meningeal artery also enters through this hole [1,2,4].

These anatomical basics are very useful, especially when placing systems for monitoring intracranial pressure (ICP) in adult and pediatric patients. It is also important to consider some cranial landmarks employed to demarcate coordinates and approaches. Within these, we find, for example, the "pterion" and "asterion" (used to position exploratory burr holes) and the "nasion", where, measuring in anterior-posterior direction, a ventriculostomy catheter is inserted (Figure 2.1).

2.2.2 Brain (Forebrain, Cerebellum and Brainstem)

The brain begins to develop in embryonic life. On day 28, the neural development of the embryo is in the so-called "3-vesicle" stage:

- The prosencephalon (forebrain) gives rise to the telencephalon (cerebral hemispheres) and diencephalon (third ventricle, thalamus and hypothalamus).
- The mesencephalon (midbrain) gives rise to the mesencephalon itsef.
- The rhombencephalon (hindbrain) gives rise to the metencephalon (pons and cerebellum) and myelencephalon which, in turn, give rise to the bulb and part of the spinal cord. The neural tube then continues its development as the spinal cord and vertebral column.

Around day 35 of gestation, the 3-vesicle embryo progresses to the 5-vesicle stage (telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon), and at day 180 starts forming sulci through growth and myelination. The meninges, in turn, form two structures, the neural crest (arachnoid and pia mater) and the mesenchyme (dura mater). The final weight of the brain on completing growth is around 1300 g in women and 1400 g in men.

The areas of intra-cortical association continue to develop even into adulthood. Growth is set to fully develop structures of the neo-cortex such as the frontal lobes, where social learning is developed. The growth of association fibres occurs mainly through three structures: the fornix, corpus callosum and anterior commissure. The general divisions of the cerebral lobes are formed from the fissures (deeper sulci), and within each lobe there are subdivisions (gyri or convolutions) formed by less deep or smaller sulci.

The lateral or Sylvian fissure divides the frontal from the temporal lobe. It is about 7 cm long.

The central or Rolandic fissure starts inside in the middle of the hemisphere and is directed downward and forward to join the Sylvian fissure.

The sulcus callosomarginalis is inside, above the cingulate gyrus.

The calcarine fissure begins at the internal occipital pole and continues forward to the parieto-occipital sulcus.

The sulcus callosomarginalis, the Sylvian fissure, the parieto-occipital sulcus and the collateral sulcus are the only ones with 100% continuity. These, along with the Rolandic and the calcarine fissures, the pre-central and the inferior temporal sulci, are the only anatomical grooves that are generally constant and present a uniform pattern in human anatomical studies [1-3].

The frontal lobes are located between the Sylvian, the Rolandic and the sulcus callosomarginalis. The parietal lobes start from the Rolandic fissure and end in the external projection of the parieto-occipital sulcus and above the projection of the Sylvian fissure. The temporal lobes are below the Sylvian fissure and are separated from the occipital lobe by an imaginary line. They have five sulci: the superior temporal; the middle temporal; the inferior temporal; the rhinal; and the collateral.

On its basal face is the "uncus" of the hippocampus, in its anterior and posterior portions, a key structure in the development of uncal herniation due to displacement of this structure against the third cranial nerve and against the cerebral peduncle in the midbrain, thus compromising pupillary contraction (dilated pupil) and the pyramidal motor pathway (contralateral hemiparesis), peculiar of this syndrome. There is a lobe within the interior of the temporal lobe called the insular lobe or Island of Reil. It is at the bottom of the Sylvian fissure and is triangular in shape, with an anterior inferior apex and a superior base. The occipital lobes have a major sulcus (calcarine fissure) and two minor sulci: the transverse occipital and the temporal occipital [1-3].

Within the association structures are three major connections between the two hemispheres and the central fibres of association. In particular:

- **Corpus callosum**: about 7 to 10 cm long, located along the ventricular system, and consists of four parts: the rostrum (adjacent to the lamina terminalis); the knee linking the frontal lobes; the body joining the parietal and temporal lobes; and the splenium joining the temporal and occipital lobes.
- **Anterior commissure**: located behind the rostrum of the corpus callosum.
- **Posterior commissure**: situated at the posterior edge of the third ventricle above the aqueduct of Sylvius.
- **Superior longitudinal fascicle**: the longest of the association fibres, arches over the insular lobe and connects the frontal with the temporal and parietal lobes.
- **Uncinate fasciculus**: a large group of fibres inside the Island connecting the basal portion of the frontal lobe with the temporal lobe.
- **Inferior occipitofrontal fasciculus**: connects the frontal with the occipital lobe running along the side of the basal ganglia.
- **Cingulum**: located in the cingulate gyrus, starts from the rostrum of the corpus callosum and runs laterally in the parahippocampal gyrus.

The cerebellum is located behind the pons and the bulb. It is separated from the forebrain by the cerebellar tentorium, which is a splitting of dural tissue that separates the supratentorial from the infratentorial structures (anterior and middle fossae from the posterior fossa). It measures about 6 x 10 x 4 cm and weighs 140 g, which corresponds to 10% of brain weight. It connects to the brainstem via three branches or peduncles: the superior cerebellar or "brachium conjuntivum" (which joins the midbrain); the middle cerebellar or "brachium pontis" (which joins the pons); and the inferior cerebellar or restiform body (which joins the brainstem). Within its development, the fourth ventricle is formed just below. Functionally, the division is established through three lobes: anterior (posture and tone fibres); posterior (vestibular fibres of balance); and medium (fibres of voluntary movement) [1-4].

The brainstem consists of four structures: the diencephalon; the midbrain; the pons; and the medulla oblongata. The diencephalon corresponds to a triangular cavity. Its side wall is formed by the two thalami; the anterior side is the anterior commissure, the posterior side is the pineal gland and the posterior commissure; the base is formed by the tela chorioidea located between the two thalami, and the vertex is above the pituitary gland.

The thalamus is a paired nucleus measuring approximately 35 x 20 x 25 mm. In back of the diencephalon is the pineal gland or epiphysis located on the quadrigeminal plate, and the hypothalamus in the anterior part located on the floor of the third ventricle and limited by the optic chiasm and the lamina terminalis. It has two units: an anterior (parasympathetic activity) and a posterior (sympathetic activity) [1-4].

The midbrain begins to develop with the closing of the alar plates to form the fourth ventricle. The cells of the plates are arranged on the ventricle to form the quadrigeminal plate, and cells of the basal lamina form the tegmentum in the ventricular floor. The mantle layer forms the cerebral peduncles to connect to the thalamus and between them are the red nucleus and substantia nigra. The red nucleus, predominantly motor, is responsible for coordinating decorticate movement which is evident in patients with acute brain injury. The dorsal surface is formed by the superior and inferior quadrigeminal colliculi, connected to vision and hearing, through the fibres of the medial and lateral geniculate bodies, and the ventral surface formed by the cerebral peduncles. The medial surface has, in the inter-peduncular sulcus, the emergence of the third cranial nerve. The lower edge is attached to the pons and on the lateral face are the pontomesencephalic sulci [1-4].

The pons originates within the pontic flexure in the rhomboid fossa of the fourth ventricle. In the basal lamina are the motor nuclei of cranial nerves VI and VII. In the alar lamina of this region are several nuclei, such as the vestibular nuclei, which coordinate a movement called "decerebration" in patients with impaired higher motor functions, the cochlear nuclei, the inferior olivary nuclei, the solitary fascicle, and the descending nucleus of the V pair. It is located under the cerebral peduncles and in front of the cerebellum. On its anterior face is the basilar artery and the apparent origin of the V pair (trigeminal). On the lateral face are the middle cerebellar peduncles that are directed towards the cerebellum. On its lower face is the pontobulbar sulcus which separates it from the medulla oblongata [1-4].

The medulla oblongata originates from the myelencephalon. The alar lamina originates nuclei for the X and XII cranial nerves. It continues in the spinal cord and separates from it by the decussation of the pyramids, an area where the fibres from the pyramidal cells in the motor cortex cross over to the contralateral side. Its anterior portion is closely related to the odontoid process or apophysis of C2 (for this reason, a high cervical injury with impaction of the odontoid directly impairs the medullary respiratory centres). On its front face are the preolivary sulci, the apparent origin of the XII cranial nerves and the bulbar pyramids. On its posterior face are the posterior lateral sulci, an area of apparent origin of the IX, X and XI cranial nerves. There are also the colliculi of gracilis fasciculus and cuneatus fasciculus (posterior cords of the spinal cord). There is also the inferior cerebellar peduncle which connects it to the cerebellum, and part of the floor of the fourth ventricle, with the acoustic striae and hypoglossal and vagal trigones. On the lateral face is the olive, the seat of the inferior olivary nuclei, and the pontomedullary sulcus, the apparent origin of the VI, VII and VIII nerve pairs [1-4].

2.2.3 Brain (Arterial and Venous System)

Understanding the arterial and venous systems is fundamental for appreciating many aspects of the pathophysiology, monitoring, and treatment of acute brain injury. Cerebrovascular emergency, for example, requires quickly correlating the anatomical aspect and the clinical location, and this must be understood by all staff involved in caring for critically ill patients. Hereafter, we will describe in detail the nomenclature and location of the major cerebral vessels, both arterial and venous.

The internal carotid artery (ICA) originates at the bifurcation of the common carotid, usually at the level of the C1-C2 disc. It has four parts: C1 (**cervical**) runs from the bifurcation of the common carotid to the external orifice of the carotid canal of the skull; C2 (**petrous**) runs from the cranial carotid canal entrance to the entrance of the cavernous sinus inside the skull; C3 (**cavernous**) runs from the entrance to the exit of the cavernous sinus; and C4 (**supraclinoid**) runs from the exit of the cavernous sinus (entry into the subarachnoid space) to its division into the middle and anterior cerebral arteries.

The supraclinoid portion consists of three segments: the lower one is the ophthalmic segment (where the ophthalmic artery arises); the middle one is the communicating segment (where the posterior communicating artery arises); and the upper one is the choroidal segment (where the choroidal artery arises). The ophthalmic segment has four to seven perforating branches directed to the pituitary stalk (superior pituitary), the optic nerve, and the chiasm. The ophthalmic artery is located below the chiasm and has a very short intracranial segment of about 3 mm before it enters the orbit. The communicating segment has some inconstant perforating arteries directed to the chiasm and the optic nerve. The posterior communicating artery (PCoA) is very important because it forms the lateral wall of the circle of Willis (Figure 2.2) connecting the carotid with the

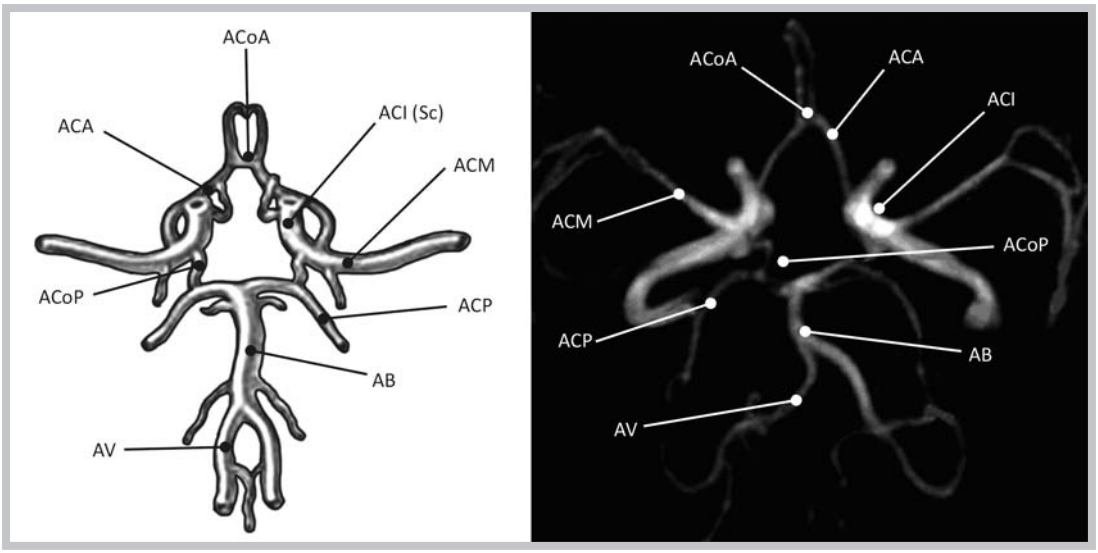

Figure 2.2. **Diagram and magnetic resonance angiography image of the arteries forming the Circle of Willis. From [1].**

ACA = anterior cerebral artery
ACoA = anterior communicating artery
BA = basilar artery
ICA (Sc) = supraclinoid internal carotid artery
MCA = middle cerebral artery
PCA = posterior cerebral artery
PCoA = posterior communicating artery
VA = vertebral artery

posterior cerebral artery, which comes from the infratentorial circulation and is a key element in collateral circulation in supratentorial cerebral ischemia [1,7,8,9].

The so-called "foetal configuration of the posterior communicating artery" occurs when the artery gives rise to the posterior cerebral artery (PCoA) rather than originate from the basilar system. This pattern t can occur in adults and is called such because it is normal in the cerebral circulation of the foetus. This segment can have about eight perforating branches directed to the third ventricle, thalamus, hypothalamus, internal capsule, pituitary stalk, and chiasm, among others. The choroidal segment has about four perforating arteries directed to the anterior perforated substance, the optic tract and the uncus. The anterior choroidal artery (AChA) provides irrigation to the choroid plexus within the ventricle temporal horn [1,12,13].

The middle cerebral artery (MCA) has an initial diameter of about 4 mm. It originates at the end of the Sylvian fissure on the inner surface of the temporal, lateral to the optic chiasm; at the level of the fissure it divides to direct to the temporal and parietal. It has four parts: M1 (sphenoidal) from the bifurcation of the ICA to the insular region within the Sylvian fissure; M2 (insular) is the segment within the Island of Reil; M3 (opercular) runs from the peri-insular region to the outside of the Sylvian fissure; and the M4 (cortical) goes from the exit through the Sylvian fissure until complete distribution on the outer face of the lobes, where it irrigates the vast majority of functional cortical areas. In 80% of cases, in the pre-bifurcation area of M1, the lenticulostriate arteries originate: they are important in hemorrhagic cerebrovascular events because they cause hypertensive hematomas at the basal ganglia level. There are approximately ten in each hemisphere [1,3,12].

The anterior cerebral artery (ACA) is smaller than the MCA. It is anterior and medial to the optic nerve. It projects forward between the two hemispheres, parallel to its contralateral, and they join through the anterior communicating artery (ACoA). It has five

parts: the A1 portion (precommunicating) from the origin to the anterior communicating artery; A2 (infracallosal) lies below the rostrum of the corpus callosum; A3 (precallosal) courses past the knee of the corpus callosum; A4 (supracallosal) runs above the corpus callosum; and A5 (postcallosal) located behind the splenium of the corpus callosum. The ACoA is the anterior portion of circle of Willis and is generally no longer than 3 mm. A1 has a branch often called the "recurrent artery of Heubner" which supplies the basal ganglia and internal capsule. This branch may be injured by searching for the ACoA during aneurysm surgery.

The pericallosal artery begins in the ACoA and around the corpus callosum. It includes the portions from A2 to A5. It has a branch called the callosomarginal artery that ascends and continues back through the cingulate sulcus. Usually it comes out of the A3 portion. The ACA also has cortical branches in the frontopolar, frontal and parietal regions [1-3].

The **vertebral arteries** (VA) originate from the subclavian arteries and enter the structure of the cervical spine through the vertebral foramen from C6, ascending to C2, where they curve medially to settle at the transverse process of C1 and then cross over the posterior arch. They enter the dura at the foramen magnum, giving rise to the **posterior spinal artery** and the **posterior meningeal artery**. The intradural segment of the VA is divided into two subsegments, the lateral and the anterior medullary, which then join with the contralateral to form the basilar artery. An additional main branch of the VA is the posterior inferior cerebellar artery (PICA) which supplies the medulla oblongata, the bottom of the fourth ventricle, the cerebellar tonsils, and the lower side of the cerebellum [1-4].

The **basilar artery** (BA) has its origin at the junction of the two VAs at the pyramidal tract of the medulla oblongata, and it ascends on the anterior surface of the pons in the so-called basilar sulcus. Its main branch is the **anterior inferior cerebellar artery** (AICA) which usually emerges in the lower third of the BA. It turns back and generally surrounds the pons, irrigating the lower two thirds of the pons and the upper third of the medulla oblongata. In the upper third of the basilar artery, before its bifurcation into the posterior cerebral arteries, the **superior cerebellar artery** emerges (SCA), which turns back on the upper level of the pons at the pontomesencephalic sulcus. This artery supplies the quadrigeminal lamina and the cerebral peduncles of the midbrain [7-9].

The **posterior cerebral artery** (PCA) emerges from the bifurcation of the basilar and meets the PCoA in the lateral region of the interpeduncular cistern. It goes through the crural and ambient cisterns in the so-called tentorial incisura (free space of the tentorium which surrounds the midbrain and connects the supratentorial and infratentorial spaces). It supplies the occipital region, thalamus, midbrain, and choroid plexus.

The P1 segment (pre-communicating) goes from the basilar bifurcation to the junction with the PcoA, is about 7 mm long, gives rise to the thalamoperforating, choroidal, quadrigeminal branches, and branches to the cerebral peduncles. The P2 segment

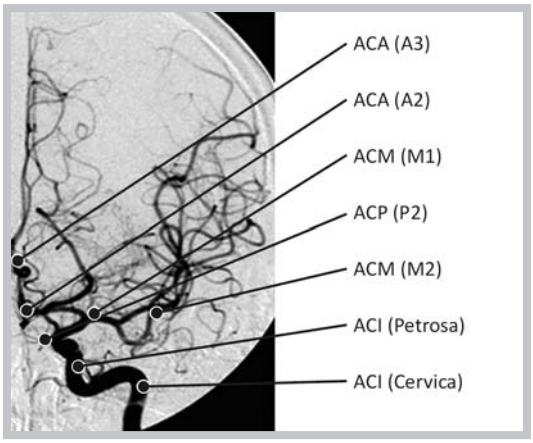

Figure 2.3. **Conventional angiography and interpretation scheme. From [1].**
ACA (A2-A3) = anterior cerebral artery, A2 and A3 portions
ACP (P2) = posterior cerebral artery P2 portion
ICA = internal carotid artery
MCA (M1-M2) = middle cerebral artery, M1 and M2 portions

(cisternal) is about 25 mm long, runs from the junction with the PCoA to the rear edge of the midbrain, and is subdivided into the P2A segment (crural) and the P2P segment (ambient). These segments give rise to the hippocampal, temporal, peduncular, choroidal, and thalamus branches. The P3 segment (quadrigeminal) is 20 mm long and runs from the posterior region of the midbrain to the calcarine fissure, crossing through the quadrigeminal cistern. It is divided into two terminal branches, the calcarine and parieto-occipital branches. The final segment, P4 (cortical), begins in the calcarine fissure on the inner surface of the occipital and runs in the occipital cortical region, giving rise to branches directed to the temporal and occipital regions [7-9]. Arterial relations are especially important in the interpretation of angiographic images in emergency situations, where it is essential to detect areas of vascular injury and collateral circulation (Figure 2.3).

The cerebral venous system comprises the surface segment (veins of the skin or scalp and muscle), the intermediate segment (veins of diploë and dura mater), and the deep segment (the cerebral veins). The surface segment generally has the same distribution as the arteries. The most important are the so-called emissary veins that connect the extracranial with intracranial drainage. In severe intracranial hypertension, especially in children, they are engorged at the frontal and temporal levels. They are located in the scalp and drain into the diploic veins which subsequently drain into the dural sinuses. In the intermediate segment are the diploic veins (venous lakes located within two cranial cortices), which are important because of the risk of air embolism in open fractures. Bleeding is easily controlled by filling the space between the two bony plates with hemostatic material. They are a frequent source of bleeding in depressed fractures. This segment also contains the meningeal arteries located between the skull and the dura. They run parallel to the arteries. They are also in the dural folds (e.g., the falx and the tentorium). The most frequent are the tentorial veins, which are a frequent source of bleeding in posterior fossa interventions [5,6,13].

The dural venous sinuses are intermediate and are grouped as follows: the **postero-superior group** comprises the superior and inferior sagittal, straight, lateral (transverse), sigmoid, tentorial and occipital sinuses; the **antero-inferior group** comprises the cavernous, sphenoparietal, intercavernous, superior petrosal and basilar sinuses.

The **superior longitudinal sinus (superior sagittal sinus)** spans the midline and runs from the frontal pole to the occipital prominence, where the confluence of sinuses is called “torcular Herophili”. It forms spaces called venous lacunae, where the meningeal veins converge and **are a source of active bleeding in fractures above the midline**. These lacunae have a triangular shape and contain the arachnoid granulations. The **inferior sagittal sinus (inferior longitudinal sinus)** starts at the lower edge of the falx cerebri (at the level of the crista galli), extends above the corpus callosum, and turns back to drain into the straight sinus. It mainly includes the draining of the pericallosal veins. The **straight sinus** originates at the splenium of the corpus callosum at the confluence of the inferior sagittal sinus and the vein of Galen. It continues posteroinferiorly in the dural junction of the falx and tentorium to come together usually in the left transverse sinus. The **transverse sinuses** originate in the torcular and run from the occipital protuberance, parallel to the outer tentorial edge; at the level of the crest of the petrous pyramid, they converge with the superior petrosal sinus to form the sigmoid sinuses. The right one is generally larger and receives drainage from the superior sagittal sinus, while the left one is smaller and receives drainage from the straight sinus. This factor should be taken into account when monitoring the jugular vein, as it originates from the sigmoid sinus drainage; therefore, the right jugular reflects more the cortical venous drainage and the left one the subcortical or deep venous drainage [5,6,13].

The **sigmoid sinuses** are the continuation of the confluence of the transverse sinus and the superior petrosal sinus. They extend along the bottom edge of the petrosal bone;

at the confluence with the inferior petrosal sinus, they enter the jugular foramen to form the internal jugular vein, where jugular venous bulb oxygen saturation is measured. The **occipital sinuses** originate from the transverse sinus, run parallel to the occipital, and drain into the sigmoid sinuses. The **tentorial sinuses** are not always present. There are two of them, with one usually located medially and the other one laterally. They are formed by the convergence of the tentorial, cerebellar, and occipital cortical veins. They have several drainage patterns. The **cavernous sinuses** are located on the sides of the sella turcica and communicate with each other through the anterior and posterior intercavernous sinuses located between the diaphragm sellae and the dura [10,11]. Recognizing them is important because they host the third portion of the internal carotid artery and cranial nerves III, IV, VI and the v1 and v2 branches of the V cranial nerve. The sphenoparietal sinuses accompany the anterior portion of the middle meningeal artery. They run through the lesser wing of the sphenoid bone and reach the cavernous sinus [10,11]. The **superior petrosal sinuses** pass along the tentorium and the edge of the petrosal bone, communicating medially with the cavernous sinus and laterally with the confluence of the transverse sinus and sigmoid sinus. The **basilar sinus** is a venous network located on the clivus. It communicates with the cavernous sinus and allows communication between the two groups of venous sinuses, upper and lower [5,6,12,13].

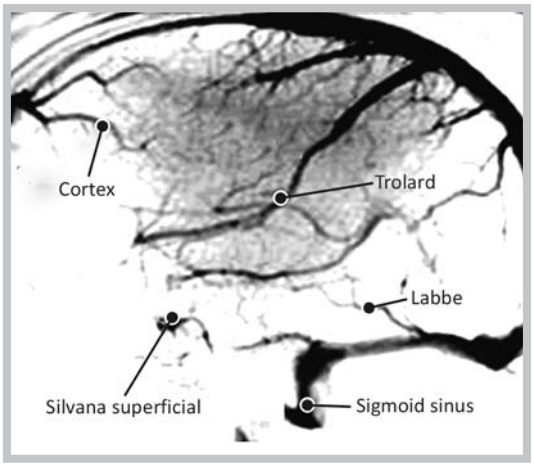

Figure 2.4. **Conventional angiogram in venous phase showing the superior and inferior anastomotic veins (Trolard and Labbe). From [1].**

The deep venous segment is subdivided into the superficial and the deep venous system. The superficial system is basically related to the cortical veins that drain mostly into the superior sagittal sinus. Within this group are the frontal, parietal (ascending and descending), temporal (ascending and descending) and occipital (lateral and medial) veins. Within this group of veins, especially at the temporal and parietal levels, attention is called to the superior and inferior "anastomotic veins":

- **Superior anastomotic vein (parietosylvian) or vein of Trolard** crosses the surface of the frontal and parietal lobes, creating an anastomosis between the Sylvian veins and the superior sagittal sinus. It may sometimes be double (Figure 2.4).
- **Inferior anastomotic vein (temporosylvian) or vein of Labbé** crosses the temporal connecting the sylvian veins with the transverse sinus. It may be double.
- **Superficial Sylvian vein** joins the previous two veins with the sphenoparietal sinus, creating a network connection between the major cerebral venous systems. Sometimes, it goes to the bottom of the Sylvian fissure directly to the cavernous sinus.

The deep venous system is formed mainly by the ventricular and the cisternal veins:

- In the anterior segment is the **basal vein of Rosenthal**, which accompanies the P2A segment of the PCA around the cerebral peduncles in the crural cistern.
- In the intermediate segment is the **great vein of Galen** formed by the confluence of the above-mentioned with the internal cerebral veins in the quadrigeminal region.
- In the posterior segment are the thalamic deep veins.

The ventricular veins are formed by tributaries of the internal cerebral veins, thalamus, basal ganglia, fornix and septum pellucidum. The **internal cerebral veins** are formed behind the foramen of Monro by the confluence of the thalamo-striatal and caudate veins.

They come together to join in the vein of Galen and **are an important intraventricular guide for detecting the foramen of Monro during endoscopic procedures**. There are also multiple cisternal veins draining into the basal vein. The vein of Galen drains into the straight sinus in the occipital region [5,6,12,13].

2.3 Key Concepts

The teams managing acute brain injury must have clear basic concepts of brain anatomy, particularly those related to the cerebral vasculature, their areas of substitution, and the functional correlations of these areas. The relationships of the cranial nerves, the holes (foramina) in the base and midline structures are also essential for a proper understanding of motor impairment and altered consciousness manifesting clinically in patients with acute brain dysfunction. Relationships such as those between the tentorial incisura and the midbrain, the temporal lobe, the third cranial nerve and the posterior cerebral artery in the pathophysiological process of cerebral hernia are examples of these essential anatomical concepts.

Neuromonitoring and emergency endovascular procedures also require an appreciation of the relationships between specific brain areas and structures according to standardized classification models developed by research groups in microsurgical anatomy, which become increasingly more familiar within the working groups of neurological care units. Normal variations, measures and differences present during the development of brain structures are important for the management of pediatric patients with acute injury in specialized units. The concepts provided in this chapter are based on definitions internationally accepted by the main groups of academic work in the area of neuroscience and should serve as a tool for correlation with subsequent chapters.

2.4 Appendix: Images

Computed axial tomography (CAT), developed by the English engineer Sir Godfrey Hounsfield in the late 1960s, was a major breakthrough in skull radiography in neurological intensive care units in the UK. Further advances in imaging techniques led to three-dimensional (3D) reconstruction of tissue and bone and computed tomography (CT) angiography with high-resolution images the brain.

With currently available technology, a CAT scan can be obtained in a few seconds, with cross-sectional and coronal images, multiplanar and 3D reconstruction at the workstation. Consistent with these new capabilities, the term “axial” has been replaced by “computed tomography.”

Computed tomography has become a highly useful, nearly indispensable tool in the management of emergency department patients, where careful clinical assessment and early confirmation of the initial diagnosis are essential: from imaging findings appropriate interventions can be initiated to change the course of a disease, thus hastening the patient’s recovery and improving outcome at discharge.

Brain CT can yield a wealth of information, as long as it is used wisely and according to established indications. The CT scanner consists of a tube that emits an X-ray beam, which, after passing through the patient, projects a shadow of the contents of the body onto the detectors on the opposite side. The attenuated radiation received by the detectors is the attenuation coefficients or “densities” of the tissues, which the scanner con-

verts into Hounsfield units (HU). This attenuation ranges over greys, from white (hyperdense) to black (hypodense). Expressed in HU, it is then interpreted by the scanner software (Table 2.1). The CT scanner can distinguish over 2000 shades of grey, as compared to the mere 30 the human eye can recognize.

In the Emergency Medical Unit, we must proceed quickly. As the initial medical diagnosis will be confirmed or ruled out on the basis of imaging findings, we must know which study is suitable for confirming our "suspicion."

Tissue	HU (-1000 to +1000)
Air	-1000
Fat	-60 to -100
Water	0 to +10
Brain: white matter	+20 to 35
Brain: grey matter	+30 to 40
Blood	+40 to + 80
Soft tissues	+50 to 80
Calcifications	+100 to +400
Bone	+1000
Metallic foreign bodies	More than +1000

Table 2.1. **Interpretation of the ranges of Hounsfield units (HU) according to tissue or element type.**

The American College of Radiology (ACR) convened imaging experts to draft consensus guidelines emergency room staff could apply in selecting the study most appropriate to evaluating a patient's clinical features.

We report here some indications from the document the neuroimaging panel issued concerning the situations where it is appropriate (suitable) to order a brain CT, which can be without contrast (simple, with bone and brain windows) and/or with contrast. Three-dimensional reconstructions of the brain are useful for elective surgery planning but not for emergencies. The following are the ACR recommendations.

Acute Ataxia

- In ataxia <3 hours, as a manifestation of cerebrovascular disease (CVD): CT angiography and CT imaging of the brain are needed. They are indicated with and without contrast, even when magnetic resonance imaging (MRI) studies may be preferred; otherwise, the beginning of treatment is delayed.
- Following head trauma, <24 hours: simple MRI of the head and CT of the temporal bone.

Cerebrovascular Disease

- All new or recent neurological deficits in the carotid or vertebrobasilar territory, stable or in progress, are to be considered an acute cerebrovascular event (CVE or stroke) and are only to be classified as transient ischemic attack (TIA) in retrospect, when symptoms resolve without intervention. In such cases, CT of the head (considering perfusion and concomitant assessment of the brain and vessels) may be ordered, together with CT angiography of the head and neck. MRI of the head with and without contrast is also indicated, as well as MR angiography (MRA) of the head and neck; otherwise, the beginning of treatment is delayed.
- When a subarachnoid hemorrhage is clinically suspected, CT of the head without contrast should be ordered, followed by CT angiography and cervicocerebral (vertebral, common carotid and its branches) arteriography for treatment planning.
- When intraparenchymal hemorrhage is clinically suspected, simple CT of the head is to be ordered.

Seizure Syndrome

- New-onset seizure: in emergency services, simple contrast-enhanced CT of the head should be ordered, as well as MRI when possible.

Focal Neurologic Deficit

- Single or multiple, sudden onset, stable or incompletely resolving, progressive, unexplained acute confusion, altered level of consciousness: in the emergency unit, CT of the head without contrast should be ordered, along with MRI of the head with and without contrast.

Headache

- Sudden onset of severe headache: CT of the head without contrast is the initially indicated study, then CT angiography or MRA with and without contrast.
- Suspected meningitis: CT of the head with and without contrast. Depending on availability, MRI should be ordered.
- New headache with suspected meningitis or encephalitis: CT of the head without contrast and MRI with and without contrast are indicated.
- In addition, some warning signs in headache should be considered:
  - Sudden onset.
  - Early morning on awakening.
  - Increase with Valsalva.
  - Onset in persons aged >45 years.
  - Signs of intracranial hypertension (IH).
  - Change in the pain pattern.
  - Abnormal neurologic examination.
  - Nonspecific diagnosis.
  - Elevated blood pressure.
- According to features over time: sudden onset headache, subacute headache gradually arising inside, important change of features, persistent headache in a patient with no history, headache awakening the patient (except cluster or hypnic headache); new in persons aged >50 years.
- According to associated signs and symptoms: fever, vomiting, pain, focalization, seizures, stiffneck, papilledema, pain and altered mental state.
- Pain and signs of temporal arteritis, headache increasing with Valsalva, recent headache in a patient with cancer (neo).

Vertigo and Hearing Loss

- In conductive hearing loss, to rule out temporal bone abnormalities and in patients with total deafness, or cochlear implant candidates in surgical planning; CT of the temporal bone without contrast should be ordered.
- In hearing loss with vertigo, history of meningitis or to rule out temporal bone anomalies, CT of the temporal bone without contrast should also be ordered.

Head Trauma

- When there is a closed head injury and carotid artery dissection is suspected, in addition to simple CT, MRA of the head and neck should also be ordered.
- All patients with head injury should undergo CT of the head without contrast.

Orbits and Visual Loss

- In amaurosis or visual acuity impairment related to a previous injury, CT of the head without contrast should be ordered.

NB: Always weigh the appropriateness versus the availability of the diagnostic method. This refers to avoiding postponing proper management of the patient, while waiting for the appropriate examination, if a useful alternative imaging method is available.

2.4.1 CT Technical Study

A brain scan is performed by placing the patient on the examination table to obtain images in the axial or the transverse plane, while taking the orbitomeatal line (Reid's base line) as a reference point (Figure 2.5). Slices are scheduled from the base of the skull to the vertex, 5 mm thick at the skull base (Figure 2.6A) in order to minimize artifacts, and 10 mm thick in the rest of the skull (Figure 2.6B).

Image contrast can be adjusted by varying the amplitude (width) of the window and the grey scale by changing the level (level) of the window. These are useful pa-

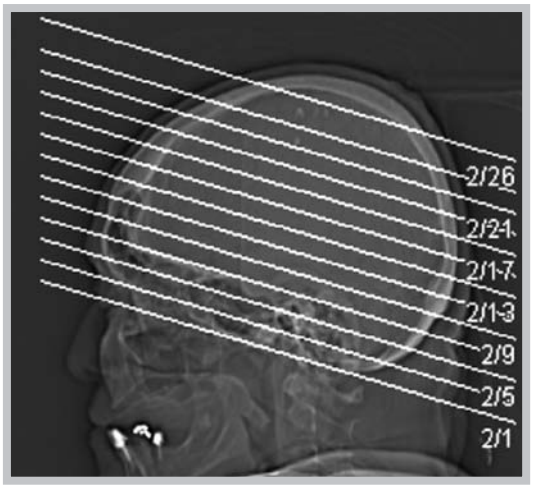

Figure 2.5. Image locator.

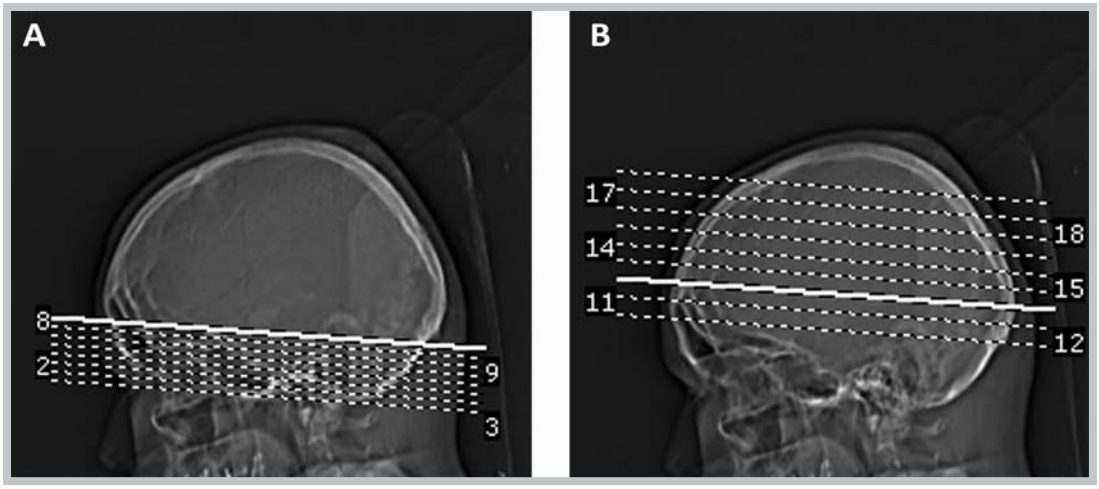

Figure 2.6. Reference lines (A and B).

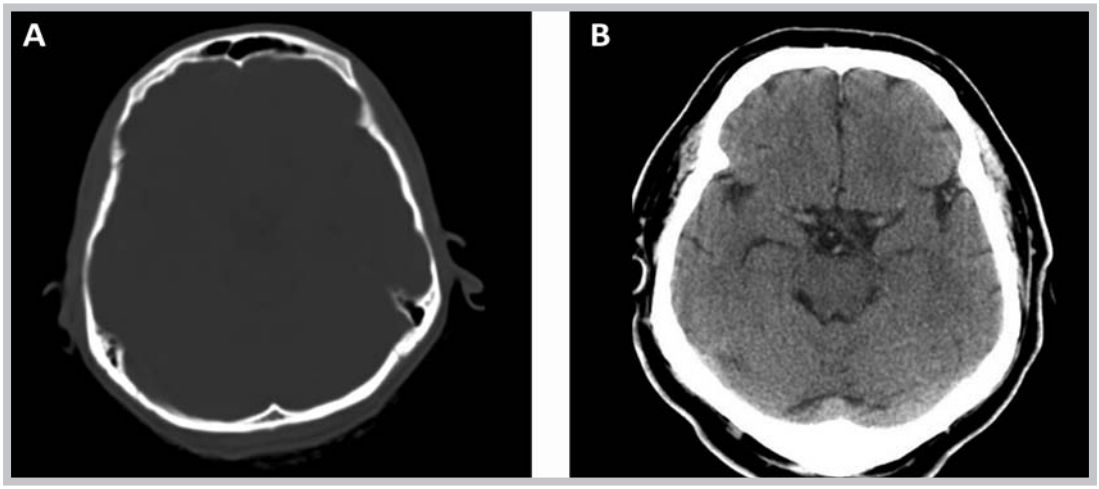

Figure 2.7. Image of bone (A) and brain (B) window.

	Width (HU)	Level (HU)
Bone window	2500	480
Brain window	80	40

Table 2.2. Bone and brain window.

rameters to select at the workstation for visualizing the tissue we need to evaluate (Figure 2.7). In this way, we modify the parameters to obtain the bone and brain window, as reported in Table 2.2. Parameters of the bone and brain window in CT scanning.

Generally, CT images of the head have very good resolution of tissues. Visualizing the skull base may be more difficult due to artifacts generated by the bone tissue in the posterior fossa, seen as hypodense bands, projected on the cerebellum, called beam-hardening artifacts. These, like other artifacts such as patient movement, partial volume and artifacts due to metal, can render diagnosis uncertain and simulate a pathology (Figure 2.8).

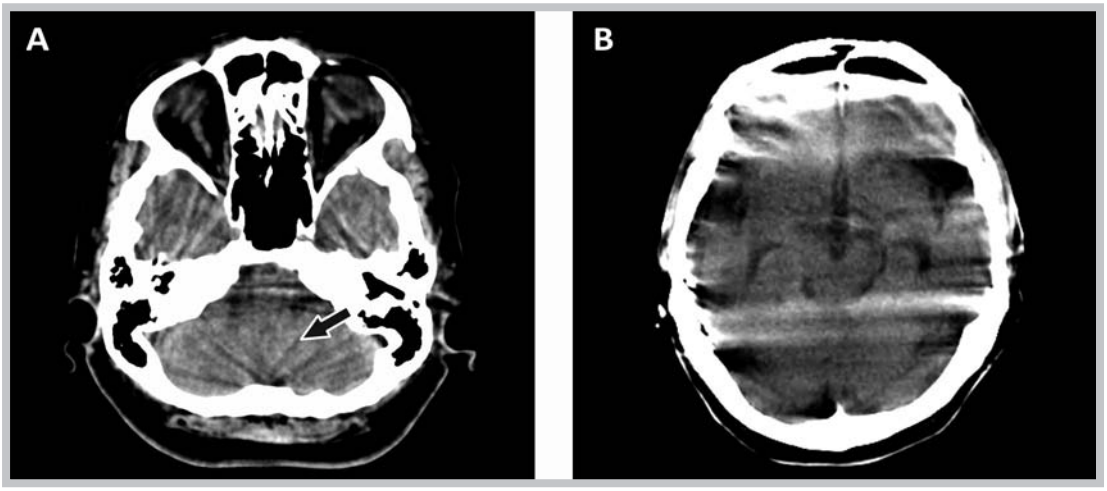

Figure 2.8. Artifacts in the posterior fossa (A) and movement artifacts (B).

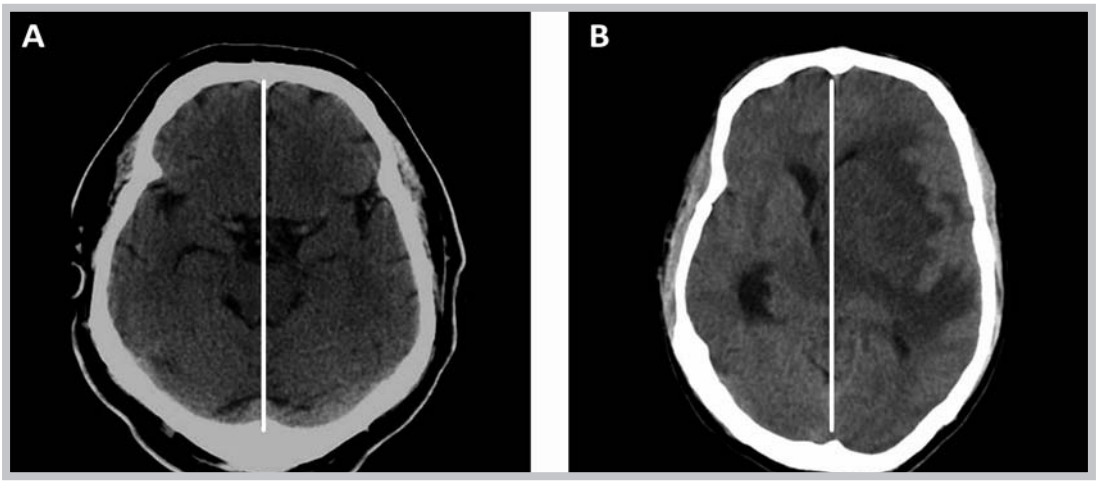

Figure 2.9. Centred (A) and displaced (B) midline.

2.4.2 Basic Radiologic Anatomy

Fortunately, tissue symmetry helps in evaluating a CT scan of the head. Both sides must be compared using the same logical order with which the examiner feels comfortable,

so that it is certain that all structures have been examined. We suggest performing an initial general evaluation and then to continue from the base of the skull to the vertex, checking each image from the centre to the periphery, starting with the brain window and then the bone window.

2.4.3 Midline

The first step is to check the central localization of the midline and to verify structure integrity (Figure 2.9).
In the evaluation of the midline, an imaginary straight line is projected along the anteroposterior (AP) axis, from the frontal crest to the occipital tubercle or to the torcular Herophili. This line should pass through the superior sagittal sinus, the falx cerebri, the corpus callosum, the vein of Galen, the septum pellucidum, the pineal, the third ventricle, the centre of the brainstem, the pituitary stalk and the cerebral aqueduct. Any deviation of structures from the midline should be interpreted as abnormal, especially if greater than 5 mm; asymmetries generating such deviations are to be sought in the brain parenchyma.

2.4.4 The Ventricular System and Cisterns

The ventricular system and the cisterns are reservoirs of cerebrospinal fluid (CSF), which has a fluid density from 0 to +10 HU (hypodense). The ventricular system consists of lateral ventricles, the third ventricle, the aqueduct of Sylvius and the fourth ventricle. The lateral ventricles are situated on either side of the midline, are generally symmetrical, have smooth edges, and consist of frontal horns (anterior), body, posterior horns, temporal horns and trigones or atria. The frontal horns have an angle between their axes; the temporal horns are usually small, almost imperceptible, and the occipital horns are bracket-shaped at the level of each respective lobe.
The atria are the junction between the body of the lateral ventricles and the posterior horns. The lateral ventricles are connected to each other and the third ventricle by the interventricular foramen or foramen of Monro, which is Y-shaped (Figure 2.10).

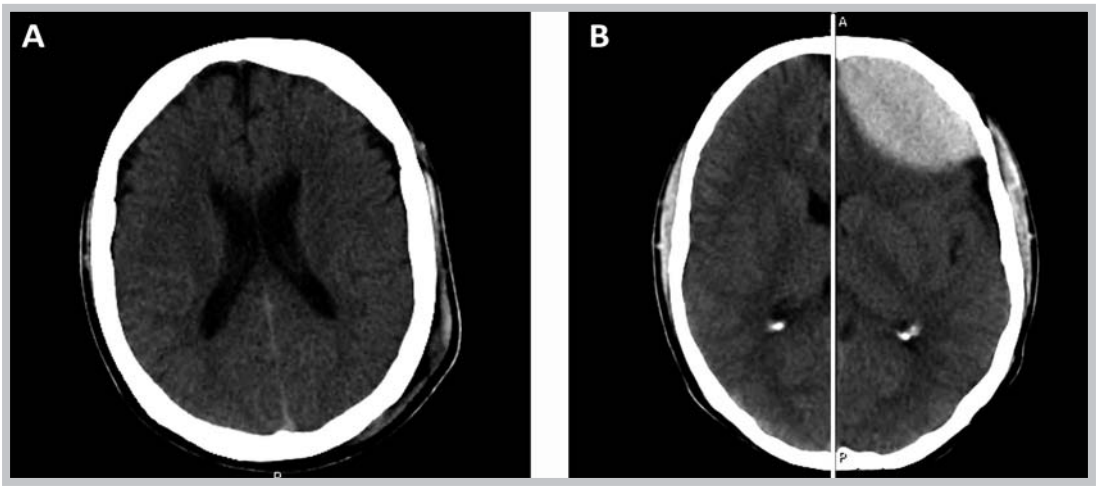

Figure 2.10. **Symmetrical (A) and asymmetrical (B) lateral ventricles.**

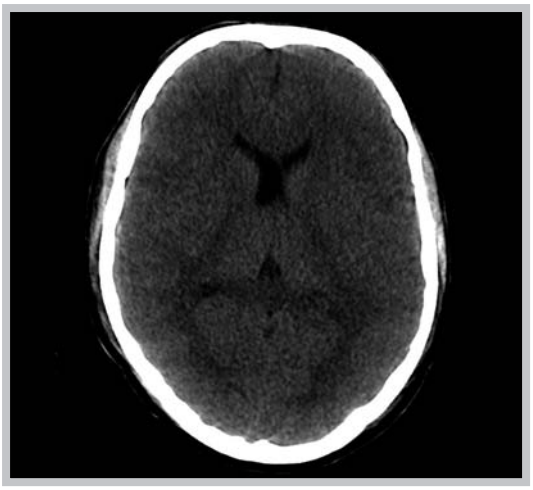

Figure 2.11. Asymmetrical frontal horns.

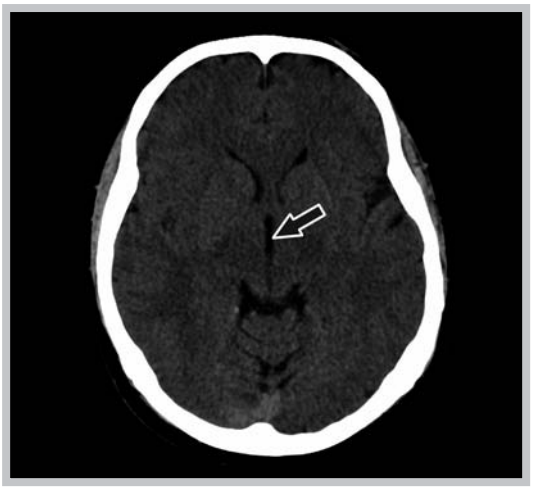

Figure 2.12. Third ventricle (arrow).

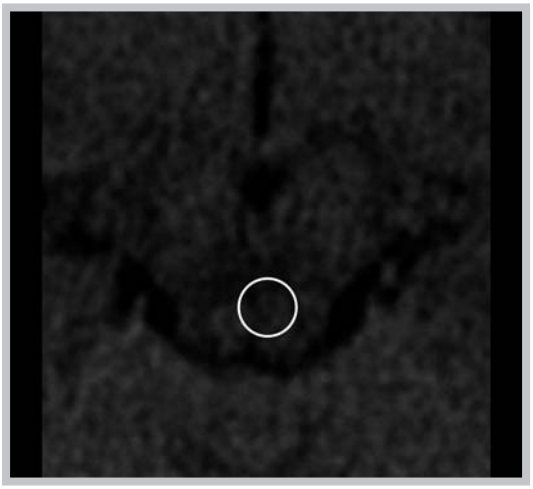

Figure 2.13. Aqueduct of Sylvius (shaded area).

Figure 2.14. Fourth ventricle (arrow).

Asymmetry in the size of the lateral ventricles should prompt an exhaustive search for space-occupying lesions, which reduce the amplitude of the ipsilateral ventricle (extra-axial collections, subacute phase of stroke, tumour, etc.), or for loss of tissue causing increased amplitude of the ipsilateral ventricle due to associated retraction changes (malacic area due to a previous stroke or tumour resection), whereas in the absence of apparent structural damage, ventricle asymmetry may be deemed a normal variant ("constitutive" variant) (Figures 2.11. and 2.12).

The third ventricle, evident in the midline, is a vertical cavity containing the interthalamic adhesion, just below the lateral ventricles, and is connected to the fourth ventricle through the aqueduct of Sylvius. It has several recesses: chiasmatic, infundibular, and suprapineal and pineal. It is important to remember that dilatation of the infundibular recess of the third ventricle is a reliable sign of acute hydrocephalus (Figures 2.13 and 2.14).

The fourth ventricle can be seen just between the middle cerebellar peduncles: it has the pons in front and the cerebellar vermis behind. The cavum septum pellucidum, the cavum vergae and the cavum velum interpositum are all normal variants in the ventricular system. The choroid plexus can be seen in the ventricular system, where the tela

chorioidea comes into contact with the ependyma, the roof of the third ventricle, the body and the temporal horn of the lateral ventricle, and the floor of the fourth ventricle. They may have calcifications and small cystic images of no pathological relevance (Figure 2.15).

The subarachnoid space lies between the pia mater and the arachnoid membrane. It contains CSF, which is compartmentalized in the cisternae thanks to membranes, septa or trabeculae. The cisternae are important because they contain key arterial and nervous structures.

Figure 2.15. Calcifications of the choroid plexus (lower arrow), pineal (middle arrow) and falx cerebri (upper arrow). The right frontal intraparenchymal calcification is not a normal variant, nor is the disproportionate expansion displayed in the lateral ventricles.

Supratentorial and Peritentorial Cisterns

- Suprasellar: infundibulum, optic chiasm and the circle of Willis.
- Interpeduncular: cranial nerve III and basilar artery.
- Ambient: cranial nerve IV, posterior cerebral artery (PCA2), superior cerebellar artery, basal vein of Rosenthal.
- Quadrigeminal: vein of Galen, posterior cerebral artery (PCA3), pineal, cranial nerve IV.
- Velum interpositum: internal cerebral veins.

Infratentorial Cisterns

- Prepontine: cranial nerves V and VI, basilar artery and anterior inferior cerebellar artery (AICA).
- Prebulbar: posterior inferior cerebellar artery (PICA), vertebral arteries, anterior spinal artery and cranial nerve XII.
- Superior cerebellar: branches of the superior cerebellar arteries and veins.
- Cisterna magna: cerebellar tonsils and branches of the PICA.
- Cerebellopontine angle: cranial nerves V, VII and VIII, AICA and petrosal vein.
- Cerebellar bulbar angle: cranial nerves IX, X and XI.

Fissures

- Interhemispheric: falx, inferior sagittal sinus and anterior cerebral artery.
- Sylvian (lateral fissure): middle cerebral artery (M1-3) and vein.

2.4.5 Basal Ganglia Region

The difference between grey and white matter is due to the presence of myelin in the white matter, which is paradoxically

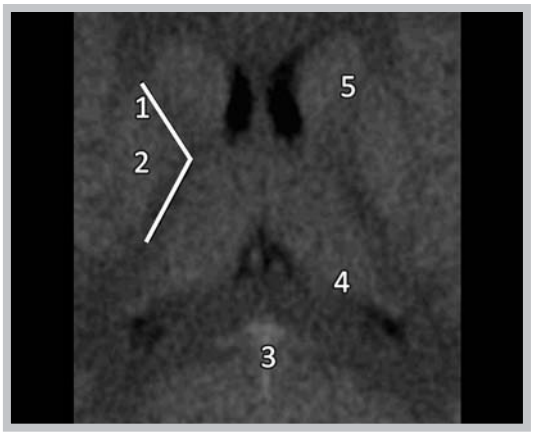

Figure 2.16. Grey basal ganglia.

1 = Internal capsule
2 = Lenticular capsule
3 = Splanius capitis cervicis
4 = Thalamus
5 = Caudate nucleus

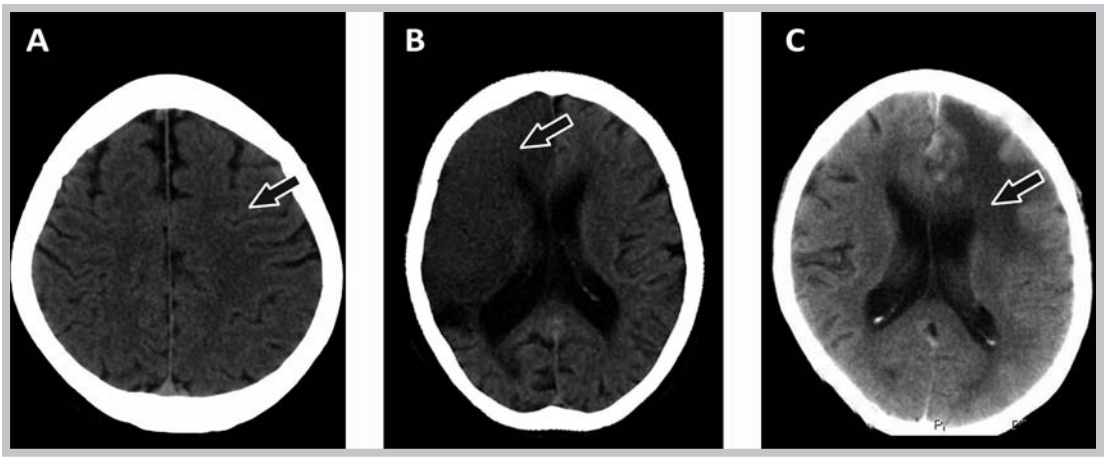

Figure 2.17. **(A) Sulci of the cerebral convexity, grey-white matter differentiation (red arrow). (B) Loss of grey-white matter differentiation due to cytotoxic edema (arrow). (C) Vasogenic edema (finger-like shape) (arrow).**

more "black" (hypodense) than the cortex, owing to its high fat content. Since the basal ganglia contain grey matter, they have the same density (isodense) as the cerebral cortex (+30 to +40 HU). They are separated by white matter tracts with lower density (+20 to +35 HU). Since the darkening of contrast between the white matter tracts and the grey nuclei suggests the presence of edema, it is very useful to evaluate these characteristic densities (Figure 2.16).

2.4.6 Cerebral Cortex and White Matter

Externally, the difference in the densities of the grey and white matter is essential for assessing the gyri, where we must clearly distinguish the cerebral cortex (higher density) from the subcortical white matter and verify the relative symmetry of the convexity sulci with the contralateral ones, the latter having liquid density. The loss of grey-white matter differentiation is abnormal and indicates edema (cytotoxic or vasogenic) or cortical dysplasia, and is associated with obliteration of the convexity sulci, whereas medial displacement, asymmetric or not, of this asymmetric line of transition indicates extra-axial collection (Figure 2.17).

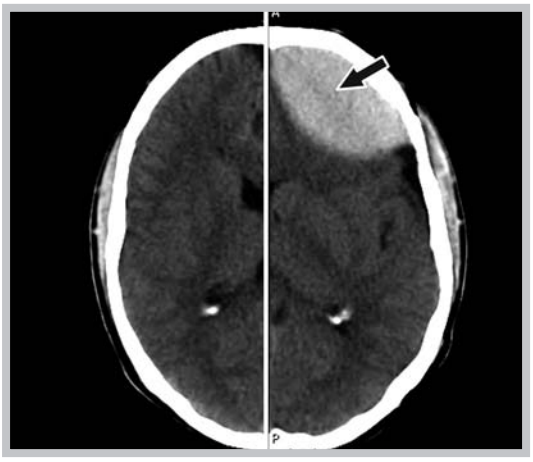

Figure 2.18. **Acute epidural hematoma (arrow). Convex with respect to the midline.**

The CSF contained in the convexity sulci or in those of the cerebellar folia changes in density (increases its density) when blood (subarachnoid hemorrhage) or purulent material (meningoencephalitis) is present. The extra-axial collections occupying the subdural space (under the dura mater) have a concave half-moon-like configuration with respect to the midline, whereas the epidural collections (external or outside the dura mater) have convex or biconvex lens settings (lentiform) (Figure 2.18). These collections of blood are highlighted by their higher density than that of the cortex in the acute phase (>5 days), are isodense to the cortex in the subacute

phase (5-15 days), and are less dense than the cortex in the chronic phase (>15 days). Finally, we present the anatomical structures present in the different slices in the transverse plane of a CT scan of the head without contrast and the circle of Willis in a contrast-enhanced CT scan of the head. These images may be a reliable reference point for image interpretation in the emergency department (Figures 2.19-2.41).

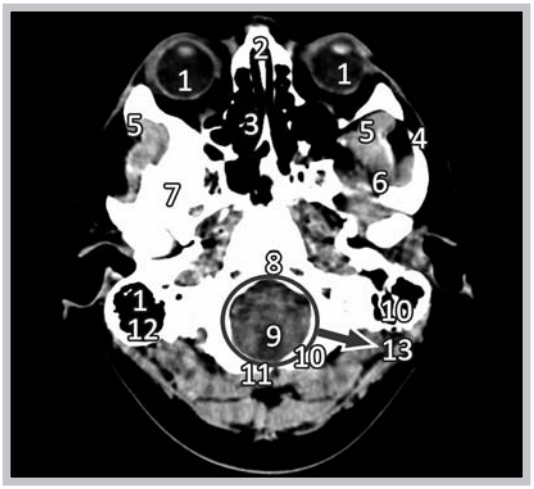

Figure 2.19

1 = Ocular globe
2 = Nasal bones
3 = Ethmoid cells
4 = Zygomatic arch
5 = Sphenoid
6 = Subtemporal fossa
7 = Temporal bone
8 = Clivus
9 = Bulb medullary union
10 = Amygdala
11 = Occipital bone
12 = Mastoid
13 = Foramen magnum

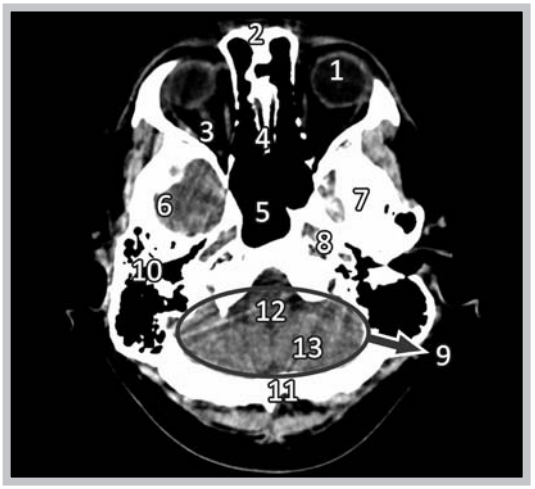

Figure 2.20

1 = Ocular globe
2 = Nasal bone
3 = Optic nerve
4 = Nasal septum
5 = Sphenoid sinus
6 = Temporal fossa
7 = Temporal bone
8 = Carotid canal
9 = Posterior fossa
10 = Mastoid
11 = Occipital bone
12 = Medulla
13 = Cerebellum

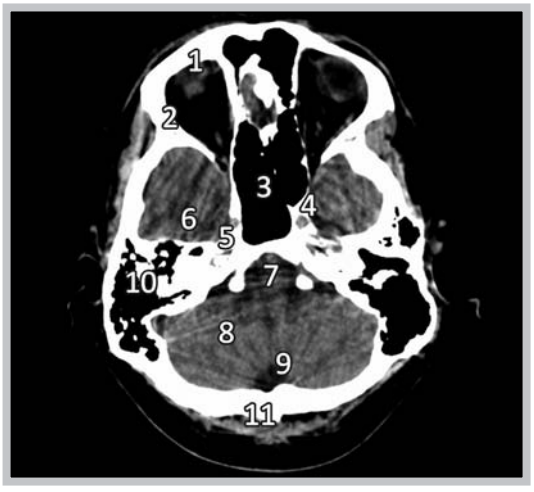

Figure 2.21

1 = Orbit
2 = Sphenoid
3 = Sphenoid sinus
4 = Cavernous sinus
5 = Tip
6 = Temporal lobe
7 = Medulla
8 = Cerebellum
9 = Cisterna magna
10 = Mastoid
11 = Occipital lobe

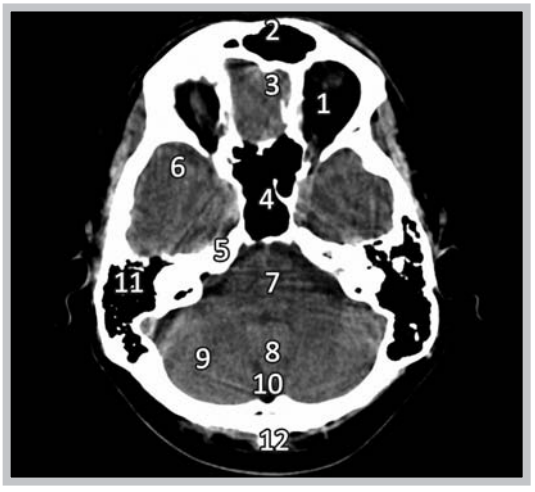

Figure 2.22

1 = Orbit
2 = Frontal sinus
3 = Frontal lobe
4 = Sphenoid sinus
5 = Tip
6 = Temporal lobe (superior gyrus)
7 = Pons
8 = Cerebellar vermis
9 = Cerebellar hemisphere
10 = Cisterna magna
11 = Mastoid
12 = Occipital

Figure 2.23

1 = Orbital roof
2 = Frontal lobe
3 = Sellae (posterior portion)
4 = Temporal lobe
5 = Tentorial edge
6 = Boulder
7 = Pons
8 = Cerebellopontine cistern
9 = Fourth ventricle
10 = Mastoid
11 = Cerebellum
12 = Occipital bone

Figure 2.24

1 = Orbital roof
2 = Frontal lobe
3 = Sellae (posterior portion)
4 = Temporal lobe
5 = Tentorial edge
6 = Pons
7 = Cerebellopontine cistern
8 = Fourth ventricle
9 = Mastoid
10 = Cerebellum
11 = Occipital bone
12 = Middle cerebellar peduncle
13 = Sigmoid sinus

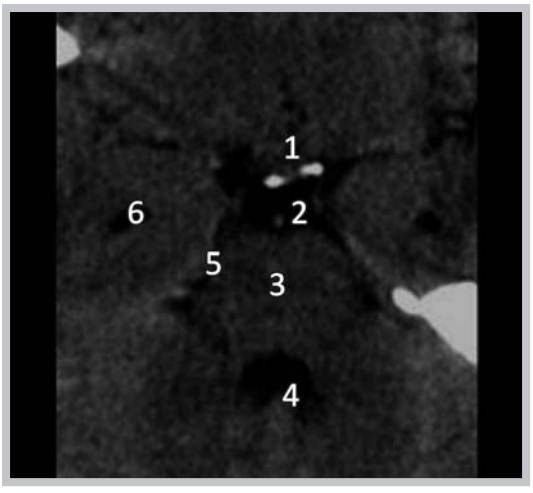

Figure 2.25

1 = Optic chiasm
2 = Basilar artery
3 = Pons
4 = Fourth ventricle
5 = Crural cistern
6 = Temporal horns

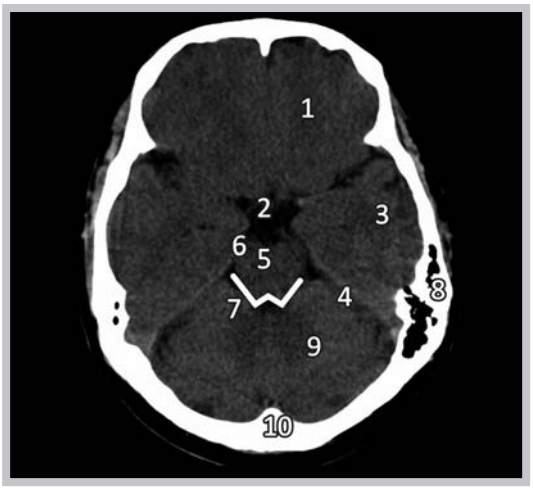

Figure 2.26

1 = Frontal lobe
2 = Suprasellar cistern
3 = Temporal lobe
4 = Tentorium
5 = Ponto-mesencephalic union
6 = Crural cistern
7 = Cisterna ambiens
8 = Mastoid
9 = Cerebellum
10 = Occipital bone

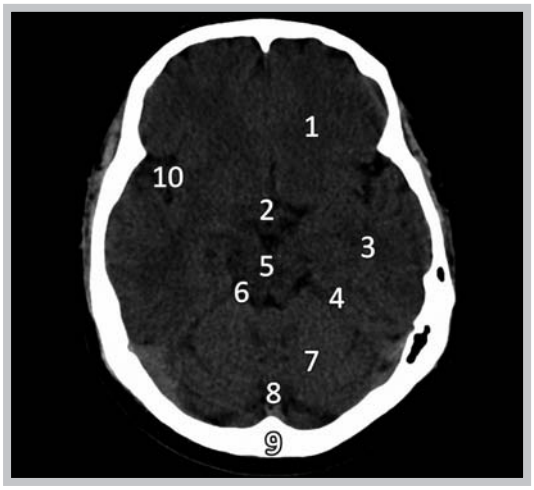

Figure 2.27

1 = Frontal Lobe
2 = Hypothalamus
3 = Temporal lobe
4 = Tentorium
5 = Midbrain
6 = Cisterna ambiens
7 = Cerebellum
8 = Torculus
9 = Occipital bone
10 = Sylvian cistern

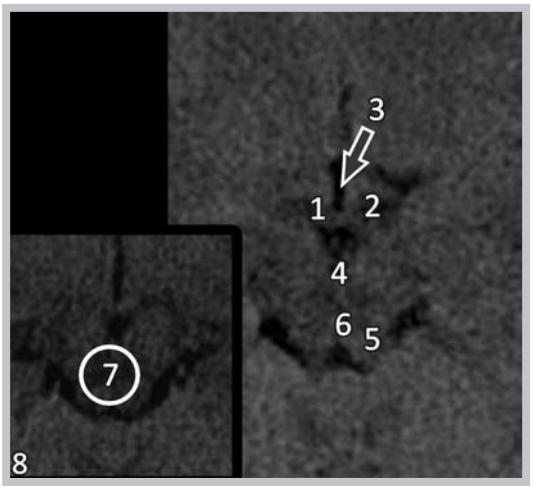

Figure 2.28

1 = Hypothalamus
2 = Optic tracts
3 = Infundibular recess of third ventricle
4 = Interpeduncular cistern
5 = Cisterna ambiens
6 = Midbrain
7 = Silvio's aqueduct

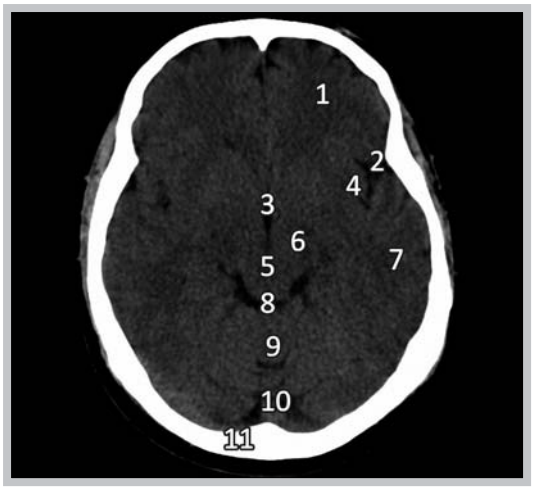

Figure 2.29

1 = Frontal lobe
2 = Sylvian cistern
3 = Third ventricle
4 = Insular cortex
5 = Midbrain
6 = Cerebral peduncles
7 = Temporal lobe
8 = Cisterna ambiens
9 = Cerebellum (vermis)
10 = Torculus
11 = Occipital bone

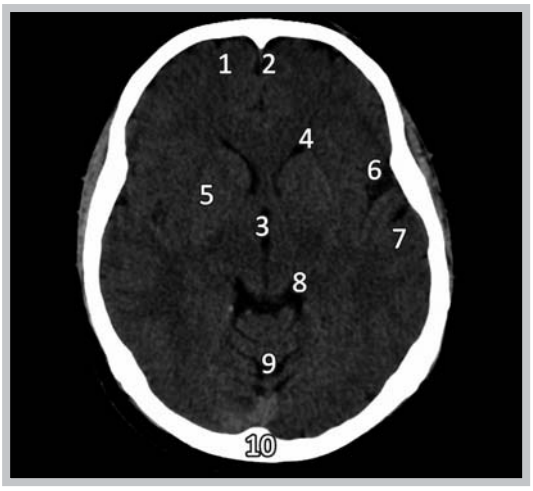

Figure 2.30

1 = Frontal lobe
2 = Falx cerebri
3 = Third ventricle
4 = Frontal horn of the lateral ventricle
5 = Lenticular fasciculus
6 = Sylvian cistern
7 = Temporal lobe
8 = Pulvinar
9 = Cerebellar vermis
10 = Occipital bone

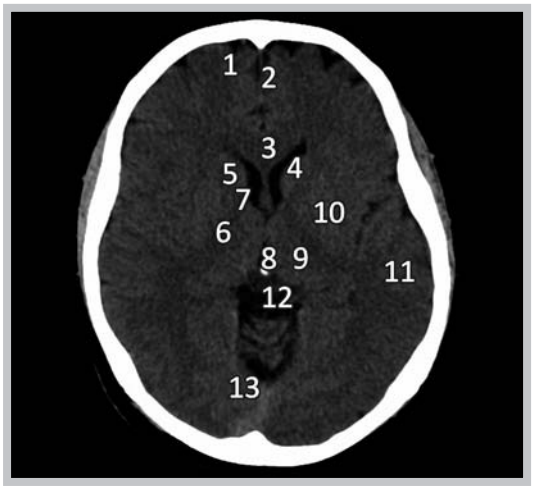

Figure 2.31

1 = Frontal lobe
2 = Falx cerebri
3 = Posterior portion of the corpus callosum ("knee")
4 = Caudate head
5 = Anterior limb of internal capsule
6 = Posterior limb of internal capsule
7 = Knee of internal capsule;
8 = Pineal recess
9 = Thalamus
10 = Lenticular fasciculus
11 = Temporal lobe
12 = Superior vermian cistern
13 = Occipital lobe

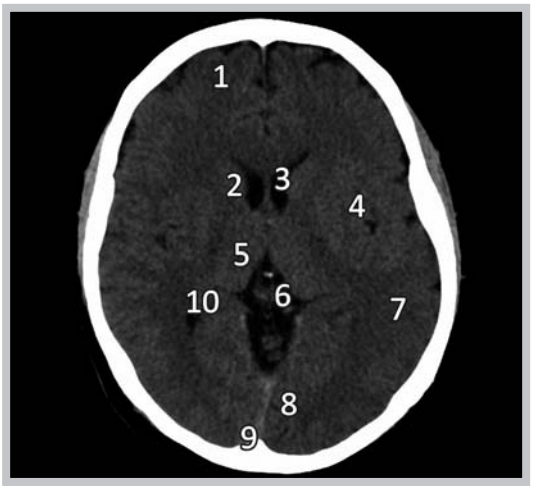

Figure 2.32

1 = Frontal lobe
2 = Caudate head
3 = Lateral ventricle frontal horn
4 = Insula
5 = Thalamus
6 = Superior vermian cistern
7 = Temporal lobe
8 = Occipital lobe
9 = Straight sinus
10 = Choroid complex

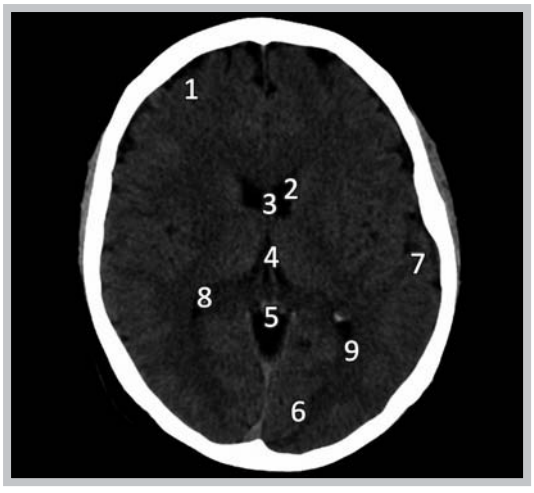

Figure 2.33

1 = Frontal lobe;
2 = Lateral ventricle frontal horn;
3 = Septum pellucidum (transparent walls);
4 = Cerebral veins;
5 = Vein of Galen;
6 = Occipital lobe;
7 = Temporal lobe;
8 = Choroid complex;
9 = Dorsal horn

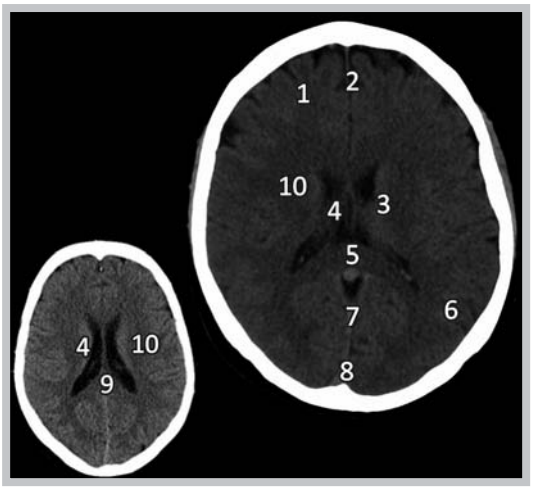

Figure 2.34

1 = Frontal lobe
2 = Interhemispheric fissure
3 = Caudate nucleus
4 = Lateral ventricle body
5 = Corpus callosum Splenium
6 = Parietal lobe
7 = Straight sinus
8 = Superior sagittal sinus
9 = Septum
10 = Corona radiata

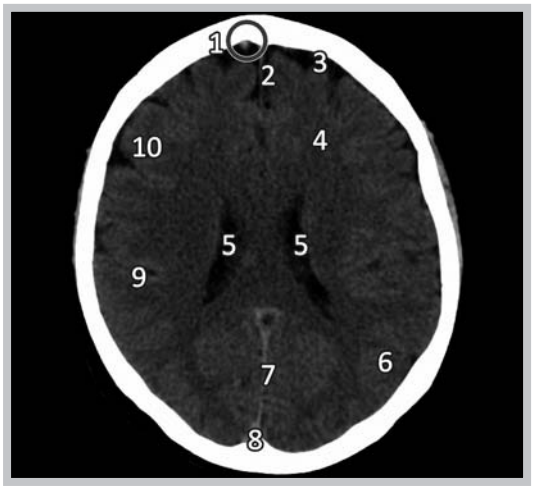

Figure 2.35

1 = Cortical vasum
2 = Falx cerebri
3 = Subarachnoid space
4 = Frontal white matter
5 = Lateral ventricle body
6 = Parietal lobe
7 = Straight sinus
8 = Superior sagittal sinus
9 = Sulcus
10 = Frontal cortex

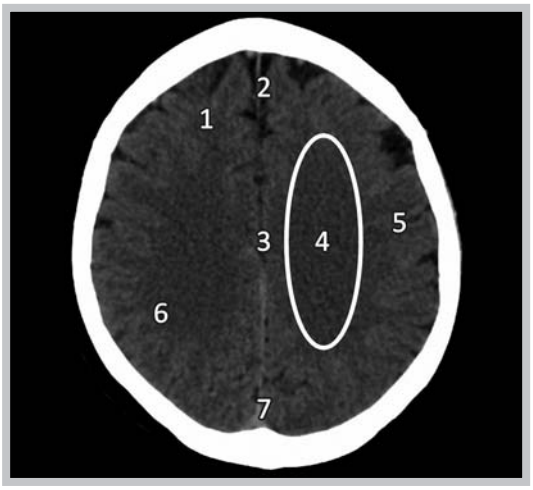

Figure 2.36

1 = Frontal llobe
2 = Falx cerebri
3 = Interhemispheric fissure
4 = Semiovale center
5 = Sulcus
6 = Parietal lobe
7 = Superior sagittal sinus

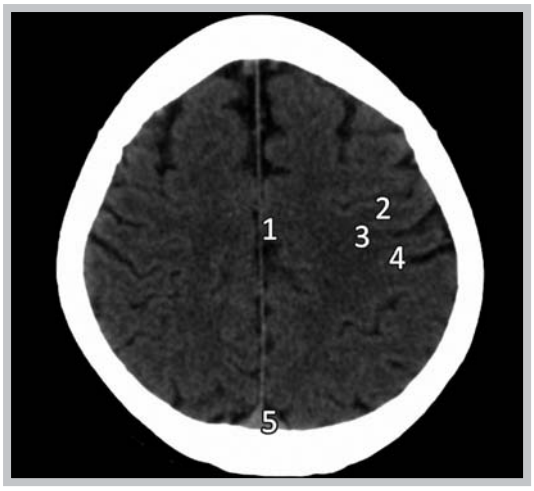

Figure 2.37

1 = Falx cerebri
2 = Central gyrus
3 = Precentral sulcus
4 = Postcentral sulcus
5 = Superior sagittal sinus

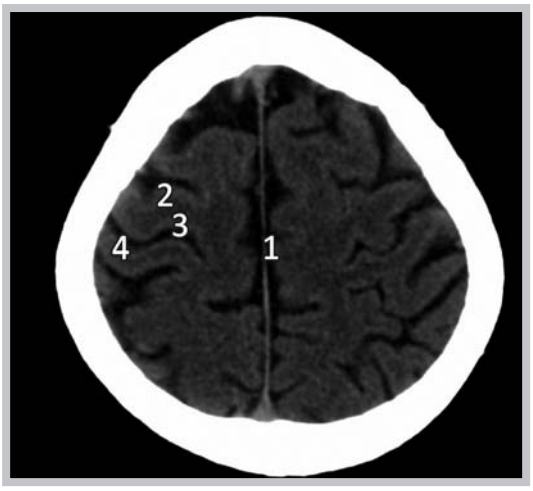

Figure 2.38

1 = Falx cerebri
2 = Precentral gyrus
3 = Centralsulcus
4 = Postcentral gyrus

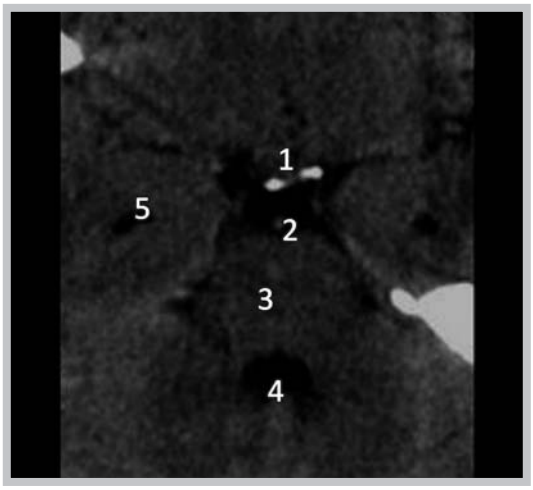

Figure 2.39

1 = Optic chiasm
2 = Basilar artery
3 = Pons
4 = Fourth ventricle
5 = Temporal horns

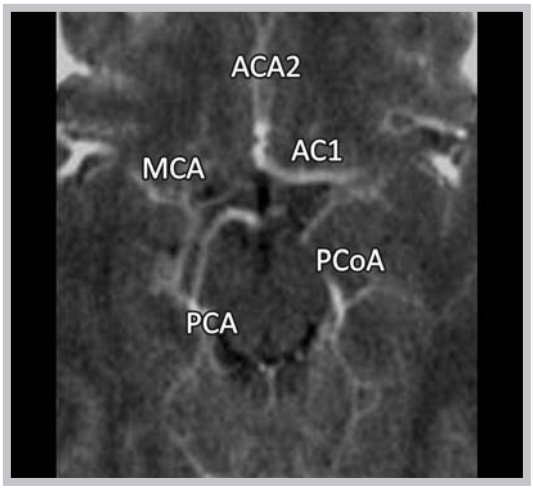

Figure 2.40

ACA1 = Segment 1 of the anterior cerebral artery
ACA2 = Segment 2 of the anterior cerebral artery
MCA = Middle cerebral artery
PCoA = Posterior communicating artery;
PCA = Posterior cerebral artery

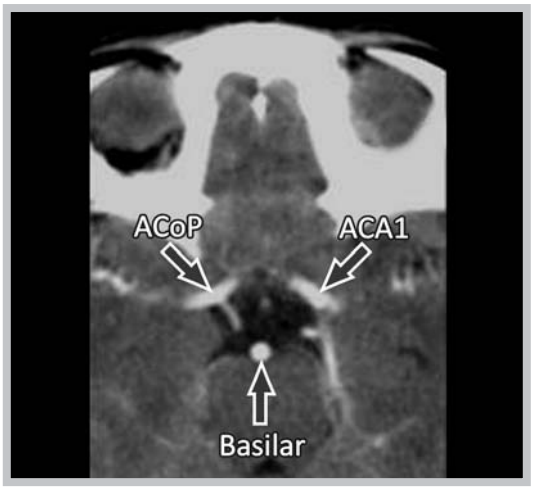

Figure 2.41

ACA1 = Segment 1 of the anterior cerebral artery
Basilar = Basilar artery

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3 Physiological Basis for the Correct Interpretation of Different Situations in Acute Cerebral Injury

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3.1 Functional and Structural Organization of the Nervous System

The nervous system is the most complex tissue of the human body. It controls and regulates numerous body functions, enabling us to interact with our environment. Within this signalling network, the brain works much as a database centre that processes the stimuli received by our sensory organs, allowing us to learn, remember, imagine, reason, and experience feelings.

From a functional point of view, the nervous system is composed of three elements: 1) neurons; 2) glia or supportive tissue; 3) blood vessels.

Neurons are the anatomo-functional unit of the nervous system. These highly specialized cells generate, transmit and receive signals along a vast communication system with other cells. The nervous system is formed by more than 9 million neurons that generate and conduct nervous impulses. The neural pool is maintained from birth, these cells have a distinctive feature: "cannot reproduce when damaged or destroyed". They have different shapes and are characterised by prolongations that can be grouped in two major classes:

- Dendrites or protoplasmatic prolongations that transmit nervous impulses to the cell body.
- Axons: unique, born of the cell body. Their grouping with others from other neurons, form the conduction pathway. Its primary function is to transmit the impulse from the cell body.

Since the dendrites transmit nerve impulses to the cell body, it is easy to understand that each neuron can receive stimuli from many different dendrites, but only one neuron can respond, because each neuron has only one axon.

According to their function, three types of neurons are distinguished:

- Afferent or sensory neurons that convert the external stimuli from the environment into internal electrical motor reflex loops and regulate involuntary activities such as breathing.
- Efferent or motor neurons carry nerve impulses away from the central nervous system (CNS) to effectors such as muscles or glands.
- Interneurons, multipolar neurons which join the afferent and efferent neurons into neural pathways.

A neuron's shape depends on its function, i.e., its position into the neuronal network and the contacts it receives. The neurons transmit information through a dense and articulated network across synapses where the impulse is mediated by neurotransmitters.

The term "**glial**" derives from the Greek word meaning "glue" or "union". The glia is a heterogeneous tissue that primarily provides physical support for neurons. Other glial cells regulate the brain's internal environment, especially the fluid surrounding neurons and others have cleaning, nutrition and defense functions. Unlike neurons, glial cells can divide and reproduce, so that they can take its place when a neuron dies. There are four types of neuroglial cells: oligodendrocytes, astrocytes, microglia, and ependymal cells. The main characteristics and functions of each type are described below.

Oligodendrocytes have a small number of prolongations and a small cellular body (the nucleus occupies the greatest part). They are mainly distributed in the white matter or at the end of nerve fibres (which is why they are called interfascicular oligodendrocytes) which synthesize the myelin sheath surrounding the axons in the CNS and the Swann cells in the peripheral nervous system (PNS). Some are thought to influence the biochemical media of the neurons. Satellite oligodendrocytes are other types of oligodendrocytes and are mainly found in the sensory and autonomic ganglia.

Ependymal cells line the ventricular cavities of the brain and the central canal of the spinal cord. On their surface in contact with the ventricles, they form a unique layer of cubical or cylindrical cells possessing microvilli and cilia which assist in the circulation of cerebrospinal fluid (CSF). The opposite cell surface forms part of the neural connective tissue.

Astrocytes are star-shaped glial cells in the brain and spinal cord. They derive primarily from the ectoderm and are twice more numerous than neurons. Their functions include biochemical support of the endothelial cells forming the blood-brain barrier, provision of nutrients to the nervous tissue, maintenance of the extracellular ion balance, and repair and scarring processes of the brain and spinal cord following traumatic injury. They have many ramifications and prolongations, known as podocytes, that surround the capillaries. They are vey important because they are thought to aid in the maintenance of the blood-brain barrier, forming high specialised regions that control the transport of glucose, oxygen, hormones and other substances essential for the nervous tissue.

There are two forms of astrocytes: protoplasmic, and fibrous. The former are found in the grey matter, possess a larger quantity of organelles, and exhibit short and highly branched cellular processes. The latter are predominantly located within the white matter, have relatively few organelles, and exhibit long unbranched cellular processes.

Astrocytes also envelope the neuronal synapses, forming a sort of network, thus regulating the ion concentration in the extracellular space.

Astrocytes possess uptake systems of neurotransmitters of high affinity, voltage-dependent ion channels, ability to generate and release neurotransmitters as well as the possibility to express in their membranes, a large number of receptors with the ability to respond to stimuli generated by the neuronal release of certain substances among which are glutamate, GABA, acetylcholine, norepinephrine and nitric oxide.

Astrocytes have the following functions:

- Assist in the elimination of cerebral metabolic waste products.
- Provide neurons with nutrients.
- Maintain extracellular space homeostasis (ions, pH).
- Are involved in the physical structuring of the brain, creating the network that sustains neurons.
- AMaintain the junction between neurons and capillaries coupling vascular and nerve functions.
- Together with endothelial cells, they form the blood-brain barrier.
- Neurogenesis.

Microglia are small cells with a dense and enlarged nucleus. Their long extensions branch into smaller vessels, lending them a ramified shape. They have a close relationship with blood vessels and are found throughout the CNS.

They store lipids, iron, and pigments and phagocytise waste products, which is why they are also known as scavenger cells. They can move and change their shape. They play a key role during embryonic development and in the secretion of growth factors which contribute to neuronal maturation and the survival of glial cells as a whole. They also assist in neuronal regeneration and plasticity. Generally, microglia are in a quiescent but alert state. When activated (like macrophages), they generate free oxygen radicals, proinflammatory proteins and cytokines such as interleukin 1 and tumour-like necrosis factor which can become detrimental for the nervous system.

3.2 The Blood-Brain Barrier (BBB)

The blood-brain barrier (BBB) was first described in 1885 by Paul Ehrlich, who experimentally demonstrated that following the injection of colorants (aniline dyes) all of the organs of some kinds of animals would stain, except the brain. The BBB forms not only a physical barrier, but also actively takes part in many different physiological, biochemical and enzymatic mechanisms that maintain homeostasis. The BBB is a dynamic structure that can quickly respond to different stimuli generated locally in the brain or the systemic circulation. Under normal circumstances, the functions of the BBB are:

- Isolation and protection of the brain against certain noxa.
- Selective transportation of substances.
- Monitoring of systemic chemical variations.
- Metabolization of different compounds.

The BBB works as both a physical and a metabolic barrier that isolates the CNS from the rest of the body. It is formed by specialized endothelial cells that cover the cerebral vascular system. This barrier have important clinical implications because an increase in its permeability can result in disease and for another side, the impermeability of an intact BBB can prevent the penetration of certain drugs, so, it is important to evaluate its degree of permeability. Several lines of evidence have suggested that astrocytic protein S100β is a potentially useful peripheral marker of BBB permeability.

From a morphologic point of view, the BBB consists of a layer of endothelial cells that covers nearly all cerebral blood vessels. The cells of the endothelium are united to each other through narrow junctions similar to those that can be found between the endothelium and astrocytes.

There are different types of junctions: a9 GAP junctions; b) adherent junctions; and c) narrow junctions.

GAP junctions are formed by transmembrane proteins (conexins) which connect the cytoplasm between endothelial cells. The adherent junctions are formed by proteins of the cadherin family, whereas the narrow junctions are composed of several membrane proteins of the zonula occludens family. The high protein expression of the narrow junctions is a fundamental and unique characteristic of the BBB, because they determine its impermeability to the majority of macromolecules.

The BBB has a very limited extracellular transportation (pinocytosis); nevertheless, it relies on highly developed specific carriers for different metabolites (e.g., glucose carrier GLUT-1). Furthermore, the BBB has many different enzymatic systems, such as the enzyme that catalyzes the conversion of $C0_2$ and H_20 into carbonic acid associated with numerous mitochondria with the high metabolic activity characteristic of endothelial cells. Closely related to endothelial cells, the podocytic processes (extensions of the astrocytes) play a protective role in the BBB, since they structure the endothelium into a barrier and regulate its response to hypoxia or hypoglycemia by modifying its permeability.

Thus, the BBB, although structurally composed of endothelial cells, is functionally regulated by neurons and glial cells.
Some specialized areas of the brain, including the hypothalamus, area postrema and subfornical and subcommissural organs, lie outside the BBB because the narrow junctions are absent. The region surrounding the ventricles and the circumventricular organs lacks the endothelium characteristic of the BBB. The choroid plexus and the neurohypophysis also lie outside the BBB. These areas are of fundamental relevance since they provide for hormonal transport and the transport of substances involved in fever onset, for example.

3.2.1 Transport Across the Blood-Brain Barrier

The permeability of the BBB depends on proprieties related to the BBB in itself and to the characteristics of various different substances. The permeability of most molecules can be predicted on the basis of their octanol/water partition coefficient. On this basis, we can distinguish two types of molecules:

- Lipophilic compounds (high partition coefficient) can easily access the brain.
- Hydrophilic compounds cannot pass the BBB and therefore cannot access the CNS (although impermeability is not total and a certain degree of diffusion exists).

Furthermore, the BBB is not permeable to high-molecular-weight compounds (MW 200-400) so, all proteins of the cerebrospinal fluid (CSF) such as albumin and immunoglobulin arise from serum ultrafiltration.
On the other hand, the majority of the hydrophilic compounds entering the CNS are proteins that pass by active or facilitate transportation. Their transport depends on ion channels, specific carriers, pumps energy-related and receptor-mediated endocytosis.
Glucose, amino acids and some intermediate metabolites enter the brain by facilitated transport, whereas larger molecules such as insulin, transferrin and other plasma proteins pass the BBB via absorptive endocytosis or with help of specialized receptors.
Further hindering our understanding, its has been noted that some highly permeable compounds are present in very low concentrations in the CNS. They are eliminated from the CNS through the blood by energy-dependent carriers such as p-glycoproteins (Pgp) in the luminal membrane of the endothelium. These mechanisms, which protect the brain, also contribute to drug resistance.

3.3 Cerebrospinal Fluid (CSF)

The brain cavity has an estimated capacity of 1600-1700 ml, 150 ml of which are occupied by CSF. The daily production of CSF is 500 ml at a rate of 0.35 ml per minute, two-thirds of which is produced by the choroid plexus and one third by the arachnoid membranes and the brain.
CSF secretion depends largely on active sodium transport in the choroid plexus. The choroid plexus epithelium secretes a major fraction of the CSF to the lumen of the ventricular system. The pivotal event in CSF secretion is the active transport of Na^+ from the epithelial cell to the CSF mediated by the apically positioned Na^+-K^+-ATPase. The apical Na^+-K^+-$2Cl^-$ cotransporter seems to contribute to Na^+ secretion, because bumetanide inhibits CSF formation when applied apically. At the same time, NKCC1 enriches the CSF with K^+ to feed the apical Na^+-K^+-ATPase. NKCC1 may alternatively take up ions from the CSF as part of regulatory cell volume increase. Cl^- is secreted through electrogenic mechanisms, likely involving one or more Cl^- channels. The above phenomenon creates

osmotic gradients that attract water. The inflow and outflow of water is tightly regulated by specific protein channels called aquaporins.

Na^+ is the main cation of CSF, and its concentration is similar to that of the plasma. In contrast, the Cl^- concentration is higher than that of the plasma because of the impermeability of the BBB to proteins and the so-called Donnan effect (the same quantity of negative and positive charges on both sides of a membrane). The normal amount of proteins ranges from 20 to 40 mg per 100 ml of CSF. The glucose reaches the CSF through a facilitated diffusion mechanism, through the GLUT transport system, its concentration being equal to 60% of that in the plasma. The CSF is limpid and colourless; its aspect is similar to water and it has practically no cells (about 8 lymphocytes/mm^3).

Experimental animal studies suggest that CSF production remains stable if the cerebral perfusion pressure (CPP = MABP – ICP) is between 50-60 mmHg, decreasing principally on the basis of blood pressure. The cells of the choroid plexus are innervated by the autonomic nervous system. The sympathetic activity is inhibitory, whereas the parasympathetic signal stimulates CSF production. Normally, only 25 ml of CSF circulate in the ventricular system; from this we can deduce that the CSF is completely replaced 3 times a day, that is to say, every 8 hours. Once in the lateral ventricles, the CSF circulates through the Monro hole to the third ventricle, which is connected to the fourth ventricle by the Sylvian aqueduct. Then the CSF drains from the fourth ventricle into the cisterna magna. The two lateral apertures (foramina of Magendie and Luschka), one on the left and one on the right, are the primary routes for drainage of CSF from the fourth ventricle into the cerebellopontine angle cistern, and subarachnoid space of the brain and spinal cord. From the basal cisterns the CSF re-enters systemic circulation and circulates toward the cortical subarachnoid space, where it is absorbed into the venous sinuses.

In 1891 Quincke was the first to measure CSF pressure by means of a water column manometer placed by lumbar puncture. In 1927, Fremont-Smith reported the values of CSF pressure in normotensive individuals without CNS pathologies. The normal CSF pressure is between 70 and 180 mmH_2O, with an average of 130 mmH_2O, equal to 10 mmHg in the horizontal position. Physiological variations are related to fluctuations in arterial blood pressure and breathing. The arterial pulsations are synchronously transmitted to the choroid plexus and then to the CSF, thus generating the intracranial pressure wave (this topic will be discussed in another Chapter).

The CSF has many different functions:

- Cushion effect. Since the brain and CSF have almost the same density, the brain "floats" in the CSF. Because of this proprety, the brain weighs 50 g (and not 1500 g) when suspended in CSF.
- Physical protection against direct or indirect impact.
- Maintain cerebral dynamics stable during changes in body position, breathing or fluctuations in arterial pressure.
- Transport substances such as neurotransmitters, hormones, etc.
- Actively assist in maintaining ion balance in the CNS.
- Since the brain has no lymphatic system, CSF assists in eliminating fluids, proteins, cells, and metabolic waste products.

3.4 Aquaporins (AQP)

The brain is composed of 70% by water, making its homeostasis essential for the survival of the cellular groups composing the CNS. Water movement across membranes is a fundamental process in all living organisms. Given this phenomenon and the impermeability of the BBB, how does the interchange of this vital element occur?

In 1988, Peter Agree discovered and described the water channel protein (aquaporin 1); this discovery earned him the Nobel prize for chemistry in 2003. Aquaporins are an integral membrane pore protein and conduct water molecules in and out of the cell. In general, they increase membrane permeability to water across facilitated diffusion, without energy costs, following osmotic gradients mainly generated by the active transport of sodium.

The brain has four types of aquaporins:

- AQP 1 is found on the epithelial cells of the choroid plexus, where they are concentrated at the apical pole; playing a principal role in CSF formation.
- AQP 4 is localized in the astrocytes and ependymal cells. They functions are: 1) BBB formation; 2) homeostatic control of water in the extracellular cerebral space; 3) regulation of extracellular potassium; 4) control of perivascular volume, a function that may be crucial for the maintenance of cells perfusion and oxygenation; 5) the high concentration of AQP4 in the hypothalamic region suggests that water channels have an active role in systemic regulation of water.
- AQP 9 can be found in astrocyte processes in the periventricular region of the parenchyma and the glia limitans bordering the subarachnoid space. It can assist in water movement between the CSF and the brain parenchyma.
- AQP 3, 5 and 8 are expressed in neuronal, astrocyte and oligodendrocyte cultures, respectively. Their physiologic role remains to be elucidated.

3.5 Intracranial Pressure

Intracranial pressure (ICP) is the pressure inside the skull and therefore in the brain tissue and the CSF as well. Each of the brain's components has a pressure. In an inextensible and rigid space, the ICP is the result of the pressure of each component of the cavity in which it is contained. According to the Monro-Kellie model, ICP is the sum of the pressure of the parenchyma, the CSF, and the blood contained inside the veins and arteries. Its value is constant.

ICP = parenchymal pressure + CSF pressure + pressure of cerebral blood volume

The percentage of the different components to ICP is:

- Glia: 700-900 ml = 45.5%.
- Neurons: 500-700 ml = 35.5%.
- Blood: 100-150 ml= 7.5%.
- CSF: 100-150 ml = 7.5%.
- Extracellular fluid: 50-70 ml = 3.5%.

Anatomically, the supratentorial space accounts for 50% of ICP, the intratentorial space for 30%, and the spinal space for 20%.

Normal values vary with age, body position, and clinical situation. In healthy persons the ICP is 7-15 mmHg In the horizontal position and negative (average, -10 mmHg) in the standing position. Normal values are 1.5-6 mmHg for term infants and 3-7 mmHg for young children.

To maintain ICP constant, any variation in the volume of one of the components will occur in relationship to a similar but opposite variation in the other components.

When this adaptation mechanism fails, the IPC rises. The structures integrating the cerebral parenchyma (glia, neurons) contribute little to the maintenance of normal ICP levels; only the CSF can contribute with a pressure gradient from the cerebral space.

The CSF and the blood contained in the cerebral veins (75% of the total blood volume) are the only components that can quickly and efficaciously decrease ICP levels by moving to the spinal compartment. Variation in CSF absorption or production doesn't play an important role. The arterial vascular compartment (25%) has a volume of 23 ml. This volume can decrease to 35% (15 ml) or increase to 172% (68 ml) depending on the decrease (vasoconstriction) or the increase (vasodilatation) in vessel diameter by means of the autoregulatory mechanism that keeps the cerebral blood flow (CBF) constant even when changes in cerebral perfusion pressure (CPP) occur (see below). Another powerful regulator of arterial vessel diameter is the partial pressure of carbon dioxide ($paCO_2$). For each mmHg of change in $paCO_2$, a blood volume change of 0.04 ml/100 g of brain tissue is produced.

Cerebral veins cannot be compressed (except in the presence of increase of ICP) and they do not react to the same stimulation as the arterial bed; for this reason, venous flow is the main determinant of intracerebral dynamics, since from its source to its mouth in the right atrium is a continuous system free of valves.

Importantly, the brain is composed of several small compartments divided by the dura mater. Therefore, the ICP is not uniformly equal in all the cavities, especially in pathological states when gradients between spaces can occur.

3.6 Cerebral Volume/Pressure Curve (V/P). Cerebral Compliance

The relationship between pressure and volume in the brain is not linear (Figure 3.1). This means that in physiological situations the brain volume can vary without causing variations in ICP thanks to compensative and mechanisms signalled previously; but after its maximum capacity has been reached, the IPC increases exponentially. In decompensated situations, even small changes in cerebral blood volume (e.g., 1 ml) can cause an increase of 7-8 mmHg in ICP. Two essential factors are not expressed in the curve: the magnitude and the time in which the changes occur. A slow-growing tumour allows the compensation mechanisms to actfully, so many remains asymptomatic because it does not change the V/P rate. In contrast, a rapidly expanding hematoma can quickly increase ICP.

Compliance is the expression of variations ICP in relationship to changes of intracranial volume:

$$\text{Compliance} = \Delta V / \Delta P$$

If the numerator changes and denominator remains unchanged, the compliance increases. This is what happens with aging. In the elderly the compliance is greater because the intracranial volume increases due to cerebral atrophy.

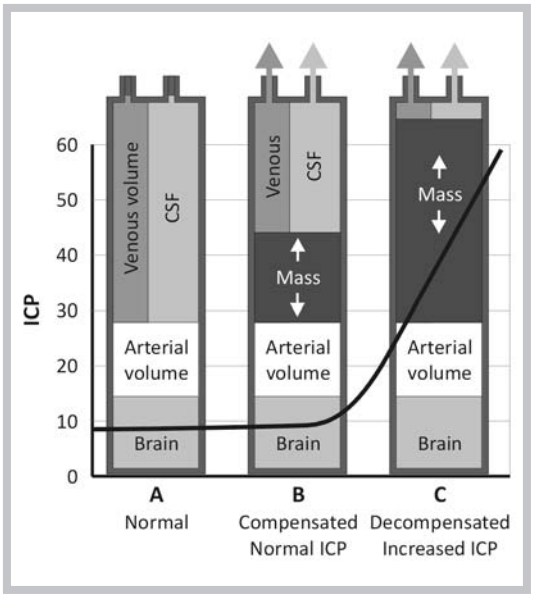

Figure 3.1. Pressure/volume curve.

On the contrary, if there is a minor increase in the numerator and a major increase in the denominator, the compliance decreases significantly.
An individual with adequate compliance has intact compensative mechanisms working. Figure 3.1 shows the three parts of the pressure-volume curve: the initial part of the curve is flat because compensatory reserves are adequate and ICP remains low despite increases in intracerebral volume (A and B in Figure 3.1).
When these compensatory mechanisms become exhausted, the pressure-volume curve turns rapidly upwards in an exponential fashion. Intracranial compliance is now critically reduced and a small increase in intracerebral volume causes a substantial increase in ICP (B and C in Figure 3.1).
Compliance should be evaluated together with ICP. There are two methods to obtain it, both of which are invasive and potentially related to risks (infections, herniation, bleeding):

- Intracranial pressure "reserve" test.
- Pression-volume index (PVI).

The intracranial pressure "reserve" test entails observing the variation in ICP while adding or removing 1 ml of fluids (saline solution of CSF). It's considered normal when the injection of 1 ml induces an increase of ICP ≤2 mmHg or when the ICP decreases with draining of 1 ml of CSF.
The pressure-volume index represents the quantity of intraventricular fluid that has to be injected to produce an ICP increase of 10 mmHg. Usually, it is equal to 25 ml. A value <10 ml indicates severely compromised compliance.

3.7 Intracranial Pressure Curve

The arterial waves hit the choroid plexus, thus generating intracranial pressure waves which are also influenced by pulsations originating from the great intracranial arteries and in a retrograde form by the venous system. The wave's components can be analysed obtain an approximately measure of the state of compliance.
The normal ICP wave has three well-defined and universally present peaks (Figure 3.2). The first reflects the arterial input, while the two others reflect venous input. The first is called the percussion wave (P1), which is well defined and wide. The second peak is P2, also known as tidal wave, and has a variable width. Finally comes the third peak (P3), often termed the dicrotic wave. As a general rule, as ICP rises, the described wave morphology changes, adopting a pyramidal shape with gradual disappearance of P1, P3 and marked rise of P2. Sometimes the ICP does not raise its absolute value but if it changes shape. If P2 is greater than or equal to P1, even with ICP values considered normal, the compliance is decreased (Figure 3.3).
In conclusion, the analysis of the ICP wave is a tool of great value to the investigation of altered states of compliance prior to dangerous increases in ICP.

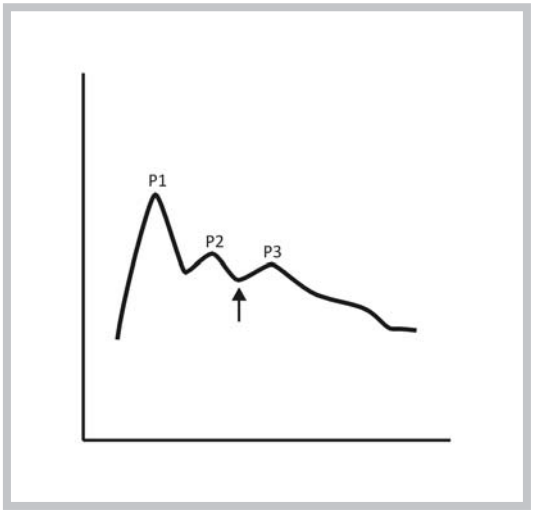

Figure 3.2. Intracranial pressure waves.

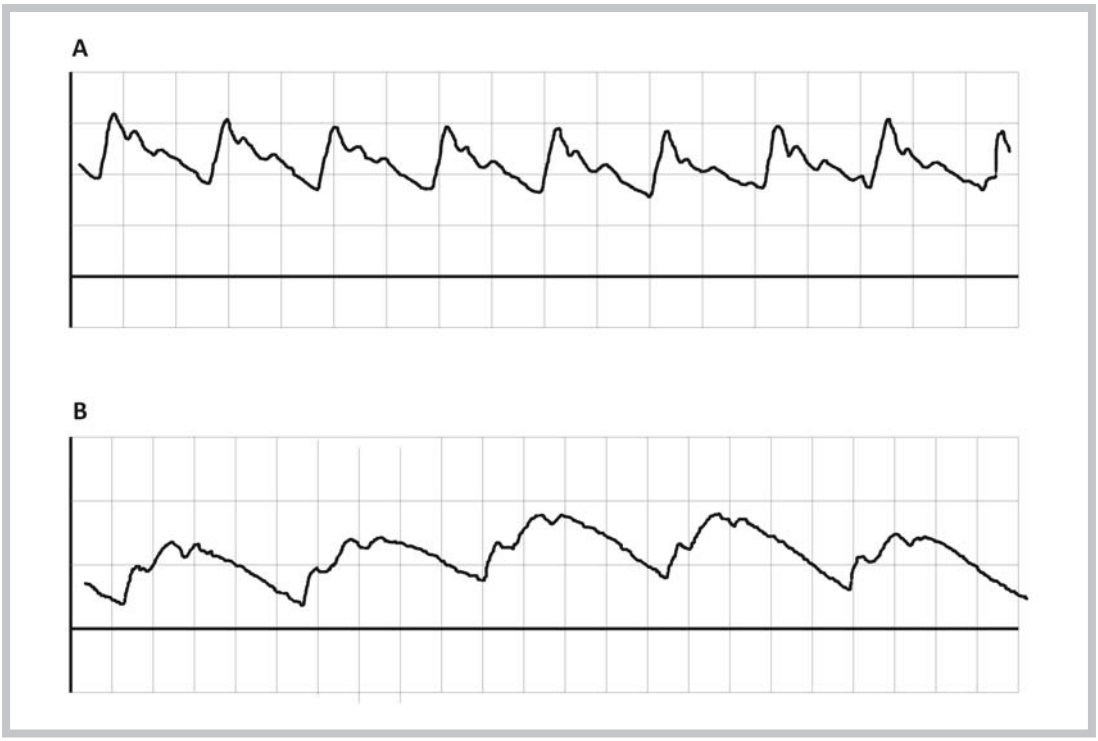

Figure 3.3. **Two patients with the same absolute ICP value (6 mmHg). (A) P1>P2>P3 indicates normal compliance. (B) P2>P1 indicates altered compliance.**

3.8 Cerebral Oxygen Metabolism

From a metabolic point of view, the brain is one of the most active and voracious organs of the human body. Although it does not perform mechanical work like skeletal or cardiac muscle, nor does it have complex enzymatic systems like the liver, it consumes 20% of total oxygen consumption.

The cerebral consumption of oxygen in a healthy and conscious individual is around 3.5 ml/100 g of tissue/min. Given that the brain weighs 1400 g on average, the total oxygen consumption is 49 ml/min. Consumption is maintained throughout a 24-hour period, even during sleep. Not all the oxygen provided is consumed, normally is extracted one-fifth to one-third that of the oxygen delivered. This difference underscores the great reserve capacity of the brain.

Oxygen is almost entirely used up in the mitochondrial oxidation of glucose to generate high energy phosphates. For each mol of oxygen, an equal amount of CO_2 is consumed, yielding a respiratory quotient of 1. The generated energy goes into maintaining the ion transmembrane gradients; therefore, the consumption of cerebral oxygen depends on cerebral activity. It has been estimated that 75% of the ATP produced is used to recover and maintain membrane potentials that take part in nervous impulse excitation and conduction. The remaining oxygen is used in several chemical reactions for the synthesis and metabolism of neurotransmitters, such as dopamine, serotonin and monoamines.

The gold standard for the measurement of cerebral metabolic rate of oxygen ($CMRO_2$) is positron emission tomography (PET), but in clinical practice it is calculated from the product of cerebral blood flow (CBF) the arterio-venous difference of oxygen ($AVDO_2$), according to the following formula:

$$CMRO_2 = CBF \times OEF$$

Though the brain does not store oxygen, it has a great need of oxygen and therefore requires its continuous supply. The availability of cerebral oxygen depends basically on two factors: the arterial content of oxygen (CaO_2) and the CBF.

3.9 Cerebral Blood Flow (CBF)

The average CBF in a healthy adult is about 55 ml of blood per 100 g of brain tissue per minute, or about 800 ml/min, corresponding to approximately 15% of the total basal cardiac output. To function adequately, the brain requires a CBF of about 54 ml/100 g brain tissue per minute. And because CBF depends on metabolic activity, CBF is greater in the gray matter (78 ml/100 g/min) than in the white matter (18 ml/100 g/min).
According to the Hagen-Poiseuille equation, the rate of laminar flow through a blood vessel is directly proportional to the existing pressure difference between the entrance and exit of the circuit (ΔP) and the diameter of the vessel (r), and inversely proportional to the viscosity of the circulating fluid (n).

$$\Delta P \times r^4$$

$$Flow = (\Delta P \times r^4) / (8 \times n \times l)$$

Under physiological conditions, the pressure gradient and the blood vessel diameter are the main determinants of CBF. The pressure gradient is obtained by calculating the difference between the mean arterial pressure (MAP) and the venous pressure; this is called the cerebral perfusion pressure (CPP). Because venous pressure is difficult to measure, ICP is measured instead. Accordingly, the CPP is obtained by calculating the difference between MAP and ICP as follows:

$$CPP = MAP - ICP$$

The cerebral blood vessels have the intrinsic capacity to maintain CBF constant, despite wide CPP fluctuations, in a range between 50 and 150 mmHg. This physiological property is called cerebral autoregulation.
Autoregulation of cerebral blood flow originates from the resistance of the arterioles which adapt their diameter in relation to different stimuli, thus determining cerebrovascular resistance (CVR). When the CPP increases to above 50 mmHg, the arterioles begin to contract, and the CVR increases in order to maintain CBF constant. By contrast, when the CPP decreases, the CVR decreases due to vasodilatation (Figure 3.4).
Under pathological conditions, the autoregulatory mechanism can be disrupted. When this happens, CBF passively follows CPP. This means that when MAP decreases, CBF decreases, and when MAP increases, CBF increases.
Thus, CBF is regulated by the control of the cerebral arteriolar tone, which is primarily modulated by CPP, in addition to other local factors such as $paCO_2$, paO_2, and pH. High CO_2 levels, acidosis and tissue hypoxia, and products of metabolic activity dilate the cerebral blood vessels and increase CBF. For this reason, the rate of formation of such products depends on the metabolic rate.
The metabolites that act in the regulation of the CBF are:

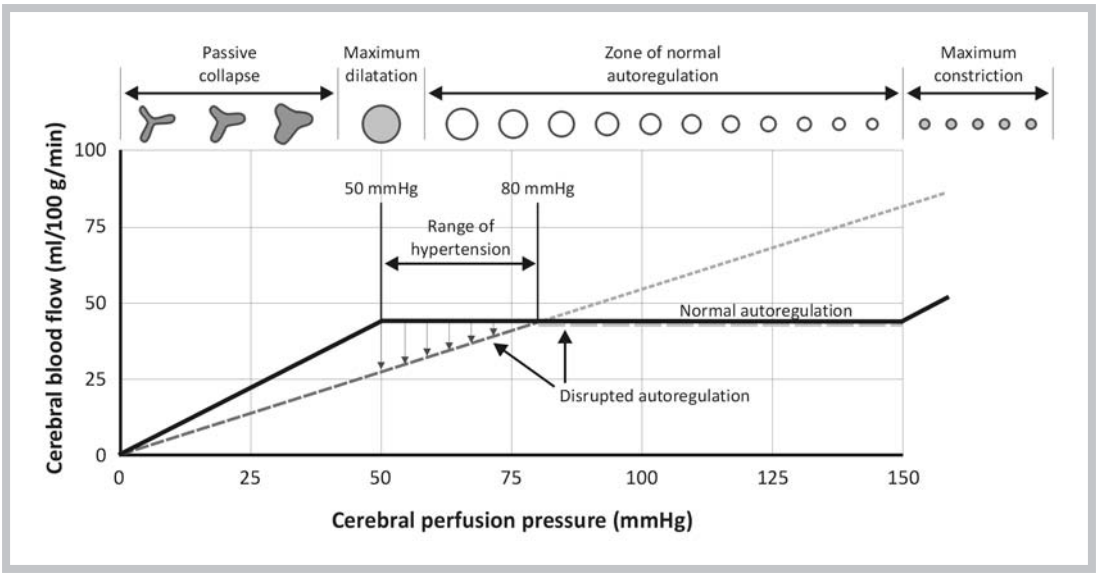

Figure 3.4. **Cerebral autoregulation curve.**

- CO_2: cerebral blood vessels are extremely sensitive to variations in CO_2 levels. This effect is related to the tissue pH values. As CO_2 levels increase, an acidic environment is created in the CSF, leading to arterial dilatation which, in turn, increases CBF.
- Potassium: a rise in perivascular potassium is a powerful stimulus to vasodilatation, as occurs, for example, in seizures or situations that cause tissue hypoxia.
- Adenosine: results from the degradation of ATP; it is a powerful vasodilator with prolonged action. Adenosine production is directly proportional to the degree and duration of tissue hypoxia.
- Nitric oxide: the cerebral vascular endothelium can express three types of enzymes called nitric oxide synthases which actively take part in CBF regulation and the transmission of impulses between neurons. It is frequently present in the prolongations of the astrocytes that form the synapses.
- Prostaglandins: another group of endogenous local acting autacoids. E2 prostaglandin and prostacyclins are both vasodilators. Experimental animal studies have demonstrated high levels of prostaglandins in CSF during arterial hypotension.

As mentioned, the brain needs a constant supply of oxygen. Oxygen transport from the air to the cerebral mitochondria depends on the correct functioning and integration of three systems: 1) respiratory; 2) circulatory; 3) hematologic.

Oxygen transport or availability (TO_2) to the brain is determined by the CBF and the arterial oxygen content (CaO_2). This depends on the main carrier: hemoglobin. Analyzing this protein, we will see that not only is its concentration important, but also its affinity for oxygen and capacity to transport it. Both properties are estimated by oxygen saturation and the oxygen-hemoglobin dissociation curve.

$$TO_2 = CBF \times CaO_2$$

$$CaO_2 = (Hgb \times 1.34 \times SaO_2) + (paO_2 \times 0.003)$$

Oxygen circulates from the atmosphere to the mitochondria by simple diffusion across concentration gradients. After crossing the alveolus-capillary barrier in the lungs, 95%

of oxygen reversibly binds to hemoglobin (Hgb), which is the main carrier of oxygen. The capacity to transport oxygen depends on the concentration of Hgb, which normally is around 15 g/100 ml of blood. Each gram of Hgb can transport 1.34 ml of oxygen.
The relationship between the carrying capacity and the amount really is transported in a given moment is referred to as arterial oxygen saturation. Its normal value is 97%.
The affinity of oxygen for Hgb is expressed by analysing the oxygen-hemoglobin dissociation curve. Its sigmoidal shape is unique: Hgb can bind to oxygen at the pulmonary level, transport it and then yield it to the cells in the capillary bed. Hemoglobin's affinity for oxygen is expressed by P50. P50 is the PO_2 corresponding to 50% saturation of Hgb. The normal value is 27 mmHg. If the P50 increases, the oxyhemoglobin dissociation curve shifts to the right.
An increased P50 indicates a rightward shift of the standard curve. This indicates a decreased affinity. In this case, the efficiency of oxygen delivery to the tissues is facilitated, as happens with an increase in body temperature, hydrogen ions, carbon dioxide or local acidosis oconcentration (the Bohr effect).
Thanks to this mechanism, the brain consumes only 33% of oxygen (cerebral oxygen extraction) and paO_2 decreases from 95 to 35 mmHg in the venous end of the capillary. Conversely, a lower P50 indicates a leftward shift and a higher affinity. A left shift of the curve is a sign of hemoglobin's increased affinity for oxygen (e.g., at the lungs). Similarly, a right shift reflects a decreased affinity.
Dissolved oxygen (paO_2) plays a secondary role in the global transport of oxygen. In order to calculate the arteriovenous oxygen difference, we need to know the oxygen content of mixed venous blood, which can be obtained with the following equation:

$$CvO_2 = (Hgb \times 1.34 \times SvO_2) + (pvO_2 \times 0.003)$$

Returning to equation 1, if:

$$CMRO_2 = CBF \times Da\text{-}vO_2$$

then:

$$Da\text{-}vO_2 = TMCO_2 / CBF$$

Ordinarily, the arteriovenous oxygen difference remains stable and equal to 4-8 ml O_2 for each 100 ml of blood. If oxygen consumption remains stable, changes in $Da\text{-}vO_2$ will reflect changes in CBF. So, if $Da\text{-}vO_2 < 4$, CBF exceeds the cerebral demand; this phenomenon is called hyperemia. Conversely, if $Da\text{-}vO_2 > 8$, this means that the oxygen supply to the brain has fallen below the demand, and this is what happens during ischemia.

3.10 Oxygen Tissue Pressure ($ptiO_2$)

Under normal conditions, there is a direct linear correlation between paO_2 and oxygen tissue pressure ($ptiO_2$). Since oxygen is consumed in the cells, $ptiO_2$ varies widely, from 90-95 mmHg in the capillaries to 30-35 mmHg in the venous district. Critical $ptiO_2$ in the brain is between 15 and 20 mmHg; nevertheless, the neuronal mitochondria require only 1.5 mmHg to maintain aerobic metabolism.
The reader is referred to the chapter on tissue oxygenation monitoring for a more detailed discussion of this topic.

3.11 Cerebral Glucose Metabolism

The brain has an enormous demand for energy. To meet this need, it requires a continuous and suitable supply of its two main nutrients: oxygen and glucose. Glucose is the basic fuel. Although the human brain accounts for only 2% of total body weight, it consumes 25% of total body glucose utilization. Only uses 10% of what is supplied.
Cerebral metabolic consumption of glucose is 5 ml per 100 g of cerebral parenchyma per minute, equal to 140 g/day.
There is a linear correlation between plasma and brain glucose concentration. The cerebral concentration is about 30% of the plasma concentration, depending on variations in blood levels. Since glucose does not readily cross the BBB, it requires a transport system. This system is formed by a family of specific, highly regulated proteins collectively referred to as glucose transporters (GLUT).
Several types are distinguished: GLUT 1 transports glucose to the endothelial cells, glial cells, and astrocytes; and GLUT 3 regulates glucose entry into the neurons. Both transport systems can increase their activity during neuronal activation to optimize glucose transport according to the supply needed.
Cerebral glucose consumption depends directly on brain activity and a sufficient supply of blood and oxygen. Since the brain lacks energy reserves, the small deposits of glycogen available mainly in the astrocytes are exhausted within about 2 minutes.
In certain circumstances, lactate and pyruvate formed during glucose metabolism can maintain neuronal activity. Nevertheless, neither crosses the BBB easily nor has specific carriers, and so cannot replace glucose as an energetic substrate in physiological situations. In some pathological states such as malnutrition or diabetes, blood ketone levels, such as acetoacetate and D-3-hydroxybutyrate in particular, are extremely high, and can be used by the brain as metabolic substrates.
Besides being the brain's primary energy source, glucose plays a major role in many other processes essential for cerebral cellular activity, including:

- Allow correct functioning of ion channels to maintain transmembrane transport.
- Production of nucleic acids, amino acids and lipids.
- Synthesis of hormones and neurotransmitters like glutamate, acetylcholine and γ-aminobutyric acid (GABA).

Cerebral energetic metabolism can be estimated by means of two techniques: the 2-deoxyglucose (2-DG) method and positron emission tomography (PET). Both have advanced our understanding of glucose with regard to: regional heterogeneity, and relationship with brain activity
The rate of glucose consumption by the gray matter varies between 5 and 15 mg per 100 g of tissue per minute, depending on the brain area studied and its specific function. By contrast, the average rate of glucose consumed by the white matter is only 1.5-2 mg/100 g/min.
Functional activity increases glucose consumption three times over the basal rate.

3.12 Cerebral Temperature

Homeothermic mammals like humans must maintain their core body temperature constant in order to survive. The body temperature depends on the balance between the production and dissipation of heat. The core temperature (trunk) varies throughout the day, from 36°C in the morning to 37.5°C in the evening. During sleep it decreases, as the rate of metabolism slows. However, the peripheral temperature (hands, feet, skin) var-

ies widely depending on environmental temperature. Some 90% of body heat is dissipated through the skin and 10% by breathing. Body heat dissipates by:

- Radiation: the most efficient. More than 60% of the heat produced is eliminated by the transmission of caloric energy by infrared radiation towards a body, object or air.
- Conduction: (5%) heat transfer by direct contact with another object of different temperature. Its effectiveness will depend on the interface surface between the two objects in contact and on the temperature gradients.
- Convection: loss of heat by air movement around the body.
- Evaporation: responsible for 20% of total heat losses. It depends on ambient humidity, exposed skin surface area, and perspiration. This mechanism is the only one that allows us to dissipate body heat when the room temperature is higher than the body temperature.

The cerebral temperature can have a static or dynamic behaviour noticeably different from the body's core temperature.

3.13 Brain-systemic Temperature Gradient

In general terms, there is a significant correlation between core temperature and cerebral temperature, albeit with differences in absolute values and speed of response. Owing to the great variability in cerebral temperature, predicting its behaviour may be impossible in some situations.

The gradient is positive when the cerebral temperature is greater than the core temperature and negative in the opposite case. In general, in injured patients, the core temperatures ranges between 36 and 38°C and there is a variable positive gradient of almost 0.3-0.5°C. In central hyperthermia, this gradient is amplified and can reach 2°C. A negative gradient occurs in spontaneous or induced hypothermia.

3.13.1 Intracerebral Gradients

The difference between the intraventricular temperature (deep) and the epidural (superficial) temperature can reach 4°C but is typically equal to 0.5°C, with the ventricular temperature being the higher of the two. The basal structures (more isolated) are warmer that those of the convexity. However, cerebral temperature is not stable, with local variations of 1 to 2°C in response to neuronal activation.

3.13.2 Factors Determining Cerebral Temperature

Factors which can affect the generation of a brain-systemic temperature gradient are: 1) cerebral blood flow; 2) temperature of the blood arriving to the brain; 3) local heat production; 4) heat isolation of the skull and other cover structures; and 5) core temperature regulation.

Cerebral Blood Flow (CBF)

CBF is the major factor responsible for the magnitude and direction of caloric interchange within the brain. The CBF is the "convective" route by which the core temperature arrives at the cerebral parenchyma. The dense capillary network of the cerebral tissue facilitates intracerebral cooling.

CBF supplies oxygen and glucose, and removes CO_2 from the cerebral tissue depending on metabolic demand. Added to these functions is the role it plays in heat "washout". A direct correlation exists between CBF, cerebral temperature, and the brain-systemic temperature gradient; thus, CBF acts as a thermal buffer.

If cerebral metabolism and temperature remain coupled, CBF rises during hyperthermia and decreases during hypothermia, when the changes in CBF predominate over those of $CMRO_2$. This relationship between CBF and cerebral temperature explains the thermopooling phenomenon, in which there is a disconnection between these variables. As a result, the brain overheats, being unable to dissipate the heat accumulated by the decrease in CBF. Another point to consider is the adaptation of the CBF over time.

Intracerebral Blood Temperature

Intracerebral blood temperature is usually 0.3 to 0.5°C less than the cerebral temperature and basically depends on two variables: core temperature and selective cerebral cooling.

Three mechanisms of selective brain cooling have been proposed:

- Pre-cooling of the arterial blood before it enters the skull due to contact with the jugular blood and the cavernous sinus, which are both cooler.
- Convective cooling by venous blood flow in the face.
- Evaporative cooling through the pharyngeal surface.

Local Heat Production

The brain consumes an enormous amount of energy and, as a result, it produces a great amount of heat. Neuronal activity requires 104 moles of ATP to transmit impulses through synapses and 107 moles to recharge a neuron after the potential of action. Almost all the energy consumed to maintain neuronal activity is transformed into heat. Evidence exists that, certain situations, the cerebral temperature is greater than the arterial temperature and that it rises before the entrance of the blood. For this reason, the available data suggest that its main heat source is the brain. Therefore, fluctuations in the intracerebral temperature result from neuronal activity.

Another important consideration is that cerebral oxygen consumption is independent of the oxygen consumption by the rest of the body. In severe neuroinjury, the $CMRO_2$ decreases proportionally to the degree of coma. But because the cerebral temperature is greater, this generates a consistent brain-systemic temperature gradient, probably as a result of increased glucose consumption, called hyperglycolysis, which increases the production of heat without consuming oxygen.

Thermal Isolation

The brain can be viewed as a box of thermal resonance with low conductivity and discharge high resistance to heat transmission.

It is isolated by: 1) scalp; 2) bone; 3) dura mater; 4) CSF.

The heat generated by the parenchyma is difficult to eliminate, as explained by the fact that the brain is not subject to superficial cooling. During neurosurgery, exposure to room temperature produces a noticeable cooling of the cerebral surface structures.

Thermal Regulation

Body temperature is controlled by the thermoregulatory centre in the hypothalamus. Injury to the centre can lead to thermoregulatory dysfunction and is generally associated with poor prognosis.

Systemic	Intracranial
• Arterial hypotension • Hypoxemia • Hypercapnia • Hypocapnia • Fever • Hyponatremia • Hypoglucemia • Hyperglucemia • Severe anemia • Acidosis • Intravascular coagulation • Systemic inflammatory response syndrome	• Intracranial hypotension • Delayed cerebral hematoma • Cerebral edema • Cerebral hyperemia • Vasospasm • Seizures

Table 3.1. Causes of secondary damage.

3.14 Concept of Primary and Secondary Injury

Primary damage occurs immediately after an injury, independently of its cause: ischemic, hemorrhagic, nontraumatic, or other. At the cellular level, damage can continue to develop during the first hours following the injury. The consequence of this phenomenon are functional or structural lesions, reversible or irreversible, focal or diffused. At the microscope, primary damage is characterized by laceration and retraction of the axons, rupture and vascular torsion. Axonal lesion constitutes the basic element of diffuse cerebral damage.

Secondary damage refers to additional damage caused by insults capable of aggravating and/or perpetuating the initial or primary damage. Its causes can be of intracranial or systemic origin. It can appear at any moment of the clinical course and due to primary injury doen't have specific treatment, prevention, detection and early treatment of secondary injuries is essential (Table 3.1).

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4 Examination of the Critically Ill Neurological Patient

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4.1 Clinical Evaluation (or Examination) of the Critically Ill Neurological Patient

The practice of neurointensive care is about the application of a methodological approach to basic routines. This includes attention to the standard ABC parameters (**A**irway, **B**reathing, **C**irculation). Since underinvestigating and undermonitoring will inevitably miss vital information, a comprehensive history and physical examination should always be obtained in a critically ill neurological patient.

4.1.1 How to Approach a Patient in the Neurological Intensive Care Unit

Because critically ill patients often have multiorgan dysfunction, the conventional approach of differential diagnosis, provisional diagnosis, investigations and final diagnosis is less relevant during acute care. In the neurological intensive care unit (NICU), however, most patients have a primary neurological disorder with medical co-morbidities as secondary complicating factors. Still, a thorough assessment of both the neurologic and systemic processes remains essential.

The Ward Rounds

The two most important parameters in the care of the critically ill neurological patient are team work and a problem-oriented approach.

History. The patient must first be stabilized. A detailed history should be obtained from eyewitnesses, paramedics or any other contacts that can furnish information about the sequence of events that led to the patient's critical state.

Sign out. If the first encounter with the patient is in the context of continuing care, a complete history should be obtained, including all the events that led to the patient's current status.

A	Airway
B	Breathing
C	Circulation
D	Disability – Glasgow Coma Scale
E	Electrolytes
F	Fluids: are they appropriate?
G	Gut: nutritional assessment
H	Hematological
I	Infection: microbiology and white blood cell (WBC) count
L	Lines: are sites clean? How long have they been in?
M	Medications: review, evaluate interactions
R	Relatives: inform relatives about patient status

Table 4.1. Problem list mnemonic.

Physical examination. Discussed later.
Review investigations. These include medications or other interventions, monitoring, laboratory and imaging studies.
List of problems and management plan. The problem sheet serves to focus the team's thoughts on an overall management strategy. A systematic approach can be created in different ways. Table 4.1 lists mnemonics to assess patient problems. Table 4.2 illustrates a systemic organ systems approach. Whenever possible, a systems-oriented approach is preferred in the NICU.

- Respiratory
- Cardiac
- Infectious
- Hematologic
- Metabolic
- Neurologic
- Alimentary
- General ICU (include ICU prophylaxis)
- Miscellaneous (allergic, orthopedic, etc.)

Table 4.2. Systems-based problem list.

4.2 General Examination

A complete physical examination should be performed during the initial evaluation after the patient has been stabilized and at least once daily in the clinically stable patient. A head-to-toe approach in the bedside examination is recommended (Table 4.3).

ABCs	• See above
Vital signs	
General examination	• Address patient by last name • Explain to the patient what you are going to do. Remember that many NICU patients may be paralyzed though not comatose • Is the patient resting comfortably or is he/she in distress?
Expose whole body	• Place the patient in an upright position (>30 degrees) if possible • Inspect skin and mucous membranes for jaundice, rashes, bruises or signs of dehydration • Inspect for pressure ulcers • Inspect intravascular lines (peripheral, central and arterial) for possible signs of infection • Inquire about frequent turning (Q2 hours)
Airway and head	• Natural airway • Artificial airway: cuff, type of tube and securing method, cuff pressure diameter • Inspect scalp, sinuses, mouth, ears, nasogastric (NG) tube, cervical nodes, eyes (any corneal ulceration as a result of drying?) • Inspect all invasive equipment sites: surgical drains; intercostal catheters (ICCs); intravenous (IV) lines, intra-arterial (IA) lines and endotracheal and tracheostomy tubes (ETTs)
Respiratory system	• Chest movement, respiratory rate, respiratory effort • Auscultate chest, particularly lung bases • Ability to cough • Secretions • Patient interaction with ventilator • Oxygenation (FiO_2, PaO_2, SaO_2) • Ventilator parameters • Chest drains • Chest X-ray – single best means of assessing respiratory status

Circulatory system, fluids and renal function	• Precordium • Neck veins • Peripheral pulses and rhythm • Peripheral edema • Auscultate precordium • Blood pressure • Urine output and other abnormal losses • Fluid input: volume and composition • Cardiac output • Is the patient on inotropes, vasopressors, vasodilators or other cardiovascular (CV) drugs? – Important in the interpretation of physical findings
Gastrointestinal system	• Inquire about NG aspirate • Efficacy of enteral feeding – is it being tolerated? • Bowel movements • Inspect for abdominal distension, wounds and drains • Inquire about the origin and the content of gastrointestinal (GI) drains • Palpate for tenderness and masses • Auscultate bowel sounds • Proper ulcer prophylaxis (e.g., H_2 antagonists or proton pump inhibitors) when indicated • Inquire about nutritional status (e.g., feeding route)
Limbs	• Any rashes, edema or wounds • Inspect wounds, remove dressing when possible • Examine for underlying fractures or peripheral neurological complications when appropriate
Nervous system	• Level of consciousness – preferable after stopping sedating medications • Brainstem reflexes • Look for lateralizing neurological signs • Glasgow Coma Scale (GCS) • Evaluate for possible seizure activity
Hematology	• Oozing or bleeding
Adequate thromboembolism prophylaxis	• Frequent turning • Mobilization • Graded compression stockings • Subcutaneous heparin, unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) • Pneumatic full-length leg compression

Table 4.3. **Head-to-toe approach in the bedside examination.**

Some important physical findings in the general examination that can suggest an underlying critical condition deserve special attention. Bounding in the neck and precordium often indicates sepsis. An indentation ring on the skin, left after listening for bowel sounds with a stethoscope, indicates extensive peripheral edema. Blue discoloration, particularly in the knees, indicates peripheral cyanosis and compromised circulation. Attempts to breathe against the ventilator, despite what appears to be adequate minute volume, is often due to severe metabolic acidosis. Rapid deterioration in cardiorespiratory signs can indicate pneumothorax or pulmonary embolism.

Always assess airway adequacy, even if the patient has an endotracheal or tracheostomy tube in place. It may be kinked or blocked.

The preferred method to assess the level of consciousness in response to pain is with nail bed pressure. Vigorous stimulation of the outer part of the orbit can cause nerve palsies and sternal rub can cause unsightly bruising.

Mental status and language function	The patient exhibited normal attention and reasoning. There was no evidence of a thought disorder. Affect and mood were unremarkable. Speech was normal and prosody was intact. Verbal expression, comprehension, repetition, reading, and writing were intact. Immediate recall, recent and remote memory were intact. There was no right/left disorientation, finger agnosia, or dyscalculia
Cranial nerves	There was no anosmia. Visual fields were normal to confrontation and visual acuity was 20/20 OU. Funduscopy was unremarkable. Pupils were of equal size (OD – millimetres, OS – millimetres) and exhibited a normal direct and consensual response to light. There was no relative afferent papillary defect (RAPD). Ocular motility was full and no nystagmus was evident. Masticatory muscle strength was normal. Facial sensation was normal. Corneal reflexes were present (direct and consensual). Facial expression was unremarkable without hypomimia and there was no facial weakness or Bell's phenomenon. Hearing acuity was normal. Palatal movements and gag reflex were intact. There was no palatal myoclonus. Sternocleidomastoid and trapezii strength were normal. Tongue protruded in the midline and showed no atrophy, tremor or fasciculations
Motor examination (bulk, tone, strength)	Motor examination showed normal muscle bulk, tone, and strength throughout. Serial finger tapping and rapid alternating movements were normal. No adventitious movements were noted
Muscle stretch reflexes (MSRS)	Muscle stretch reflexes were symmetric and normoactive. Plantar responses were flexor bilaterally. No pathologic reflexes were appreciated
Sensory	Normal light-touch, pinprick, temperature, vibration, and position sense. Graphesthesia, stereognosis, and two-point discrimination were unremarkable. There was no extinction to double simultaneous tactile stimulation
Cerebellar and coordination	Coordination examination showed normal rapid alternating movements. Finger-finger, finger-nose, and heel-knee-shin testing were unremarkable
Romberg test	Romberg test was negative
Gait and station	Erect posture was normal. There was no postural instability. There was no festination. Tandem, heel, and toe walking were unremarkable

Table 4.4. Neurological examination.

4.3 Comprehensive Neurological Examination

Guidelines for a comprehensive neurological examination have been published by the American Academy of Neurology (AAN). Much information regarding a patient's mental status will be obtained during history taking.

This chapter is intended just as an overview of the neurological examination. For a more detailed description, which is beyond the scope of this chapter, one should refer to several texts designed for this purpose, including: DeMyer's The Neurologic Examination. A Programmed Text, Sixth Edition; DeJong's The Neurologic Examination by William W. Campbell; and Localization in Clinical Neurology by Paul W. Brazis, Joseph C. Masdeu and Jose Biller. Table 4.4 illustrates an example of a detailed normal neurological examination used at the Department of Neurology, Loyola University Medical Center.

4.4 Routine Investigations of the Neurocritical Patient

Several parameters, including laboratory testing (e.g., glucose levels), physiological (e.g., EKG) and imaging (e.g., chest X-ray), serve as an extension of the physical examination in the evaluation of the critically ill neurological patient. Table 4.5 summarizes these tests. Obtaining routine microbiologic tests daily is not recommended, since the results must be interpreted based on clinical impression.

Frequency	Test
Every four hours	Glucose levels
Daily	• Arterial blood gases • Potassium • Creatinine • Blood urea and nitrogen (BUN) • Sodium and chloride • Hemoglobin • White cell count and platelets • Magnesium • Calcium and phosphate • 12-lead EKG • Chest X-ray
Twice weekly	Liver function tests: serum billirubin, alkaline phosphatase, aminotransferase activities and serum albumin levels
Continuous monitoring	Cardiac telemetry, pulse oximetry, blood pressure, cardiac rhythm

Table 4.5. **Examinations in the critical ill neurological patient.**

Blood pressure	Maintain normotension
Symptoms and signs of myocardial ischemia	Continuous EKG monitoring Have low threshold to obtain 12-lead EKG and cardiac enzymes (troponins, CK-MB)
Cerebral ischemia	Frequent neurochecks
Hypoglossal neuropathy	Localized loss of conduction that causes short-term paralysis. There is no degeneration of the axon and complete recovery is usual
Early signs of bleeding around operative site	Risk of upper airway obstruction Intubation is extremely difficult; consider ear-nose-throat (ENT) consultation at this point

Table 4.6. **Key points to remember when taking care of the postoperative carotid endarterectomy patient.**

4.4.1 Monitoring Potential Complications in Intubated Patients

When evaluating intubated patients it is important to look for potential complications. General complications of endotracheal and tracheostomies are: malposition; dislodgment; disconnection; obstruction; infection; local damage to larynx and trachea; interference with humidification; and warming of inspired gases.

4.4.2 Postoperative Care Following Carotid Endarterectomy

Table 4.6 summarizes the most important points to remember when taking care of the postoperative carotid endarterectomy patient.

4.5 Focused Neurological Examination of Selected Topics

The neurological examination of the critically ill neurological patient should focus on the initial impression provided by the clinical history. The approach to a comatose patient differs from a history suggestive of acute cord compression. The following topics will summarize the recommended approach to a focused neurological exam depending on the initial suspected condition.

4.5.1 Coma

Syndromes of global cerebral dysfunction related to critical illness embrace such acute disorders as coma and delirium, and chronic processes with various degrees of cognitive impairment. Global cerebral dysfunction can result from direct cerebral damage, but in many instances it develops as a consequence of a systemic insult.
Coma often evolves into clinically diverse disorders of consciousness and must be differentiated from situations where awareness is preserved, as in the deafferentate state. Coma and delirium have been independently linked to increased short-term mortality.
Different terms have been used to describe disturbances of global cerebral dysfunction: coma, delirium, encephalopathy, acute confusional state, and ICU psychosis. Etiology-specific terms (e.g., septic encephalopathy or hepatic encephalopathy) have been used when there is a well-grounded suspicion regarding the causal mechanism.
There are two interconnected domains of neurologic function that describe consciousness: arousal or wakefulness, and awareness, often termed "the content of consciousness". Awareness, in turn, has many components, including perception, attention, memory, executive function, and motivation. The anatomic substrate of arousal is the ascending reticular activating system, a set of connections of neurons extending from the pontine and midbrain tegmentum and projecting to the cerebral hemispheres through the thalamus.
Coma is characterized by a profound disturbance of the reticular activating system. Duration of greater than 1 hour differentiates coma from transient states such as syncope or concussion. Coma is a transitional state that can evolve into recovery of consciousness, vegetative state, or brain death. Plum and Posner proposed a simple, four-part neurologic evaluation of the comatose patient [1]. These parameters are: assessment of the level of consciousness; brainstem function; motor activity; and respiratory pattern.

Activity	Score
Eye opening	
None	1 = Even to supra-orbital pressure
To pain	2 = Pain from sternum/limb/supra-orbital pressure
To speech	3 = Non-specific response, not necessarily to command
Spontaneous	4 = Eyes open, not necessarily aware
Motor response	
None	1 = To any pain; limbs remain flaccid
Extension	2 = Shoulder adducted and shoulder and forearm internally rotated
Flexor response	3 = Withdrawal response or assumption of hemiplegic posture
Withdrawal	4 = Arm withdraws to pain, shoulder abducts
Localizes pain	5 = Arm attempts to remove supra-orbital/chest pressure
Obeys commands	6 = Follows simple commands
Verbal response	
None	1 = No verbalization of any type
Incomprehensible	2 = Moans/groans, no speech
Inappropriate	3 = Intelligible, no sustained sentences
Confused	4 = Converses but confused, disoriented
Oriented	5 = Converses and oriented

Table 4.7. Glasgow Coma Scale [2].

Eye response (E)	E4 = Eyelids open or opened tracking or blinking to command E3 = Eyelids open but not tracking E2 = Eyelids closed, open to loud voice, not tracking E1 = Eyelids closed, open to pain, not tracking E0 = Eyelids remain closed with pain
Motor response (M)	M4 = Thumbs up, fist or peace sign to command M3 = Localizing to pain M2 = Flexion response to pain M1 = Exterior posturing M0 = No response to pain or generalized myoclonus status epilepticus
Brainstem reflexes (B)	B4 = Pupil and corneal reflexes present B3 = One pupil wide and fixed B2 = Pupil **or** corneal reflexes absent B1 = Pupil **and** corneal reflexes absent B0 = Absent pupil, corneal, and cough reflex
Respiration (R)	R4 = Not intubated, regular breathing pattern R3 = Not intubated, Cheyne-Stokes breathing pattern R2 = Not intubated, irregular breathing pattern R1 = Breathes above ventilator rate R0 = Breathes at ventilator rate or apnea

Table 4.8. **FOUR score coma scale [3,4].**

Terms such as somnolence, lethargy, obtundation and stupor have been used to describe different degrees of decreased level of consciousness. Nevertheless, the reliability of such terms is poor and their use should be discontinued in medical practice. The use of scoring systems such as the Glasgow Coma Scale (GCS, see Table 4.7) increases reliability and decreases interrater variability. Nonetheless, the GCS has limitations, including a low sensitivity to subtle changes in arousal, a failure to assess brainstem function, and the difficulty with obtaining a verbal score in intubated, sedated, or aphasic patients. Other scoring systems that incorporate brainstem findings include the **F**ull **O**utline of **U**nresponsiveness (**FOUR**) score (Table 4.8) and the Glasgow Liege Score. The GCS and the FOUR score can be used as part of the serial examination of the patient and are also useful measures for prognostication of outcome.

Although coma is frequently reported in clinical studies of patients who have primary neurologic dysfunction, fewer reports have evaluated the epidemiology and impact of coma in the general medical or surgical ICU. Up to 90% of postcardiac arrest patients are comatose for varying lengths of time. In a study of sepsis-associated encephalopathy, 16% of patients who had sepsis were comatose and the level of consciousness was closely associated with mortality. The presence of coma has prognostic significance in patients with either primary or secondary mechanisms of brain injury. Coma has been identified as a powerful predictor of death and functional outcomes in patients who have stroke, traumatic brain injury, or cardiac arrest.

Clinical Evaluation of the Comatose Patient: History

The cause of coma might be obvious during initial assessment (e.g., cardiac arrest, drug intoxication or trauma). If the cause is unclear, initial history taking should focus on the most potentially treatable causes of coma. The most pertinent information to gather is about circumstances and rapidity of neurological dysfunction, antecedent symptoms, medications, illicit drugs or alcohol use; and past medical history, particularly heart, liver, kidney, and lung disease. If information cannot be obtained from the patient, it is of paramount importance to contact family members and interrogate paramedics about the circumstances in which the patient was found.

General Physical Examination

After establishing adequacy of the ABCs, the next step should be to obtain vital signs (temperature, pulse, respiratory rate and pattern, and blood pressure). Obtaining glucose level should be done along with vital signs. The steps approach in the general examination was mentioned earlier. Some important findings in the general examination of the comatose patient are summarized in Table 4.9.

Finding	Neurological causes	Medical or other non-neurological causes
Increased body temperature (fever, hyperthermia)	• CNS infection (e.g., meningitis, meningoencephalitis, cerebral abscess) • Neuroleptic malignant syndrome • Serotonin syndrome • Malignant hyperthermia • Heat stroke (temperature can be as high as 42-44°C; associated with dry skin) • Anticholinergic drug intoxication (associated with dry skin) • Hypothalamic temperature-regulating centres (central fever)	• Systemic infection • Non-infectious inflammatory conditions (e.g., systemic lupus erythematosus, thrombotic thrombocytopenic purpura)

Decreased body temperature	• Hypothalamic damage
	• Hypothermia itself causes coma only when the temperature is <31° C
	• Wernicke's encephalopathy
	• Myxedema coma
	• Panhypopituitarism
	• Thyroid encephalopathy
	• Acute renal failure (Addisonian crisis)
		• Environmental
		• Sepsis (peripheral circulatory failure)
		• Drug intoxication:
		  · alcoholic
		  · barbiturate
		  · sedative
		  · phenothiazine
		• Hypoglycemia
		• Hypothyroidism

Hypoventilation	• Medullary cardiorespiratory centre structural damage (e.g., ischemic stroke, hemorrhage, compression due to cerebellar herniation) • Upper cervical spinal cord damage	
Tachypnea		• Systemic acidosis • Pneumonia
Shallow, slow, but regular breathing		• Metabolic encephalopathy • Drug depression
Cheyne-Stokes respirations (crescendo/decrescendo with alternating apnoea episodes)	• Bihemispheric damage (usually accompanies "light coma")	• Heart failure • Severely ill elderly patient
Rapid, deep (Kussmaul) breathing	• Pontomesencephalic lesions	• Metabolic acidosis
Ataxic breathing	• Progressive rostrocaudal damage of the brainstem • Agonal gasps indicate medullary damage	
Arterial hypertension	• Reactive hypertension from intracranial hemorrhage, ischemic stroke or as part of the Cushing reaction	• Hypertensive encephalopathy

Arterial hypotension	• NOTE: In adults, intracranial hemorrhage would not lead to hypotension since the cranial cavity is not large enough	• Cardiogenic shock • Hypovolemic shock • Septic shock • Others: alcohol or barbiturate intoxication; profound hypothyroidism; Addisonian crisis
Raccoon's eyes, Battle sign, otorrhoea, rhinorrhoea,	• Skull base fracture	
Petechia, ecchymosis	• Meningococcemia	• Coagulopathy that can result in intracranial hemorrhage, e.g.: thrombotic thrombocytopenic purpura, bleeding diathesis
Purpura with fever and nucal rigidity	• Meningoencephalitis	
Splinter, plantar hemorrhages. Rhot spots		• Endocarditis that can result in cardioembolism of infective material and resultant brain abscess and infectious vasculitis
Funduscopic examination: subhyaloid hemorrhages	• Subarachnoid hemorrhage	
Funduscopic examination: papilledema	• Increased intracranial pressure	

Table 4.9. **Summary of general physical examination.**

Focused Neurological Examination

General observation of the patient should be followed by assessment of level of arousal, brainstem reflexes and muscle tone.

Level of Arousal

The threshold for arousal and the optimal motor response is evaluated by applying a sequence of increasingly intense stimuli to each side of the body. Serial examinations are useful to detect variability in the level of consciousness. A moderate stimulus to arousal is tickling the nostrils with a cotton wisp. Nail bed or knuckle pressure is another form of painful stimulation. The GCS and/or the FOUR score provide a quantitative measure of the level of arousal. Even though the GCS was initially designed to evaluate traumatic brain injury, the scale (as well as the newer FOUR score) can be utilized in serial assessment of non-traumatic causes of coma.

Differential Diagnosis of Coma

Coma must be differentiated from brain death, vegetative state, minimally conscious state (MCS), akinetic mutism, pharmacologically induced states of decreased arousal, and the locked-in syndrome (LIS). Table 4.10 summarizes the differences between these clinical states.

Definition	Level of consciousness	Brainstem functions	Motor function	Note
Brain death				
Complete and irreversible loss of brain and brainstem function	Abolition of consciousness	Absent cranial nerve activity Absent spontaneous breathing	Absent motor function	Before a diagnosis can be made, conditions that can confound neurologic assessment must be ruled out, in particular: • Physiologic or metabolic derangements • Severe hypothermia (temperature <32°C) • Recent exposure to toxic or pharmacologic agents that might impair consciousness or neuromuscular transmission
Vegetative state				
Global impairment of consciousness, wherein awareness of self or the environment is absent, but signs of arousal are retained. Results from extensive damage to the cerebral cortex, with relative sparing of the brainstem	Opens eyes spontaneously, but does not react in any meaningful way to environmental cues. Does not follow any commands	Intact reflex brainstem activity, including breathing		Vegetative state longer than 1 month is classified as a persistent vegetative state
Minimally conscious state (MCS)				
Occurs in the setting of catastrophic hemispheric brain injury, with intact brainstem function and preservation of some corticocortical and corticothalamic circuits	Global alteration of consciousness with elements of arousal. Intermittent evidence of self or environmental awareness. Might sporadically follow commands, attend to recognizable objects or voices, initiate meaningful speech, or engage in purposeful movement	Intact		Long-term outcomes of patients in MCS have not been studied well

Akinetic mutism				
Typically the result of injury to the bilateral frontal lobes	Profound deficiency in executive function Unable to initiate speech Does not exhibit any motor or verbal response to verbal or noxious stimulus		Unable to initiate movement Seems on the verge of initiating activity, yet this is never accomplished	Neurologic recovery has been reported
Pharmacologically induced coma				
Deliberate induction of a coma-like state with the use of sedative or anesthetic agents	Virtually any clinical evidence of brain or brainstem activity can be abolished	Virtually any clinical evidence of brain or brainstem activity can be abolished		Agents commonly used for pharmacologically induced coma include barbiturates, propofol, and midazolam. Confounds the clinician's ability to diagnose coma or even brain death
Locked-in syndrome (LIS)				
Focal injury to the ventral pons	Preserved arousal and awareness	Anarthria Preserved vertical eye movements and eye blinking Alternative presentations may occur in patients with injury of the rostral pons and midbrain, in whom even eye movements are lost (''total LIS'')	Quadriplegia	In its classic presentation, patients with LIS can express themselves only by blinking and with vertical eye movements States analogous to LIS: • Guillain-Barré syndrome • Neuromuscular-blocking drugs without appropriate sedation

Table 4.10. **Differences between brain death, vegetative state, minimally conscious state (MCS), akinetic mutism, pharmacologically induced states of decreased arousal, and the locked-in syndrome (LIS).**

Brainstem Reflexes

Easily examined brainstem reflexes are pupillary light reflexes, eye movements (spontaneous and elicited), corneal reflex, and respiratory pattern. If these brainstem activities are preserved, the lesion causing coma is probably due to bilateral hemispheric dysfunction. At the other end of the spectrum, the absence of these reflexes indicates a lesion primarily originating or externally affecting (e.g., transtentorial herniation) the brainstem.

Respiratory Patterns

In comparison to other brainstem signs, these are of less localizing value. See the table above for a summary of abnormal respiratory patterns. Aside from the abnormal respiratory patterns mentioned above, other cyclic breathing variations have been described but their importance is less significant.

Pupillary Signs

Pupil shape, size, symmetry and response to light provide valuable information about brainstem function. Pupillary reactions are examined with a bright, diffuse light (not an ophthalmoscope). Normal size, reactive and round pupils fundamentally exclude midbrain damage.

Table 4.11 summarizes the localization value of pupillary abnormalities in a comatose patient. As a general rule, the pupillary light reflex is resistant to metabolic disturbances. An exception to this rule is pharmacologic iridoplegia. Administration of 1% pilocarpine can be used to differentiate pharmacologic iridoplegia (failure to constrict) from anoxic pupillary dilatation (preserved response). The ciliospinal reflex, instead of pharmacological dilation, can be used as an alternative method to dilate the pupils. It is important to recognize the patient in a locked-in state due to a midbrain syndrome with abnormal pupillary abnormalities or due to profound peripheral neuropathy as occurs in a patient with severe Guillain-Barré syndrome.

Abnormal pupillary finding	Lesion localization
Reactive and bilaterally small (1-2.5 mm) but not pinpoint pupils	• Metabolic encephalopathies • Bilateral hemispheric lesions (e.g., hydrocephalus or thalamic hemorrhage)
Small and reactive	• Diencephalon (“diencephalic pupils”) • Sleep can also cause this finding • Metabolic coma
Oval and slightly eccentric pupil	• Transitional sign that accompanies early midbrain-third nerve compression

Midposition, unreactive and hippus (spontaneous oscillations in size). Pupils become larger with ciliospinal response	• Midbrain tectum (structural lesion of midbrain or oculomotor nerve)
	• Pharmacologic iridoplegia:
	  ▪ Atropine (e.g., during cardiopulmonary arrest)
	  ▪ Glutethimide
	  ▪ Barbiturates
	  ▪ Succinylcholine
	  ▪ Lidocaine
	  ▪ Phenothiazines
	  ▪ Methanol
	  ▪ Aminoglycosides

Midposition, irregular, unreactive and displacement of one pupil to one side (corectopia)	• Midbrain tegmentum
Unilateral or bilateral oval pupils. May be fixed to light	• Oculomotor or pupillomotor fibres
Large, unreactive and dilated (due to sparing of the sympathetic pathways) pupil ipsilateral to the side of the lesion (Hutchinson’s pupil)	• Fascicular or compressive peripheral cranial nerve III palsy
Pinpoint (<1 mm) and reactive	• Pons (due to sympathetic damage and parasympathetic irritation) • Narcotic or barbiturate overdose • NB: Response to naloxone and the presence of reflex eye movements distinguish these two entities
Ipsilateral Horner syndrome	• Hypothalamic damage • Lateral pontine • Lateral medullary • Ventrolateral cervical cord

Table 4.11. **Localization value of pupillary abnormalities in a comatose patient.**

Ocular Movements

Spontaneous Eye Movements

Elevate patient eyelids and note the resting position and spontaneous movements of the globes. Lid tone progressively decreases as coma deepens. Table 4.12 summarizes spontaneous eye movement abnormalities.

Brainstem reflex eye movements and the corneal reflexes

The physiological arch of the oculocephalic reflexes relays signals through the ocular motor nuclei and their midbrain, pons and medulla interconnections. During a normal response, the examiner observes evoked eye movements in the direction opposite to head movement (either vertical or horizontal head movement). These reflexes are normally inhibited or suppressed in the alert patient. Intact oculocephalic reflexes in a comatose patient indicate intact brainstem function and imply that the underling etiology of coma is cerebral bihemispheric dysfunction. The absence of these reflexes indicates brainstem damage in most cases. Overdoses of certain drugs can also result in absent oculocephalic reflexes. If the cause is due to a drug reaction, pupillary size and light reaction would be normal in most cases.

The vestibulo-ocular response (also called the oculovestibular response) tests the physiological integrity of similar brainstem tracts, but the initial stimulus is thermal and is therefore also referred to as “caloric” testing. Thermal stimulus is stronger than head movements. After documenting intact tympanic membranes, the auditory canal is instilled with 50 ml of cool water with the patient’s head angled 30 degrees to the horizontal plane. This stimulus induces convection currents in the labyrinths that travel through the vestibular nerve to the brainstem pathways that stimulate the brainstem oculomo-

Abnormal spontaneous eye movements	Lesion localization
Horizontal divergence of the eyes at rest	• Normal in drowsiness
Conjugate horizontal ocular deviation to one side	• Ipisilateral frontal lobe lesion • Contralateral pons lesion • Contralateral frontal lobe irritation (e.g., seizure activity) • Other: contralateral hemisphere lesion, paradoxical response ("wrong-way eyes")
Periodic alternating gaze (ping-pong pupil) or conjugate horizontal roving	• Bihemispheric damage • Posterior fossa (rare)
Repetitive divergence	• Metabolic encephalopathy
Nystagmoid movements of one eye	• Middle pons lesion • Lower pons lesion
Small amplitude vertical eye movements	• Diffuse encephalopathy
Ocular bobbing	• Pontine lesion • Posterior fossa • Diffuse encephalopathy

Inverse ocular bobbing ("ocular dipping")	• Diffuse encephalopathy:
	  ▪ Anoxic brain injury
	  ▪ Post status epilepticus

Reverse ocular bobbing	• Diffuse encephalopathy • Pontine lesion (rarely)
Converse ocular bobbing	• Diffuse encephalopathy • Pontine lesion (rarely)
Pretectal pseudobobbing (V-pattern)	• Pretectal lesion
Vertical ocular myoclonus	• Pontine lesion

Table 4.12. **Spontaneous eye movement abnormalities.**

tor nuclei. The normal response is a brief latency, followed by ipsilateral horizontal tonic eye deviation and contralateral horizontal nystagmus to the side of cool-water irrigation (sensory nerve stimulation), respectively. One mnemonic medical students use to remember the response of nystagmus to thermal stimulation is COWS (Cold Opposite, Warm Same). A common error when interpreting clinical findings is to "reverse the concept" of the normal direction of the tonic and nystagmus response to cold water. Loss of tonic conjugate eye deviation indicates brainstem damage. The absence of nystagmus in spite of tonic conjugate eye deviation indicates that the cerebral hemispheres are dysfunctional or metabolically inhibited.

The blink reflex is probably mediated by the superior colliculus. It is elicited by stimulating the eye with bright light. A tonically retracted eyelid suggests pontine damage (particularly infarction) as a result of failure to inhibit the levator palpebrae muscles. The normal response to stimulation of the cornea by gentle touch with a wisp of cotton is a brief bilateral lid closure. The corneal reflexes depend on the pathway integrity between the fifth (afferent) and both seventh (efferent) cranial nerves in the pons. In conjunction with reflex eye movements, the corneal reflex is useful in clinical tests to evaluate pontine function. CNS depressant drugs can diminish or eliminate the corneal responses quickly after reflex eye movements are affected but before the pupillary light reflex is dysfunctional.

Motor Activity of the Body and Limbs

The localizing value of clinical observation of limb movements, tone and reflexes is less clear than the other neurological examination findings mentioned above. Metabolic coma is the most common cause of bilateral decerebrate (extensor) and decorticate (flexor) posturing. Also, the value of other motor findings (e.g., hemiparesis due to hypoglycemia) can be misleading.

Motor response should be elicited by assessing first for spontaneous movements followed by the response to increasing degrees of stimulus (verbal, then non-painful sensory, then painful stimulus). The man-in-the-barrel syndrome (bilateral arm weakness with spared lower extremity strength) suggests an anoxic lesion affecting the watershed area of the anterior cerebral and middle cerebral artery. Decorticate rigidity (arm adduction, elbow flexion, pronation and flexion of the wrist, and hip and knee extension) suggest a contralateral diencephalic and cerebral hemispheric lesion. Decerebrate rigidity (elbow extension, wrist flexion and pronation, and extension of the hip, knee and feet plantar flexion) can be due to a severe metabolic disorder or a structural upper brainstem lesion (below red nucleus but with intact pontine reticular formation).

Opisthotonus (periodic hyperextension of the trunk and hyperpronation of the arms, usually in response to painful stimulus) suggests dysfunction of the corticoreticular fibers (between the upper and lower colliculus) and has been described in cases of traumatic brain injury and tetanus. In neonates, opisthotonus is most likely secondary to meningitis, kernicterus or tetanus. Lesions in the pontine tegmentum can cause abnormal extension of the arms usually associated with weak flexion of the lower extremities. A flaccid quadriplegia, particularly if associated with areflexia, can be due to poliomyelitis or poliomyelitis-like syndromes (e.g., West Nile virus [WNV]), critical illness neuropathy, critical illness myopathy, or due to an acute demyelinating or axonal neuropathy (e.g., Guillain-Barré syndrome).

4.5.2 Evaluating the Patient With Suspected Central Nervous System Infection

The approach to the patient with suspected CNS infection begins with an evaluation of the clinical features that provide critical information leading to etiologic diagnosis. Iden-

tifying infectious agents in CNS infection depends largely on cerebrospinal fluid (CSF) and blood culture analyses, but biopsy of brain, spinal cord, or meningeal tissue may occasionally be needed

Clinical Presentation

Table 4.13 summarizes the main CNS infectious syndromes that should be suspected in the critically ill neurological patient.

Clinical history	Physical exam	Risk factors	Comments
Acute septic meningitis			
Classic triad: fever, neck stiffness, altered mental status Triad has a low sensitivity for diagnosis; only 44% of cases have the full triad. 95% of episodes had at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. Seizures reported in 5-28% of cases	Potential lack of a febrile response in elderly patients, the immunocompromised or patients inadequately treated with antibiotics Cranial nerve palsies Signs of increased intracranial pressure (ICP)	Risk factors for unfavourable outcome: • advanced age • presence of osteitis or sinusitis • absence of rash • low admission GCS • tachycardia • positive blood cultures • elevated erythrocyte sedimentation rate • thrombocytopenia • low CSF white cell count	Mortality and morbidity rates of 25 and 60%, respectively The best parameter to differentiate viral from bacterial meningitis is **severity** (defined by one of four findings at admission: altered consciousness, seizures, focal neurologic findings, and shock) and CSF absolute neutrophil count >1000/mm^3 were predictive of bacterial meningitis
Encephalitis			
• Should be suspected in a febrile patient presenting with altered mental status or other signs of diffuse cerebral dysfunction • Headaches • Myalgia • History of mild respiratory infection • Seizures, both focal and generalized, are a common manifestation	• Fever • Decreased level of consciousness may be followed by focal neurological signs • Parotitis associated with mumps • Herpetic rash associated with HSE • Signs of increased ICP	• Mosquito vector (e.g., WNV) • HIV • Blood transfusions and donated organs	• Most commonly caused by viruses (HSV, VZV, CMV, and WNV among others) • Immune-mediated conditions such as ADEM, paraneoplastic or autoimmune limbic encephalitis also cause encephalitis. • HSE is the most important form of treatable encephalitis
Brain abscess			
• Commonly present with site-specific focal neurologic deficits, such as aphasia and weakness • Seizures in up to 40% of cases (59)	• Fever less common than in meningitis • Neck stiffness in 25% of cases (indicates associated meningitis) • Focal examination may be absent. • Signs of increased ICP		• Brain abscesses are focal, purulent infections of brain parenchyma

Cranial epidural abscess			
• Headache • Fever • Nausea	• Fever • Signs of increased ICP	• Trauma • Neurosurgery • Nearby infections, e.g., meningitis, sinusitis • Other extra-cranial sources	• Extra-axial infection in the virtual space between the dura mater and the skull • Usually occurs in the frontal region • The most common infectious pathogens include streptococci, staphylococci, and anaerobes; infections are often polymicrobial
Subdural empyema			
• Altered level of consciousness • Focal neurologic deficits • Seizures	• Fever • Signs of increased ICP	• Sources of infection include: ▪ Paranasal sinuses ▪ Hematogenous spread through emissary veins in the subdural space ▪ Postoperative setting	• An infection in the potential space between the dura mater and the arachnoid mater • Unlike the epidural space, the subdural space is less restrictive than the epidural space, resulting in a wider spread of empyema, which can cause inflammation of the brain parenchyma, septic thrombophlebitis, and venous infarction • High mortality rate (34%)
Ventriculitis			
• Headache • Fever • Nausea	• Fever • Signs of increased ICP	• Bacterial meningitis • CSF shunt • External ventricular drainage (EVD) • Other intracranial device	• Infection of the ventricular system of the brain • Complication of meningitis in 30% of adult cases • The most common pathogens involved in EVD and CSF shunt infections are gram-positive organisms such as *Staphylococcus epidermidis* and *S. aureus*

Table 4.13. **Main CNS infectious syndromes that should be suspected in the critically ill neurological patient.**

ADEM = acute disseminated encephalomyelitis
CMV = cytomegalovirus
HIV = human immunodeficiency virus
HSE = herpes simplex encephalitis
HSV = herpes simplex virus
ICP = increased intracranial pressure
VZV = varicella-zoster virus
WMV = West Nile virus

4.5.3 Intracranial Hypertension and Herniation Syndromes

Clinical signs and symptoms suggesting increased intracranial pressure include headache, nausea and vomiting, and bradycardia with or without increases in arterial blood pressure. Brain herniation corresponds to a shift of the normal brain through or across regions to another site due to mass effect. It is usually the result of focal structural pathology (e.g., tumour, trauma, infection, etc.), but it can also be due to a diffuse, more physiological process (e.g., encephalitis). Four major categories of herniation syndromes are distinguished: transtentorial, subfalcine, foramen magnum, and alar or sphenoid herniation.

Brain imaging serves as an extension to the clinical examination in the evaluation of these syndromes. Either CT or MRI of the brain can reveal signs of impending herniation before patients start demonstrating clinical signs. Although the use of "screening brain imaging" for possible or probable brain herniation in high-risk patients has not been validated, it is done frequently as a matter of routine. An example of this situation is ordering a "follow-up CT head" in a patient admitted with putaminal hemorrhage who is otherwise clinically doing well. Tables 4.14-4.16 summarize the clinical and imaging findings, as well as the potential complications of the mayor types of herniation syndromes.

Clinical findings	Imaging findings	Complications
• Ipsilateral dilated pupil • Contralateral hemiparesis • Ipsilateral hemiparesis if Kernohan's notch is present (false localizer)	• Ipsilateral ambient cistern widening • Ipsilateral prepontine cistern widening • Uncus extending into the suprasellar cistern • Contralateral temporal horn widening	• Occipital infarct due to posterior cerebral artery compression

Table 4.14. Transtentorial herniation (central or uncal).

Clinical findings	Imaging findings	Complications
• Nausea • Vomiting • Obtundation	• Spinning top appearance of midbrain • Narrowing of bilateral ambient cisterns • Filling of the quadrigeminal plate cistern	• Hydrocephalus • Rapid onset of obtundation and possibility of death

Table 4.15. Ascending cerebellar transtentorial herniation.

Clinical findings	Imaging findings	Complications
• Headache • Contralateral leg weakness	• Amputation of the ipsilateral aspect of the frontal horn • Asymmetric anterior falx • Obliteration of the ipsilateral atrium of the lateral ventricle • Septum pellucidum shift	• Ipsilateral anterior cerebral artery (ACA) infarction as ACA is entrapped under the falx • Other associated herniations

Table 4.16. Subfalcine herniation.

Clinical findings	Imaging findings	Complications
• Bilateral arm dysesthesia • Obtundation	• Cerebellar tonsils at the level of the dens on axial images • Cerebellar tonsils on sagittal images 5 mm below the foramen magnum in adults; 7 mm below in children	• Obtundation • Death

Table 4.17. Cerebellar tonsils herniation (foramen magnum herniation).

4.5.4 Acute Ischemic Stroke

History

This topic is covered in more detail in a separate chapter. The neurointensivist must always keep in mind the diagnosis of ischemic stroke when the initial presentation reveals an acute focal neurological deficit. The clinical approach to a patient with an acute focal neurological deficit should be systematic. The first step is localization of the lesion. This is of paramount importance, since obtaining the wrong imaging study could result in permanent but otherwise preventable neurological damage. There is a tendency for the general practitioner to assume that an acute focal neurological deficit means acute ischemic stroke. It is of utmost importance to always consider the possibility of a "stroke mimic." Table 4.18 lists common acute stroke mimics.

Table 4.19 lists the salient elements from history taking of a suspected stroke patient. Establishing the time of symptom onset is essential in order to decide patient eligibility for IV thrombolysis or endovascular therapy. Ideally, symptom onset is obtained directly from the patient. The use of cues (e.g., "before or after going to the bathroom?" or "before or after breakfast?") may be helpful for inferring an estimated time of onset from those circumstances in which the precise time of symptom onset is difficult to establish.

Obtaining history from eyewitnesses, preferably family members, is of utmost importance to corroborate the patient's report or to establish the time of symptom onset. Reaching a family member by telephone may be necessary if no one is immediately available. If a precise time of symptom onset is impossible to determine, history should focus on identifying when the patient was last seen neurologically normal. In patients awakening with symptoms, the time of onset becomes the time at which they were last seen normal (i.e., when they went to sleep). If the presentation is "waxing and waning symptoms" suggestive of transient ischemic attack/s; it is necessary to ensure complete resolution before the clock can be "reset."

A detailed description of the nature of symptom onset should be obtained. Abrupt onset suggests a vascular etiology, whereas "marching symptoms" (beginning in one region and gradually spreading to involve other areas) may support an alternate etiology (i.e., seizure or migraine). Inquiry should be made regarding risk factors for vascular disease, as well as any history of seizures, migraine, insulin use or drug abuse that may support an alternate cause for the patient's symptoms. Eligibility for thrombolysis must be ob-

- Seizures (postictal state)
- Hypoglycemia
- Metabolic encephalopathy
- Exacerbation of previous deficits
- Intracranial neoplasia
- Intracranial abscess
- Other intracranial mass lesion
- Hemiplegic migraine
- Subarachnoid hemorrhage
- Hypertensive encephalopathy
- Peripheral vestibulopathy
- Conversion reaction

Table 4.18. Common acute stroke mimics.

History of present illness	• Time of symptom onset • Evolution of symptoms • Convulsions or loss of consciousness at onset • Headaches • Chest pain
Past medical history	• Prior intracranial hemorrhage • Recent stroke • Recent head trauma • Recent myocardial infarction
Past surgical history	• Recent surgical puncture • Arterial puncture (non-compressible)
Medications	• Anticoagulant therapy
Review of systems	• Gastrointestinal or genitourinary bleeding

Table 4.19. Salient elements from history taking of a suspected stroke patient.

Left middle cerebral artery	• Right gaze and head preference • Aphasia • Right hemiparesis • Right hemisensory loss • Right homonymous hemianopsia
Right middle cerebral artery	• Left gaze and head preference • Left hemiparesis • Left hemisensory loss • Left spatial hemineglect • Anosognosia • Left homonymous hemianopsia
Left anterior cerebral artery	• Abulia • Incontinence (usually due to bilateral damage) • Right hemiparesis • Aphasia (transcortical motor or sensory) • Callosal apraxia
Right anterior cerebral artery	• Abulia • Incontinence (usually due to bilateral damage) • Left hemiparesis • Callosal apraxia
Left posterior cerebral artery	• Right homonymous hemianopsia • Pure alexia (alexia without agraphia)
Right posterior cerebral artery	• Left homonymous hemianopsia • Left visual neglect
Vertebrobasilar system	• Binocular blindness (e.g., due to the tip of basilar occlusion) • Diplopia • Dizziness/vertigo • Nausea • Dysarthria/dysphagia • Hemiparesis or quadriparesis • Hemisensory loss • Limb or truncal ataxia • Long tracts and cranial nerve findings (sensory or motor) • Decreased level of consciousness
Small vessel disease (lacunar stroke)	• Pure sensorimotor • Pure motor • Pure sensory • Ataxia-hemiparesis

Table 4.20. **Clinical signs and symptoms of the most common arterial ischemic stroke syndromes.**

tained in a structured fashion to minimize the possibility of overlooking critical information.

Some accompanying symptoms that suggest other diagnosis warrant further exploration. Thunderclap headache should alert the clinician to the possibility of subarachnoid hemorrhage. Small bleeds or sentinel leaks from unruptured intracranial aneurysms may not be evident on the CT scan. Additional evaluation with lumbar puncture to rule out the presence of subarachnoid hemorrhage may be warranted.

Focused Neurological Examination

The examination should focus on identifying signs of lateralized hemispheric or brainstem dysfunction consistent with focal cerebral ischemia. Phenomenological presenta-

tions of ischemic compromise in different anatomical regions of the cerebral and spinal circulation are extensive. Table 4.20 summarizes the clinical signs and symptoms of the most common arterial ischemic stroke syndromes.

The National Institute of Health (NIH) Stroke Scale (NIHSS) is a 15-item scale that assesses key components of the standard neurological examination and measures stroke severity. The scale should be performed rapidly and it serves to predict short-term and long-term neurologic outcomes. Table 4.21 illustrates the components of the NIHSS. Its drawbacks include a lack of detailed cranial nerve assessment, sensitivity for mild deficits (e.g., hand dexterity), underestimation of stroke severity in right hemispheric as well as posterior circulation ischemic strokes, and pertinent changes in serial neurological exams.

1a	Level of consciousness (LOC)	0=alert and responsive; 1=arousable to minor stimulation; 2=arousable only to painful stimulation; 3=reflex responses
1b	LOC questions: ask patient's age and month. Must be exact	0=both correct; 1=one correct; 2=neither correct
1c	Commands: open/close eyes, grip and release non-paretic hand	0=both correct; 1=one correct; 2=neither correct
2	Best gaze: horizontal extraocular movement by voluntary or doll's eye	0=normal; 1=partial gaze palsy; abnormal gaze in one or both eyes; 2=forced eye deviation or total paresis which cannot be overcome by doll's eye
3	Visual field: use visual field threat if necessary. If monocular, score field of good eye	0=no visual loss; 1=partial hemianopia, quadrantanopia, extinction; 2=complete hemianopia; 3=bilateral hemianopia or blindness
4	Facial palsy: if stuporous, check symmetry of grimace to pain. Paralysis (lower face)	0=normal; 1=minor paralysis (normal looking face, asymmetric smile); 2=partial; 3=complete paralysis (upper and lower face)
5	Motor arm: arms outstretched 90° (sitting) or 45° (supine) for 10 sec. Encourage best effort, note paretic side	0=no drift; 1=drift but does not hit bed; 2=some antigravity effort, but cannot sustain; 3=no antigravity effort, but even minimal movements count; 4=no movement at all; X=unable to assess due to amputation, fusion, etc.
6	Motor leg: raise leg to 30° supine for 5 sec	
7	Limb ataxia: check finger-nose- finger; heel-shin; score only if out of proportion with paresis	0=no ataxia (or aphasic, hemiplegic); 1=ataxia in upper or lower extremity; 2=ataxia in upper and lower extremity; X=unable to assess as above
8	Sensory: use safety pin. Check grimace or withdrawal if stuporous. Score only stroke related losses	0=normal; 1=mild to moderate unilateral loss but patient aware of touch (or aphasic, confused); 2=total loss, patient unaware of touch. Coma, bilateral loss
9	Best language: describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis	0= normal; 1=mild-mod aphasia (comprehensible); 2=severe aphasia (almost no information exchanged); 3=mute, global aphasia, coma
10	Dysarthria: read list of words	0=normal; 1=mild-mod slurred; 2=severe, unintelligible or mute; X=intubation or mechanical barrier
11	Extinction/neglect: simultaneously touch patient on both hands, show fingers in both visual fields, ask about deficit, left hand	0=normal, none detected (or visual loss alone; 1=neglects or extinguishes to double simultaneous stimulation in any modality; 2=profound neglect in more than one modality

Table 4.21. National Institute of Health Stroke Scale (NIHSS) [5].

The neurovascular examination can reveal clues of the underlying mechanism of ischemic stroke. The presence of a cervical bruit, cardiac murmur, or irregular heart rhythm suggests artery-to-artery thromboembolism or cardioembolism, respectively. Unequal extremity pulses suggest aortic dissection. Funduscopic examination may reveal signs of chronic hypertensive arterial disease or endocarditis. Signs of head or neck trauma suggest occult cervical spine injury.

Further Evaluation

Brain imaging is the only reliable means to differentiate between ischemic and hemorrhagic stroke and is therefore mandatory prior to thrombolytic therapy. Refer to the chapter on stroke for further discussion on neuroimaging of acute stroke. As previously mentioned, the main purpose of evaluating a patient with suspected acute ischemic stroke is to determine the eligibility for thrombolysis.

Table 4.22 lists the inclusion and exclusion criteria for the use of intravenous thrombolysis after thrombolysis within 3 hours of symptom onset. Intravenous recombinant tissue plasminogen activator (r-tPA; alteplase) is also recommended in selected patients with acute ischemic stroke within 3 to 4.5 hours of symptom onset.

After stabilizing and admitting the patient it is important to estimate disease severity and likelihood of recovery of the neurological deficit. Scales commonly use to evaluate prognosis in patients with stroke are available by accessing www.strokecenter.org.

Inclusion criteria	• Clinical diagnosis of ischemic stroke causing measurable neurologic deficit • Onset of symptoms <3 h before beginning treatment; if the exact time of stroke onset is not known, it is defined as the last time the patient was known to be normal.
Exclusion criteria	**Patient's history** • Stroke or head trauma in the previous 3 months • Any history of intracranial hemorrhage • Major surgery in the previous 14 days • Gastrointestinal or urinary tract bleeding in the previous 21 days • Myocardial infarction in the previous 3 months • Arterial puncture at a non-compressible site in the previous 7 days **Clinical** • Minor or rapidly improving neurologic deficits (controversial) • Seizure at the onset of stroke is an exclusion if the residual impairments are due to postictal phenomenon; seizure is not an exclusion if the clinician is convinced that residual impairments are due to stroke and not to postictal phenomenon • Symptoms suggestive of subarachnoid hemorrhage • Persistent elevated blood pressure (systolic ≥185 mmHg, diastolic ≥110 mmHg) • Active bleeding or acute trauma (fracture) on examination **Laboratory** • Platelets <100,000/mm^3 • Serum glucose <50 mg/dl (<2.8 mmol/l) • International normalized ratio (INR) >1.7 or prothombin time >15 seconds if on oral anticoagulant • Elevated partial thromboplastin time (aPTT) if on heparin **Head CT** • Evidence of hemorrhage • Evidence of major early infarct signs such as diffuse swelling of the affected hemisphere, parenchymal hypodensity and/or effacement of >33% of the middle cerebral artery territory

Table 4.22. **Inclusion and exclusion criteria for the use of intravenous thrombolysis.**

4.5.5 Intracranial Hemorrhage (Subarachnoid and Intraparenchymal Hemorrhage)

Intracranial hemorrhage can be the result of bleeding into different compartments, including the epidural space, the subdural space, the subarachnoid space, the intraparenchymal space and the intraventricular space. Detailed history about symptoms onset, medical risk factors, anticoagulation, drug abuse, and head trauma should be obtained. Overall, the most common cause of intracranial hemorrhage is trauma, but the cause varies depending on the specific location. Given the numerous possible locations and the variety of potential causes of intracranial hemorrhage, associated clinical presentations are diverse. Suspected diagnosis depends on the presence of appropriate signs and symptoms, pertinent patient history (hypertension, prior hemorrhage, drug use, anticoagulation, and trauma) and appropriate diagnostic imaging. Once intracranial hemorrhage is suspected, a head imaging study must be obtained immediately. In most cases, CT of the head is the initial imaging test of choice. Preliminary laboratory testing should include coagulation parameters (prothrombin time [PT], international normalized ratio [INR], and partial thomboplastin time [PTT]), complete blood cell count, electrolytes, liver function tests and drug screen.

The most common cause of subarachnoid hemorrhage (SAH) is head trauma. Worldwide, the incidence of nontraumatic SAH is approximately 6/100,000/year. It is more commonly seen in patients less than 60 years of age. The principal cause of spontaneous SAH is a ruptured aneurysm (85%). Several factors influence the incidence of developing SAH (e.g., gender, race, and family history of SAH). Women are at greater risk of developing SAH than men and blacks are at greater risk than whites.

First-degree relatives with a history of SAH is the most important nonmodifiable risk factor. Important modifiable risk factors are heavy alcohol consumption, hypertension, and smoking. Headache is the most common presenting complaint for SAH.

The classical presentation of nontraumatic SAH is an acute severe “thunderclap” headache that usually is described by patients as “the worst headache of my life.” Headache usually reaches maximum intensity over seconds to a few minutes. Conversely, only 1 in 10 patients presenting with thunderclap headache actually have SAH. In up to 33% of SAH cases, headache may be the sole presenting symptom. Signs and symptoms of meningeal irritation can also occur, including meningismus, photophobia, prominent neck or upper back pain, seizures, and obtundation. Serious consequences can occur as a result of failure to detect acute aneurysmal SAH, exposing the patient to

Grade	Neurological status
I	Asymptomatic or minimal headache and slight nucal rigidity
II	Moderate to severe headache; nuchal rigidity; no neurologic deficit except cranial nerve palsy
III	Drowsy; minimal neurologic deficit
IV	Stuporous; moderate to severe hemiparesis; possibly early decrebrate rigidity and vegetative disturbances
V	Deep coma; decrebrate rigidity; moribund appearance

Table 4.23. Hunt and Hess Classification Scale [6].

WFNS Grade	Glasgow Coma Scale Score	Major focal deficit
0	-	-
1	15	Absent
2	13-14	Absent
3	13-14	Present
4	7-12	Absent or present
5	3-6	Absent or present

Table 4.24. World Federation of Neurologic Surgeons (WFNS) Subarachnoid Hemorrhage Grade [7].

a risk of recurrent SAH of up to 50% in the first year. The patient's level of consciousness is a cardinal determinant of outcome after SAH and can affect treatment decisions as well as prognostication.

The Hunt and Hess grade (Table 4.23) and the World Federation of Neurological Surgeons scoring system (Table 4.24) are the most frequently used assessment scales [6,7]. Cases of cranial neuropathies may represent elevated intracranial pressure (abducens or oculomotor nerve palsy) or aneurysmal compression (oculomotor nerve compression due to a posterior communicating artery or superior cerebellar artery aneurysm). The amount of SAH is evaluated with the Fischer grading system, which has a prognostic value in predicting the risk of vasospasm and overall patient outcome (Table 4.25) [8].

Fisher Group	Blood on Computed Tomography
1	No subarachnoid blood detected
2	Diffuse or vertical layers ≤1 mm thick
3	Localized clot and/or vertical layer >1 mm
4	Intracerebral or intraventricular clot with diffuse or no SAH

Table 4.25. Fisher Grading Scale [8].

Hypertension is the most common cause underlying nontraumatic intracerebral hemorrhages (50-60%). Cerebral amyloid angiopathy (CAA) is the second most common cause of nontraumatic intraparenchymal hemorrhage. The incidence of both (hypertensive hemorrhage and CAA) increases with age. Other causes of parenchymal hemorrhage are venous thrombosis, underlying neoplasm (either primary or metastatic), vascular lesion (e.g., vascular malformations), and inflammatory lesions (e.g., herpes simplex infection, aspergilosis). Common presenting symptoms of intraparenchymal hemorrhage include nausea and vomiting, headache, seizure activity, altered cognition, with or without associated focal neurologic deficits. When the volume of the hemorrhage is large, clinical sequelae often reflect the local mass effect, any associated herniation (transfalcine, transtentorial, and tonsillar), hydrocephalus, diffuse intraventricular extension, and/or diffuse increased intracranial pressure.

The volume of intracerebral hemorrhage can be calculated in cubic centimetres using the following equation: Volume = (A X B C)/2, where A is the maximal diameter of hematoma in centimetres on its largest axial cut; B is its diameter in centimetres in the dimension perpendicular to A on the same axial cut; and C is the height of slices on which the hematoma is visible (excluding the first and last cuts just showing its extremes) by the slice thickness of the CT scans in centimetres. The estimated hematoma volume in cubic centimetres is an important prognostic indicator.

4.5.6 Overview Motor Examination in the Critically Ill Patient

Motor function examination in the NICU setting is a critical component of daily evaluation. Spontaneous and stimulus-induced movements of the face and extremities should be observed in detail. Motor deficits may affect a single limb (monoplegia), one hemibody (hemiplegia), bilateral lower limbs (paraplegia) or all four extremities (tetra or quadriplegia). The distribution, progression and onset of deficits are important to properly localize the possible pathology. The initial step in assessment is to determine if a central process or a peripheral neuromuscular problem is the cause of weakness. This may be difficult, as patient presentation may be complicated by encephalopathy, intubation or sedation in the ICU setting.

Clinical examination should concentrate on findings, such as muscle wasting or swelling, muscle tenderness, muscle tone, fasciculations, myokymia, percussion myotonia, tendon reflexes, and skin lesions. Important skin lesions include the heliotrope rash of dermatomyositis (DM), exanthematous rashes associated with viral infections, purpura or

petechiae, telangiectasias, digital ulcers or splinter hemorrhages, and Janeway's lesions or Osler's nodes in infective endocarditis.

The most common neurologic complications in the ICU are metabolic encephalopathy, seizures, hypoxic-ischemic encephalopathy, and stroke. Some can manifest with generalized weakness. Nonetheless, generalized weakness in is associated more commonly with neuromuscular or peripheral nerve injury. Careful clinical examination aids to localize limb weakness to spinal cord, roots, plexus or peripheral nerves.

Since the differential diagnosis of a patient presenting with acute flaccid paralysis in the NICU setting is quite large, clinical, epidemiologic, biochemical studies, neuroimaging, and electrophysiologic studies help to delineate the etiology (Table 4.26).

When assessing a patient with motor weakness, the patient's age may point towards inflammatory or demyelinating lesions, which are more common in the young as opposed to neoplastic and vascular etiologies in the elderly. The Guillain-Barrè syndrome (GBC) manifests with subacute onset of progressive weakness over days to weeks. Botulism mimics GBS but has additional features of ophthalmoplegia, with pupillary involvement and autonomic features such as dry mouth and paralytic ileus. Rapid nerve stimulation on electromyography/nerve conduction velocity (EMG/NCV) testing shows features of a presynaptic neuromuscular junction disorder. Botulinum toxin can be identified in stool, serum, or suspected food samples.

Marked asymmetry and acute rapid progression of symptoms should always alert the clinician to consider cerebrovascular disease in the differential diagnosis of a peripheral neuropathic process. Posterior circulation strokes (especially pontine infarctions) can result in a locked-in state, where patients are able to communicate only via eye blinks. Multiple strokes can be seen in patients who have underlying infective endocarditis or have undergone cardiac surgery. Asymmetric weakness is another feature which may help in the differential diagnosis, as poliomyelitis or polio-like virus infection (including West Nile virus) cause asymmetric paresis. West Nile Virus infection results in a meningoencephalitis and acute flaccid asymmetric paralysis, accompanied by fever, encephalopathy and predominantly proximal, asymmetric weakness. Electrophysiologic studies show evidence of axonopathy, and CSF analysis shows lymphocytic pleocytosis with elevated proteins.

The distribution of weakness may point toward a specific diagnosis, such as acute intermittent porphyria, in which patients present with painful, often asymmetric weakness frequently beginning in the upper extremities. Patients usually experience severe colicky abdominal pain accompanied by psychiatric disturbances prior to the development of neuropathy. The combination of abdominal pain and neuropathy makes this clinical presentation similar to heavy metal intoxication.

Magnesium is a competitive blocker of calcium at the presynaptic junction, preventing calcium entry into the presynaptic neurons. Hypermagnesemia should be suspected in patients with renal failure and taking receive magnesium-containing laxatives or antacids or patients with eclampsia who receive magnesium sulphate for seizure control.

Peripheral neuropathy is a well-recognized consequence of systemic vasculitis due to peripheral nerve infarction with Wallerian degeneration. Rarely, neuropathy is the sole manifestation of vasculitis, referred to as nonsystemic vasculitic neuropathy. Patients present with painful, stepwise progressive, distal-predominant, asymmetric or multifocal neuropathy, with sensorimotor deficits evolving over months to years. Laboratory tests often indicate features of systemic inflammation, such as an elevated sedimentation rate or positive anti-neutrophil cytoplasmic antibodies. Peripheral neuropathies associated with HIV infection can be divided into three major groups: distal, symmetric peripheral neuropathy; chronic, relapsing polyradiculoneuropathy; and more rarely as mononeuritis multiplex.

Diagnosis	Clues in diagnosis	Treatment
Guillain-Barré Syndrome	Antecedent "flu-like" illness, vaccination	IVIG or plasma exchange
Spinal cord compression	History of trauma or cancer	Corticosteroids and surgical decompression
Basilar artery occlusion	Cardiovascular risk factors, prior history of stroke	Thrombolytic or thrombus removal treatment if appropriate, antiplatelets
Vasculitic neuropathy	History of systemic vasculitis or rheumatologic disorder	Immunosuppressant drugs
Myasthenia gravis	Muscle fatigability, ocular and bulbar involvement	Anticholinesterase drugs, plasma exchange or IVIG
Hypophosphatemia	Chronic alcoholism, intravenous hyperalimentation without phosphate, and chronic ingestion of antacids	Phosphate supplementation
Hypermagnesemia	Renal failure, eclampsia	Cessation of magnesium therapy, hemodialysis or IV calcium
Polio-like viral infections including West Nile virus	Summer months; asymmetric weakness and rapid progression of symptoms	Supportive treatment
Critical illness neuromyopathy and/or myopathy	NICU admission, sepsis, multiorgan dysfunction syndrome, status asthmaticus, NMB agents	Supportive treatment
Botulism	Contaminated food exposure, honey	Antitoxin administration and supportive care
Lyme disease	Recent travel to endemic areas, tick bites	Antibiotics
HIV infection	Risk factor, prior history of drug abuse or blood transfusion	HAART
CMV infection in the immunocompromised	Solid organ transplant, HIV infection	Ganciclovir or foscarnet
Inflammatory myopathies	Rash, proximal weakness, high CPK	Corticosteroids, immunosuppressant drugs
Heavy metal intoxications (arsenic, gold, thallium)	Occupational exposure	Elimination of continued exposure, dimercaptosuccinic acid or penicillamine
Paraneoplastic disorders	Known history of cancer	Treatment of primary malignancy

Table 4.26. **Common causes of acute flaccid paralysis in the ICU.**

HAART = highly active antiretroviral therapy
IVIG = intravenous immunoglobulin
NMB = denotes neuromuscular blockage

Inflammatory myopathies may manifest as preferential and prominent proximal muscle weakness and rash without involvement of the face or ocular muscles. The rash is erythematous, periorbital, and purplish and can be accompanied by rashes over the knuckles (Gottron's sign) or subcutaneous calcification. CK levels often are significantly elevated. Rhabdomyolysis often presents with focal rather than generalized weakness. This entity should be considered in the presence of arterial occlusion, compartment syndromes or trauma. It often manifests with swollen, tender muscles, focal weakness, and elevated CK levels (>10,000 IU).

The lack of sensory complaints and abnormalities during sensory examination provide powerful localizing information. Spinal cord lesions, regardless of the cause, usually re-

sult in sensory as well as motor dysfunction. History of known malignancy and associated lower back pain at the time of presentation may suggest metastatic epidural spinal cord compression.

Progressive polyradiculomyelopathy due to infection with cytomegalovirus (CMV) presents with rapid onset lower extremity and sacral paresthesias. Progressive paraparesis ensues rapidly, with concomitant areflexia, ascending sensory loss, and sphincter dysfunction. It generally occurs with advanced immunodeficiency. An important clue to the presence of this potentially treatable illness is a polymorphonuclear pleocytosis in the CSF.

Electromyography (EMG) and nerve conduction studies (NCS) serve as an extension of the physical examination and often allow refinement of the diagnosis. It needs to be emphasized, however, that electrodiagnostic testing may be insensitive in the acute period but after 4-5 days. EMG/NCS testing provides accurate localization of the motor unit lesion, establishes the presence or absence of demyelination or conduction block, and helps establish a prognosis. Electrodiagnostic testing may confirm the lack of sensory involvement and asymmetry.

Magnetic resonance imaging (MRI) of the brain or spinal cord should help to determine whether the process is central in origin. CSF analysis is usually indicated in suspected acute idiopathic neuropathies or myopathies. CSF protein in the Guillain-Barré syndrome is elevated without pleocytosis, but this is a non-specific finding. If CSF pleocytosis is present, HIV infection, Lyme disease, cytomegalovirus (CMV), West Nile virus (WNV) or leptomeningeal carcinomatosis should be considered in the differential diagnosis. Serologic testing should be guided by the presumptive diagnosis, as many metabolic abnormalities leading to weakness can be excluded with initial chemistries. The combination of elevated liver enzymes and pancytopoenia should trigger an investigation of arsenic intoxication.

4.5.7 Acute Spinal Cord Injury

The most common cause of acute spinal cord injury is trauma secondary to motor vehicle accidents, falls, recreational injuries or acts of violence. The appropriate localization of the spinal cord lesion requires understanding spinal cord and vertebral anatomy, organization and blood supply. Since spinal cord injuries are common in patients with polytrauma, MRI should be considered in these patients. Non-traumatic cord compression encompasses a variety of etiologies and clinical presentations and includes compressive, malignant, infectious, vascular and inflammatory causes.

Careful examination for overlying vertebral spine tenderness may suggest an underlying destructive process such as a neoplasm or infection as the etiology, and pain that lessens with sitting or standing is suggestive of a malignancy. Acute intervention for spinal disk disease is rare with only 0.25-1.0% of patients presenting with rapidly deteriorating neurological symptoms.

Spinal-cord compression due to malignant disease accounts for approximately 20,000 cases annually in the United States. It is a relatively common complication of cancer and may be the presenting sign in up to 30% of patients. The most common level of metastatic epidural spinal cord compression (MESCC) involvement is the thoracic spine (59-78%), followed by the lumbar (16-33%) and the cervical spine (4-15%), while multiple levels are involved in up to half of patients. Most patients present with back pain, which worsen after a period of lying down because of distension of the epidural venous plexus. MESCC at or above the conus medullaris leads to weakness of the upper motor neuron and is usually symmetric. Usually, the iliopsoas muscles are preferentially affected, and

weakness is most severe with thoracic MESCC. Treatment consists of rapid initiation of corticosteroid therapy, followed by direct decompressive and maximal-debulking surgery with intra-operative stabilization of the spine (in appropriate cases) and postoperative radiation therapy. The use of high-dose steroids based on the Bracken protocol (30 mg/kg methylprednisolone in the first hour, followed by 5.4 mg/kg methylprednisolone in the next 23 h in patients presenting within 8 h of spinal cord injury) has been much debated.

Despite flaws in the initial studies and subsequent criticism, such treatment is still common practice in the US. Nevertheless, it is appropriate to give at least high doses of dexamethasone in patients with suspected traumatic or nontraumatic (especially related to tumour) cord compression pending a definitive diagnosis. Steroid administration need not be deferred till after imaging, but it should be given empirically. All patients with suspected spinal cord injuries should also be assessed for urinary and rectal tone. Urinary function can be assessed by measuring the residual amount of urine after voluntary voiding. A volume >100 ml of urine found by straight catheterization is considered an abnormal post-void residual.

4.5.8 Spinal Cord Syndromes

Complete Cord Transection

The finding of a sensory level with pinprick loss is the most valuable finding to identify the spinal cord as the lesion site in a patient with weakness. Weakness, either paraplegia or tetraplegia, occurs below the level of the lesion due to interruption of the descending corticospinal tracts. Sensory loss involving all modalities below the level of the lesion is noticed. Initially, the paralysis may be flaccid and areflexive because of spinal shock, but hypertonic, hyperreflexive paraplegia or tetraplegia eventually occurs, with bilateral extensor toe signs, loss of superficial abdominal and cremasteric reflexes, and extensor and flexor spasms. Urinary and rectal sphincter dysfunction with incontinence, sexual dysfunction, and signs of autonomic dysfunction can also be demonstrated below the level of the lesion.

Brown-Sequard Syndrome

A hemisection of the spinal cord results in the Brown-Sequard syndrome (BSS), with loss of pain and temperature sensation contralateral to the side of injury due to interruption of the crossed spinothalamic tract. Usually, a clinical sensory level is one or two segments below the level of the lesion, reflecting the ascending nature of this crossing tract.

Below the lesion site there is ipsilateral loss of proprioceptive function due to interruption of the ascending fibres of the posterior columns. Ipsilateral weakness below the lesion reflects the interruption of the descending corticospinal tract. Only a limited number of patients in the NICU setting have the pure form of BSS. Far more often the Brown-Sequard plus syndrome is seen, with a relative ipsilateral hemiplegia and a relative contralateral hemi-analgesia.

Anterior Spinal Artery Syndrome

The vascular nature of this syndrome is reflected in its abrupt onset occurring within minutes or hours from its initiation. Clinically, the syndrome presents with back or neck pain and at times in a radicular pattern, usually followed by a flaccid paraplegia and less commonly tetraplegia. Urinary and bowel incontinence are usually present. A sensory

level to temperature and pinprick reflects involvement of the spinothalamic tracts bilaterally, but posterior column modalities of sensation remain relatively intact. The initial motor presentation progresses from a flaccid paraplegia to one of spasticity with hyperreflexia and Babinski signs.

Central Cord Syndrome

The central cord syndrome is characterized by disproportionately more motor impairment of the upper than in the lower extremities, bladder dysfunction, usually urinary retention, and varying degrees of sensory loss below the level of the lesion. The syndrome is classically known to affect older persons with cervical spondylosis and a hyperextension injury, wherein the cord is compressed between the bony spurs anteriorly and the infolded ligament flavus posteriorly.

Posterior Column Syndrome

This process involving the posterior columns is characterized by loss of position sense, vibration sense, and two-point discrimination. The lack of proprioceptive information and feedback to the motor system affects the muscle groups required for discriminative movements, resulting in a sensory ataxia. Gait is described as ataxic (or stomping), and the deficit can be more prominent in darkness or with eyes closed, as visual cues can no longer assist in maintaining body balance. The affected limbs may become hypotonic but are usually not weak. At times, other spinal cord lesions can produce a truncal ataxia but without the associated proprioceptive difficulties. In such cases, spinocerebellar tract dysfunction, as a manifestation of spinal cord compression, appears to be responsible for this clinical syndrome.
With dysfunction of the posterior columns in the cervical region, neck flexion may elicit an electric-like sensation that radiates down the back or into the arms (Lhermitte's sign). It is thought to represent increased mechanosensitivity of the dorsal columns, with neck flexion further activating those sensory pathways.

4.5.9 Guillain-Barré Syndrome

Once used interchangeably with the term "acute inflammatory demyelinating polyneuropathy (AIDP)", the Guillain-Barré syndrome (GBS) now encompasses any acute, idiopathic inflammatory polyneuropathy that produces progressive muscle weakness and areflexia, regardless of whether the underlying neuropathy is demyelinating or axonal. The annual incidence of GBS is reported to be 1.2-2.3 per 100,000 in different parts of the world and accounts for one of the most common causes of paralysis among NICU patients. The constellation of rapidly progressive symmetrical weakness in the arms and legs, with or without sensory disturbances, with or without involvement of respiratory or cranial nerve muscles, hyporeflexia or areflexia, in the absence of a CSF cellular reaction, remains the hallmark for the clinical diagnosis of GBS. The most frequently identified cause of infection is *Campylobacter jejuni*. Other well-defined infections related to GBS are cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*, and *Hemophilus influenzae*. GBS represents a true case of molecular mimicry and antibody cross-reactivity. The diagnosis is usually made on clinical grounds, with CSF typically showing normal pressure, few (<10 mm^3) or no pleocytosis with elevated protein concentration. EMG/NCV shows nerve conduction abnormalities with conduction block, prolonged F waves, absent H waves or evidence of proximal demyelination at the root level and somewhat typical sural sparing.

There are a number of other GBS variant patterns. The Miller-Fischer variant accounts for approximately 5% of all cases of GBS. Patients develop the triad of ophthalmoplegia, ataxia, and areflexia, with varying degrees of limb weakness associated with IgG antibodies to GQ1b. Although there is usually bilateral involvement of the oculomotor, trochlear, and abducens nerves, partial and asymmetric syndromes also exist. Facial and bulbar weakness is also common. Other variants are acute motor axonal neuropathy (AMAN), acute sensory neuropathy (ASAN), acute sensorimotor axonal neuropathies (AMSAN), and pharyngeal-cervical-brachial neuropathy. Generally, the non-demyelinating (axonal) variants are associated with a worse prognosis for recovery.
Rapidly progressive weakness is the core clinical feature of GBS. Typically, weakness peaks within 4 weeks, but neurological deficits often worsen within 2 weeks, followed by a plateau phase of varying duration from days to several weeks. In 10% of cases the plateau phase may persist for months. This phase is followed by a usually much slower recovery phase of varying duration, usually within 6 months. About 65% of patients have persistent minor problems, such as weakness, fatigue or distal numbness. Permanent disabling weakness or severe neurological deficits occur in about 5-10 % of patients.

4.5.10 Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular transmission involving the production of autoantibodies directed against the nicotinic acetylcholine receptor. The hallmark of the disease is fluctuating or fatigable muscle weakness. Acetylcholine receptors antibodies are detectable in the serum of 80-90 % of persons affected with the disorder. The most common symptoms of focal muscle dysfunction, in order of decreasing frequency, involve the ocular, bulbar, neck, limb, girdle distal limb and trunk muscles. Patients present with ptosis, diplopia, dysarthria, dysphagia or dyspnoea. The symptoms tend to progress later in the day and improve with rest. Iatrogenic MG has been associated with the use of D-penicillamine, alpha-interferon therapy, and chronic graft versus host disease (GVHD) in bone marrow transplantation patients. Respiratory failure is the presenting symptom in 1% of cases.
The diagnosis is based on a history of fluctuating weakness with corroborating findings on examination. The most commonly used confirmatory study is the Edrophonium (Tensilon) test. The use of this rapidly acting anticholinesterase drug (5-10 mg IV over 1 min) should improve muscle power within minutes.
Electrophysiological testing is widely available and provides further confirmatory evidence. Slow repetitive motor nerve stimulation will demonstrate a decline in muscle action potentials. Single-fibre EMG has a sensitivity of about 90%. Acetylcholine receptor (AchR) antibodies are highly specific for MG and are detected in about 80% of patients. About 15% of MG patients do not harbour these antibodies. The anti-muscle specific tyrosine kinase (MuSK) antibody needs to be considered in patients presenting with AchR-seronegative clinical syndromes. Patients with MuSK-MG have marked weakness and atrophy, especially of the facial or oropharyngeal muscles. They tend to present with respiratory symptoms or neck extension weakness. They may respond poorly to acetylcholinesterase inhibitor therapy and develop profuse fasciculations with acetylcholinesterase inhibitors.
The long-term natural course of MG is not clearly established other than being highly variable. Symptoms may remain confined to ocular muscles in 15-20% of cases (ocular myasthenia), but most patients with initial ocular involvement develop generalized

forms of the disease within 1 year. Maximal weakness occurs within 2-3 years into the disease, but spontaneous remission has been observed. Table 4.27 lists the drugs to avoid in patients with MG.

Critical Illness Polyneuropathy/Myopathy

Critical illness polyneuropathy (CIP) and its muscle counterpart, critical illness myopathy (CIM) are among the most common disorders resulting in weakness in ICU patients. CIP is a predominantly motor, axonal polyneuropathy occurring in 30-60% of patients who are critically ill with sepsis, multiorgan dysfunction syndrome, status asthmaticus and receiving medications, such as NMB agents, corticosteroids, and cytotoxic drugs. In severe CIP, patients have flaccid areflexic quadriparesis with weak or absent limb movements, even when the limbs are stimulated distally by pressure over the nail beds. Patients with CIM/ CIP typically have sparing of the cranial nerves and a variable sensory examination. Often, the only clinical sign of CIP is respiratory muscle weakness which manifests as difficulty in weaning from the mechanical ventilator after pulmonary or cardiac causes are excluded. The polyneuropathy tends to be more severe the longer the stay in the ICU.

Nerve conduction studies show low compound muscle action potential (CMAP) amplitudes, with preservation of sensory nerve action potential (SNAP) amplitudes in CIM and absent SNAPs in CIP. The duration of the compound muscle action potential (CMAP) may be prolonged, suggesting primary dysfunction of the muscle fibre membrane in addition to denervation. Even in the more advanced stages of CIP, conduction velocity and distal latencies remain relatively normal, emphasizing the purely axonal, degenerative nature of the neuropathy.

Unlike patients with CIP or CIM, those with GBS have weakness prior to ICU admission, conspicuous cranial nerve involvement, and evidence of demyelination on nerve conduction studies. The pathogenic mechanism underlying CIP is unknown. Primary axonal damage may be due to involvement of axonal transport systems, which are known to be energy-dependent; this fact may explain why distal nerve segments are predominantly involved.

- Alfa-interferon
- Aminoglycosides
- Beta-blockers
- Botulinum toxin
- Calcium channel blockers
- Chloroquine
- Chloroquine
- Corticosteroids
- D-penicillamine
- D-tubocurarine
- Erythromycin
- Fluoroquinolones
- Lithium
- Magnesium-containing laxatives, antacids
- NMBs
- Pancuronium
- Phenytoin
- Polymyxin antibiotics
- Procainamide
- Propanolol
- Quinidine
- Quinidine, quinine
- Quinine
- Quinolones
- Telithromycin

Table 4.27. Drugs to avoid in patients with MG.

Critical illness myopathy may occur independently of, or in association with, CIP. The major feature is diffuse flaccid weakness involving all limb muscles and the neck flexors, as well as the facial muscles and diaphragm, which often makes weaning patients off the mechanical ventilator difficult. Ophthalmoplegia may also be present. Nerve conduction studies reveal low-amplitude CMAPs, some of which may be of long duration. Fibrillation potentials and positive sharp waves will be present in both CIM and CIP. In CIM, motor unit potentials are of low amplitude and short duration, with high-frequency components. Markedly elevated CK levels suggest a necrotizing myopathy. Muscle biopsy is helpful in subtyping CIM. Neither the nerve nor the muscle shows any evi-

Frequency	Main clinical features	EMG features	Muscle enzymes	Muscle biopsy	Outcome
Thick-filament myosin loss					
Common with steroids, neuromuscular blocking agents, and sepsis	Flaccid limbs and respiratory weakness	Abnormal spontaneous activity	Mildly elevated	Loss of thick (myosin) filaments	Good
Rhabdomyolysis					
Rare	Flaccid limbs	Near normal	Markedly elevated (myoglobinuria)	Normal or mild necrosis	Good
Necrotizing myopathy of intensive care					
Rare	Flaccid weakness and myoglobinuria	Severe myopathy	Markedly elevated, myoglobinuria	Marked necrosis	Poor
Disuse (cachectic) myopathy					
Common?	Muscle wasting	Normal	Normal	Normal or type II fibre atrophy	Good
Combined polyneuropathy and myopathy					
Common	Flaccid limbs and respiratory weakness	Indicate combined polyneuropathy and myopathy	Variable	Denervation atrophy and myopathy	Variable

Table 4.28. Critical illness myopathy.

dence of inflammatory changes. Four main subtypes of crtitical illness have been identified on muscle biopsy: necrotizing, cachectic, acute rhabdomyolysis, and thick filament (myosin) loss type (Table 4.28).

The use of IV corticosteroids or neuromuscular-blocking agents has been associated with the development of CIM as compared to the use of these agents in patients with CIP. Treatment of these syndromes mainly is supportive and rests on aggressive management of the underlying sepsis or the systemic inflammatory response syndrome (SIRS). Intravenous immunoglobulin (IVIg) is not useful in patients with CIP or CIM. The long-term outcome after CIP is better than that after CIM.

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5 Evaluation Scales in Neurocritically Ill Patients

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5.1 Objectives

Accurate assessment of the clinical condition of critically ill neurological patients is an essential part of intensive care. The application of clinical rating scales and the evaluation of their results have become common practice for health professionals caring for severely ill neurological patients. Evaluation scales serve different purposes. Understanding their implications is essential for communication between professionals from different areas and institutions. This chapter describes and discusses the most frequently used scales in assessing acute and subacute critical neurological patients.

5.2 Introduction

The usefulness of clinical rating scales and outcome is manifold. Comparison between different series of patients is possible. Some scales are clinical, others are based on images, and others still use a combination of different variables. Scales may be useful for classifying patients, establishing prognosis, helping in decision making. For example, the Fisher scale is used specifically to assess the risk of vasospasm in patients with spontaneous subarachnoid hemorrhage (SAH). In patients with traumatic brain injury (TBI), a score on the Glasgow Coma Scale (GCS) <9, GCS=9-12, GCS=14-15 will reflect severe, moderate, or mild illness, respectively. This has implications for decision making: patients with severe TBI and a GCS ≤8 must be intubated and mechanical ventilation initiated. Some of the scales are specific to certain diseases and seek to assess their clinical aspects. In contrast, other scales are more generic and are applicable not only for evaluating different diseases but also different stages of neurological processes. For example the GCS, which was initially devised for assessing patients with TBI, has been extended to include other pathologies such as neurological damage of vascular origin.

5.3 Evaluation in the Acute Phase

5.3.1 Clinical Scales for the Evaluation of Altered Consciousness

Assessment schemes for the evaluation of consciousness disorders provide quantitative measures of the severity of coma in the acute phase and have proved useful in studies predicting functional sequelae after hospital discharge. The development of coma scales continued in response to the need for reliable, standardized data that could in-

form safe therapeutic measures and facilitate the design of protocols for clinical performance. Point scales serve to: 1) standardize levels of awareness in clinical research, thus allowing their comparison and replication across studies; 2) monitor the clinical course of the disease; 3) facilitate performance and decision making; and 4) predict outcome.
One advantage of coma scales is that they allow statistical analysis of the data for testing their reliability, validity and clinical significance. One drawback of point scales is that each measure is based on the clinician's experience, knowledge and observation. The ideal coma scale should meet the requirements of: 1) high validity; 2) classification of severity; 3) reliability; 4) linearity (additivity and homogeneity); 5) association with disease outcome; 6) ease of application; 7) simplicity; 8) yield; and 9) minimum redundancy.
Even with the use of these scales, however, the assessment of coma is not without controversy. Different scales have been designed to improve the GCS. For example, the Glasgow-Liège Scale evaluates indicators of brainstem function.
Other requirements of any assessment tool are that the scale items are representative of each construct, are clearly observable, and have a clear clinical interpretation. From the assumption that normal consciousness and coma constitute two ends on a continuum of human brain functional states and that consciousness involves two distinct but related attributes (alertness and content), some degree of caution is necessary when evaluating responsiveness since any response will need to be set somewhere along this continuum. From this, we can infer that, depending on the alterations in central nervous system (CNS) function, a scale will have different answers that may correspond to some alteration of consciousness. Since alertness and monitoring overlap, identifying specific indicators for exclusive categories in scale design is difficult. The result is the conceptualization of alertness and vigilance variables as one entity. In addition to indicators of neurological functions, other variables in medical and neurological examination seek to capture aspects of the etiology and diagnosis of coma motor responses, such as pupillary size and reactivity and ocular motility.
In reality what we actually see, however, are the pathophysiological and neuroanatomical correlates that provide a reliable localization and characterization of the illness. The responses to each item are organized hierarchically on a continuum from normal responses to a progressive impairment of brain function that ends in brain stem reflex movements or even their absence.
The higher functions (contents of consciousness) refer to a wide range of human behavioural characteristics such as cognitive, emotional, and sensory perception, motor functions, etc.).

Glasgow Coma Scale

The Glasgow Coma Scale (GCS) is widely used for assessing the level of consciousness in patients with neurological disorders of diverse etiology. Originally developed by Jennett and Tesdale and published in 1974, it measures the level of consciousness in TBI patients. Although the original scale had a maximum score of 14 points, with subsequent refinements the authors expanded the section on the assessment of motor response to 6 points (initially consisting of a maximum of 5 points). The descriptors currently included in the GCS evaluate: 1) motor activity; 2) verbal response; and 3) eye opening (Table 5.1). The total score is the sum of the points assigned for each activity examined (range, 3-15). The severity of head injury can be established by scoring sections. There is also consensus that a patient with a GCS score <9 will have a level of consciousness that can be considered as "coma". A description of the scale scoring system is given below.
Eye opening: 4 points are assigned for spontaneous eye opening; these patients still have eye fixation and eye tracking, although it is not necessary to consider the existence of eye opening. The presence of eye opening and staring suggests an intact optic path-

Score	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously		
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	
Motor	Makes no movements	Extension to painful stimuli	Abnormal flexion to painful stimuli	Flexion Withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

Table 5.1. **Glasgow Coma Scale (GCS).**

way and visual cortex; 3 points are recorded if the patient opens his eyes in response to a verbal command. This usually occurs in patients with drowsiness who respond to an auditory stimulus to open their eyes. A score of 2 points is recorded when the patient opens his/her eyes only in response to painful stimuli. These states are compatible with more severe brain dysfunction. A score of 1 is recorded when there is no eye opening in response to various intense stimuli.

Motor response: this is the most important section of the GCS from which the level of stimulus processing at the neuraxis can be inferred more accurately. Clinical examination of motor response in certain patients can be likened to an examination by somaesthetic evoked potentials. The integrated motor responses within the GCS (GCSm) may suggest the highest level of neural signal processing in patients with acquired acute brain damage.

On stimulation, the limb should be brought to cross the midline. Alternatively, if the upper limb has been placed on the root of the lower limb and the stimulus is applied to the upper chest, the hand will be elevated above the umbilical line. The score reflects an intact cortex and cortical pathways but is associated with brain dysfunction within a hemisphere. When there is a simple withdrawal response to pain or a stereotyped or classifiable response, 4 points are assigned, which should suggest cortico-subcortical location as the highest level of neurological processing. It should be remembered that to establish that the patient actually performs a "withdrawal response" the browser should monitor the elbow movement. Accordingly, a response is considered as "withdrawn" if the elbow is away from the axis of the body, regardless of whether that movement is associated with a forearm flexion. The typical response in flexion (bending or decortication) (rated with 3 points) is a motor response to noxious stimuli. It should be noted that decorticate flexion of the elbow involves the approach toward the major axis of the body associated with a forearm and often bending flexion of the wrist. This type of response is often observed in subacute neurological processes of vascular origin not common in traumatic events. A motor response is assigned 2 points if, after nociceptive stimulation, the patient performs a pronoextension extensor response of the upper limb, from which it can be inferred that the highest level of processing does not exceed the mesencephalic level. A score of 1 is recorded for the absence of motor response to painful stimuli; this indicates very severe bilateral hemispheric involvement or brainstem damage. Elicitation of the verbal response in intubated patients should not be limited to a repertoire of three questions that explore temporo-spatial orientation: "What is your name?", "Where are you?" and "What year is it?". If the patient speaks in an oriented and conversant manner, the maximum score of 5 is recorded, 4 points will be given when the patient is disoriented and conversant, 3 points when words are inappropriate (intelligible but inappropriate to the situation); 2 points for unintelligible sounds, and 1 point for no verbal response.

The GCS measures the degree of neurological dysfunction as a global function of "consciousness" at the time of examination. However, its prognostic value in TBI and other acute neurological processes mainly relates to the score after all extracranial factors that can influence the level of consciousness have been controlled. The effect that certain factors may have on the level of consciousness is well known. Hypotension, hypoxia, sedative drugs, toxic or postcritical state can all influence the GCS score. The GCS, which may be called "Score Collection Glasgow", or first aid, has the same prognostic ability as the Glasgow score obtained once these factors have been controlled.

Notes for Using the Glasgow Coma Scale

As initially described, the GCS was, and retains its main indication in the evaluation of decreased level of consciousness in patients in the acute phase of TBI. The ubiquity of the scale has facilitated its spread to other groups of severe neurological processes of diverse etiology such as ischemic or hemorrhagic cerebrovascular accidents, CNS infections, or acute complications of intracranial neoplasms. It is also often applied in other circumstances for evaluating only functional alterations of cerebral metabolism or causes of a systemic nature, coma, renal failure, hepatic, pulmonary, metabolic diseases, in the context of septic shock. It is also useful in cases of alcohol intoxication or drug abuse.

The GCS has also been combined with other scales to assess acute and severe neurological conditions. Thus, in evaluating patients with spontaneous SAH, the GCS has been included in one of the major scales assessing its severity, the scale of the World Federation of Neurosurgeons.

Limitations of the Glasgow Coma Scale

There are some limitations to the implementation of the GCS. For example, neurological disorders not directly altering the level of consciousness may interfere with the examination: for instance, aphasia, sensory deficits such as deafness or blindness, psychiatric disorders, and mental deficit can all add to the difficulty of the clinical examination. The verbal component of the GCS may be precluded in intubated patients. In such cases, the verbal component can be removed from the scale, and an "I" (intubated) noted on the evaluation form, without assessing this parameter, or otherwise make inferences from other responses. Hence, eye opening in response to verbal commands and pain is assigned an overall score of 12 points, while the total GCS score is 7 points for eye opening in response to pain and stereotyped flexing of the extremities.

Another possible limitation to the GCS is the fact that the motor component may also present difficulties in evaluation due to the presence of immobilizing splints or traction for the treatment of orthopedic injuries. Other difficulties in motor evaluation include motor deficits, such as pyramidal tract lesions or intracerebral lesions which do not affect consciousness but can alter the motor response. So it is not uncommon to find patients with motor responses resulting from diffuse axonal injury type which interfere with the evaluation of consciousness according to the GCS. You can see how some patients with axonal injury similar to pronoextension objectified in the responses of decortication, but with a different meaning. In the case of decerebrate bending, a mechanism involved in the genesis of motor response is the cessation of the connection between the cerebral cortex and the reticular substance due to an acute hemispheric process that intercepts the control and inhibition of intrinsic muscle tone and the substance, manifested by an abnormal motor response. In contrast, in patients with diffuse axonal injury and pronoextension these responses often manifest as spontaneous activity due to diencephalic substance that directly stimulates the brainstem internuncial neurons, generating pronoextension responses. Such situations and others like them must be taken into account when assessing the state of consciousness in patients with axo-

nal injury. Only then can a judicious interpretation be made of the meaning of this type of response.

The ocular component of the GCS may be difficult to assess in patients with facial trauma in which the upper third of the facial mass is seriously injured or eyelid edema occludes the eyelids and makes eye opening impossible, or also in patients presenting with congenital or acquired amaurosis, as well. In such cases, consideration should be given to the component of eye opening; assessment of the level of consciousness will have a maximum total of 11 points, including verbal and motor response.

In any case, it should be noted that of the three sections composing the GCS, the motor component has the highest profile and greatest weight in the evaluation of global CNS dysfunction. For some authors, the motor component of the GCS itself contains all the necessary information even in cases suggesting that, given the prognostic capacity of this section, it would replace the entirety of the scale in predicting the evolution of TBI patients

Training in the application of the GCS is key to increasing its reliability. Its application by a well-trained staff ensures adequate reliability, although major disagreements have been described: one series reported that between 20 and 35% of patients evaluated were rated differently and by different evaluators. It is therefore important not only to adequately train the examiners but also harmonize interpretation of the responses and the intensity and characteristics of the stimuli applies to the patient.

Although the GCS has a capacity of major global prediction when analyzing large series of patients, it should not be used in predicting the prognosis of specific individuals with critical neurological process such as TBI. In fact, we find patients with very low scores due to the development of acute extra-axial lesions, extradural hematoma, who, when treated quickly and the masses are evacuated, will have a good long-term prognosis. Consequently, the ability to forecast the GCS should be used primarily in the study of patient groups.

Innsbruck Coma Scale

Like the GCS, the Innsbruck Coma Scale (ICS) was developed to evaluate TBI patients. The ICS is a summative scale; scores

Item	Factor	Score
Eye opening	Spontaneous	3
	To acoustic stimuli	2
	To painful stimuli	1
	None	0
Reaction to acoustic stimuli	Turning towards stimuli	3
	Better-than-extension movements	2
	Extension movements	1
	None	0
Reaction to pain	Defensive movements	3
	Better-than-extension movements	2
	Extension movements	1
	None	0
Body posture	Normal	3
	Better-than-extension movements	2
	Extension movements	1
	None	0
Pupil size	Normal	3
	Narrow	2
	Dilated	1
	Completely dilated	0
Pupil response to light	Sufficient	3
	Reduced	2
	Minimum	1
	None	0
Position and movements of the eyeballs	Fixing of the eyes	3
	Sway of eyeballs	2
	Divergent	1
	Divergent fixed	0
Oral automatisms	Spontaneous	2
	To external stimuli	1
	None	0

Table 5.2. Innsbruck Coma Scale (ICS).

range from 0 to 23 points, with a minimum score of 0 (no response) and a maximum of 23 (patient oriented). The scale takes the same values (Table 5.2) as the GCS for ocular and motor responses, in addition to eye position, pupil size, pupil response to light, and oral automatisms. In the lower ranges of scores in the evaluation of the patient on admission, the ICS is highly predictive of patient mortality at 21 days of stay.

Edinburgh Coma Scale-2

The Edinburgh Coma Scale-2 (E2CS) is the best answer as long as the patient is considered valid to classify according to an ordinal system, where a higher score indicates lower level of consciousness. The system assigns a single score in a continuous exploration from a lack of any response to the responses of patient orientation. It has the advantage over previous scales that it does not add co-variable factors. Its shows good correlation with the GCS and the Glasgow Outcome Scale (GOS) for mortality and morbidity levels organized in a proper order. For 1 to 3, the ratio increases rapidly for morbidity, but mortality is <30% for a score of 5, then non-linear up to 100% with a score of 10. A drawback to the E2CS is that it assumes that in patients obeying orders the verbal response is preserved in the absence of obtaining the same or the wrong answer. Another drawback is that an intubated patient cannot be expected to give a verbal response, unless, perhaps a response is elicited and a lower score assigned. The scale takes the values specified in Table 5.3.

	Item	Score
The patient answers to a set of questions about temporal and personal orientation	Answers correctly to both	0
	Answers correctly to either	1
	Answers incorrectly to both	2
Two sets of commands (close and open hands, close and open eyes)	Obeys correctly to both	3
	Obeys correctly to either	4
	Neither correct	5
Strong pain	Localizing	6
	Flexion	7
	Extension	8
	None	9

Table 5.3. Edinburgh-2 Scale (E2CS).

Other Scales

The Glasgow Coma Scale-Liège (Born, 1988), designed on the GCS, is based on the fact that, in the first 24 hours after brain injury, the study of the brainstem reflexes index provides a good prognosis and that early mortality rates are associated with brainstem reflex disorders (Table 5.4).

The Reaction Level Scale (RLS85) (Table 5.5) is another scale that assesses the level of response in patients with acute brain injury. It was developed for use in instances where evaluation can be problematic, as in intubated patients or patients with

Best eye response (1-4)	1. No eye opening 2. Eye opening to pain 3. Eye opening to verbal command 4. Eyes open spontaneously
Best verbal response (1-5)	1. No verbal response 2. Incomprehensible sounds 3. Inappropriate words 4. Confused 5. Orientated
Best motor response (1-6)	1. No motor response 2. Stereotyped extension to pain 3. Stereotyped flexion to pain 4. Withdrawal from pain 5. Localizing pain 6. Obeys commands
Brainstem reflexes (0-5)	0. No brainstem reflex 1. Oculocardiac reflex 2. Horizontal oculocephalic or oculovestibular reflex 3. Pupillary light reflex 4. Vertical oculocephalic or oculovestibular reflex 5. Fronto-orbicular reflex

Table 5.4. Glasgow Liege Scale (GLS).

Grade	Description
1	Alert, with no delay in response (responds without stimulus)
2	Drowsy or confused, but responds to light stimulation
3	Very drowsy or confused, but responds to strong stimulation
4	Unconscious; localizes (moves a hand towards) a painful stimulus but does not ward it off
5	Unconscious; makes withdrawing movements following a painful stimulus
6	Unconscious; stereotypic flexion movements following painful stimuliery
7	Unconscious; stereotypic extension movements following painful stimuli
8	Unconscious; no response to painful stimuli

Table 5.5. **Reaction Level Scale (RLS85).**

eye swelling. The scale has a good reliability for various etiologies of brain injury such as head trauma and stroke. The main assumption in the scale's design is that there is a continuum in the level of consciousness, alertness and orientation to non-response to noxious stimulation. Similarly, it is assumed that the reverse sequence must occur in the patient with impaired recovery of consciousness. Based on theoretical considerations and clinics, each change in degree on the scale can be considered a reflection of a real change in the patient's condition. It is also assumed valid to consider the best response of the patient. The scale has 8 categories of bedside assessment.

5.3.2 Hunt and Hess Scale

Based on the classification of Botterell and Lougheed, the Hunt and Hess scale was published in 1968 and has been several subsequently amended. It was initially designed to determine the risk of surgery that a ruptured aneurysm and timing of surgery carry. Although several factors such as age and number of days elapsed since bleeding are involved, WE Hunt and RM Hess estimated that the intensity of meningeal inflammation, the severity of neurological deficit, and the presence or absence of neurological disease were clinical data that were better able to predict surgical risk. The scale was derived from the data on 275 consecutive patients and surgical intervention, either early (in patients with grades I and II), or delayed (reserved for patients with grade III or higher awaiting neurological improvement). Neither patient age nor aneurysm location were determinants of surgical risk. The number of days since bleeding was not considered an important prognostic element.

The Hunt and Hess classification is structured on 5 grades depending on the level of intensity of clinical manifestations such as headache, stiff neck, focal neurologic deficit or altered level of consciousness (Table 5.6). The first 2 grades include patients without altered consciousness or stiff neck graded as minimal to moderate while headache can be graded mild or moderate to severe. Such patients have no focal deficits but may have paralysis resulting from cranial nerve compression due to aneurysmal growth. Grade I and II patients were submitted to early surgery in the Hunt and Hess series.

Grade	Description
I	Asymptomatic, mild headache, slight nuchal rigidity
II	Moderate to severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
III	Drowsiness/confusion, mild focal neurologic deficit
IV	Stupor, moderate-severe hemiparesis
V	Coma, decerebrate posturing

Table 5.6. **Hunt and Hess Scale.**

Indications for the Use of the Hunt and Hess Scale

The principal indication for the Hunt and Hess scale is to predict surgical-risk patients with recent subarachnoid hemorrhage (SAH). According to initial studies, an increase in the clinical grade is associated with an increased risk of mortality. However, this scale was developed before the implementation of navigation techniques or endovascular coiling. Therefore, the recommendation that aneurysm exclusion techniques should be limited to Hunt and Hess <grade III have become obsolete, owing to the significantly lower risk for patient undergoing an endovascular technique. Although not intended for this purpose, the scale has been frequently used to assess the overall clinical risk of SAH. However, new scales may be more accurate in predicting surgical risk.

Limitations of the Hunt and Hess Scale

As discussed above, the Hunt and Hess scale was not intended as a predictor of the clinical course of patients with spontaneous SAH, although it often has been used for such purposes.

The Hunt and Hess scale should be used judiciously in those patients in whom the level of consciousness may be affected not only by the bleeding but also by its accompanying complications. It's not uncommon to see patients with SAH and spontaneous seizures in whom the level of consciousness during and after the seizures is influenced by the epileptic activity and not by a decreased level of consciousness produced directly by bleeding. The development of hydrocephalus, which progress over time, also significantly influences the level of consciousness, without implying a worsening of prognosis derived directly from SAH but indirectly from hydrocephalus. After placement of a cerebrospinal fluid shunt, consciousness returns to the previous level in relation to the SAH. That "restored" level of consciousness should be the one that really establishes the clinical prognosis.

Certain symptoms such as stiff neck or headache pain, for example, have a subjective component. Probably it is the subjectivity of both the physician and the patient in the interpretation of certain symptoms included on the Hunt and Hess scale that justifies in part the further development of other scales such as the World Federation of Neurological Surgeons (WFNS), with its more quantitative measurements that were introduced to overcome the problem of interobserver variability in the interpretation of certain signs and symptoms.

5.3.3 World Federation of Neurological Surgeons Scale

This scale was introduced in 1988 in an attempt to have a simple scale that could estimate the prognosis of a patient with SAH and could be used as a means to quantify changes in the patient's clinical status throughout the acute phase. The scale needed to be reliable and, above all, allow its combination with other methods of clinical evaluation of SAH, which until then had been developed along the lines of Hunt and Hess for the Cooperative study.

The WFNS Scale was developed on the basis of the GCS. Unlike the Hunt and Hess scale, it does not take into consideration the presence of signs such as stiff neck or symptoms such as headache. The Surgeons Committee had to choose at the outset between the proposed Kassell and Torner stratification (5 grades) and that of Jagger et al. (7 grades) of spontaneous SAH, agreeing finally on the scheme presented in Table 5.7.

As can be seen from the table, set up in 5 grades, an unruptured aneurysm was considered as one grade, the GCS was taken for assessing level of consciousness, given the scale's widespread application in the evaluation of head injury, and was used only for high-grade focal deficits (aphasia, hemiparesis, and hemiplegia), which differ in grades II and III on this scale.

Grade	Glasgow Coma Scare score	Motor deficit
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

Table 5.7. **World Federation of Neurological Surgeons scale.**

Special attention should be drawn to the fact that ptosis and ocular adduction difficulty (third cranial nerve palsy or oculomotor internal) are not considered suggestive of focal data but instead the result of direct compression of the third cranial nerve due to the growth of the aneurysm in the posterior circulation, thus keeping the patient in group II on the WFNS scale. The WFNS scale provides some advantages over the Hunt and Hess scale, such as greater simplicity and lower interobserver variability.

The WFNS scale was later modified by Sano and Tamura to improve the discriminatory power of each grade. With this modification, the WFNS scale was restructured into 6 grades by subdividing grade III and redefining grades I and II. In this new scheme, patients with a GCS score of 15 and neurologically intact are categorized in grade I, although some may have cranial nerve palsies that do not involve increasing severity (as in third nerve palsy secondary to the sudden growth of aneurysms of the posterior communicating arteries). Grade II patients, including those with a GCS score of 15, have a clinically intense headache and/or stiff neck. Grade III, (GCS score 13-14) is divided into two subgroups: IIIA if no focal deficit and IIIB if focal deficit is present. In grade IV (GCS score 7-12), the upper and lower scores coincide with the WFNS scale, without changing the GCS score for patients with sufficient consciousness but may lose the swallow reflex and so will require admission to the ICU. Finally, grade V (GCS score <7) includes patients in deep coma with abnormal motor reactions.

Indications for Use and Limitations of the WFNS Scale

The WFNS scale should be used for the evaluation of the clinical severity of patients with spontaneous SAH during the acute phase. The WFNS clinical scale is now better able to establish the prognosis of patients after neurological examination in the acute period of SAH.

Possible limitations of the WFNS scale are: 1) absence of clinical significance in the scale because highly symptomatic patients with severe headache and severe neck stiffness, who are nevertheless classified as grade I, may not have altered level of consciousness or motor deficits; 2) assessment of the level of awareness is important for the prediction of death and disability; however, the presence of focal signs such as hemiplegia, hemiparesis and/or aphasia is important in the development of disabilities ensuing from acute neurological process, making it less reliable in predicting mortality; 3) detected inconsistencies in the cut-off scores on the GCS to differentiate between grade II and III and IV characteristic of these groups because they have the same neurological status with the only difference being the focus. Group IV has a much broader neurological status comprising a GCS score of 7 and a GCS score 12 which denotes a confused state; 4) adds defects attributable to the GCS. Thus, it is advisable to collect individual components of the GCS (eye, motor and verbal responses) as the same overall score; the different prognoses will depend on the score of each of the three components.

5.3.4 The Johns Hopkins Classification

One of the more recently developed scales for the assessment of patients with spontaneous SAH is the Johns Hopkins classification published by Tamargo R et al. in 1997 (Table 5.8) and proposed as an alternative to the two most commonly used scales hitherto, Hunt and Hess and WFNS.

Based on the GCS, and like the WFNS scale, it attempts to discern the severity within the group of patients with grade IV SAH on the WFNS scale. On the latter, grade IV is made up of patients with severe coma, a score of 6, and others with much less involvement (score of 12) that only have a certain degree of drowsiness. In contrast, the Johns Hopkins scale segregates patients with a GCS score of 6 to 8 (grade IV) from those with a score <6 (grade V).

The Johns Hopkins scale solves the problem of classification of patients with very different prognoses within the same group, and differentiating between mild, moderate and severe illness, compared with the lack of resolution that the WFNS scale has. Although the scale has not been evaluated in large series, it is remarkable for its simplicity and ease of use by clinicians.

The indications for its use are similar to those mentioned for the WFNS scale, i.e., evaluation of the severity and clinical impact of SAH bleeding. Like all scales, including the GCS, there are limitations to its use.

Grade	Description
0	Unruptured aneurysm
I	15 points GCS
II	12-14 points GCS
III	9-11 points GCS and/o focal deficit
IV	6-8 points GCS
V	3-5 points GCS

Table 5.8. Johns Hopkins scale.

5.4 Imaging-based Assessment Scales

5.4.1 Traumatic Coma Data Bank Scale

The Traumatic Coma Data Bank (TCDB) scale is currently the most widespread tool in the evaluation of computed tomography (CT) of TBI. The scale was presented in 1991 by Marshall, et al. and was initially developed to evaluate through CT images in the acute phase of patients with head injury, intracranial lesions in these patients. The classification is intended to include the universe of all patients with closed head injuries and classify them according to prognostic features and therapeutic orientations. The initial justification for the development of the scale was twofold: to establish subgroups of patients with head trauma who have a similar risk of neurological impairment, and to identify groups of trauma patients with similar clinical medium and long-term prognosis. The scale was developed exclusively for blunt trauma, excluding injuries caused by firearms, and was initially implemented only for patients with severe head trauma, i.e., with a GCS ≤8. It has a direct relationship with the level of consciousness disorder as assessed by GCS, specifically the GCSm and different categories of the TCDB classification. Likewise, the various levels of this classification scheme are associated with mortality rates significantly different from each other. According to CT findings, the diagnostic classification includes six categories, four of which pertain to predominantly diffuse lesions and predominantly focal injuries. Diffuse lesions (types I to IV) may include low-volume mass lesions (limit, 25 cc), but with diffuse brain injury as a predominant lesion. Also considered for this classification in addition to the mass lesion volume are: midline shift (more or

Cathegory	Cranial CT
Diffuse injury I (pathology not visible)	No visible pathology on CT
Diffuse injury II	Cisterns present with midline displacement of 0-5 mm and/or dense lesions present. No injuries or mixed high density of more than 25 cc. Bone fragments and foreign bodies can be present
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift of 0-5 mm. No injuries or mixed high density of more than 25 cc
Diffuse injury IV (shift)	Displacement of the midline of more than 5 mm. No injuries or mixed high density of more than 25 cc
Evacuated mass lesion	Any lesion surgically evacuated
Non evacuated mass lesion	Injury high or mixed density of more than 25 cc not surgically evacuated

Table 5.9. **The Traumatic Coma Data Bank (TCDB) scale.**

less than 5 mm) and compression of mesencephalic cisterns. One advantage of the TCDB scale is its widespread use in centres caring for TBI patients. Besides its clinical applicability, another factor contributing to its dissemination is that there is a high correlation between CT scan readers when analyzing the images in trauma patients. This degree of agreement is higher when there are mass lesions and when lesions are classifiable as diffuse brain injury (grades I to IV). Table 5.9 presents the different categories of the TCDB classification.

As mentioned above, the different categories are associated with different rates of mortality; the mechanism most probably involved is the presence of intracranial hypertension. Thus, mortality increases progressively in the different categories of diffuse injury, reaching a mortality of 56% in type IV diffuse lesions, comparable to the mortality of injured patients with evacuated masses (53%). In grade III and IV diffuse injury, the most important predictor of evolution is the intracranial pressure, whereas in the other age groups, the GCS and pupil reactivity predict the prognosis better. It is therefore evident that the TCDB classification informs us of the likelihood of intracranial hypertension and mortality; however, there are many other factors such as patient age, previous trauma, and comorbidities which also have a role in the outcome.

Indications for Use and Limitations of the Traumatic Coma Data Bank Scale

The TCDB scale should be used for estimating the risk of death and intracranial hypertension in patients who have suffered a head injury. It was designed to be applied to the first CT scan obtained during the acute phase of injury, since the TCDB classification includes only primary traumatic injuries. On the other hand, although the scheme was developed for evaluating patients with severe head trauma, i.e., with a GCS score ≤8, its use has been extended to other groups of TBI patients (moderate and mild) to describe intracranial lesions. Moreover, although the TCDB scale was not designed for that purpose, certain categories in the scheme are associated with certain therapeutic or monitoring procedures. Thus, the presence of type III diffuse injury is associated with the presence of intracranial hypertension, and linked to intracranial pressure monitoring. Similarly, the presence of space-occupying lesions (<25 cm^3) requires a surgical therapeutic approach, which undertaken or not, leads to a reclassification of the patient within the TCDB classification.

It should be noted that the TCDB classification is a dynamic rating system; therefore, given the possibility of development of traumatic intracranial lesions either spontaneously

or during intervening events, it is possible to reclassify patients throughout the process. Thus, in patients in whom a CT scan was obtained immediately after trauma, the scan may not show intracranial lesions that can develop during the first 3-12 hours after the trauma. So some authors propose a reclassification based on the features of the last or the worst CT performed in the acute phase.

There are some other limitations of the TCDB classification. The classification takes a primarily surgical approach without considering some TBI of great clinical relevance and, above all, of great prognostic importance. This is the case of traumatic subarachnoid hemorrhage (tSAH), which currently enjoys a significant prognostic role, and was not considered in the initial TCDB classification. Currently, traumatic SAH is usually classified as diffuse brain injury type II. Other injuries often not sufficiently weighted in the classification are tomographic lesions associated with diffuse axonal injury, especially those located in the brainstem or corpus callosum. According to the TCDB classification, the presence of such lesions, often small hemorrhagic lesions on the CT scan, would be included under type II diffuse injury, which could lead to prognostic expectations anyway, but may be established a priori by the tomographic images. It is well known that in patients with diffuse axonal injury mainly affecting central brain structures, the prognosis for recovery in the medium term is uncertain. Conversely, larger hemorrhagic lesions due to concussions may be associated in general with a better clinical outcome. Hence, the TCBD classification is less powerful when used for evaluating mild TBI.

5.4.2 Greene Scale for Assessing Posttraumatic Subarachnoid Hemorrhage

The presence of tSAH on a CT scan has gained increasing relevance. Although an association between prognosis and the presence of tSAH has been demonstrated, it is equally true that there is consensus on how to classify and evaluate the presence of such lesions on the CT scan. Moreover, the clinical significance of posttraumatic SAH differs from spontaneous SAH owing both to blood volume and location. In most trauma cases, the subarachnoid blood does not usually enter the basal cisterns but rather mixes with the supratentorial and spinal fluid surrounding the cerebral hemispheres. Less frequently it is located at the level of the cisterns of the skull base, where bleeding is probably due to a different mechanism.

Greene et al. proposed in 1995 a model for weighing and assessing the severity of this entity based on a series of 252 patients at St. Joseph's Hospital and Medical Center in Arizona enrolled over 3 years. The study included only patients with non-penetrating head wounds and abnormal CT, regardless of the degree of altered consciousness. Although the study was not designed to show a scaled analysis of SAH itself, the aim was to study whether CT findings can be considered useful in the evaluation of traumatic SAH. The main contributions of this study are that it established a systematic way to analyze traumatic SAH and that it defined a severity scale for traumatic SAH in terms of intensity in association with other pathological findings on the CT scan.

The proposed scale of CT analysis focuses on the presence or not of SAH and, if present, the evaluation of its thickness (≤5 mm or >5 mm), and its location. The anatomical locations imaged for the presence of subarachnoid blood are the interhemispheric fissure, fissure frontobasal, frontal fissure, occipitoparietal fissure, base of the Sylvian fissure, Sylvian fissure, insular cistern, suprasellar cistern, ambiens cistern, interpeduncular cistern, prepontine cistern, transverse cerebral fissure, supracerebellar cistern, and cerebral convexity. With this type of analysis, we can distinguish between those regions including the basal cisterns, vertical regions of cerebrospinal fluid, the Sylvian fissure and

bleeding. Based on this distinction, the location is classified in a hierarchical manner and assigned scores of 1 to 3, where 1 refers to the presence of traumatic SAH in the hemispheric region only, 2 only located in the basal region, and 3 presence of SAH in the basal interhemispheric regions. Besides these aspects, also evaluated are the presence or absence of associated brain edema, obliteration of basal cisterns associated with SAH, mass lesions such as epidural or subdural hematoma, or the presence of concussion and midline shift >5 mm, or ≤5 mm (toward the septum pellucidum). Table 5.10 shows the Greene Scale for the classification of tSAH.

Grade	Description
1	Traumatic SAH ≤5 mm
2	Traumatic SAH >5 mm
3A	Traumatic SAH ≤5 mm, median line deviation ≤5 mm and mass lesion
3B	Traumatic SAH ≤5 mm, median line deviation >5 mm and mass lesion
4A	Traumatic SAH >5 mm, median line deviation ≤5 mm and mass lesion
4B	Traumatic SAH >5 mm, median line deviation >5 mm and mass lesion

Table 5.10. **Greene classification of traumatic subarachnoid hemorrhage.**

Greene KA et al. found a direct relationship between the degree on the scale and the level of consciousness (GCS) on admission of the patient. The scale also correlated statistically with the outcome, as measured by the Glasgow Outcome Scale (GOS).
The significance of SAH in patients with TBI is different in patients with spontaneous subarachnoid bleeding due to rupture of intracranial aneurysms. Both its location and because of its pathophysiology, the relationship between posttraumatic vasospasm and SAH is not as clear as it is in spontaneous SAH. Traumatic SAH is a marker of a brain damage mechanism of relevance. Thus, the presence on CT of traumatic SAH has been considered an element suggestive of mechanisms of acceleration/deceleration in the genesis of trauma, and therefore not infrequently associated with the presence of diffuse axonal injury.

5.4.3 Gennarelli Scale for Rating Diffuse Axonal Injury

Gennarelli developed a scale based on previous anatomo-pathological findings by Adams in patients with diffuse axonal injury. It was the primary basis for classifying diffuse axonal injury and scales with radiological and clinical variables were later developed. Table 5.11 presents the Gennarelli classification based on pathologic findings from studies in primates, which was subsequently modified. Although initial studies were conducted in experimental animals, the results were then extrapolated to imaging studies using CT, in which it was observed that CT showed moderate sensitivity for the detection of white matter lesions accompanying diffuse axonal injury. These chances of detecting axonal injury were later exploited with the advent of magnetic resonance imaging (MRI).
The Gennarelli scale for evaluating diffuse axonal injury is currently the most widely used tool for assessing injury severity, as it indicates a direct relationship between the lesion severity and long-term neurological and functional outcomes.
In 1987, Gentry et al., using MRI studies in the acute phase of injury and comparing the radiographic findings with clinical findings, described traumatic axonal injury lesions and their most frequent locations: lobar white matter (frontal, temporal, parietal and occipital), corpus callosum (splenium, body and knee), corona radiata (anterior and posterior), capsula (internal and external), brain stem and cerebellum.
The radiological approach to the study by Gentry along with Gennarelli's anatomical classification allows stratification of lesions secondary to diffuse axonal injury along a sliding scale, so that peripheral lesions in the lobar white matter are classified in the range of the

less serious, while central brain lesions and those of the brainstem are associated with greater clinical severity.

Grade	Description
I	Deep small hematoma diffused in crerebral hemispheres These lesions are widely distributed in the white matter of the hemispheres (including the corpus callosum), stem and cerebellum. In less severe cases, it affects only the paramedian white matter
II	Since this is a staging of the same problem, grade II lesions are observed only after the Grade I lesions are present, when hemorragic lesions aggregate in the corpus callosum
III	Grade I and II lesions are present. Furthermore, focal hemorrhagic lesions are present in the dorsal lateral quadrant of the midbrain or upper third of the bulge

Table 5.11. **Morphological classification of axonal diffuse region. Gennarelli classification modified.**

5.4.4 Fisher Scale

Developed by Fisher et al. in 1980, this scale assesses the location and extent of SAH visualized by CT, based on the observed changes in CT scans of a verified case of ruptured intracranial aneurysms, and the relationship with cerebral vasospasm (Table 5.12).

Divided into 4 grades, the scale relates the amount of blood visualized on a CT scan at the level of the cisterns, sulci and ventricles, with the possibility of developing arteriospasm. Analysis of the presence of blood should include at least the following locations: 1) frontal interhemispheric fissure, including the immediate region of the genu of the corpus callosum; 2) basal frontal fissure, including the inferomedial boundary region of the hemisphere, close to the anterior communicating artery; 3) occipitoparietal fissure (posterior interhemispheric fissure); 4) base of the Sylvian fissure (horizontal portion of the Sylvian fissure around the proximal middle cerebral artery bifurcation); 5) Sylvian cistern (bottom of the Sylvian fissure adjacent to its base and the main divisions of the middle cerebral artery); 6) insular cistern (subarachnoid space vertically oriented on the surface of insula); 7) part of the Sylvian fissure oriented horizontally and superimposed on the upper surface of the temporal lobe; 8) suprasellar cistern (region of the circle of Willis); 9) ambiens cistern (perimesencephalic space vertically oriented); 10); quadrigeminal cistern (subarachnoid space adjacent to the quadrigeminal bodies); 11) transverse cerebral fissure between the corpus callosum and the fornix above and below the diencephalon; 13) prepontine cistern located ventral to the base of the pons and superior cerebellar cistern; 14) surface of the brain.

In cases where the amount of blood that is not noticeable or is so diffuse that it forms clots >1 inch thick (grade 1 and 2, respectively), the rate of vasospasm is very low. In cases where the accumulation of blood is greater (grade 3), the risk of vasospasm increases as does ischemic neurological deterioration even more if blood occupies

Grade	Appearance of hemorrhage
1	None evident
2	Less than 1 mm thick
3	More than 1 mm thick
4	Diffuse or none with intraventricular hemorrhage or parenchymal extension

Table 5.12. **Fischer scale.**

Grade	Criteria
1	Absence of subarachnoid hemorrhage and ventricular invasion
2	Minimal subarachnoid hemorrhage without ventricular invasion
3	Minimal subarachnoid hemorrhage with ventricular invasion in both lateral ventricules
4	Dense subarachnoid hemorrhage with ventricular invasion in both lateral ventricules

Table 5.13. **Fischer revised scale.**

the wells in the vertical plane (interhemispheric fissure, insular cistern, ambiens cistern) or >3 x 5 mm in the longitudinal cisterns (Sylvian and interpeduncular).

Indications for Use and Limitations of Fisher's Scale

The Fisher scale has its main indication in assessing the risk of developing vasospasm according to CT findings in the acute phase of aneurysmal SAH, and so may n estimate of the risk of developing ischemic focal neurological deficits associated with this situation. The Fisher scale should not be used as a scale to estimate clinical severity or for evaluating neurological complications of spontaneous SAH. Furthermore, accurate estimation of the amount of subarachnoid bleeding as assessed by CT is not always easy. The problems for quantification are diverse: 1) irregular size of the cisterns and fissures; 2) planes that do not correspond to the inclination of the CT court; 3) difference in blood concentration in each of these regions; 4) inaccuracy in measuring the intensity in Hounsfield units (HU) due to the frequent coexistence of partial volume effect due to both the proximity of the bone and the cerebral cortex; and 5) increasing trend of isodensity of bleeding with the time.

5.4.5 Graeb Scale

In 1982 Graeb published a retrospective study of CT findings of 68 patients with intraventricular hemorrhage caused by aneurysm rupture (25%), trauma (25%), hypertensive hemorrhage (20%) and other miscellaneous causes. The mortality rate was 50%, whereas 21% of patients who recovered didn't have sequelae or had only mild disability. Since the development of hydrocephalus is an important factor in the prognosis of patients with blood in the ventricles, the authors proposed a classification to assess its risk. The classification is based on the amount of blood invading the ventricles (Table 5.14). One consideration to take in mind is the "blood-filled and expanded ventricle " which implies that the presence of ventricular dilation is directly attributable to bleeding, and not to the possible co-existence of hydrocephalus. The maximum score is 12 points, and there is some consensus that a score ≥7 allow us to evaluate this bleeding as high risk, frequently associated with a severe clinical picture. The risk of hydrocephalus is low when the score is between 1 and 4, moderate between 5-8, and severe when the total score is 9 to 12.

The main objective of Graeb's Scale is to quantify intraventricular blood associated with spontaneous SAH, intraparenchymal hematomas, or other processes such as tumours, and arteriovenous malformations; therefore, it may be used to estimate the risk of developing obstructive hydrocephalus.

	Item	Score
Lateral right ventricle	Traces of blood	1
	Less than half of the ventricle filled with blood	2
	More than half of the ventricle filled with blood	3
	Ventricle filled with blood and expanded	4
Lateral left ventricle	Traces of blood	1
	Less than half of the ventricle filled with blood	2
	More than half of the ventricle filled with blood	3
	Ventricle filled with blood and expanded	4
III ventricle	Blood present, ventricle size normal	1
	Ventricle filled with blood and expanded	2
IV ventricle	Blood present, ventricle size normal	1
	Ventricle filled with blood and expanded	2

Table 5.14. Graeb grading scale.

5.4.6 Le Roux Scale

In 1992, Le Roux published the results of a series of patients with intraventricular hemorrhage secondary to head injury. This study utilized a risk scale somewhat similar to that Graeb had published 10 years earlier. The study population was 43 patients. The blood was distributed in one or both ventricles in 25 patients; in the third or fourth ventricle in 4, and in all the ventricles in 14. There were also 3 intracerebral hematomas and 14 in the basal ganglia. The presence of ventricular blood in each ventricle was evaluated on a scale with a score between 0 (no ventricular hemorrhage) and 4 (maximum degree of ventricular invasion), with a total score range from 0 to16 (Table 5.15).

Item	Score
Traces of blood	1
Less than half of the ventricle filled with blood	2
More than half of the ventricle filled with blood	3
Ventricle filled and expanded with blood	4

Table 5.15. Le Roux grading scale.

5.4.7 Spetzler-Martin Scale

This scale was devised by Spetzler and Martin in 1986 to establish surgical risk and treatment recommendations for arteriovenous malformations (AVM). It combines clinical and radiological variables.

This grading system (Table 5.16) establishes the risk of morbidity and mortality and the most appropriate form of treatment of AVM. AVMs are classified according to the total score, based on the following criteria: size of nidus, type of venous drainage, and eloquence of adjacent brain area.

The size of the lesion is usually determined by the size of the malformation, which is defined on angiography: small, <3 cm (1 point); medium, 3-6 cm (2 points); and large, ≥6 cm (3 points). In general the overall AVM size is related to the number of afferent arteries.

The pattern of venous drainage is also determined by arteriography. A superficial directed to cortical venous system, straight or transverse sinus is assigned 0 points; a deep pattern (deep venous drainage, internal, basal cerebral veins or cerebellar or paracentral veins) is assigned 1 point.

The following regions are considered eloquent: sensorimotor cortex, language and visual area; hypothalamus; thalamus; internal capsule; brainstem, cerebellar peduncles; and deep nuclei. An AVM affecting an eloquent areas is assigned 1 point and 0 if no eloquent areas are affected.

	Item	Score
Size of arteriovenous malformations	Small (<3 cm)	1
	Medium (3-6 cm)	2
	Large (>6 cm)	3
Location	Noneloquent site	0
	Eloquent site	1
Venouse drainage	Superficial	0
	Deep	1

Table 5.16. Spetzler Martin Grading scale.

5.4.8 NIH Stroke Scale (NIHSS)

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was originally designed as a research tool, but now has other potential utilizations such as: clinical assessment, determining treatment appropriateness (thrombolytics), and predicting outcome.

Variable	Definition	Score
Level of consciousness	Alert	0
	Somnolent	1
	Stupor	2
	Coma	3
Level of consciousness (questions)	Answers both questions correctly	0
	Answers one question correctly	1
	Answers neither question correctly	2
Level of consciousness (commands)	Performs both tasks correctly	0
	Performs one task correctly	1
	Performs neither task correctly	2
Best gaze	Normal	0
	Partial gaze palsy	1
	Forced deviation	2
Visual	No visual loss	0
	Partial hemianopia	1
	Complete hemianopia	2
	Bilateral hemianopia	3
Facial palsy	Normal	0
	Minor paralysis	1
	Partial paralysis	2
	Complete paralysis of one or both sides	3
Motor arm	No drift	0
	Drift	1
	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
Motor leg	No drift	0
	Drift	1
	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
Limb ataxia	Absent	0
	Present in one limb	1
	Present in two limbs	2
Sensory	Normal	0
	Mild-to-moderate sensory loss	1
	Severe or total sensory loss	2
Best language	No aphasia	0
	Mild-to-moderate aphasia	1
	Severe aphasia	2
	Mute, global aphasia	3
Dysarthria	Normal	0
	Mild-to-moderate dysarthria	1
	Severe dysarthria	2
Extinction and inattention	No abnormality	0
	Visual, tactile, auditory, spatial, or personal inattention	1
	Profound hemi-inattention or extinction to more than one modality	2

Table 5.17. NIH ictus scale.

The NIHSS can be used as a clinical aid to evaluate and document neurological status in acute stroke patients, and it is valid for predicting lesion size and stroke severity. The scale is designed to be a simple, valid, and reliable tool that can be used at bedside from physicians or nurses.
The scale is composed of 15 items for neurologic examination to evaluate the effect of cerebral ischemia on levels of consciousness, language, neglect, visual-field loss, extra-ocular movement, motor strength, ataxia, dysarthria, and sensory loss. Each item on the scale is scored from 3 to 5 with 0 as normal (Table 5.17). Assessment takes less than 10 minutes to complete.

5.4.9 ICH Score

In 2000 Hemphill, working at the University of California, San Francisco (UCSF), developed an outcome risk stratification scale (the ICH Score) based on 5 variables determined to be independent predictors of 30-day mortality. The variables are: GCS, age, localization, volume of hemorrhage, and presence of intraventricular extension of bleeding. Each parameter is assigned points according to the strength of association with outcome. The ICH Score is the sum of the points of the various characteristics (Table 5.18).
The GCS was divided into 3 subgroups (GCS scores of 3-4, 5-12, and 13-15) to reflect the influence of the GCS score on outcome. Age ≥80 years was also strongly associated with 30-day mortality, so1 point was assigned for this situation. Intraventricular hemorrhage (VH), infratentorial origin of ICH, and ICH volume had relatively similar strengths of outcome association. IVH and infratentorial origin of ICH are dichotomous variables with points assigned only when present. ICH volume was dichotomized to <30 and ≥30 cm^3. Thirty cubic centimetres was chosen because it represented a cut-off point for increased mortality in the UCSF ICH cohort.
The ICH Score was an accurate predictor of outcome assessed as 30-day mortality. The range of ICH scores was 0 to 5. No patient with a score of 0 died, whereas all patients with an score of 5 died. Thirty-day mortality rates for patients with 1, 2, 3, and 4 points were 13%, 26%, 72%, and 97%, respectively. This grading scale has been validated worldwide.

	Component	Points
GCS score	3-4	2
	5-12	1
	13-15	0
ICH volume, cm^3	≥30	1
	<30	0
Intraventricular hemorrhage	Yes	1
	No	0
Infratentorial origin of ICH	Yes	1
	No	0
Age, years	≥80	1
	<80	0
Total ICH Score		0–6

Table 5.18. Determination of the ICH score.

5.5 Scale of Evolution, Evaluation of Consciousness in Advanced Stages of Brain Injury Outcome Scales

5.5.1 Glasgow Outcome Scale (GOS), GOS-Extended and Extended Glasgow Outcome Scale of Edinburgh (EEGOS)

The need to evaluate the health outcomes in patients who had suffered brain damage was the major reason that Jennett and Bond developed a 5-point scale that included neurological dysfunction is both intellectual and physical aggression produced by the brain. In 1975 the Glasgow Functional Outcome (GOS) scale was introduced (Table 5.19). It is now a general evaluator of spontaneous and traumatic brain lesions. Researchers working on the development of the scale considered impaired social interaction of the patients as the most important element that could evaluate the final results of the clinical process. For practical purposes, the scale includes 5 categories, ranging from Category I (death of the individual) to category V (good recovery). Category II includes persistent vegetative state, meaning a patient with no cerebral cortex functions and no reasonable behaviour even if it does not necessarily imply that the cerebral cortex is not grossly intact. Category III includes patients with severe disability, defined generically as "conscious but disabled". This implies that such patients are independent for activities of daily living despite cognitive deficits or physical deficits. Category IV includes patients with moderate disability defined as "disabled but independent patient." Such patients can travel by public transport and can perform work in a suitable environment and therefore are independent in these activities, but can present physical and intellectual abilities or personality changes. Category V includes patients with good recovery. Such patients return to their pre-injury activity well without cerebral deficits or with smaller physical or psychological deficits.

The categories in the original scale were considered by some as too broad and therefore felt they could include within the same category patients with significant clinical differences. In 1981 a new version of the scale, the Glasgow Outcome Scale-Extended, was developed which includes 8 points on the scale. Death, vegetative state, complete dependence on others, dependence on others for some activities, inability to return to work or participate in social activities, return to work with reduced capacity, and reduced participation in social activities, good recovery with mild mental and social deficits and good recovery with no deficit. The extended GOS scale (GOS-E) was completed by introducing the implementation of a standardized interview format that improves the reliability and validity of results. Thus, these corrections to the original scale were intended to solve, on the one hand, the low sensitivity to reflect changes experienced by the patient, and on the other, the low reliability due to the absence of a structured interview. Compared with the GOS, the GOS-E has shown greater sensitivity to assess changes due to mild and moderate injuries.

In addition to the above, also worthy of mention is an expanded version of GOS, the so-called extended GOS Edinburgh (EEGOS) and Signorini Hellaell proposed in 1997. It establishes an 8-point scale divided into a summation of functional, behavioural, cognitive and of physical parameters.

The GOS and GOS-E scales were designed to describe the social impact that occurs

Grade	Description
1	Death
2	Vegetative state
3	Severe disability
4	Moderate disability
5	Good recovery

Table 5.19. Glasgow Outcome Scale.

as a result of brain damage of traumatic origin rather than vascular origin. Currently they are still employed in the evaluation of neurologic and mental disabilities resulting from brain damage of any origin. Important to note is how much of the GOS and the GOS-E presents the individual's interaction with his or her environment. So, the dysfunction that may occur in this interaction may be due to psychological, physical deficits, or both.

However, these scales have attracted criticism that they focus more on physical aspects than neuropsychological deficits, and this despite the recommendations of the scales' authors, pointing to the increasing impact of intellectual changes on physical limitations in terms of disability caused by brain damage. These scales have also received criticism that they are difficulty to use especially in children with head injuries.

5.5.2 Revised Neurological Assessment Instrument (NAIr)

The Neurological Evaluation Scale revised uses different elements to assess consciousness. The theoretical basis of the scale incorporates the physiological and neuroanatomical correlates of levels of consciousness based primarily on Plum and Posner´s publications. The scale was originally designed to assess neurological function in adults with acute brain injury. The scale items were selected to capture different aspects of the CNS and assess awareness along a continuum from alertness to coma. The clinical variables reflect the brain state, respiratory rate, pupil size and reactivity, eye movements and motor responses, operationalized nervous system functions, neuroanatomical and physiological correlations that facilitate the identification of pathology. The responses in each category are organized hierarchically, ranging from normal reflexes to the brain and progressive dysfunction of brainstem structures. The level of awareness concerning the characteristics of degree of alertness related to the brainstem reticular formation and adjacent structures ranging from the half-bridge to the hypothalamus. This level cognitive functions and emotional concerns have significant roles in attention, memory and executive functions. Eye opening, counselling skills and communication, and behavioural responses reflect a measure of vigilance. The behaviour of localization involves the integration of functions of the brainstem and cerebral cortex of both hemispheres, the spinal cord and peripheral structures. This involves the integration of motor responses and eye functions of the pupils. The original scale consisted of 10 items. The selection of these criteria was based on strong correlations with the GCS and predictive validity criteria with the GOS.

Based on the nature of consciousness and the need for establishing a minimum alert sequence to apply the scale, one must first examine the response of eye opening, eye items, and the contents of alertness, evaluating the motor responses in the last phase. When used by trained observers, evaluation with the NAIr takes <3 minutes. The evaluation study of the NAIr scale included patients with conditions of different etiology. The study population was 39 patients, of which 18 presented with stroke, 12 with brain tumours, 7 with metabolic encephalopathies, and 2 with TBI. The mean age was 60 years (range, 20-87). The authors reported no significant differences between patients with structural or metabolic injury and suggested that the instrument is valid for the evaluation of both types of patients. They recommend that the items to be included are motionless pupil in mid-position as the lowest score of the scale in the category of ocular motility, which is associated with a lesion located in the lateral pontine tegmentum. The NAIr is a summative scale, with scores ranging from 8-37, with a minimum of 8 (no answers) to 37 (oriented patient). The scale items take the values specified in Table 5.20. The scale combines 8 items reflecting motor activity, verbal and brainstem function. The

results show that the NAIr is a valid scale (r=0.9189, Pearson coefficient), reliable (r=0.9057, Pearson coefficient) and easy to administer, in the assessment of awareness levels in adults with structural or metabolic brain injury.

Variable	Description	Score
Eye opening	Spontaneous	5
	Voice	4
	Voice and touch	3
	Pain	2
	Without response	1
Pupils reactivity	Light	3
	Slow	2
	No reactivity	1
Verbal communication (orientation)	Appropriate language, orientated	5
	Appropriate language, disorientated	4
	Confused, inappropriate words	3
	Inappropriate sounds	2
	Without response	1
Differential size of the pupils in millimeters	1 mm	5
	2 mm	4
	3 mm	3
	4 mm	2
	>4 mm	1
Eye motility	Ocular motility	5
	Spontaneous fixations to order	4
	Horizontal or vertical nistagmus	3
	Conjunction with lateral deviation	2
	Lack of coordination of both eyes	1
Motor response (arms)	Normal	5
	Does not obeys to commands and doesn't localize	4
	Flexion	3
	Extension	2
	Without response	1
Motor response (legs)	Normal	5
	Does not obeys to commands and doesn't localize	4
	Flexion	3
	Extension	2
	Without response	1
Responses to verbal or tactile stimulation	Oriented and recognizes stimuli	5
	Scared, attempts to locate the stimulus source	4
	Restless	3
	Low activation, subtle movements	2
	No answer	1

Table 5.20. NAIr scale.

5.5.3 Behavioural Assessment Scale (NAS)

The Behavioural Assessment Scale was developed to measure the range of behavioural functions ranging from alert to coma. The authors assessed 60 patients under the effect of sedation for maxillofacial interventions. The scale was compared with the GCS and the key test of WAIS numbers. Statistical analysis showed: a Pearson correlation coefficient of 0.97 ($p < 0.05$) for interobserver reliability, correlation coefficient, -0.90 ($p < 0.05$) for the correlation between the NAS and the GCS; a Pearson correlation coefficient -0.62 ($p < 0.05$) for the correlation between the NAS and the key test of the WAIS numbers. The latter was taken as a measure of behavioural validity. The scale is reliable and valid. The NAS differentiates between two levels of sedation: high and mild sedation. Furthermore, the scale discriminates between different levels of sedation in patients with mild sedation.

In its standard form, the scale is a brief interview conducted by an observer to evaluate four categories of responses: alert/sedation, orientation, speech and motor responses. If the patient is asleep, the evaluator tries to wake him by calling him by name in a normal tone. If the patient does not respond, he is woken up. If the patient is awake, the observer must induce pain by placing pressure on a fingernail with a pencil or other hard object. Otherwise a response to painful stimulus can be elicited by pinching the trapezius muscle in the side of the base of the neck. During the interview, the patient is asked: his or her name, where he or she is including the name of the city, and the date, including year, month and day of the week. The question of why he or she is here evaluates

Item	Description	Score
Alertness/sedation (defects in the perception of the environment, drowsiness)	Not present, awake and alert	1
	Alert patient but slow, sleepy voice answered	2
	Asleep, arousable to touch and voice	3
	Arousable only to pain	4
	Not arousable to pain	5
Level of orientation (confusion or loss of appropriate personal associations, spatial and temporal)	Normal, facing the person, space and time	1
	Oriented to person and place, but not in time	2
	Oriented in person, but not in place and time	3
	Oriented or not the person, place and time, but awake	4
	No answer	5
Level of communication (poor articulation, pronunciation or substitution of sounds that affect the intelligibility regardless of context)	Normal	1
	Forced speaking with pronunciation errors but intelligible	2
	Forced speaking with moderate errors even if some words are intelligible	3
	Unintelligible speaking, poorly pronounced	4
	No answer	5
Psychomotor level (loss of spontaneous movement, decreased facial expression, decreased emotional tone)	Normal	1
	Moderate speed and slow movements, blunted affect	2
	Movements and moderate to severely speed slow, low energy and oscillation of affection	3
	No spontaneous movements	4

Table 5.21. NAS evaluation scale.

aspects of speech, and consistency of thought. The patient is ask to repeat the phrase "neither yes or no, but not" taken from the Spanish version of the Folstein Mini Mental State Exam.

The NAS (range, 4-19) is the sum of the scores for each of the 4 categories that the scale assesses. A score of 19 represents non-response for each category. Of the 4 categories, the study of the scale, orientation highlights (confusion or loss of ability to be personal, spatially and temporally). The categories alert, oriented and speaks explain 97% of the variance. The category of motor responses is only 2%. That is, of the 4 categories, 3 seem essential to the overall score. The scale's authors suggest that the NAS may be appropriate to the extent that it measures changes in the levels of neurobehavioral functions of patients during the recovery process and monitors them (Table 5.21).

5.5.4 Ranchos Los Amigos Levels of Cognitive Functioning Scale

Cognitive Scale developed by the Rancho Los Amigos (LOCF) is used to classify patients with brain injury according to their behaviour. It is based on the deterioration of the brain capacity to process information after brain injury. Generally, as a result of severe brain injury there is unusual behaviour and difficulty in self control. This scale describes the stages of recovery from coma to independent functioning on 8 levels, ranging from lack of answers to an patient awake, oriented, and resolved with appropriate behaviours. The scale takes the values shown in Table 5.22. It has good properties of concurrent validity and test-retest unreliability. However, it does not reflect small changes in cognitive functions and has very broad categories where a patient can be in several at one time. Another drawback of the scale is that it does not measure physical function.

Level	Response
I	No response
II	Generalized response
III	Localized response
IV	Confused-agitated
V	Confused-inappropriate
VI	Confused-appropriate
VII	Automatic-appropriate
VIII	Purposeful-appropriate

Table 5.22. **Ranchos Los Amigos Scale of Cognitive Functioning.**

5.5.5 Disability Rating Scale

The Disability Rating Scale (DRS) assesses 8 items from alertness, awareness and capacity of motor responses to cognitive skills for self-care and personal independence and social adaptability. Several studies have shown its reliability, validity and good yield. It is classified into 10 levels of disability: no disability, disability, mild, moderate, moderately severe, severe disability, severe, vegetative state, severe vegetative state patient died. The scale variables are shown in Table 5.23.

5.5.6 Coma/Near-Coma Scale

Coma/Near-Coma (CNC) scale was designed to measure small clinical changes in patients with severe brain injury of traumatic and nontraumatic origin, with features close to the vegetative state or in this state. Many of the patients in a vegetative state have a stable phase (in terms of clinical rehabilitation), some are better and others are worse or die. A scale that reflects small changes has a prognostic value and views the outcome of

the disease as the great value to all involved in the rehabilitation of these patients. Moreover, this scale is helpful in making therapeutic decisions by the patient management clinical team, in addition to funding agencies responsible for the care and rehabilitation treatment of patients. The scale was intended to be an extension of the CNC lev-

Variable	Description	Score
Eye opening	Spontaneous	0
	To speech and/or sensory stimulation	1
	To pain	2
	None.	3
Communication ability	Oriented	0
	Confused	1
	Inappropriate	2
	Incomprehensible	3
	None	4
Motor response	Obeying	0
	Localizing	1
	Withdrawing	2
	Flexing	3
	Extending	4
	None	5
Feeding (cognitive ability only)	Complete	0
	Partial	1
	Minimal	2
	None	3
Toileting (cognitive ability only)	Complete	0
	Partial	1
	Minimal	2
	None	3
Grooming (cognitive ability only)	Complete	0
	Partial	1
	Minimal	2
	None	3
Level of functioning (physical, mental, emotional or social function))	Completely Independent	0
	Independent in special environment	1
	Mildly dependent-limited assistance (non-resid – helper)	2
	Moderately dependent-moderate assistance (person in home)	3
	Markedly dependent-assist all major activities, all times	4
	Totally sependent-24 hour nursing care	5
"Employability" (as a full time worker, homemaker, or student)	Not restricted	0
	Selected jobs, competitive	1
	Sheltered workshop, non-competitive	2
	Not employable	3

Table 5.23. Disability Rating Scale (DRS).

els Disability Scale with more discriminative power in patients in a vegetative state. In fact, it was initially recommended for use in patients with scores between 21 and 26 on the Disability Scale. The scale is divided into 5 levels (no comma, near-coma, coma, moderate, severe and extreme) as is the score for the 11 items that compose it. These items reflect the observations of sensory and perceptual reflex responses.

The information provided on this scale is useful for reducing the risk in advance to guide patients to lower levels of care or withdraw from more intense rehabilitation programs. The scale was designed to provide rapid assessment of reliable and valid progress or deterioration in patients with severe brain injury. In the evaluation of coma and vegetative states, the rehabilitation staff reports that the scale is useful for discriminating between patients with low or very low awareness and those who will progress beyond these levels. The scale is easy and quick to apply. It allows the omission of some items such as the vocal response in patients with a tracheotomy, without losing reliability and ability to predict clinical changes.

For each variable a small scale test is performed with the patient, some of which require up to 5 trials. Each scale variable is assigned a score of 0, 2 or 4. The score on the scale indicates classify the patient according to 5 levels of consciousness: no comma, near-coma, coma, moderate, and severe. The scale evaluates the following: responses to auditory stimuli, verbal orders, a light stimulus for light stimulus orientation, defence reflex, olfactory responses in orientation to tactile contact, nasal reflex, moderate pain, strong pain, and vocalization.

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Section 2.
Neuromonitoring

6 Neuroimage Monitoring in the Management of Neurocritical Care Patients

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6.1 Introduction

The development of the CT scanner was not only a milestone in medical diagnoses, but also a key piece in the development of modern neurology. The British engineer Godfrey Newbold Hounsfield was the director of the team that developed the first applicable CT scanner prototype. In 1967, Allan M. Cormack published the first relevant paper that was the point of departure for the works of Hounsfield, who designed the first feasible CT scanner in 1972. That same year, Hounsfield put into operation the first CT scanning device that combined electronic calculation techniques and X-ray procedures, ushering in the most important advance in radiological diagnosis since the discovery of X-rays in 1885 by the German physicist Wilhelm Konrad Roentgen.

For the machine to work appropriately, the body part under study had to be completely immersed in water. Early CT studies took almost 24 hours to complete. In 1973 the first cerebral CT scanner in a clinical setting was installed at the Mayo Clinic in the United States. In 1979 Hounsfield received recognition for his research with the Nobel prize in Physiology or Medicine, along with the Most Excellent Order of the British Empire in 1979 for the invention of the CT scan.

The clinical impact of CT scanning increased over the years, transforming the concept of the intervening diagnosis based on image findings. As it gained application in other areas of medicine, it revolutionized neurology and neurosurgery and launched the development of new areas of knowledge such as neurocritical care medicine.

The physics of CT is similar to that of conventional radiology: the radiated X-rays cross the human body; the radiation is visualized on a film and measured with a specific device. Unlike conventional radiology, radiation in CT is not collected on a radiographic film but by radiation detectors. The rotational motion of an X-ray tube around the human body, while the radiation detector turns in the opposite direction, makes the human anatomy visible. The radiation detector consists of a measurement system that quantifies the X-ray intensity the organism tissues have absorbed.

The basic elements of a CT scanner are: a bed where the patient is positioned; an X-ray generator (gantry) where the X-ray tube is located; the electronic detectors that measure the radiation intensity; and a computer that converts into images the radiation measured by the detectors.

The radiation received by the detectors is recorded by an analogical-digital converter that turns it into a binary signal for processing by a computer. Collimation of the system allows for varying the thicknesses of the slices. The radiation absorption coefficients

of the body tissues are associated to each other in pixels along a grey scale which are shown in a radiological image.

Each axial slice is composed of a number determined by volumetric elements with specific radiation absorption. Each volumetric element, called a voxel, is composed of three-dimensional elements. On the scanner screen the image is reproduced in two-dimensional elements called pixels.

The intensity of radiation absorption is expressed in Hounsfield units or HU (unit of radiation absorption). There are 2000 levels of radiation absorption, ranging from the air to the bone (maximum and minimum radiation absorption; for example, water absorbs 0 HU). In CT scans of the intracranial structures in a healthy individual, the radiation absorption is between 0 and +50 HU. Figure 6.1 presents the scale of radiation absorption of various different intracranial structures. The cerebral white matter absorbs approximately +25 HU, grey matter absorbs +40 HU, while the cerebrospinal fluid absorbs between 0 and +5 HU.

In pathological situations, recent intracranial hematomas may absorb +70 HU or more due to their hypercellularity, the ferric component of hemoglobin, and the concentration of calcic elements. Therefore, the radiation absorption is high and shows up as a hyperdense image. In ischemic or edematous areas of the brain, these regions have a lower radiation absorptive capacity, with absorption of +20 HU or less. Therefore, the range of values of Hounsfield units that we should select to study intracranial physiological structures must be between 0 and +50 HU, including in this exam the cerebrospinal fluid, normal brain, or hypodense brain (as in brain damage of ischemic origin). If the diagnosis includes the possible presence of hemorrhagic lesions, the range of HU should be set between 0 and +100 HU. Within this range, hemorrhagic injuries can be observed as images with less radiological density than skull bone.

The range of HU values is called a "window." In addition, the computer system enables the operator to decide which anatomical structure corresponds to the grey scale medium (between black and white; a scale of 40 levels of grey are easily perceptible to the human eye). If the operator decides that the medium average is a normal cerebral tissue (around +45 HU), the grey matter can be observed as a hyperdense image. Inversely, areas such as the white matter or injuries with larger water content, as in brain edema, can be observed as hypodense images.

Another relevant technical aspect of CT scanning is the orientation of the slice to the major axis of the body. Before selecting the slice orientation, we should establish the diagnostic suspicion and the potential intracranial location of the lesion. In general, the standard slice orientation for acute neurocritical patients should be the cantomeatal orientation, which follows an imaginary line from the external auditory channel to the eye. Other orientations such as the neuro-orbitary, the biauricular orientation, and the occipital-temporal orientation can also be useful in the diagnosis of other types of intracranial lesions in neurocritical patients.

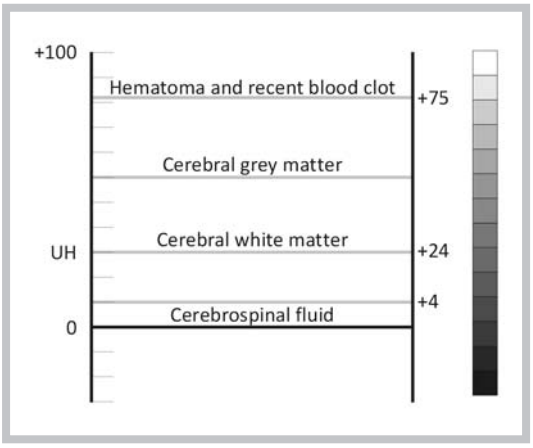

Figure 6.1. **Scale of absorption of intensity of intracranial structures expressed in Hounsfield Units (HU).**

A standard CT scan will include a scout view (simple X-ray image in a sagittal section) and a series of CT slices on the axial axis. In CT studies in critical emergencies,

4-8 mm thickness slices in the supratentorial region and 4 mm slices in the posterior fossa are advisable; however, intravenous contrast material should not be used unless brain abscess, isodense subdural hematoma or other lesions are suspected.

6.2 CT in Head-injured Patients

A significant advance in the diagnosis of consequences of head injury was the ability to scan and monitor intracranial pressure. In the early 1980s the usefulness of CT in head-injured patients was proved not only because of the efficacy of the CT scan to demonstrate the presence of hemorrhagic intracranial lesions amenable to surgical removal, but also its capacity to evidence other kinds of lesions with prognostic relevance.
The technical aspects of CT in patients with head injuries does not substantially differ from those of other neurological critical situations: a window between +90 HU and +100 HU; centre in +40 HU; cantomeatal orientation; 4-8 mm slices in the supratentorial region; and 4 mm slices in the infratentorial region, without the use of intravenous contrast material. A scout view of the cervical spine should be also included. A CT scan with a bone-like window must complete the radiological exam in order to diagnose the possible presence of injuries or cranial fractures. The frequent association of ffacial injuries with head injury, makes advisable a facial CT scan, including paranasal sinus.
There are several approaches to interpreting the CT scan of patients with head injury in the acute phase. The most widely used classification of CT scan findings in such patients is the Traumatic Coma Data Bank classification (TCDB) (Table 6.1). According to this scheme, injuries are categorized into two basic groups: 1) diffuse lesions, including low-volume intracranial space-occupying lesions and diffuse brain damage prevailing over the focal damage; 2) high-volume intracranial space-occupying lesions.
The first group comprises predominantly diffuse injuries or predominantly focal lesions without significant mass effect (known as diffuse brain injury) and is further subdivided into four categories. In high-volume focal lesions (volume >25 ml), mass effect can be due to purely hemorrhagic lesions or mixed density lesions. These injuries are grouped into two categories depending on whether they can be surgically removed or not.
The TCDB classification takes into account a direct relationship between four diagnostic categories of diffuse brain injury and the risk of death. Similarly, when the TCDB system is used together with the traditional classification of intracranial hemorrhages (epidural hematoma, subdural hematoma, intracerebral hematoma), the risk is higher if accom-

Category	CT scan
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen
Diffuse injury II	Cisterns present with midline shift 0-5 mm and/or lesion densities present; no high or mixed density lesion >25 ml; may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0-5 mm; no high or mixed density lesion >25 ml
Diffuse injury IV (midline shift)	Midline shift >5 mm, no high or mixed density lesion >25 ml
Evacuated mass	Any lesion that can be surgically evacuated
Non-evacuated mass	High or mixed density lesion >25 ml that cannot be surgically evacuated

Table 6.1. **Classification of CT findings according to the Traumatic Coma Data Bank classification.**

panied by intracranial hypertension. According to the TCDB's designers there is a direct relationship between the Glasgow Coma Scale (GCS) score (mainly its motor component) and categorization according to the TCDB classification. The TCDB authors admit that the scheme's categories are arbitrary; however, they underline the high prognostic value of the four groups of diffuse brain injury the classification distinguishes (Table 6.1):

- CT scan normal for age and previous health status (diffuse brain injury I).
- Pathological CT scan with mixed or low-volume hypodense lesions (<25 ml) without compression of the cisterns or significant midline shift (0-5 mm) (diffuse brain injury II).
- CT scan with or without injuries similar to diffuse brain injury type II but in which there is compression or absence of the cisterns (diffuse brain injury type III or diffuse injury with cerebral swelling).
- Pathological CT scan with mixed or low-volume hypodense lesions (<25 ml) but with midline shift >5 mm (diffuse brain injury IV or diffuse brain injury with midline shift).

The TCDB classification has been criticized for its fundamentally surgical orientation, omitting in the analysis of the CT scan some injuries that cannot be surgically treated but with a known impact on prognosis.

In the TCDB classification, diffuse axonal injuries localized mainly next to the midline are considered as small-volume hemispheric injuries, in spite of the differences in clinical prognosis. Similarly, brainstem injuries (of significant relevance for prognosis) are not included. Nevertheless, the TCDB classification is universally accepted and has become a standard reference for CT evaluation of traumatic brain injury. On the other hand, one of the advantages of the TCBD classification is its high level of interobserver agreement, where the degree of concordance in mass lesions (concordance, 0,94-0,91) is higher than in diffuse brain injury (categories I-IV) (concordance, 0,71-0,67).

Some of the limitations of implementing the TCDB classification have been overcome in daily clinical practice. Traumatic subarachnoid hemorrhage, which has a recognized impact on prognosis, is included among type II lesions; and significant brainstem injuries are considered as unclassifiable injuries in the TCDB system.

When using the TCDB scheme it is advisable not to classify mass injuries in numeric expressions as in diffuse lesions, which definitely fall under diffuse brain injuries I-IV. High-volume mass injuries do not have a numerical categorization.

It should also be remembered that the TCDB system is a dynamic classification and can therefore vary in each patient depending on the clinical course. Accordingly, if the volume of a diffuse brain injury type II increases, it should be reclassified as a mass injury (evacuated or not evacuated).

In patients with head injury, interpretation of the CT scan should be extended beyond categorization by the TCDB scheme to include other levels of analysis. From a pathophysiological perspective, study of the CT scan of a head-injured patient should include the search for the presence or absence of anatomic structures. This first exam should include a revision of normal cerebral structures and the normal location and amount of cerebrospinal fluid. Only thereafter should the analysis of pathological images start. Table 6.2 illustrates a systematic protocol for interpreting pathological lesions on the CT scan. The protocol includes the following lesions: 1) high-volume hemorrhagic injuries and, therefore, potentially surgically evacuable lesions; 2) hypodense lesions of different cause (hypodensities of vascular distribution, simple contusions, etc.); 3) single or multiple injuries, frequently of low volume and usually associated with diffuse axonal injury. This step in the description of lesions on the CT scan must be followed by a second step in which the presence or absence of pathophysiological conditions frequently associated with head injury (e.g., intracranial hypertension, cerebral herniation or others) must be inferred.

Hemorrhagic injuries that are potentially surgically removable	• Subdural hematoma • Epidural hematoma • Hemorrhagic contusion/intraparenchymal hematoma
Hypodense space-occupying injuries	• Simple contusion • Hemispheric swelling • Hypodensities with vascular distribution
Lesions frequently correlated with axonal injury	• Injury of the corpus callosum • Injury of the brainstem/mesencephalon • Lesions of the basal nucleus • Intraventricular hemorrhage • Subarachnoid hemorrhage • Injuries of the grey matter/white matter interface

Table 6.2. **Initial data to analyze on the CT scan of head-injured patients.**

6.2.1 Potentially Removable Hemorrhagic Lesions

There are several types of hemorrhagic injuries consequent to head injury, each of which with different clinical and prognostic meanings. Hyperdense lesions, as an extra element in the intracranial content, have been frequently associated with space-occupying mass lesions, and intracranial hypertension by analogy to neoplasms. Often, the increased volume accompanying such lesions after head trauma will lead to intracranial hypertension. Another point to consider is that the presence of such a lesion is a marker for the presence of other lesions, less eloquent on the CT scan but with relevant prognostic significance. Table 6.3 lists hemorrhagic injuries commonly detected in the CT scan of head-injured patients.

- Hematoma epidural
- Subdural hematoma
- Hemorrhagic contusion
- Intracerebral hematoma
- Hemorrhagic injuries associated with diffuse axonal injury:
  - Hemorrhage of the corpus callosum
  - Capsular hemorrhage
  - Intraventricular hemorrhage
- Subarachnoid hemorrhage

Table 6.3. **Most frequent hemorrhagic injuries after traumatic brain injury.**

6.2.2 Epidural Hematoma

Epidural hematoma is an extra-axial hemorrhage in the external region of the dura mater. It carries two main risks: it can evolve into a rapid-growing intracranial lesion and it may reach a very high volume. Subsequently, epidural hematoma carries a high risk of intracranial hypertension, with the consequent risk of compression of cerebral structures of clinical (mesencephalon, brainstem) and functional importance. At attenuation values of approximately 50-100 HU, the morphology of an epidural hematoma is typically a biconvex lens (Figure 6.2), generally with clear-cut borders and usually adjacent to a fracture

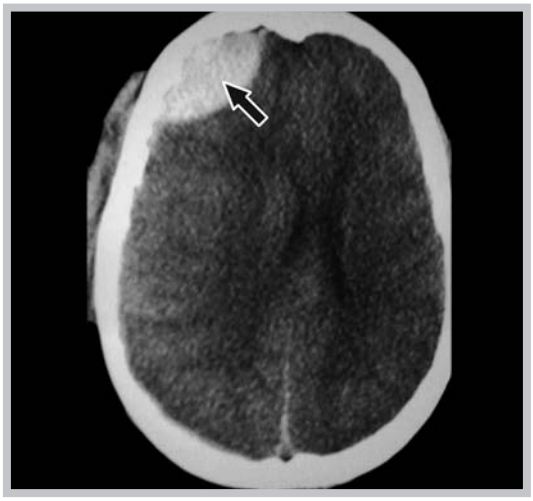

Figure 6.2. **Frontal epidural hematoma. Morphology of biconvex lens (black arrow). Midline shift.**

Figure 6.3. **Extensive right parieto-occipital subdural hematoma. Typical morphology (black arrow). No midline shift.**

line. The density is frequently homogenous. Usually unilateral, it can increase substantially in volume, compressing the ipsilateral ventricle and shifting the septum pellucidum significantly.

The presence of a heterogeneous epidural hematoma suggests active bleeding. The most frequent location is the temporoparietal region (75% of epidural supratentorial hematomas occur next to the temporal bone). In most cases, epidural hematoma results from damage of the meningeal arteries. Less frequent localizations are the frontal and occipital regions (8 and 5% of all epidural hematomas, respectively). Posterior fossa epidural hematomas have a higher incidence than subdural or vertex hematomas and suggest damage to the sagittal venous sinus or lateral venous sinus.

Besides morphology, other data can aid in the differential diagnosis between epidural hematoma and subdural hematoma. If a hematoma crosses major sutures of the skull and extends to both sides of the tentorium, the probability of an epidural location of the hematoma is higher than subdural. The coexistence of ipsilateral epidural and subdural hematomas is not uncommonly associated with epidural hematoma; however, much more frequent is epidural hematoma and contralateral subdural hematoma, which results from blow and counterblow injuries.

In most cases, epidural hematoma is the only intracranial lesion observed after traumatic brain injury. Its association with significant intra-axial lesions is less than 15%. Prompt surgical evacuation of epidural hematoma is normally associated with good prognosis. Irrespective of the surgical delay in this type of injury, a correlation exists between delay and increased mortality. Similarly, epidural hematomas >2 cm, with areas of different densities (suggestive of active bleeding) and midline shift are usually associated with poor outcome unless promptly removed.

6.2.3 Subdural Hematoma

Subdural hematoma may be considered similar to epidural hematoma because it arises in adjacent anatomical structures; however, it carries a different prognosis and pathogenetic meaning. There are small superficial cerebral veins that flow toward the large venous sinuses, crossing the subarachnoid and the subdural spaces. These veins are relatively straight lines and very susceptible to rotation, deceleration and traction motions that occur in traumatic brain injury. Tearing of bridging veins is the most common cause of hematoma in the subdural space. This virtual space is only evident due to the mechanism of increased pressure that allows it to be revealed. A less frequent mechanism of subdural hematoma is cerebral contusion adjacent to the subdural space, with bleeding into the subarachnoid-pia mater space.

Occasionally, subdural hematomas can be observed after rupture of a large intracerebral hematoma in the subdural space. Although a subdural hematoma can arise in the cranial region that has been directly hit, it is more commonly found in the counterblow re-

gions. Typically, the morphology of subdural hematoma on a CT scan is a hyperdense lesion next to the bone, with a lens convergent-shaped opacity of homogenous density; at high attenuation it appears on the CT scan with less neat borders than an epidural hematoma. Acute subdural hematomas (Figure 6.3) are more frequently located at a brain convexity, mainly in the parietal region and less frequently in the frontal lobe and occipital area. Sometimes, subdural hematomas can be difficult to identify on the CT scan due to subjacent cranial bone. In order to minimize this effect, the signal amplitude and the CT scan window need to be adjusted to better identify the injury.

The second most frequent location of subdural hematoma is the tentorium, evidenced as an asymmetry in the typical "Y" morphology of the tentorium surrounding the vermis. Less frequent is an interhemispheric location (due to laceration of the veins draining into the sagittal sinus). Interhemispheric subdural hematomas are frequently associated with coagulopathy or platelet dysfunction. It is not unusual to observe acute subdural hematomas of atypical morphology. Sometimes, acute subdural hematomas of heterogeneous density, with a mixture of low and high attenuation areas, suggest active bleeding or a subarachnoid leak into the subdural space. Frequently, hyperacute subdural hematomas do not present a morphology typical of subdural hematoma, but a lens-shaped form instead. Although the exact mechanism underlying this morphology is unclear, intense bleeding (minutes after the accident) and blockage of the subdural space due to arachnoid adherences are thought to be involved. One characteristic of acute traumatic subdural hematoma is its frequent association with other intracranial lesions. Posttraumatic acute subdural hematoma is seldom an isolated lesion. Like single traumatic intracranial lesions, posttraumatic acute subdural hematomas are not usually associated with relevant trauma, anticoagulant or anti-platelet aggregation therapy. In more than 80% of traumatic injuries, subdural hematomas and intracerebral lesions are adjacent, the latter sometimes involved in the genesis of the subdural hematoma. This is one of the reasons why traumatic subdural hematomas have a worse prognosis than epidural hematomas. The poor prognosis of subdural hematoma is mainly due to two factors: mass effect (surgical evacuation in the first 4 hours after trauma carries a better prognosis); and its association with other intracranial lesions that result in compression of the lateral ventricles, midline shift, and intracranial hypertension among others.

6.2.4 Cerebral Contusion and Cerebral Hematoma

Cerebral contusion is the second most frequent intracranial lesion after head trauma. Cerebral contusion can be defined as a cerebral lesion due to a direct blow to the head. CT scans of cerebral contusions show images of a mixture of hypo- and hyperdensities due to dispersed multiple petechial injuries in the damaged area, associated with areas of edema and/or tissue necrosis (Figure 6.4). Depending on its location and the mechanism of injury, cerebral contusions can be classified into different groups. When the contusion results from the direct effect of bone impact on the brain, the contusion underlies the

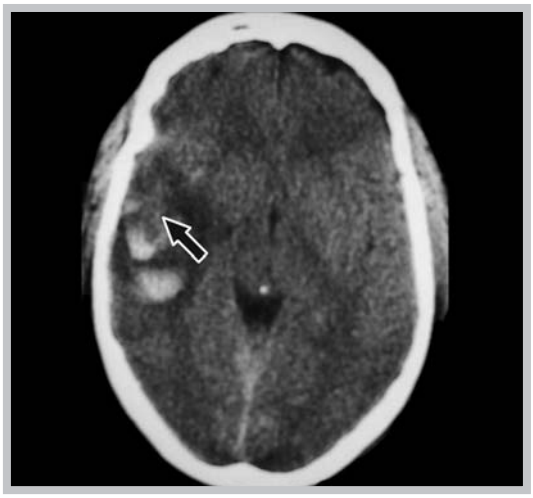

Figure 6.4. **Image of mixed contusion in the right temporal lobe (black arrow).**

bone. Cerebral contusions resulting from counterblow may be located in the contralateral region of impact. The precise mechanism of injury is not clear; however, the gradients of negative pressure generated during the blow may play an important role.
Although cerebral contusions can occur in any part of the brain, the regions most often affected in traumatic brain injury are the inferior areas of the frontal and the temporal lobes. This is probably due to the regions sliding over the surface of the anterior and temporal fossa during sudden acceleration/deceleration accompanying the trauma. The regions most often involved are the brain areas subjacent to bones (inferior frontal bone, petrosal crest, etc.). The parasagittal region is also frequently damaged, whereas the cerebellum and occipital areas are less often affected.
Intracerebral hematoma is seen on the CT scan as a hyperdense intracerebral area with sharp borders at an attenuation between +70 and +90 HU. If an intracerebral hematoma is observed on the CT scan, it has to be >25 ml in volume to be included in the TCDB classification as a significant mass lesion. This value is arbitrary and probably reflects more a distinction of surgical relevance rather than a neuroanatomical difference. The CT scan can show key characteristics of an intraparenchymal cerebral hematoma to aid in deciding whether to remove the hematoma. Besides volume, tomographic data need to be taken into consideration in hematoma removal. A midline shift of >7 mm is a relevant element to support the decision for surgical removal. The location of cerebral contusions is also important when establishing the indication for surgery. Voluminous hemorrhagic contusions in the temporal lobe compressing the basal cisterns, even without midline shifting, correlate with sudden deterioration in consciousness. Therefore, this kind of cerebral contusion must also be considered as potentially surgically removable.

6.2.5 Increase in Cerebral Volume After Traumatic Brain Injury

Increased cerebral volume due to either brain edema or a rise in cerebral blood volume causes the cerebrospinal fluid (CSF) to move out of the skull toward the spinal spaces. On the CT scan the increase in cerebral volume is mainly shown by the absence of CSF in its usual position. Absent or decreased CSF on the CT scan may not only be due to brain edema but it can be also associated with an intracranial increase of the intravascular compartment, which frequently occurs in posttraumatic cerebral hyperemia.

Figure 6.5. **Image suggesting intracranial hypertension (black circle), with absence of the ambiens cistern.**

For the tomographic diagnosis of an increase in cerebral volume, the following data are relevant: absence or decrease in the size of the ambiens cistern, absence or decrease in the size of the third ventricle, absence or decrease in the size of the lateral ventricles, absence of perihemispheric CSF (Figures 6.5 and 6.6), and/or decrease in the size of the cistern of the great cerebral vein of Galen.
Some practical aspects should be considered before evaluating the absence of CSF as a clue to increased cerebral volume. When estimating the size of the lateral ventricles, the patient's age should always be taken into account: CSF volume is lower in the lateral ventricles of young

patients. The absence of perihemispheric CSF is a sensitive finding to establish the suspicion of increased cerebral blood volume; however, this high sensitivity is accompanied by a low specificity because the cerebrospinal spaces can be reduced by hypoventilation and/or other mechanisms that will transiently increase cerebral blood volume.

In contrast, the decrease or absence of the basal cisterns and a decrease in the size of the third ventricle (specifically defined as a relevant element suggestive of type III injury in the TCDB classification) are the most specific indicators of an increase in cerebral volume due to a pathological mechanism. Analysis of the cistern of the internal cerebral vein deserves special mention, as it is often present even in patients with intracranial hypertension and cerebral herniation. Its absence is highly suggestive of large supratentorial masses not always clearly visible on the CT scan, like subdural hematomas close to the vertex.

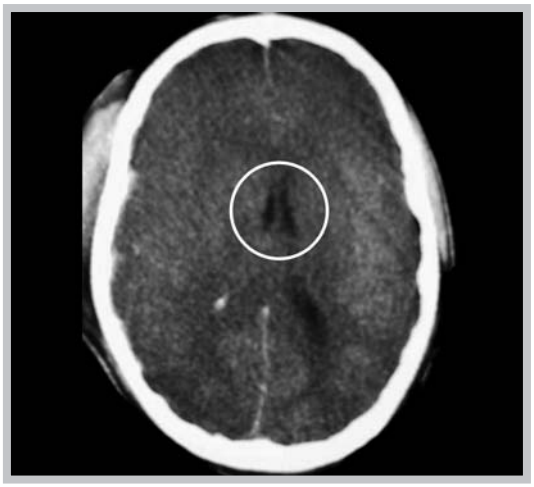

Figure 6.6. **Generalized increase in cerebral volume. Absence of the cerebral sulci. Decrease in the size of the lateral ventricles (black circle).**

6.2.6 Injuries Compatible With Diffuse Axonal Injury

The term diffuse axonal injury was coined by S.J. Strich in 1956 to describe a series of injuries, usually of small volume, subsequent to head injury and sometimes associated with severe neurological dysfunction and occasionally irreversible. Some authors hold that there is a certain degree of axonal injury in all severely head-injured patients. The predominant locations of diffuse axonal injury are: the parasagittal white matter close to the grey matter; the corpus callosum; the pontine-mesencephalic union; and the cerebellar peduncles. In white matter damage, the most frequent location is the frontal region and periventricular regions of the temporal lobes, normally next to the temporal horn of the lateral ventricle.

Adams classifies axonal diffuse injury into three grades of severity: mild, moderate and severe. In this classification scheme, mild injury (grade I) is characterized by microscopic changes in the white matter of the cerebral cortex, the corpus callosum, the brainstem and occasionally the cerebellum. Moderate diffuse axonal injury (grade II) is defined as the presence of evident focal changes in the corpus callosum. Severe axonal diffuse in-

Degree	Description
I	Evidence of axonal injury consisting of small lesions in the white matter of the cerebral hemispheres, the corpus callosum, the brain stem and, occasionally, the cerebellum
II	Focal macroscopic lesions in the inferior part of the corpus callosum, sometimes on one side of the midline but extending over several centimetres rostrocaudal, and in the white matter of the cerebral hemispheres
III	I and II degree lesions may be present, as well as evidence of hemorrhagic focal injuries in a dorsal lateral quadrant of the mesencephalon or the superior third part of the protuberance

Table 6.4. **Morphologic classification of diffuse axonal injury based on Gennarelli's classification.**

jury (grade III) comprises grade II lesions plus injuries in the dorsolateral region of the brainstem, usually in the superior cerebellar peduncles.

Table 6.4 shows the modified Gennarelli's classification system. Gennarelli's classification is based on anatomical findings; however, it is the basis for radiological approaches to the classification of diffuse axonal injury. In addition to the elements included in Gennarelli's classification, injuries in the anterior commissure, the septum pellucidum and the fornix are frequently associated with corpus callosum lesions.

The principal mechanism involved in diffuse axonal injury is the shearing of the axonal structures or the stretching of these regions in which axons are predominant. Diffuse axonal injury is generated by rotation and acceleration/deceleration movements of the skull, which stretch and break the nerve fibers. It is accepted that the severity of diffuse axonal injury is higher after oblique and lateral impacts of the head than after a sagittal impact.

CT is not the best radiological technique for the diagnosis of diffuse axonal injury. Often, small hypodense lesions will not show up on a CT scan because the lesions present an attenuation indistinguishable from normal cerebral tissue. Nevertheless, the CT scan can be useful to suspect the existence of diffuse axonal injury as much for radiological direct signs as indirect signs. The CT scan can more easily reveal diffuse axonal injuries with hemorrhagic components, and it is less sensitive in the diagnosis when radiological hypodensity predominates. Since most axonal diffuse injuries are small lesions and less than 30% of them are hemorrhagic, CT is not the best method for their diagnosis.

The most frequent locations of diffuse axonal injury are the lobar white matter, the corpus callosum, and the brainstem. The junction between the grey matter and the white lobar matter, because of the abrupt change in tissue density, is the zone where axonal diffuse injuries are most frequently observed. They appear as small ovoid lesions with their major axis directed towards the axon affected. This type of injury has a certain predilection for the parasagittal region.

The area with the second highest incidence of axonal diffuse injury is the corpus callosum and the splenius zone in particular. The two hypotheses that reasonably explain this localization are: 1). The direct impact of the falx cerebri on the corpus callosum; 2). The rotational forces transmitted to the corpus callosum.

Diffuse axonal injury in the corpus callosum most often appears as a focal lesion, midline placed, frequently situated on the splenius and less often in the body or the genu of the corpus callosum. Occasionally, it is accompanied by intraventricular bleeding due to rupture of subependymal veins.

Diffuse axonal injury can be accurately diagnosed using magnetic resonance instead of CT. Magnetic resonance is sensitive enough to detect hemorrhagic and non-hemorrhagic lesions; however, several sequences are necessary to obtain a precise diagnosis.

Brainstem lesions, the most severe axonal diffuse injuries, are usually associated with multiple hemorrhages in the white matter and the corpus callosum. For this reason, they are considered sensitive indicators of axonal diffuse injury. The most frequent location of diffuse axonal injury in the brainstem is the dorsolateral region of the mesencephalon, although it is sometimes difficult on a CT scan to differentiate between the mesencephalon and the perimesencephalon) (Figures 6.7 and 6.8). Also frequent are injuries in the posterior limb of the internal capsule due to small lacerations of the lenticulostriate arteries that irrigate this zone. Less frequent injuries are those of the lenticular nucleus, the external capsula and/or the thalamus.

In patients with axonal diffuse injury, there are other radiological signs that, although not strictly injuries of the cerebral parenchyma, are usually associated with axonal damage. Among these, intraventricular hemorrhage and subarachnoid hemorrhage should be mentioned. Intraventricular hemorrhage is often produced by blood coming from a

cerebral hematoma into the intraventricular space and less frequently due to laceration of the subependymal veins. The clinical picture of this injury depends on concomitant injuries and/or the presence of hydrocephalus.

Posttraumatic subarachnoid hemorrhage appears on the CT scan as a hyperdense area of irregular distribution that spreads out around the cerebral hemispheres and into the cistern spaces; it can be caused by blow and counterblow injuries and can be observed in sites distant to the area of impact. Typical locations are the interpeduncularis cistern and the sulcus lateralis (fissure of Sylvius), often without generating mass effect. The clinical picture of posttraumatic subarachnoid hemorrhage is related to the risk of vasospasm and the symptoms arising from concomitant injuries. Traumatic subarachnoid hemorrhage has been demonstrated to be an independent factor for poor prognosis after traumatic brain injury. The coexistence of these lesions on a CT scan is associated with very poor outcome.

Diffuse axonal damage, because it produces defects in intrahemispheric and interhemispheric communication, is one of the most clinically relevant findings in the prognosis of head-injured patients. In general, complete recovery varies individually. Nevertheless, an inverse relationship has been observed between the Glasgow Coma Scale (GCS) score at admission and the Glasgow Outcome Scale (GOS), with a worse functional outcome for patients with brainstem injuries.

Figure 6.7. **Brainstem injury (1) with secondary intracranial hypertension that generated distortion of the perforating arteries. Increase in volume of both temporal lobes and temporal fracture (2).**

Figure 6.8. **Small hematoma in the mesencephalon.**

1 = Hematoma

2 = Fracture with small subdural hematoma in the right temporal lobe

6.3 CT in Patients With Cerebrovascular Hemorrhagic Disease

6.3.1 Spontaneous Subarachnoid Hemorrhage

Spontaneous subarachnoid hemorrhage is a hemorrhagic cerebral disease that can be easily diagnosed at CT. The present generation of scanners can establish a diagnosis of intracranial subarachnoid hemorrhage in almost 100% of cases. The absence of subarachnoid blood on a CT scan, associated with bleeding demonstrated by lumbar

puncture, correlates with low hematocrit (<23%), in which bleeding can be principally isodense. Where CT cannot be diagnostic for subarachnoid hemorrhage is in patients with severe coagulopathy or in those under anticoagulation therapy.

Similarly, subarachnoid hemorrhage detected by lumbar puncture without evidence of blood on the CT scan should prompt us to suspect subarachnoid hemorrhage due to extra-cranial bleeding (arteriovenous spinal malformation, etc.). It is also possible that blood not appearing in the subarachnoid space on the CT scan could be due to the occurrence of bleeding several days before; nevertheless, blood in the subarachnoid space can be detected on the CT scan even at the end of the first week after bleeding in almost 50% of cases.

Within days after the hemorrhage, the blood in the subarachnoid space decreases and the subarachnoid hemorrhage observed on the CT scan becomes isodense in relation to the parenchyma, which appears as a false image of obliteration of the cortical subarachnoid spaces and basal cisterns, simulating diffuse brain edema and suggesting an increase in intracranial pressure.

Magnetic resonance imaging (MRI) is more sensitive than CT to detect small subarachnoid hemorrhages in the subarachnoid spaces. An additional advantage is MRI's ability to identify small calcifications sometimes associated with vascular disease.

One of the classic classification systems for the evaluation of spontaneous subarachnoid hemorrhage according to CT scan findings is Fisher's classification (Table 6.5). Fisher designed this system to predict the development of vasospasm according to four risk categories from lowest to highest as follows: 1) no subarachnoid hemorrhage; 2) diffuse bleeding or a thin blood layer in the vertical subarachnoid structures <1 mm thick; 3) localized clots and/or vertical layers of blood in the subarachnoid vertical structures >1 mm thick; 4) diffuse bleeding or absence of subarachnoid blood but with intracerebral clots or intraventricular hemorrhage.

According to Fischer's classification, the presence of blood should be checked in at least the following locations: 1) frontal intercerebral fissure, including the region next to the genu of corpus callosum; 2) basal frontal fissure, including the inferomedial region of the hemisphere next to the region of the anterior communicating artery; 3) parieto-occipital fissure (posterior intercerebral fissure); 4) base of the sylvian fissure, (horizontal portion of the sylvian fissure around the proximal part of the middle cerebral artery and its bifurcation); 5) sylvian cistern (inferior part of the sylvian fissure adjacent to the middle cerebral artery); 6) insular cistern (subarachnoid space guided vertically on the surface of the insula); 7) sylvian fissure (part of the sylvian fissure superior to the surface of the temporal lobe); 8) suprasellar cistern (Circle of Willis region); 9) ambiens cistern (perimesencephalic space vertically guided); 10) quadrigeminal cistern (subarachnoid space adjacent to the quadrigeminal bodies); 11) cerebral transverse fissure between the corpus callosum, fornix and diencephalon; 12) prepontine cistern ventral to the base of the protuberance; 13) cerebellar superior cistern on the surface of the brain.

Degree	Characteristics
1	No bleeding on the CT scan
2	Diffuse bleeding or thin blood layer in any one of the vertical subarachnoid structures (intercerebral fissure, insular cistern, cistern ambiens) <1 mm thick
3	Localized clots and/or vertical layers of blood in the subarachnoid vertical structures ≥1 mm thick
4	Diffuse bleeding or absence of subarachnoid blood, but with intracerebral or intraventricular clots

Table 6.5. Fisher's scale.

Grade	Characteristics
0	No subarachnoid hemorrhage or intraventricular hemorrhage
1	Minimal/thin subarachnoid hemorrhage, no intraventricular hemorrhage in both lateral ventricles
2	Minimal/thin subarachnoid hemorrhage, with intraventricular hemorrhage in both lateral ventricles
3	Thick subarachnoid hemorrhage, no intraventricular hemorrhage in both lateral ventricles
4	Thick subarachnoid hemorrhage, with intraventricular hemorrhage in both lateral ventricles

Table 6.6. **Revised Fisher's scale.**

Fisher's classification was derived from a study that had limitations which aroused objections, including: 1) it did not involve a consecutive series of patients, which can be inferred from the high incidence of vasospasm in the series; 2) the high rate of patients grouped in risk category I probably due to the scanner generation in use at that time; 3) the inclusion of patients within 1-5 days after clinical signs of bleeding, which probably facilitated the clearance of blood in the subarachnoid space and therefore on the CT scan.

A later modified Fisher's Scale (Table 6.6) incorporated elements known to influence the etiology of cerebral ischemia. These elements quantify the intensity of subarachnoid hemorrhage (including the impact of intraventricular hemorrhage on prognosis). Their relevance for prognosis in the prediction of neurological deficits after subarachnoid hemorrhage has been also tested.

The magnitude of blood on the CT scan after a subarachnoid hemorrhage is a general indicator of the severity of the clinical process (Figures 6.9 and 6.10).

Patients with subarachnoid hemorrhage with relevant bleeding on a CT scan have a worse outcome. In fact, Fisher's classification seeks to establish a direct relationship between the amount of bleeding visible on the CT scan and the risk of vasospasm over the following days.

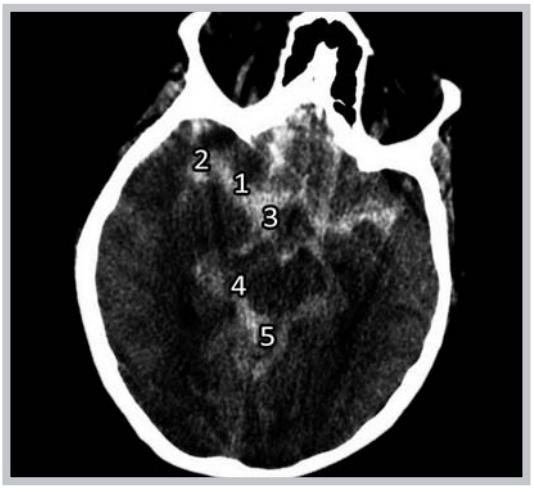

Figure 6.9. **Spontaneous subarachnoid hemorrhage with bleeding in the sylvian fissure.**

1 = Trunk
2 = Sylvian fissure (lateral)
3 = Suprasellar cistern
4 = Ambiens cistern
5 = Quadrigeminal cistern

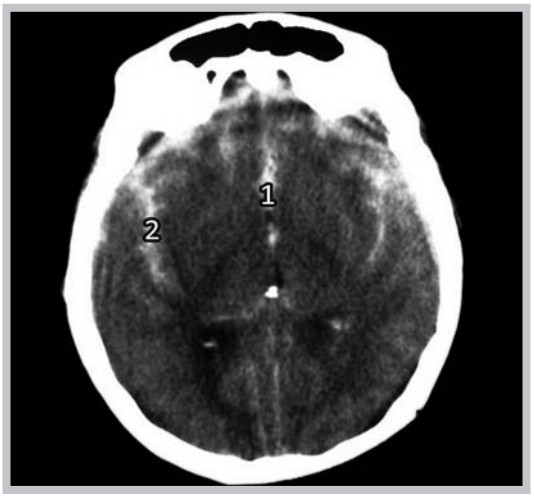

Figure 6.10. **Spontaneous subarachnoid hemorrhage with bleeding.**

1 = Intercerebral fissure
2 = Sylvian fissure (lateral)

Estimating the exact amount of blood in the subarachnoid space on a CT scan is not easy because of: 1) irregular distribution of cisterns and fissures; 2) CT cross-sections do not correspond to the anatomical distribution of the subarachnoid spaces; 3) different amounts of blood in the subarachnoid regions; 4) inaccuracy in the measurement of the intensity in HU or the frequent coexistence of the partial volume effect; 5) progressive tendency to isodensity of bleeding over time.

To quantify the intensity of the bleeding in the basal cisterns in patients with subarachnoid hemorrhage, Hijdra et al. developed a quantitative system that could be used to score the extent of bleeding in 10 subarachnoid spaces close to the circle of Willis. Blood should be quantified in the following spaces: frontal intercerebral fissure; lateral sylvian fissures; basal sylvian fissures; suprasellar cistern (bilateral quantification); ambiens cistern (bilateral quantification); and quadrigeminal cistern. Bleeding intensity is scored as follows: no blood in the subarachnoid space (0); small quantity of blood (1); moderate quantity (2); a subarachnoid space completely filled with blood (3).

The range of the intensity of a subarachnoid hemorrhage is between 1 and 30 points on this scale. The location of bleeding on a CT scan in subarachnoid hemorrhage can aid in detecting an aneurysm in the circle of Willis. In a bleeding aneurysm of the anterior communicating artery, the hyperdensity is usually located in the suprasellar cistern and the frontal intercerebral fissure, with spread to the frontal regions and less frequently to the pericallosal cistern and the sylvian fissure. In severe bleeding of the anterior communicating artery, intracerebral hematomas in the frontobasal regions are frequently observed. A bleeding internal carotid artery aneurysm in the supraclinoid segment shows a variety of locations of blood on the CT scan, including: the suprasellar cistern; the interpeduncularis cistern; the sylvian fissure; and the anterior intercerebral fissure. In middle cerebral artery bleeding, the most frequent locations of blood are the sylvian fissure and the suprasellar cistern. Intracerebral hematomas in the parasylvian areas are also common in sylvian aneurysms. Hemorrhage due to an aneurysm of the distal segments of the basilar artery often evidences blood in the suprasellar cistern, the perimesencephalic cistern, and the interpeduncular cistern, while in bleeding aneurysms of the posteroinferior cerebellar artery, blood is typically revealed in the prepontine and the pericerebellar cistern.

6.3.2 CT in the Diagnosis of Intraventricular Hemorrhage

Intraventricular hemorrhage is a frequent finding after a subarachnoid hemorrhage. The higher incidence of intraventricular bleeding after an aneurysm rupture is associated with an aneurysm of the anterior communicating artery in which the lateral ventricles and the third and fourth ventricles are flooded with blood. This type of bleeding is also frequent in rupture of carotid aneurysms and sylvian aneurysms. In subarachnoid hemorrhage due to an aneurysm of the posteroinferior cerebellar artery, the bleeding often affects the third and fourth ventricles, without extension to the lateral ventricles. The increase in resistance to the physiological circulation of CSF due to ventricular bleeding and altered fluid reabsorption frequently correlates with hydrocephalus.

Severe spontaneous intracerebral hemorrhage is also frequently associated with ventricular bleeding. The incidence of intraventricular hemorrhage is higher in thalamic hematoma or in putamina hematoma with thalamic extension. In interventricular hemorrhage associated with brain injury, the incidence is lower than in cerebrovascular hemorrhagic disease. Traumatic intraventricular hemorrhage is often associated with mechanisms of acceleration/deceleration that frequently cause diffuse axonal injury and is often due to rupture of the subependymal veins.

Site	Characteristics	Score
Right lateral ventricle	Trace of blood or mild bleeding	1
	Less than half of the ventricle filled with blood	2
	More than half of the ventricle filled with blood	3
	Ventricle filled with blood and expanded	4
Right lateral ventricle	Trace of blood or mild bleeding	1
	Less than half of the ventricle filled with blood	2
	More than half of the ventricle filled with blood	3
	Ventricle filled with blood and expanded	4
Third ventricle	Blood present, ventricle size normal	1
	Ventricle filled with blood and expanded	2
Fourth ventricle	Blood present, ventricle size normal	1
	Ventricle filled with blood and expanded	2

Table 6.7. **Graeb's scale. Each lateral ventricle is scored separately. The maximum score is 12 points.**

In 1982, Graeb et al. reported on the relevance of interventricular bleeding in acute neurological patients and developed a classification scheme to quantify intraventricular bleeding in patients with cerebrovascular disease and head trauma. Because of the high incidence of intraventricular bleeding in subarachnoid hemorrhage and spontaneous intracerebral hemorrhage, Graeb's classification is chiefly used in patients with spontaneous intracranial hemorrhagic. Table 6.7 illustrates the scoring system according to CT scan findings.

The maximum score is assigned for blood flooding the lateral ventricles, including also the presence of blood in the third and fourth ventricles. It is important to emphasize that "ventricles full of blood and expanded" indicates the presence of a ventricular dilatation directly attributable to bleeding and not to the possible coexistence of hydrocephalus. The maximum score is 12 points. There is general consensus that a score >7 implies intraventricular bleeding associated with clinical severity.

A similar scale described by Le Roux et al., although initially used to assess ventricular hemorrhage associated with traumatic brain injury, has been frequently used to evaluate intraventricular hemorrhages due to spontaneous subarachnoid hemorrhage. Le Roux's scale quantifies between 1 (minimal quantity of blood) and 4 (completely full ventricle) the invasion by blood into the third, fourth and each of the lateral ventricles. The score range on the Le Roux scale is 1-16 points.

6.3.3 CT in Spontaneous Intracerebral Hematoma

Compared with normal parenchyma, spontaneous intracerebral hematoma appears on the CT scan as a hyperdense area inside the cerebral parenchyma, usually generating mass effect. The hyperdensity is due to the presence of hemoglobin (90%) and only partially to the iron concentration (8%). Clot retraction causes a substantial increase in blood cell volume and therefore an increase in radiological density (+90-100 HU). Generally, small-volume intracerebral hematomas present with a rounded or oval shape, with relatively neat borders, whereas high-volume hematomas show irregular and indistinct borders, as well as asymmetric morphology. In 88% of cases, spontaneous intracerebral hemorrhage occurs inside the cerebral hemispheres, 8% in the cerebellum, and 4% in the brainstem.

The precise location of intracerebral hematoma on the CT scan is relevant to determine:

- Etiology, pathogenesis of the hematoma and its possible association with arterial hypertension. These last hematomas are usually located in the basal ganglia, whereas hematomas with an etiology other than hypertension, as for example, neoplasia or arteriovenous malformations, will vary in location (lobar hematoma, posterior fossa, etc.).
- Clinical picture should agree with the location of the hematoma in terms of the brain structures affected by the bleeding.
- Outcome, which obviously correlates with the location and extension of the intracerebral hemorrhage.
- Treatment which will differ according to hematoma location and volume, the clinical picture, etc.

Hypertensive hematomas are more often situated in the putamen (lateral location) and the thalamus (medial location). Thalamic hematomas account for 15-25% of these hematomas, often smaller than putaminal hematomas due to the smaller size of the nucleus and due to its fibre content, which makes the diffusion of blood difficult. Most putaminal hematomas (60%) present with ventricular bleeding which in more severe cases spreads out toward the mesencephalon.

Putaminal hematoma has a higher incidence than mesencephalic hematoma. Most high-volume putaminal hematomas tend to affect adjacent neurological structures (Figure 6.11) and only a low percentage (17%) remain confined exclusively to the putamen. Around 10% extend to the external capsula. Putaminal-capsulae hematomas have a worse outcome when they extend to the semi-oval centre. Nevertheless, the poorest prognosis is associated with putaminal hematomas with hemispheric extension (20% of cases) and putaminal-thalamic hematomas (about 20% of these hematomas). The former tend to extend toward the cerebral hemispheres and the corona radiate, the latter also to the thalamus and the intraventricular space.

Lobar intracerebral hemorrhage (Figure 6.12) has a predominant parietal (30%) and frontal location (20%), although they can sometimes be situated in more than one cerebral lobe. Less frequently they are found in the occipital region (15%). The intraventricular extension of bleeding is less frequent in lobar hematomas than in basal ganglia hematomas.

Figure 6.11. **Left putaminal hematoma (black arrow) with compression of the external capsule and ventricular bleeding.**

CT in patients with spontaneous intracerebral hemorrhage does not differ from that for head-injured patients, except that in the cases of hypertensive etiology, contrast-enhanced CT is advisable. Generally speaking, the use of contrast-enhanced CT scan is indicated in: 1) patients younger than 40 years of age; 2) patients without a clinical history of high blood pressure; 3) hematoma of atypical morphology or with extensive invasion of the subarachnoid or subdural space; 4) patients with previous comorbidities such as neoplasms, bacterial endocarditis, arteritis or others.

In spontaneous intracerebral hemorrhage the volume of the bleeding is recognized as a key element with a better prognosis and therapeutic relevance. The location also has relevance for prognosis and ther-

apeutic approach. Table 6.8 lists the most frequent topographic locations of spontaneous idiopathic intracerebral hematoma. Evaluation of the CT scan of a patient with a high-volume spontaneous intracerebral hematoma would be incomplete without an analysis of the phenomena that the hematoma generates in adjacent and contiguous brain structures. Here it is essential to evaluate: midline shift, effacement of the cerebral sulci, and compression of the cisterns of the skull base. The ambiens cistern is frequently compressed in high-volume spontaneous intracerebal hemorrhages, and compression or absence of the cistern suggests a high risk of transtentorial herniation. In hematomas of the posterior fossa, estimating the volume is especially relevant due to potential compression or disappearance of the cerebellar superior cistern and the magna cistern.

Figure 6.12. Occipital lobar hematoma (black arrow) with ventricular bleeding.

Among the major factors in the outcome of cerebral spontaneous hematoma there are its volume and its influence on key brain structures. There are several methods to facilitate quantification of intracerebral hematoma volume.

Broderick's Formula. Investigating the influence of the volume (ml) of spontaneous intracerebral hemorrhage 30 days after bleeding, Broderick et al. used the formula of the ellipsoid: 4/3 ∏ABC, wherein A is the largest diameter of the hemorrhage (cm); B the diameter of the hemorrhage 90º to A, and C the height (cm) of the hematoma calculated by multiplying the number of slices involved with the slice in thickness.

Formula of Kothari. In 1996 Kothari et al. developed a method to estimate hematoma volume on the CT scan according to the ABC/2 method, wherein A is the greatest hemor-

Lobar hematoma	• Parietal • Frontal • Occipital
Thalamus	• Type I: Thalamus • Type II: Thalamus and internal capsule • Type III: Thalamus extending to mesencephalon/hypothalamus
Caudate nucleus hematoma	
Putamen nucleus hematoma	• Putamen nucleus • Lateral putaminal hematoma • Anterior putaminal hematoma • Posterior putaminal hematoma • Medial putaminal hematoma • Putaminal-thalamic hematoma • Putaminal-hemispheric hematoma
Cerebellar hematoma	• Vermis • Cerebellar hemisphere hematoma • Vermis and cerebellar hemisphere hematoma
Brainstem hematoma	

Table 6.8. Classification of spontaneous intracerebral hematomas according to CT scan findings.

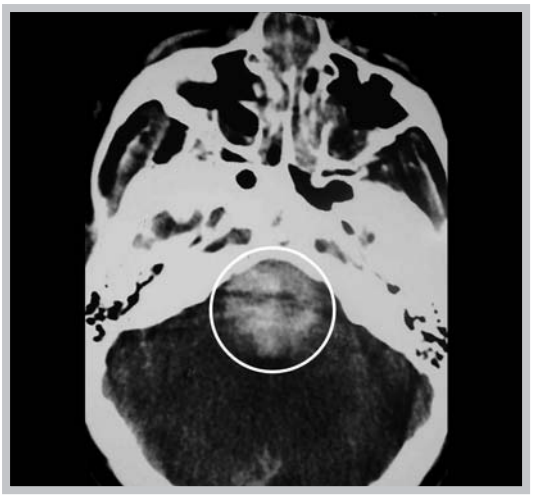

Figure 6.13. **Hematoma of the brainstem (black circle).**

rhage diameter by CT; B is the diameter of the 90 degrees to A; and C is the approximate number of 10-mm CT slices where the hematoma can be observed. With regard to C, if one slice of the hemorrhagic area is >75% of the area observed in slice A, the value of C is 1. If the area is between 25 and 75% of the maximum area, C is 0.5; if the area is <25%, then C is not considered at this level. In all cases, the values of A and B are measured in centimetres on the CT image, bringing the values nearer to 0.5 cm.

Formula of the sphere. A simpler way to calculate hematoma volume is by approximation of the volume by "transforming" the hematoma into a sphere. To do this, the diameters A, B and C are estimated, and the average thereof is calculated. Once one diameter is known, the formula is used to calculate the sphere. The formula is: volume of the sphere $4/3\prod r^2$, wherein r is the average radius of the theoretical sphere. In patients with acute neurological deficit, CT is useful to rule out the presence of infratentorial hematoma. A cerebellar hematoma can be located in the cerebellar hemispheres, the vermis or in both. According its location and size, cerebellar hematoma can be amenable to surgical treatment. Therefore, it is very important to make an early diagnosis of the size of volume and diameter of a cerebellar hematoma. Mesencephalic and brainstem hematomas are only susceptible to medical treatment, and in many cases are associated with poor outcome (Figure 6.13).

6.4 CT in the Diagnosis of Acute Ischemic Cerebrovascular Diseases

The early diagnosis of acute ischemic cerebral disease is based on the CT scan. Despite the limitations of CT in the early diagnosis of some ischemic brain lesions, an imaging study should be performed as an emergency procedure before the suspicion of acute ischemic cerebrovascular disease. Therapeutic and prognostic implications can be derived from an early CT scan and accurate interpretation of the images. Accuracy in the diagnosis of ischemic stroke is high when CT and MRI are combined. Nevertheless, the lack of accessibility to MRI in most hospitals means that CT is the most useful technique for emergency department physicians.

CT scan findings in patients with neurological deficits due to ischemic stroke are not always correlated with the clinical picture. Patients with eloquent deficits may not have clear pathological findings on the CT scan. Similarly, it is not infrequent to find on the CT scan of these patients some clinically silent ischemic lesions (probably old lesions). CT can be very useful not only to establish a diagnosis of cerebral ischemia secondary to occlusion of a great vascular territory, for example, the middle cerebral artery, etc, but also of small terminal arterial territories (Heubner's artery, perforating arteries, etc.). CT can also evidence ischemia of border vascular territories (watershed infarct), for exam-

ple, the territory between the middle cerebral artery and the anterior cerebral artery, the region of the girus angularis, etc.

A CT scan without contrast, with a window between 0 and +70 HU, may be a standard procedure in the first approach to a patient with suspected acute ischemic stroke. On the other hand, a window between +0 and +70 HU provides a higher number of the "range of grey" to distinguish between normal cerebral structures and hypodense cerebral structures resulting from cerebral ischemia. CT without contrast is significantly less useful in the diagnosis of cerebral ischemia in the posterior fossa processes due to the lack of spatial resolution and the radiological bone-generated artifacts. Apart from the clinical presentation, the clinical data that should be considered in order to identify cerebral ischemia signs on the CT scan of a patient with acute cerebrovascular symptoms are: 1) location of hypodense areas; 2) morphology of hypodense areas; 3) the presence of mass effect.

Table 6.9 illustrates a schematic approach to a patient with suspected acute ischemia. The vascular territories most frequently affected in acute ischemic diseases are the middle/cerebral artery, the posterior cerebral artery, the anterior cerebral artery, and the basilar artery.

The early changes that occur after acute cerebral ischemia must often be inferred from indirect radiological signs. The radiological signs start in the grey matter, with decreasing radiological intensity. Therefore, a decrease in the differentiation between white matter and grey matter is a frequently described sign suggestive of ischemia. Direct measurement of the radiation absorption units on CT scan can aid in the diagnosis of ischemia. In normal conditions, the grey matter has an attenuation coefficient between +30 and +35 HU, while that of the white matter is between +20 and +25 HU. In ischemia, the attenuation decreases and the contrast between the grey matter and the white matter is lower.

The sensitivity of a CT study can be improved by decreasing the radiological window to a nonstandard window. For example, a window of +50 HU and a centre in +35 HU improves the discriminating capacity without losing specificity. The loss of differentiation

CT scan in the early phase of ischemic stroke	Early hypodensity	• Lack of definition of the insular cortex: "insular ribbon sign" • Hypodensity of the lentiform nucleus • Other hypodensities
	Early signs of mass effect	• Effacement of the cerebral sulci • Effacement the lateral ventricle • Compression of the rhombencephalon
	Hyperdensity of the middle cerebral artery, basilar artery	
CT scan in the late phase of ischemic stroke	Location of hypodensity	• Middle cerebral artery: subcortical, subcortical • Other arterial territories • Watershed ischemia
	Size of the infarct	• Estimation of volume • Percentage of the vascular affected territory: • Less than 1/3 • More than 1/3
	Hemorrhagic transformation	• None • Petechial • Hematoma • Mass effect

Table 6.9. **CT scan findings in ischemic stroke.**

between the white matter and the grey matter in the insular cortex, the hypodensity of the lenticular nucleus or the effacement of sulci can often be detected in the first 6 hours after stroke in almost 80% of patients with occlusion of the great intracranial arteries.

Radiological signs suggestive of acute ischemia in the territory of the middle cerebral artery are:

- The insular ribbon sign in which the ribbed edge of the insular cortex (grey matter), which is normally slightly hyperdense, disappears, becoming indistinguishable from the white matter. The absence of perfusion in this territory is due to decreased blood flow to the cortical insular area, turning it isodense as compared to the adjacent white matter.
- The decrease in radiological intensity (relative hypodensity) of territories of the basal nucleus, mainly of the lenticular nucleus and posterior limb of the internal capsule.
- Occasionally, acute ischemia can be diagnosed from the observation of embolic material in the middle cerebral artery or anyone of its branches. This material, more radio-intense than the normal brain tissue, can be evidenced in the proximal middle cerebral artery as a linear hyper-density (hyperdense middle cerebral artery sign). Some studies have demonstrated the high specificity of this sign as a key evidence for middle cerebral artery occlusion, but its sensitivity is <30%.

Embolic hyperdense material in the more distal branches of the middle cerebral artery (sign of the middle cerebral artery) inside the sylvian fissure can sometimes be observed. Some authors give more value to this sign than to the hyperdense middle cerebral artery because it can be present in 15% of patients in which the CT scan was performed within the 3 first hours. The presence of embolic material in the middle cerebral artery has been associated with a worse clinical outcome after fibrinolytic therapy. The sign of the hyperdense artery can be also observed in the basilar artery (Figure 6.14).

In acute cerebrovascular disease, CT findings such as early signs of cerebral ischemia (early signs of infarct) and signs of arterial occlusion (sign of vascular hyperdensity) can aid in making treatment decisions. Tomographic evidence of edema and mass effect is associated with a significant increment in hemorrhagic risk after thrombolytic treatment. Estimating the percentage of ischemic territory is also relevant. It has been observed that after recombinant tissue plasminogen activator (rt-PA) fibrinolysis, the risk of poor outcome is higher in cases presenting hypodense areas more than one third of the territory of the middle cerebral artery.

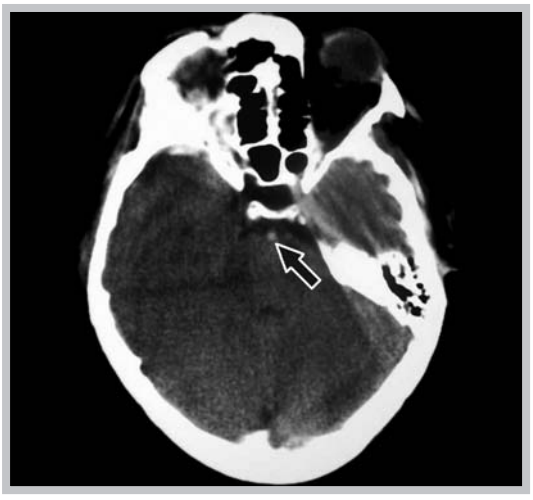

Figure 6.14. **Thrombus in the basilar artery (arterial hyperdensity) (black arrow).**

In massive cerebral infarction, it is also important to note any signs of cerebral suffering, intracranial hypertension, or risk of cerebral herniation.

These signs are similar to those described in the section on traumatic brain injury. Therapies such as decompressive craniectomy are partially based on CT scan findings. The quantification of the midline shift, the decrease in perihemispheric CSF, and the presence of subtle or advanced signs of cerebral herniation are also relevant.

6.4.1 Magnetic Resonance Imaging

Nuclear magnetic resonance (NMR), or magnetic resonance imaging (MRI), is a noninvasive and non-ionizing radiation procedure that has a unique way of contrasting tissues and offers higher spatial resolution. MRI uses radio waves and strong magnets. The technique is based on the interaction between the external magnetic field and the core with a magnetic moment different from zero. The hydrogen nucleus seems to be the best target for MRI, as it has the following advantages: 1) present in all the nuclei in human tissues and generates more signal; 2) gives the best contrast. The magnetic field forces the hydrogen atoms in the body to align in a certain way (similar to the way a compass needle moves when held near a magnet). Radio waves are sent toward the aligned hydrogen atoms, they bounce back, and a computer records the signal. Different types of tissues send back different signals. Each tissue, according to its abundance of protons and the time lapse between stimulation and return to rest (T1 and T2 sequences), emits a signal of varying intensity that is captured by the equipment. Classic MRI sequences called spin echo are being replaced by fast turbo spin, spin echo or echo, since they are faster and retain many of the signal's characteristics.
The following table details the basic signs of some tissues in the study of the central nervous system in different spin echo sequences. T1 and T2 and fluid-attenuated inversion recovery (FLAIR) is widely used because of it high sensitivity and an inversion time (the water), so that the water in the cavities and the CSF have a low FLAIR signal (black). This enhances sensitivity, particularly for subtle cortical and periventricular lesions, which may go unnoticed in T2 sequences (Table 6.10).

Requences	T1	T2	FLAIR
Water in the cavities	↓	↑	↓
Edema (free water)	↓	↑	↑
Grey matter	Grey	Grey	Light grey
White matter	White	Black	Dark grey
Calcium	↑/↓	↓	↓
Fat	↑	↑	↑
Sensibility	↓	↑	↑↑
Resolution	↑↑	↑	↓

Table 6.10. MRI sequences.

6.4.2 Advantages of MRI

Better spatial resolution and contrast of different brain structures. It provides excellent anatomic images of the posterior fossa and allows simultaneous measurement of cerebral blood flow and volume. It can visualize the arterial and venous vasculature and its anatomic relationships. It allows early detection of ischemic injury and increased water content. Higher sensitivity and specificity to show diseases of the spinal cord. Better long-term predictive power in relation to CT.

6.4.3 Disadvantages of MRI

It takes time (''Time is brain''). It cannot be performed in complex patients with pacemakers, prostheses or alongside standard equipment in critical care units. If other organ systems need to be studied at the same time, the information provided is not as complete as with CT. It does not have good resolution for bones or blood in the subarachnoid spaces. It is not available in all centres and is expensive. It usually requires a neuroradiologist to assist in the interpretation of the results and decide which sequence is most convenient.

6.4.4 Indications for Emergency

Pathologies of the posterior fossa, vertebrobasilar territory:

- Ischemic stroke and previous thrombolysis.
- Diffuse axonal injury.
- Subdural hematomas of the vertex or isodense areas.
- Herpetic encephalitis.
- Multiple sclerosis.
- Spinal cord injury.
- Cerebral venous thrombosis.
- Brain tumours.
- Secondary brain hemorrhage (arteriovenous malformation, cavernomas, etc.).

6.5 Conclusions

CT, a key technique in the development of neurocritical care, must be a part of special training for doctors involved in the management of acute neurological patients.
The technical specifications of the CT scan are key components for improving the performance of the diagnosis for neurocritical patients.
CT scan findings of head-injured patients must be assessed against the criteria of the TCDB classification and with a pathophysiological approach.
For the analysis of the CT scan in spontaneous subarachnoid hemorrhage, Fisher's scale, modified Fisher's scale, and Hijdra's scale must be used.
The CT scan in patients with acute cerebrovascular ischemic diseases can be valuable in formulating the prognosis and therapeutic strategy.

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7 Intracranial Pressure Monitoring. Acute Cerebral Injury: the First 48 Hours

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7.1 Intracranial Pressure

An understanding of the principles that determine ICP and its waveforms are important for optimal management of a patient with intracranial hypertension. Intracranial pressure is determined by the effects of atmospheric pressure, the volume of the intracranial contents, the hydrostatic pressures determined by the effect of gravity or weight on the mass of the craniospinal axis, and the elastance of the brain.

The Monro-Kellie hypothesis describes the skull as a semi-closed compartment containing the brain and interstitial fluid, cerebrospinal fluid (CSF), and blood. In a normal adult, approximately 87% of the intracranial space is occupied by the brain, 4% by the blood (60 ml), and 9% by the CSF which is estimated to be about 100-150 ml. Water composes approximately 80-90% of the volume, since the brain parenchyma contains 75-80% water.

Increases in the volume of an intracranial component, such as intravascular blood during vasodilation, or in a pathological condition, such as extravascular blood, tumour or edema, must result in the displacement of other intracranial components such as the CSF or intravascular blood (vasoconstriction) to maintain ICP normal. The CSF flows from the ventricles to the cisterna magna, basilar cisterns and subarachnoid space of the brain and spinal cord and is removed by bulk flow reabsorption over the convexities of the hemispheres in the arachnoid villi found in the walls of the dural veins. Higher hydrostatic pressure in the CSF space can drive the bulk flow and displace CSF by increasing reabsorption. At CSF pressures <5 mmHg, CSF reabsorption may diminish or cease. Increased dural sinus pressure may potentially also decrease CSF reabsorption.

Patient positioning, such as placing a patient in a head-down or Trendelenberg position, can cause an increase in ICP by increasing the hydrostatic pressure of the brain due to gravity. In addition, this position may impede venous outflow. Such venous congestion increases cerebral venous blood volume and, depending on cerebral elastance, it can also increase ICP.

Elastance describes the relationship of ICP as a result of a change in volume. The elastance of the craniospinal axis is dependent on the distension of the dura mater and, primarily, on the displacement of fluids (e.g., blood or CSF). In brain atrophy, elastance is low and changes in volume may little effect ICP. However, when compensatory mechanisms are overwhelmed, even small changes in volume may cause large increases in ICP. Normal ICP ranges between 5 and 10 mmHg. The upper limit of normal in adults and older children is 15 mmHg. During a Valsalva maneuver or sneezing, the ICP can exceed 30-50 mmHg, but it rapidly returns to normal in a brain with normal elastance.

7.2 Techniques for Monitoring Intracranial Pressure

There are various options for monitoring ICP invasively either placed intraoperatively or, more commonly, at the bedside through a burr hole. Anatomic locations of placement include ventricular, parenchymal, subarachnoid, subdural and epidural sites (Figure 7.1). Modalities include: 1) fluid-coupled monitoring; 2) fiberoptic monitoring which utilizes a reflected laser beam; and 3) piezoelectric crystal transducers which, when compressed, produce a voltage proportional to the degree of compression.

Fibre optic and piezoelectric monitors do not require other external transducers and are calibrated or "zeroed" prior to intracranial placement. These monitors are placed into the brain parenchyma and have the advantage that changes in the head of bed do not require re-levelling of a transducer. However, there may be some drift in the system over time, which causes inaccurate readings, and these monitors cannot be recalibrated. If inaccuracy due to drift is suspected, the intraparenchymal component of the monitor must be replaced with the attendant costs and potential complications of reinsertion. These monitors also have no ability to drain CSF.

The zero point for the fibre optic or electronic monitor is at the tip of the catheter. If the monitor is placed deeply compared to a more superficial placement, the measured ICP may be higher by several mmHg due to the hydrostatic weight of the brain above the monitor tip.

A fluid-coupled ventricular monitor is positioned with its tip in the frontal horn of a lateral ventricle. It is connected to an external strain gauge transducer and can be recalibrated and used to drain CSF, which will help with the treatment of intracranial hypertension. Both reliable and accurate, this technique is traditionally considered the gold standard for ICP monitoring. The transducer is calibrated to the level of the foramen of Monro. The tragus, which lies just anterior to the external auditory meatus, serves as the external anatomical landmark for the foramen of Monro. One disadvantage of a fluid-coupled monitor is potential obstruction by brain tissue, blood or bone especially during placement. Other drawbacks are that air within the system will dampen the waveform and artificially lower the pressure, and changes in head position require re-zeroing the transducer. When the ventricles are small and significantly compressed, placement of an intraventricular catheter may be difficult. Fluid-coupling also increases the risk of infection. Some studies have shown that the risk of infection increases with lon-

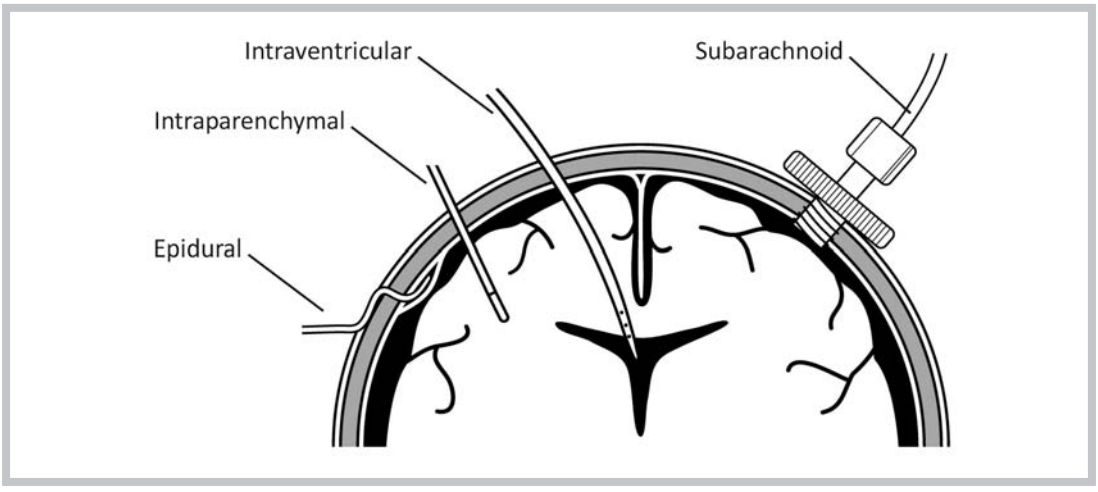

Figure 7.1. Intracranial pressure monitoring placement.

ger duration of catheter placement; however, other studies have reported that infectious risk is highest within the first 10 days and decreases thereafter. This would suggest that the infection is introduced at the time of catheter insertion. Periodic flushing with antimicrobials or routine replacement do not appear to reduce the risk of infection. The use of prophylactic antibiotics is often limited to periprocedural administration just prior to placement, since antimicrobial treatment for the duration the catheter is in place likely increases the risk of resistant organisms and may not reduce the risk of catheter-related ventriculitis. Removing the catheter as soon as possible and minimizing the frequency of opening and accessing the system may reduce the risk of infection. Subcutaneous tunnelling of the catheter away from the insertion site may also lower the risk of infection. Newer antibiotic-impregnated catheters are available.

A subarachnoid screw or bolt is a fluid-coupled metal tube secured in the skull through a burr hole and is connected to an external pressure transducer. These do not effectively drain the CSF and are less accurate than a ventricular monitor, since at higher pressures the screw becomes obstructed with brain tissue.

Subdural monitors can be placed during surgery but are not typically used as they can become obstructed and are considered less accurate.

Epidural catheters are also less accurate due to compartmentalization by the dura from the intraparenchymal space. Because there is a theoretically lower risk of hemorrhage during placement compared to an intraparenchymal monitor, epidural catheters were historically used in patients with coagulopathy who required urgent monitoring (e.g., hepatic encephalopathy and cerebral edema). But because of their inaccuracy, they are not commonly used today.

The semi-rigid dura mater creates compartments within the cranium. The falx cerebri, which is a sagittal fold of the dura mater, splits the supratentorium into two halves. The tentorium cerebelli is a fold of the dura mater that separates the occipital lobes from the cerebellum. The free edges of the tentorium cerebri bilaterally leave an opening that is traversed by the midbrain. Understanding the semi-rigid nature of the dura creating these compartments is relevant during ICP monitoring, since pressure differentials occur in different compartments. A parenchymal monitor in a frontal lobe may not detect elevation of pressure on the contralateral side or infratentorially in the cerebellum. Similarly, a fluid-coupled catheter placed into a lateral ventricle and passed too deeply past the third ventricle may not detect intracranial hypertension occurring in the supratentorium.

Lumbar drains cannot reliably measure intracranial pressure in herniation, when the intracranial and intraspinal spaces become further compartmentalized. In addition, placement of a lumbar catheter can precipitate cerebral herniation when ICP is high and removing CSF from below can create a pressure gradient with a downward shift of the brain.

7.3 The ICP Waveform

Cardiac and respiratory activity creates the pulsatile components of the ICP waveform. The normal ICP waveform has three major components: the percussion wave (P1); the tidal wave (P2); and the dicrotic wave (P3) (Figure 7.2). The percussion wave is the most constant in amplitude and results from systolic pulsation in the large intracranial arteries. The second or tidal wave (P2) is a result of the elastance of the brain. P2 and the dicrotic wave (P3) are separated by the dicrotic notch, which corresponds to the dicrotic notch of the arterial pressure waveform due to closure of the aortic valve during diasto-

le. The dicrotic wave is considered venous in origin. Respiratory contribution to ICP has a tidal variation that is dependent on changes in cerebral venous outflow due to intrapleural pressures that result from changes in intrathoracic and intraabdominal pressure during the ventilatory cycle.

The morphology and pulse pressure of the ICP waveform can be indicative of pathological states. As noted above, elastance describes the change in pressure per unit change in volume. Elastance is dependent on the capacity to displace CSF or intravascular blood when one component of the intracranial compartment increases. Since the ICP waveform results from a bolus of blood from the heart into the intracranial vault, the waveform reflects the elastance. When the elastance increases, the pulse amplitude of the ICP waveform also increases (Figure 7.3).

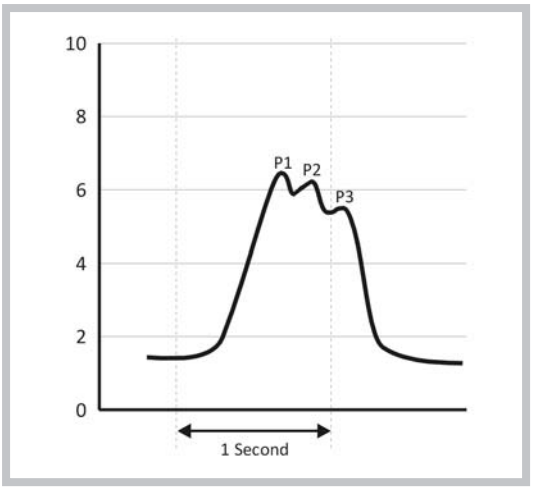

Figure 7.2. **Normal ICP waveform (in mmHg). P1 corresponds to the percussion wave, P2 the tidal wave, and P3 the dicrotic wave.**

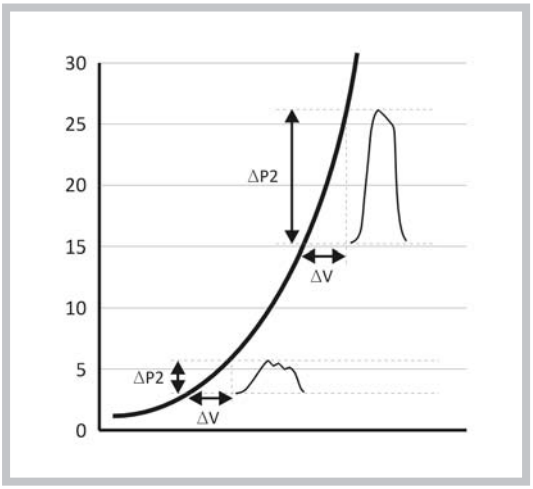

Figure 7.3. **Volume to pressure relationship curve. At low elastance, a change in volume, as depicted by ΔV, increases the intracranial pressure (ICP) by ΔP1; however, at higher elastance when there is less ability for the brain to displace other intracranial components, the same ΔV results in a much greater change in pressure: ΔP2>>ΔP1. Of note is that the pulse pressure of the waveform is much greater and the waveform morphology changes such that the percussion and tidal wave become confluent.**

Attempts have been made to predict impending intracranial hypertension when the pressure level is still normal. Increasing elastance is indicative of impending intracranial hypertension. Techniques to detect this include: 1) measurement of the pressure response to the infusion or withdrawal of fluid; 2) ICP pulse amplitude analysis; and 3) ICP waveform analysis.

There are various methods for the instillation or withdrawal of fluid or CSF to evaluate the pressure response. Marmarou proposed the “pressure-volume index” (PVI), wherein a standard amount of fluid is instilled to determine the volume of fluid needed to raise the opening pressure 10 times. In this calculation, the mathematical log of the ICP is linearly related to the volume with a slope equal to the PVI. A decrease in the PVI indicates increasing elastance and correlates with the development of intracranial hypertension and poorer outcome. Miller induced a “volume-pressure response” by rapidly infusing a set amount of fluid into the CSF space, from which he observed that a greater than 3 mmHg rise in pressure for each millilitre infused would predict increasing elastance and worsening ICP. The obvious complications associated with this technique are infection and potential precipitation of sustained ICP elevation, also known as plateau waves, described below.

Another method to detect impending intracranial hypertension that does not re-

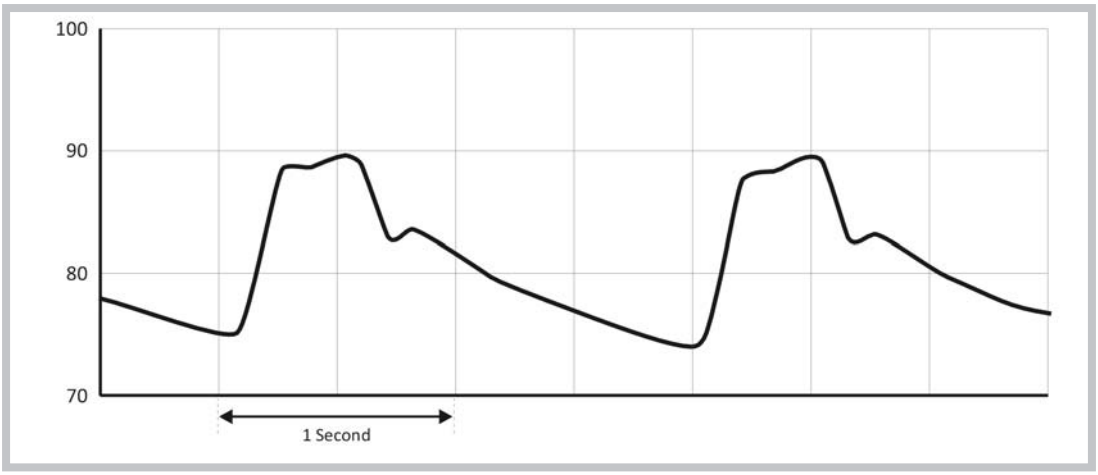

Figure 7.4. **Elevated intracranial pressure wave (in mmHg). Note the change in morphology from the normal pressure wave seen in Figure 2. The tidal wave, P2, increases in amplitude and becomes confluent with P1, the percussion wave. The pulse pressure, or the difference between the lowest and highest amplitudes of the waveform, is also larger.**

quire infusion of fluid into the CSF is analysis of the pulse amplitude and variance in ICP. Increasing pulse amplitude and increased ICP variance can be caused by worsening elastance or cerebral vasodilation. It has been proposed that a cardiac to respiratory wave amplitude ratio >2 indicates cerebral vasodilation, while a lower ratio is indicative of increasing elastance.

Finally, when ICP is elevated, the waveform morphology changes further. P2, the tidal wave, becomes more prominent, increases in amplitude, and merges with P1, which results in a widening and rounding of the waveform (Figure 7.4).

But even with the use of these various techniques, the clinical relevance of determining increasing elastance is unclear, since it is uncertain which therapies should be initiated, and how aggressive they should be, to prevent worsening of ICP.

7.4 Elevated Intracranial Pressure and Pressure Waves

Lundberg observed the ICP waveforms of 143 patients with intracranial tumours, spontaneous hemorrhages or head trauma and described three patterns of ICP waveforms as a function of pressure and time (Figure 7.5).

The Lundberg A wave, also called a plateau wave, persists for 5 to 20 minutes at amplitudes of 50 to 100 mmHg. Lundberg B waves are moderately elevated to about 50 mmHg and persist only over 30 seconds to a few minutes. Lundberg C waves occur approximately 6 to 10 times a minute and have amplitudes of 20 mmHg.

Lundberg hypothesized that the A wave is a result of cerebral autoregulation and an increase in CBV due to vasodilation. Elevation in ICP results in decreased cerebral perfusion pressure. Cerebral vessels dilate to maintain cerebral blood flow constant. This results in prolonged elevation of ICP and the plateau wave. This prolonged elevation may be aborted by draining the CSF or other rapid maneuvers to lower ICP. When elastance is high, hypercarbia or other maneuvers that cause cerebral vasodilation can produce plateau waves. The plateau wave may eventually resolve spontaneously, as the prolonged elevation of ICP results in cerebral ischemia which, in turn, produces an adrenergic discharge, an increase in mean arterial pressure (MAP), and restoration of CPP. When the

CPP is adequate, the cerebral vessels constrict and CBV and ICP both decrease. Since ischemia is often associated with Lundberg A waves, they may be associated with permanent cerebral injury. Cerebral ischemia may result in more edema and increased elastance. Plateau waves may be a sign of impending herniation.

Lundberg B waves have no significant clinical effects, but they are considered a sign of cerebral dysfunction. They are seen in comatose patients with Cheyne-Stokes respirations. Variation in CBF occurs in synchrony with B waves. In animal studies, B waves are associated with oscillations in the diameter of the pial vessels and CBV but not with blood pressure or $paCO_2$.

Lundberg C waves correlate with Traube-Hering waves, which are rhythmic oscillations in blood pressure that occur every 6 to 10 times per minute as a result of fluctuations in vasomotor tone and they are independent of the respiratory cycle. They are seen in normal individuals and are not pathological.

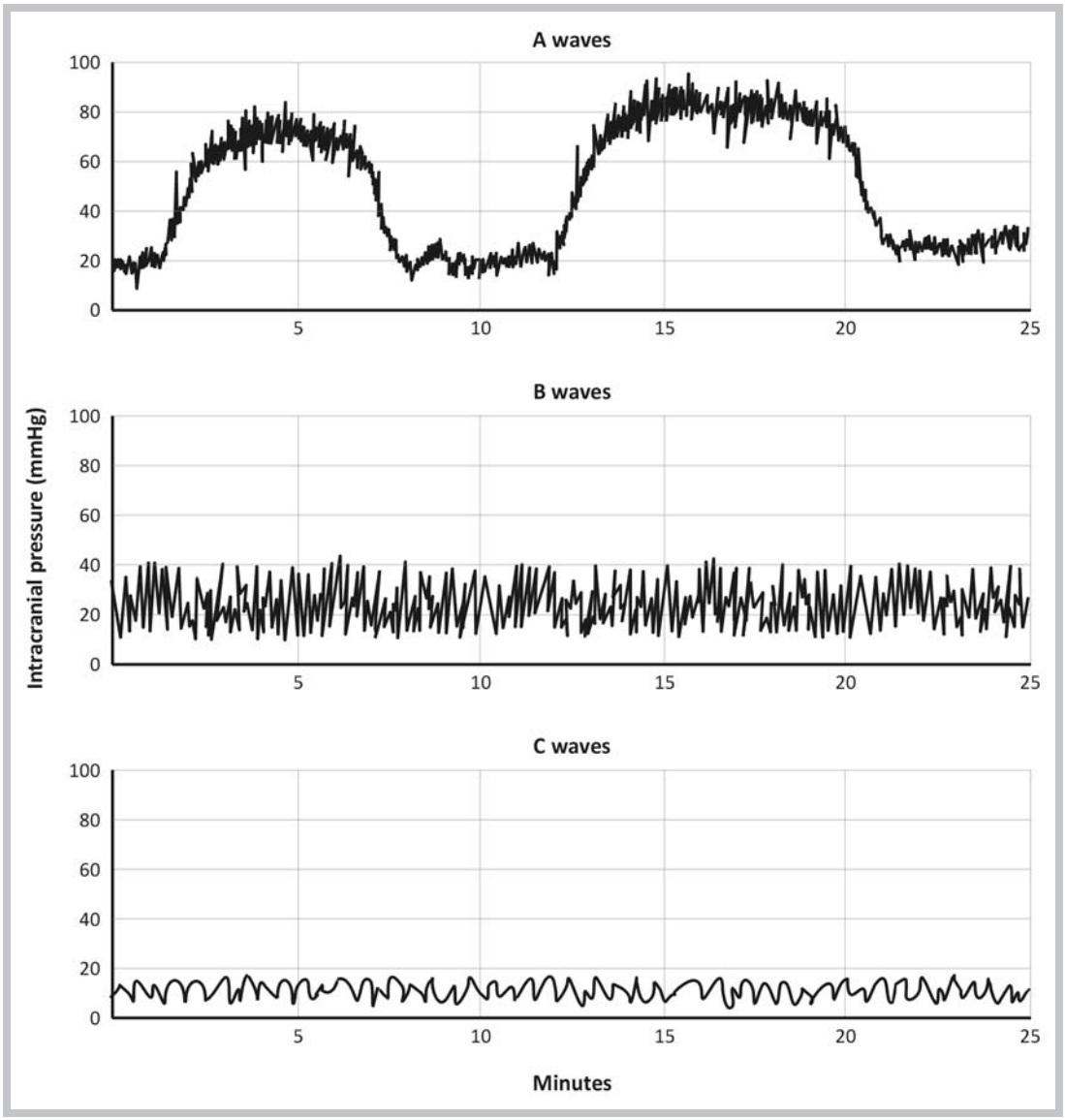

Figure 7.5. Lundberg waveforms.

7.5 Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP) can be calculated with placement of an ICP monitor. CPP is the difference between MAP and ICP. When measuring systemic MAP by an invasive technique, the fluid-coupled transducer is zeroed at the phlebostatic axis in the midaxillary line; however, when measuring MAP to determine the CPP, the invasive arterial line transducer, similarly to the fluid-coupled ICP monitor, is calibrated to the tragus, which corresponds to the foramen of Monro.

Normal CPP is between 70 and 100 mmHg. A CPP of 50-60 may be adequate, but ischemia ensues at a CPP <40 mmHg.

When the central venous pressure (CVP) is elevated, venous outflow from the brain is impeded. The resultant increase in CBV elevates ICP. When the CVP exceeds the ICP, the CPP is instead determined by calculating the difference between the MAP and the CVP.

Positive end-expiratory pressure (PEEP) during mechanical ventilation can affect ICP but it is less frequently seen that one might expect. For PEEP to be clinically relevant to ICP, it must increase the intrapleural pressure. This occurs in patients with compliant lungs but poor chest wall compliance. Studies suggest that ICP is affected by PEEP in situations where PEEP exceeds 20 cmH_20 and when the chest wall is stiff. In this situation, the right atrial pressure and the superior vena cava pressure both increase and venous outflow from the brain is reduced. In conditions where the mean airway pressure is elevated with increased intrapleural pressure, ICP may be affected in the same manner.

Intraabdominal hypertension and the abdominal compartment syndrome seen in multitrauma or patients with severe ileus can also increase ICP by increasing intrapleural pressure. This pressure is transmitted across the walls of the thoracic vasculature. The CVP rises and again impedes cerebral venous outflow, impeding venous return from the brain and increasing ICP. Elevated intraabdominal pressure also reduces venous return to the heart and can decrease systemic blood pressure, thereby also causing a decrease in CPP.

7.6 Cerebral Autoregulation

In steady-state conditions, cerebral blood vessels dilate or constrict to maintain cerebral blood flow constant. When cerebral autoregulation is intact, vasoconstriction ensues with rising MAP to maintain CBF at approximately 50 mg/100g/min. When the blood pressure decreases, vasodilation will maintain CBF at the same level. In normotensive individuals, autoregulation typically occurs between a MAP of 50-150 mmHg (Figure 7.6). The relevance of this for ICP occurs at times of low compliance or high elastance, when increases in MAP result in vasoconstriction which decreases both CBF and CBV, thereby lowering ICP. Conversely, low blood pressures cause autoregulatory cerebral vasodilation and increased ICP (Figure 7.7).

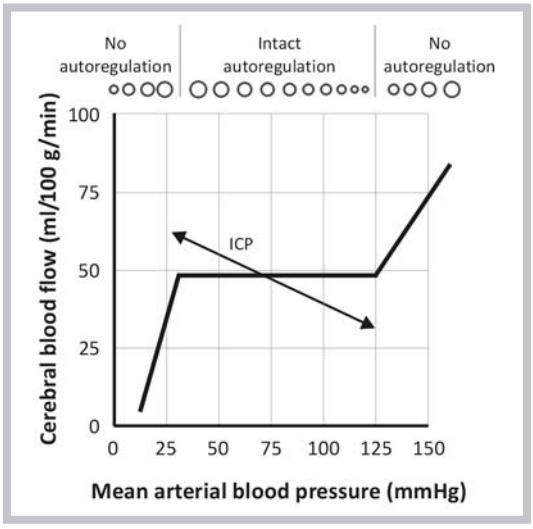

Figure 7.6. Normal autoregulation curve.

In the pathological state, autoregulation is disrupted and CBF cannot be maintained constant. In this situation, decreases in blood pressure directly result in decreased CBF and ischemia. Increases in MAP will increase both CBF and CBV and can result in elevation of ICP. Increases in MAP will also raise the risk of cerebral edema and hemorrhage.

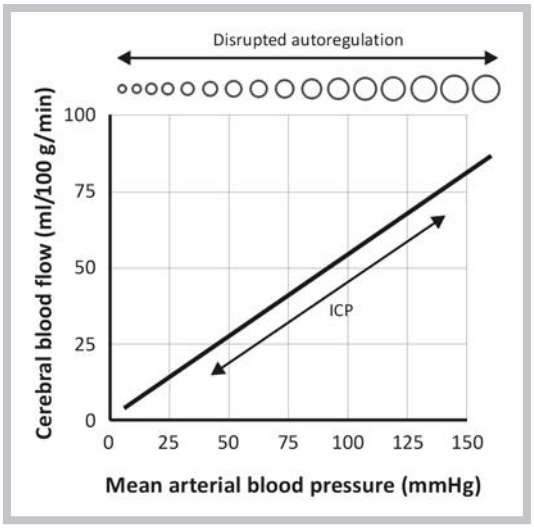

Figure 7.7. **Disrupted autoregulation. Autoregulatory curve in areas of brain injury, such as the core of an ischemic stroke or an area of cerebral contusion in traumatic brain injury, where the cerebral vasculature is disrupted.**

7.7 Indications for ICP Monitoring

Since secondary brain injury such as ischemia can occur in patients with intracranial hypertension, traumatic brain injury (TBI) guidelines recommend the placement of a monitor when the Glasgow Coma Scale score is ≤8 in a patient with an abnormal computed tomography (CT) scan or even when the scan is normal but the patient is aged over 40 years, has unilateral or bilateral motor posturing or systolic blood pressure <90 mmHg. Normal ICP is <10 mmHg. In the Traumatic Coma Data Bank, 72% of patients with severe TBI had an ICP >20 mmHg. Since numerous studies have shown worsened outcome with ICP above 20-25 mmHg, the published guidelines use this as the threshold to treat.

There are no randomized clinical trials to create a strong level of evidence supporting the use of ICP monitoring in other disease states such as ischemic and hemorrhagic stroke (ICH). However, ICP monitoring is considered an option in the 2007 American Heart Association/American Stroke Association guidelines for the management of spontaneous ICH in adults. There are some data to support the use of monitors in hepatic encephalopathy stage IV patients. A contraindication to placement of an ICP monitor is a bleeding diathesis or coagulopathy.

7.8 Conclusions

Intracranial pressure monitoring may be helpful in managing patients with suspected intracranial hypertension. Treating elevated ICP and maintaining adequate CPP may prevent secondary brain injury due to ischemia. An ICP monitor can detect elevations in cerebral pressure before a clinically significant herniation syndrome occurs. Familiarity with the types of monitors available and recognition of waveforms and their patterns can help the clinician to troubleshoot the technical problems that occur during monitoring and to detect worsening of edema.

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8 Update on Brain Tissue Oxygen Monitoring in TBI and Other Acute Cerebral Disorders

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8.1 Introduction

Traumatic brain injury (TBI) is one of the leading causes of mortality and morbidity in the developing and developed countries [1-3], and its impact on the economy, family and personal life is huge. In the developed countries, preventive measures, education, organization of health care and treatment based on invasive and non-invasive monitoring have reduced morbidity and mortality [4-7]. In some developing countries, improvements have come about only in some specialized centres mainly through the better organization of health systems and from the prevention and correction of common secondary injury factors such as hypotension and hypoxia [2,8,9].

The implementation of intracranial pressure monitoring is recommended in severely injured patients. Besides guiding treatment to reduce intracranial hypertension (ICH), it may even be beneficial simply by favouring increased contact with patients and by offering a better understanding of the disease process [10,11]. However, ICP monitoring is costly and many specialists in the developing countries, although not openly discussed, consider such invasive neurological monitoring a low priority, or even superfluous, in an era of scarce budgets, organization and time [11-13]. Such attitudes are reflected in comments often heard from physicians – such as: "I prefer the CT scan", or "There are flaws in calibration", or "The waves are full of artefacts" – and in complaints from administrative staff – such as: "Too much time is spent on this kind of monitoring" [1,13]. Attempts to introduce new monitoring methods to evaluate blood flow and metabolism, such as cerebral oxygenation, are met with even greater controversy [14-17].

The introduction of brain oxygen monitoring as a method to prevent or detect ischemia has followed a similar course as ICP, with many factors unavoidably contributing to mistrust and doubt as to its utility [15,17-19]. TBI is a notoriously heterogeneous disease with a very mixed pathology and variations in severity and histopathology in different areas. In a post mortem neuropathological study, Teasdale and Graham [20,21] described diffuse axonal injury in 92% of cases, hypoxic injury in 54%, focal lesions in 94% and congestion in 28%. In most patients, four or more abnormalities co-existed. Because of such heterogeneity, we do not really know what kind of monitoring is specific for and representative of a given type of brain injury [22,23]. For example, the Glasgow Coma Scale (GCS) provides an indication of severity and prognosis, but it does not identify the specific type of injury nor the kind of monitoring to implement [22,24]. The same GCS score may be observed in different types of injury. Moreover, computed tomography (CT) imaging yields only a momentary picture and is not continuous [22]. There is urgent need for a more multimodal approach to capture and monitor the disease profile [17,25].

The first reports of brain tissue oxygen monitoring ($ptbO_2$) date back 15 years [15], and studies continue to describe the technique and explore associations with other monitoring modalities and different imaging studies [26-29]. Some report on treatment response, but few build on previous experience, for example, taking the time curve into consideration [16,30,31]. Starting in 2009, papers began to appear in the US in which $ptbO_2$ was proposed as a guide for treatment [16,17,32], but they failed to sufficiently take into account the heterogeneity of TBI and cerebral aneurysms. Nor did they relate treatment thresholds to the known profiles of $ptbO_2$ trend differentiation underlying the causes of low oxygen tension values [16,31]). These indiscriminate approaches highlight the complexity of TBI and suggest that we should focus on strategies targeted to the needs of the individual patient rather than on standardized solutions which may be correct for an **average** patient but may not apply to others. The interpretation of findings and how these are translated into clinical practice for the individual patient is therefore relevant when evaluating the cost-benefit ratio of this monitoring system.

Compared to studies from the developed countries, several conducted in Latin America reported that $ptbO_2$ monitoring showed a higher occurrence of secondary injury factors [33-37]. Outcome improved [34-37] but not to the same level as in the most experienced centres [16,17]. It is unknown whether the improved outcome observed after the introduction of brain tissue oxygen monitoring in the developing countries is attributable to a more cohesive team effort and attention to care or to specific treatment goals. Whatever the cause of the decline in mortality, the experience of the developing countries is sufficient to motivate the purchase of monitoring equipment. Greater familiarity with multimodality monitoring can guide the therapeutic decisions by neurosurgeons and intensivists along the time evolution curve and monitoring trends, regardless of clinical grade or sedation level. Within our collaboration, we have compared the experience with $ptbO_2$ monitoring between developed and less developed regions. In this review, we will describe the classical initial reports on $ptbO_2$ monitoring and the more recently published studies. We will define which standards of analysis of $ptbO_2$ can help us to define better treatment approaches. Based on our over 15 years of experience in monitoring $ptbO_2$ we will compare current developments and trends against initial experience. We will also review new areas of application, limitations, and briefly discuss the position of local measurement approaches, such as $ptbO_2$, in relation to more global approaches, such as jugular oximetry.

8.2 Approaches to Monitoring Cerebral Oxygenation

Two different approaches to the study of cerebral oxygenation can be distinguished: global and regional. In global monitoring, oxygen saturation is measured in cerebral venous blood by means of continuous or intermittent monitoring of SjO_2 (jugular bulb oxyhemoglobin saturation) and derived parameters. The most common technique for regional monitoring is to measure the brain oxygen tension ($ptbO_2$). Near-infrared spectroscopy (NIRS), which combines a mix of global and regional monitoring, will not be addressed in this review, as it has not been adequately validated for TBI [38]. The purpose of global monitoring (SjO_2) is to ensure general cerebral oxygenation. In local monitoring ($ptbO_2$) the aim can be either to position the probe in a relatively undamaged part of the brain [39], in which case the values obtained reflect global cerebral oxygenation [15], or to position the probe in the penumbra of a lesion, with the intent to guide therapy to limit the development of local secondary damage [39,40] (Figure 8.1).

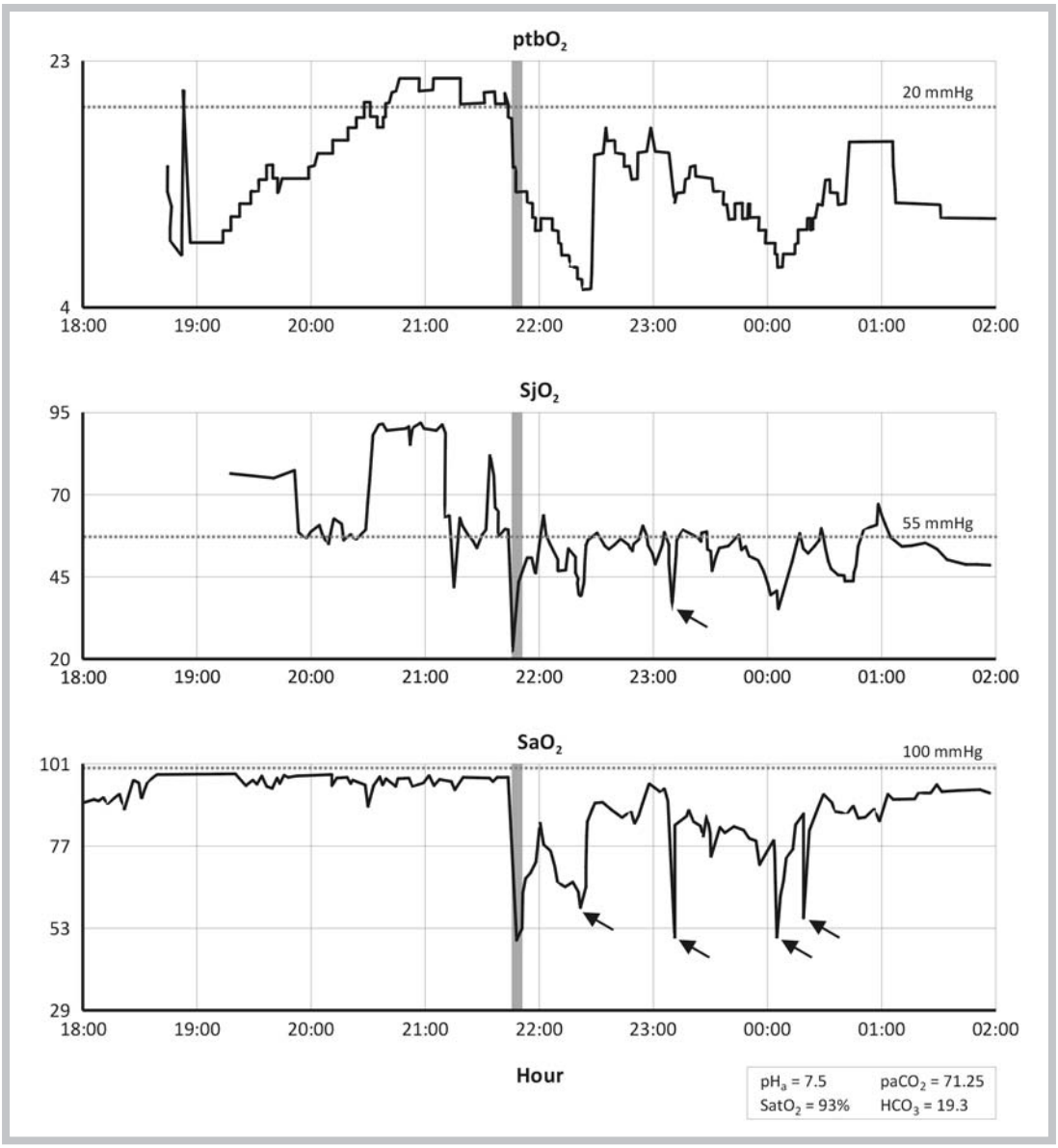


Figure 8.1. **Multiple episodes of systemic hypoxia with ischemic brain. In 30% of cases, these episodes are related to systemic desaturation (lower Figure, SaO_2 and arrows). Decrease in SjO_2 (gray arrow) shows foreseen events. The answer in tissue oxigenation shows a a decrease of more than 20 mmHg after 21 hours. The starting "hyperemia" peak (SjO_2 >85%) is related to psychometric agitation and should be read in relation to median arterial pressure.**

8.2.1 Global Approach: Jugular Bulb Oxygen Saturation

Introducing a catheter into the jugular venous bulb provides access to cerebral venous blood and thus permits indirect measurement of brain metabolism and/or an estimate of the amount of oxygen bound to hemoglobin. This amount is expressed as a percentage rather than by the partial pressure. According to the saturation curve of hemoglobin and oxyhemoglobin at the venous end, a partial pressure of oxygen of 40 torr corresponds to a saturation of 75% [42]. The frequent occurrence of artefacts and the wide variability in venous drainage of the brain produce inconsistencies in the values mea-

sured and reduce the reliability of SjO_2 measurements [43]; nonetheless, the knowledge derived from SjO_2 measurement can be useful in neurocritical care. It is essential that the catheter be positioned (and maintained) in the jugular bulb, as placement in a more proximal position can contaminate it with extracerebral venous blood, making values inaccurate and non-representative of the cerebral condition. By applying the Fick principle to this monitoring technique, changes in cerebral blood flow (CBF) can be inferred, adding more information to support the treatment of TBI and other entities than would be available from ICP monitoring alone [44,45]. Such inferences are valid only when the rate of oxygen consumption and transport, the amount of dissolved oxygen in the blood, the hemoglobin level, and the degree of decoupling of the saturation curve of hemoglobin are all stable [42,46]. Under evolving conditions, these factors need to be considered when interpreting SjO_2 – a step which is not always taken. The global cerebral oxygen status in healthy individuals reflects the balance between oxygen supply and demand and is dependent on cerebral blood flow and metabolism. The cerebral metabolic rate of oxygen ($CMRO_2$), expressed as ml/100 g/min, is calculated by multiplying CBF by the oxygen content difference between arterial and venous jugular oxygen (ΔAjO_2). The equation is expressed as:

$$CMRO_2 = CBF \times \Delta AjO_2 \text{ or } CMRO_2 = CBF \times (CaO_2 - CjO_2)$$

where: CaO_2 = arterial oxygen content; CjO_2 = jugular venous oxygen content; and ΔAjO_2 = arteriovenous jugular difference of oxygen.

In normal conditions, when metabolism is coupled with flow, the $CMRO_2$ will not change [47]; hence, ΔAjO_2 is constant. The normal value is 6.3±1.2 vol. /100 ml of blood [47,48]. In pathological conditions, however, CBF regulation may be abnormal and the coupling between flow and metabolism partly lost. For example, in patients with TBI, CBF can be increased or decreased regardless of $CMRO_2$ [48,49]. Assuming a normal arterial oxygen content, narrowing of the ΔAjO_2 with a SjO_2 >75% indicates that the CBF is too high (>50 ml/100 mg/min) in relation to metabolic requirements and suggests hyperemia. Hyperemic values would be considered when the ΔAjO_2 is <4 ml/dl. Conversely, a wide ΔAjO_2 >9 ml/dl or a low SjO_2 <55% suggests that the CBF is too low to meet metabolic needs and is indicative of hypoperfusion [48].

When regulatory mechanisms are intact, there is an inverse relationship between ΔAjO_2 and CBF. When CBF falls, the brain extracts a greater amount of oxygen and ΔAjO_2 increases. However, when oxygen extraction is already high and the compensatory mechanisms are exhausted, a further decrease in CBF causes a decrease in $CMRO_2$. Therefore, in cerebral ischemia, the oxygen uptake is dependent on the input and the relationship between CBF and ΔAjO_2 and it is also unpredictable. This situation is associated with increased lac-

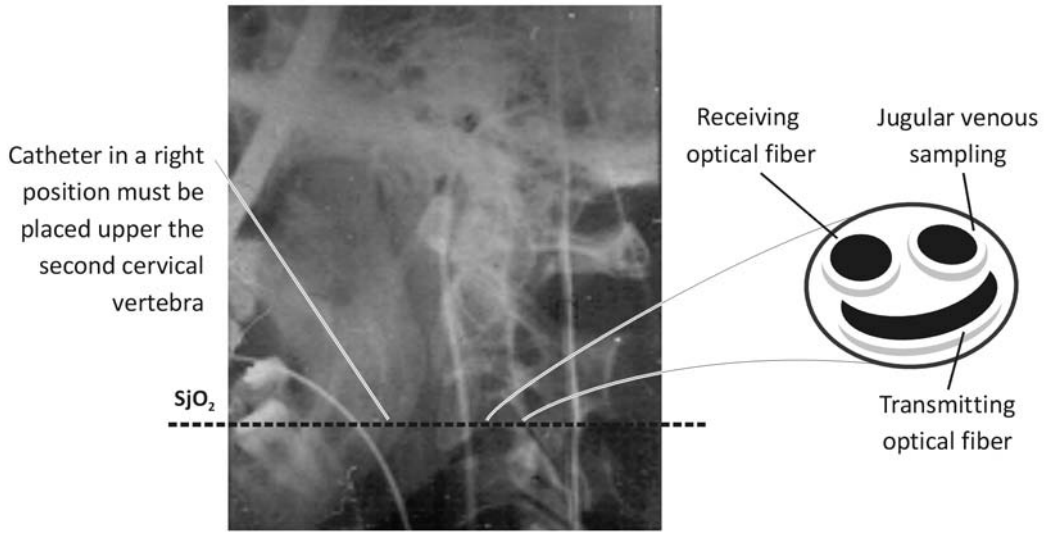
Normal parameters	Hypoperfusion	Hyperemia	References
ΔAjO_2 2.9-6.3±1.2 ml/dl or 1-3 µmol/ml	6.8 ml/dl or 3 µmol/ml	<3 ml/dl or <3 µmol/ml	[48]
CBF 42±12 ml/100 g/min	23 ml/100 g/min	53 ml/100gr/min	[48]
SjO_2 60-75%	<55%	75%	[50,51]
Lactate oxygen index=LOI $AV\Delta/Aj\Delta O_2$ <0.8	Lactate index ≥0.8 Ischemic-infarct pattern	Normal LOI	[40,54]
Cerebral Oxygen Extraction=CEO 35% (24-42%) adults 26% (17-35%) infants	>35%	<26%	[51,52,53]

Table 8.1. Normal and pathological oxygen values in TBI.

tic acid production and can be detected by calculating the lactate-oxygen index (AVΔL/AjΔO_2). A lactate-oxygen index ≥0.8 indicates the presence of ischemia [40,48,54].

In TBI patients, a ΔAjO_2 <2.9 ml/dl corresponds to an average CBF of 53±18 ml/100 g/min, a ΔAjO_2 between 2.9 ml/dl and 6.8 ml/dl corresponds to a CBF of around 42±12 ml/100 g/min, and a ΔAjO_2 >6.8 ml/dl corresponds to a CBF of about 23 ml/100 g/min [48]. Although calculating ΔAjO_2 provides detailed information, drawing blood involves a heavy workload, so continuous SjO_2 monitoring is preferable.

In summary, the SjO_2 can be influenced by many variables involved in global oxygen supply and consumption. It reflects the balance between cerebral oxygen supply and metabolic rate when oxyhemoglobin saturation, hemoglobin concentration and the hemoglobin dissociation curve remain constant. A decrease in SjO_2 reflects a decrease in oxygen supply to the brain or increased metabolic activity. Any disturbance that increases the demand or decreases the oxygen supply may decrease SjO_2. Likewise, a disorder that decreases $CMRO_2$ or increases the oxygen supply can increase the SjO_2.



SjO_2 <55%

- Is it an artifact? (May need catheter repositioning, recalibration of continuous fiberoptic catheter
- Recollect blood sample/Correct estimated value
- Consider the corrected calculated SjO_2 value
- Select the parameter:
  - SjO_2 <55% for 15 minutes
  - ΔAjO_2 > 6.8 vols.
  - ECO_2 > 24
  - $CMRO_2$ increased or decreased
- Before the treatment decision, take into account other parameters: ICP, mean ABP, level of sedation ICP, CPP, ptO_2, anemia, vascular autoregulation and clinical condition

SjO_2 >75%

- Is it an artifact?
- Recollect blood sample/Correct estimated value
- Consider the corrected calculated SjO_2 value
- Select the parameter:
  - SjO_2 >75%
  - ΔAjO_2 <3 vols.
  - ECO_2 >42%
  - $CMRO_2$ decreased
- Before the treatment decision, take into account other parameters: ICP, mean ABP, level of sedation ICP, CPP, ptO_2, anemia, vascular autoregulation and clinical condition

Figure 8.2. **Key points in SjO_2 monitoring. Main questions and management flow chart.**

For a better understanding of the relationship between CBF and $CMRO_2$, we may consider cerebral hyperemia as being similar to the hyperdynamic state in sepsis, in which cardiac output is high with a narrow ΔAjO_2, with poor oxygen consumption and arteriovenous shunting [55]. In contrast, prolonged ΔAjO_2 with SjO_2 <65%, corresponds to a hypodynamic state, with pump failure and extensive extraction [56]. Clearly, this is only a comparison, because the vascular autoregulation in the brain is very different from that in other parts of the body (Figure 8.2).

8.2.2 Practical Approach: Hyperemia with SjO_2 >75%

To properly interpret SjO_2 measurements, it is necessary to consider other variables of multimodality monitoring, and ICP monitoring in particular. A SjO_2 >75 % (ΔAjO_2 <3 vols.) which coincides with an increase in ICP should be initially treated with rapid correction of hyperthermia, if present, and a moderate degree of hyperventilation [57,58] ($PaCO_2$ 30-35 mmHg) as the main agent. Increased sedation may be appropriate if levels are considered insufficient to reduce agitation [59,60]. Prior to initiating treatment, it is necessary to:

- Check for possible jugular catheter malposition.
- Check the calibration: ensure that the value estimated by the fiberoptic catheter does not vary by more than 4% compared to the saturation measured by the co-oximeter, while slowly withdrawing blood from the catheter tip [43].

It is recommended to calibrate the SjO_2 monitor with the co-oximeter every 6 hours when changes in SjO_2 occur and prior to initiating therapeutic changes. Rotation movements of the neck or cervical extension facilitate the loss of the optical signal, since the fiberoptic catheter then touches the walls of the vein (Figure 8.3).

Clots can also alter the light transmission of the optical fibre [43]. Table 8.2 shows important factors for the treatment decisions of patients with SjO_2 >75 % and SjO_2 <55 % by means of other elements of multimodality monitoring.

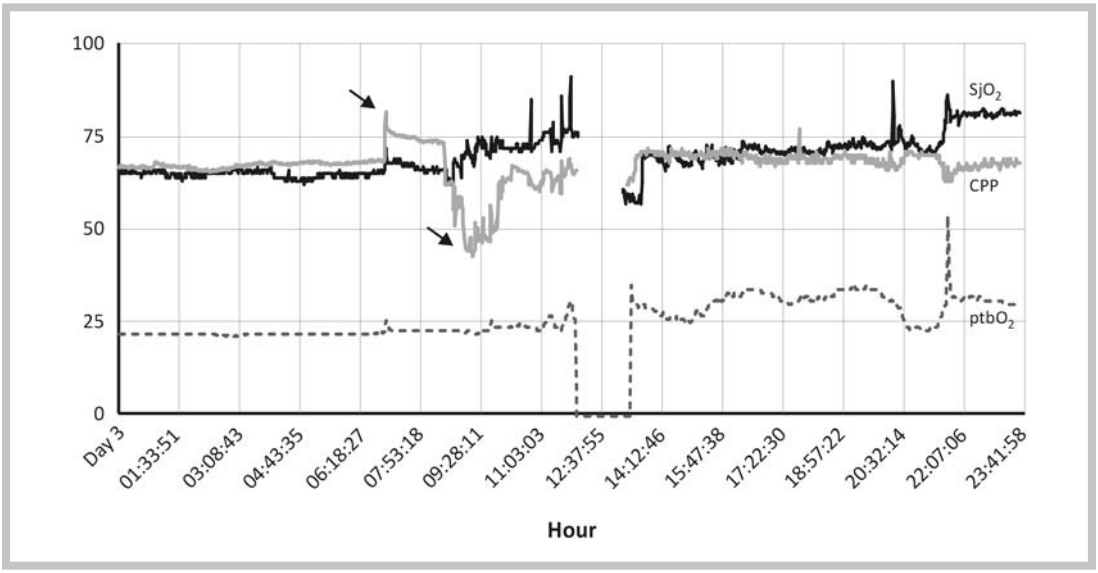


Figure 8.3. **SjO_2 monitoring and common artefacts. During the bath, SjO_2 (previously increased with CPP, first arrow) decreased by 45 mmHg (second arrow). No consistent variation in CCP in relation to $ptbO_2$ was observed. With the fast and inexplicable fall of SjO_2, blood was extracted and SjO_2 changed. Between 6.18 and 7.53 hrs, with the aspiration of secretions, SjO_2 increased, suggesting hyperemia. The period of monitor disconnection shows $ptbO_2$ reliability and recalibration of SjO_2 (registered between 12.37 and 14.12 hrs).**

Factors favoring SjO_2>75%	Factors favoring SjO_2 <55%

• Permissive hypercarbia
• Psychomotor agitation and pain
• Postoperative areas
• Underlying surgery
• Defective vascular autoregulation
• Decreased cerebral metabolic rate
• Venous outflow obstruction or cranial cervical
• Seizures
• Metabolic acidosis
• Hyperoxemia 100%
• Uncal herniation and brain death
• Alveolar recruitment with CO_2 retention
• Fever poorly controlled
• Spesis
• Common artifacts:
  ▪ Bath immersion
  ▪ Mobilization of the catheter
  ▪ Catheter lumen obstruction
  ▪ Patient transfer
  ▪ Suctioning
	• Arterial hypotension
	• Hypocapnia <30 mmHg
	• Intracranial hypertension
	• Decreased CBF
	• Real hypoxia with or without hypotension
	• CSF Leake
	• Oversedation
	• Low cardiac output
	• Hypothermia
	• Chills after removal of hypotermia
	• Cerebral vasospasm
	• Dehydration and Hypovolemia
	• Heart failure
	• Increased viscosity
	• Common artifacts:
	  ▪ Bath immersion
	  ▪ Mobilization of the catheter
	  ▪ Obstruction of the light emitted
	  ▪ Patient transfer
	  ▪ Suctioning

Table 8.2. **Factors decisions in Hyperemia and Hypoperfusion interpreted by SjO2 in TBI.**

8.2.3 Theoretical Approach: Hyperemia With SjO_2 >75%

Hyperemia is common in the immediate postoperative period after craniotomy [61]. The CBF in the area adjacent to a craniotomy may increase which – particularly in combination with an increase in blood pressure – can lead to vasogenic edema. When the brain

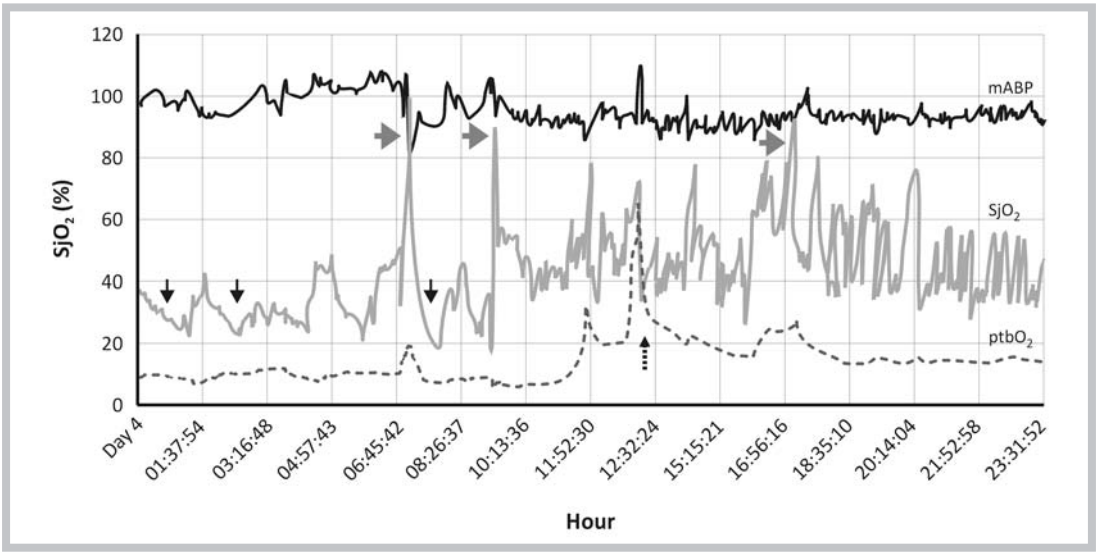


Figure 8.4. **Male, 15 years old, with GCS 8, CT Scan with diffuse small hemorrhagic points after traffic accident. Several events of hyperemia (gray arrows) and hypoperfusion (black arrows) in TBI patient, not fully sedated and febrile. The repercussion in $ptbO_2$ was evident; $ptbO_2$ decreased by 5 mmHg with an associated reaction in SjO_2. Dotted arrow shows fest FiO_2 100%. The blood pressure had an increasing pattern trend. Hypoperfusion (black arrows).**

is decompressed following the removal of a space-occupying lesion [5], the ICP decreases, sometimes leading to an abrupt increase in perfusion. This type of hyperemia can be indirectly detected with SjO_2 (high values), but SjO_2 may later decrease when the metabolic reserve is exhausted and CBF has become insufficient [62,63]. Blood pressure control becomes critical at this moment in order to limit the development of vasogenic edema. Because agitation and pain may cause increased blood pressure, it is better to initiate appropriate levels of sedation and analgesia before treating hypertension with antihypertensive drugs such as nifedipine or nicardipine [64-66] (Figure 8.4).

in 30% of patients with severe TBI, nursing procedures such as tracheal suctioning in the first 36 hours posttrauma increased blood pressure, ICP and SjO_2. ICP remained elevated for 11±6.1 minutes by 5 mmHg or more (mean increase of 16.6±10.2 mmHg) and SjO_2

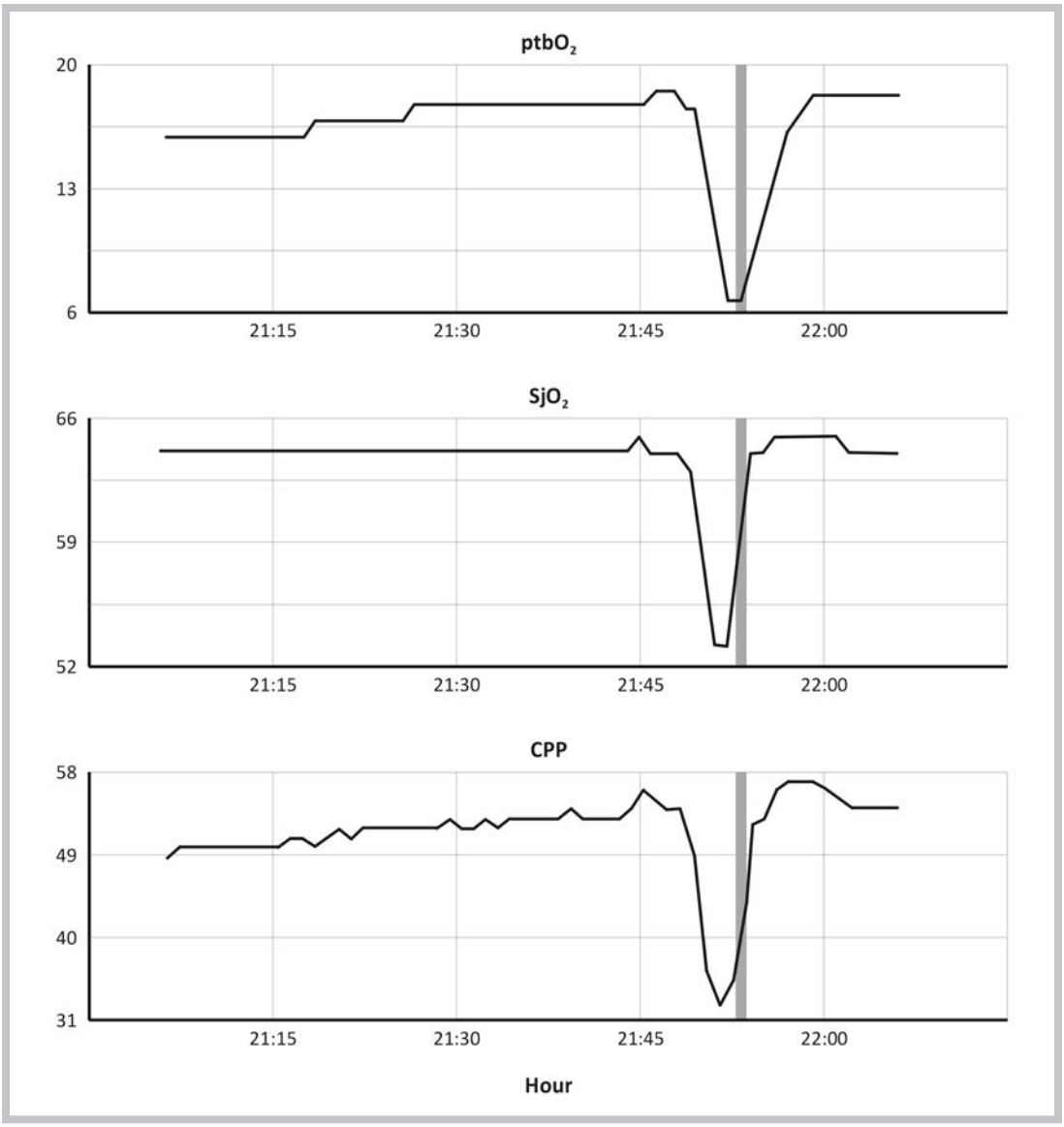


Figure 8.5. **Evident disfunction in cerebrovascular autoregulation. The cerebrovascular autoregulation is dependent from the cerebral pressure perfusion (CPP), especially in cases with vasopressors. In this case, CPP was really low, below the normal range. SjO_2 and $ptbO_2$ decreased at the same time of CPP (21.45 h).**

for 15.0±12.4 minutes, rising from 62±10 to 77±10%. The blood pressure increased for at least 10 minutes (average, 16.0±8.0 minutes) during and after 94 of the 120 aspirations, resulting in an increase in cerebral perfusion pressure (CPP) from 80.7±11.9 to 97.4±18 mmHg. The sustained rise in SjO_2, with increased perfusion pressure during and after suctioning, suggests disturbed vascular autoregulation [67]. The impact that such events may have on outcome is uncertain. Sometimes, autoregulation can partially self-regulate; increasing the blood pressure with vasopressors may reduce ICP and improve the SjO_2.

It should be remembered, however, that a single determination of SjO_2 >75% by itself does not imply a correct CPP nor does it define the prognosis [68].

Much can be learned about the incidence of hyperemia in TBI as determined by SjO_2 from studies by Robertson et al. [69]. A total of 2799 samples were taken from 450 patients in the first 5 days after trauma. Normal values were found in 342 patients (76%), high values (>75%) in 86 (19.1%), and low values (<55%) in 22 (4.9%) (Figure 8.6).

The distribution of SjO_2 values was found to change over time. On days 1 to 5 posttrauma, about 30% of patients had a SjO_2 >75%. No clear correlation was found between SjO_2 and CBF, however [42,69]. Low CBF values occurred at high values of saturation and high CBF values at lower SjO_2 values. Patients with an average SjO_2 >75% had a poorer outcome, most likely secondary to a depressed metabolic rate rather than due to hyperemic CBF. In this study, SjO_2 >75% was not clearly associated with hyperemia, although some authors consider it a major cause of intracranial hypertension [70,71].

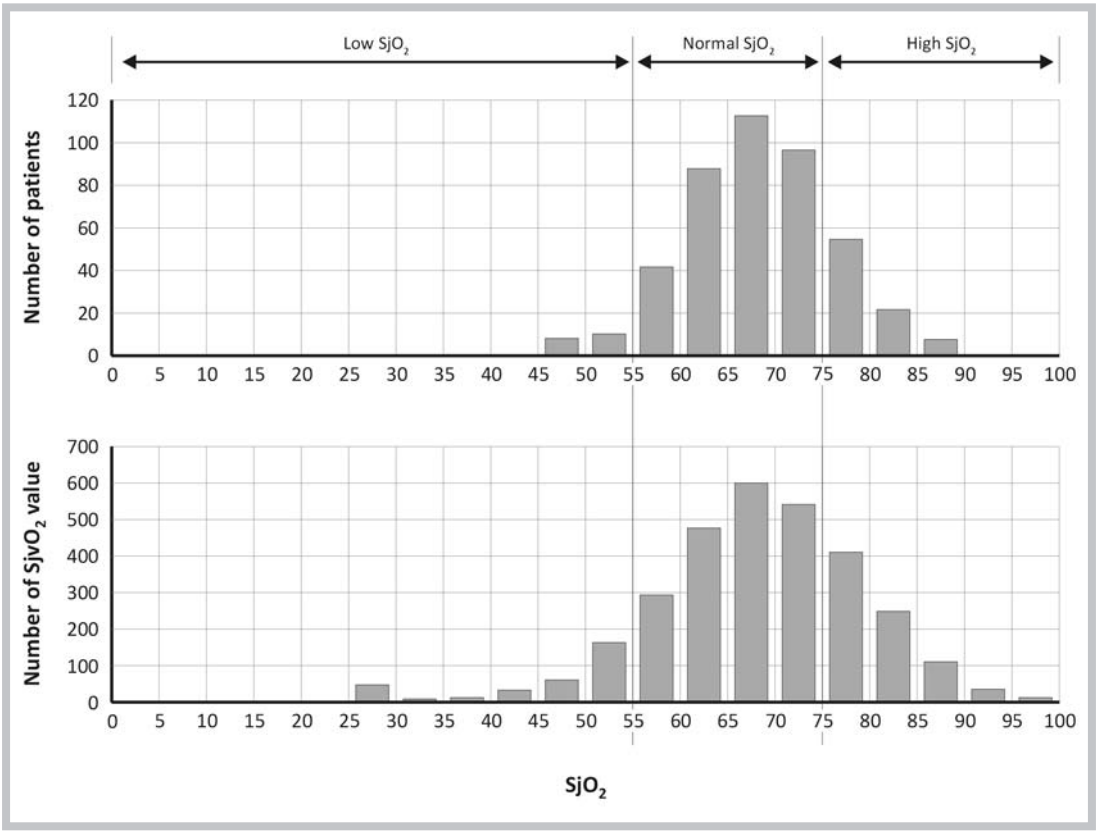


Figure 8.6. **Graphs showing the distribution of the SjO_2 values among the 450 patients (upper) and distribution of the 2799 SjO_2 individual measurements (lower), with division into three groups with low, normal, and high SjO_2 values.**

Also, a wide range of CPP values was found at elevated SjO_2 values, indicating that hyperemia cannot be accurately identified by measuring SjO_2. Regional CBF can be high in some parts of the brain but low in others [49,72]. These findings stand in contrast to those of other studies, where a closer association between SjO_2 and hyperemia was found in smaller groups of patients. What we can conclude is that hyperventilation or other treatments to induce vasoconstriction should be initiated to decrease suspected hyperemia if patients are adequately monitored [59,60]. This makes a strong case for multimodality monitoring as a basis for treatment decisions [73].

In 1982, Chan [49] investigated the association between CPP and SjO_2 in 41 TBI patients by means of continuous transcranial Doppler measurement to determine the optimal CPP level. At a given SjO_2 level, the average velocity in the middle cerebral artery was measured and the pulsatility index calculated. The pulsatility index is defined as:

Pulsatility index: systolic velocity – diastolic velocity/mean velocity

(normal value = 0.9±0.2 in 20 subjects)

Regression analysis demonstrated that a decreased CPP, due either to an increase in ICP or a drop in blood pressure, increased the pulsatility index and reduced the SjO_2. Decreases in SjO_2 occurred more frequently at CPP levels <70 mmHg. At CPP levels >70 mmHg, however, there was no correlation between the pulsatility index and SjO_2. Transcranial Doppler studies and calculation of the pulsatility index may therefore provide support in the search for an optimal CPP at a given level of SjO_2.

8.3 Hyperemia and Arterial pCO_2

Vascular tonus is strongly dependent on arterial pCO_2. Increasing pCO_2 and hypercarbia ($PaCO_2$ >45 mmHg) causes vasodilatation, with an increase in cerebral blood volume and an increase in CBF. For each mmHg increase in $PaCO_2$, CBF increases by 3 to 4% and cerebral blood volume by 0.72±0.42 [74,75]. Changes in arterial CO_2 concentration affect its influence not only on vascular tone through changes in pH, but also through altered concentrations of adenosine and nitric oxide mediators which are considered mediators of vascular tonus [76]. An increase in $PaCO_2$ raises ICP because increases in blood volume lower the volume-pressure index (see explanation in Annex 1) and spatial compensation capability.

The reduced reserve capacity to deal with increased volume at higher levels of arterial pCO_2 has direct relevance for clinical management [59,60]. In situations of increased arterial pCO_2, relatively minor and otherwise innocent increases in cerebral blood volume, which may be caused by the use of positive end-expiratory pressure (PEEP), venous obstruction, flexing of the neck or recruitment maneuvers, may lead to an unacceptable increase in ICP [77,80]. Therefore, caution is recommended in the use of permissive hypercapnia and lung-protective maneuvers in these situations [81].

Pulmonary problems caused by aspiration, contusion, rib fractures and atelectasis are common in TBI patients. Adjuvant CO_2 retention with a decreased vital capacity and an increase in dead space may cause secondary brain damage due to increased cerebral blood volume, ICP and SjO_2. Acute elevations of arterial pCO_2 which increase ICP can generally best be managed by short-duration manual ventilation with an Ambu bag. Monitoring the effect of such maneuvers is important, as excessive vasoconstriction may result in cerebral ischemic events (Figure 8.7).

There are reports of the use of airway pressure release ventilation (APRV) mode to protect against elevation of ICP and to promote the elimination of pCO_2 [82,83]. Impor-

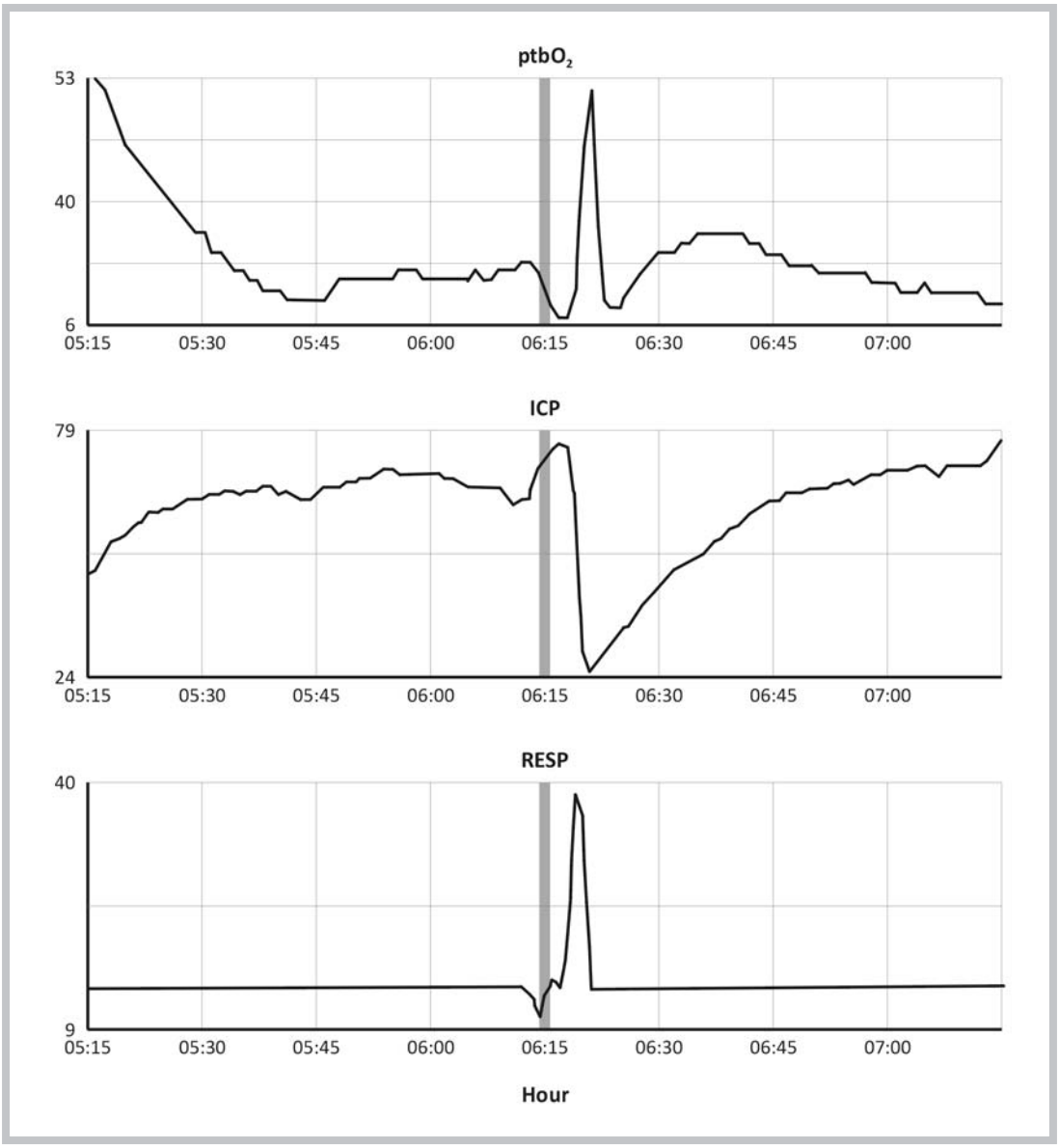


Figure 8.7. **Refractary ICP and hyperventilation maneuver. The Ambu bag maneuver decreased ICP from 79 to 24 mmHg (6.15 hour). The initial elevation of mean ICP (5.15 h) was associated with a dropping trend of $ptbO_2$. Later $ptbO_2$ reached 53 mmHg with hyperoxia FiO_2 100%. With Ambu bag maneuver (RESP=40) ICP decreased for around 15 minutes (6.15 h), and $ptbO_2$ had a "superficial" improving pattern.**

tantly, however, any process that increases the alveolar pressure will also increase the pressure in the pulmonary artery and veins, thus carrying some risk for hypercarbia and suboptimal perfusion due to increased alveolar dead space. Much uncertainty exists on the effects of alveolar plateau pressure levels and the consequent production of CO_2 during recruitment maneuvers in ICP.

An artificial maneuver that may mimic hyperemia is the administration of 100% oxygen prior to suctioning procedures. In hyperoxia, SjO_2 increases markedly, thus potentially minimizing the risk of temporal dysperfusion and cerebral hypoxia in compromized patients [84,85] (Figure 8.8).

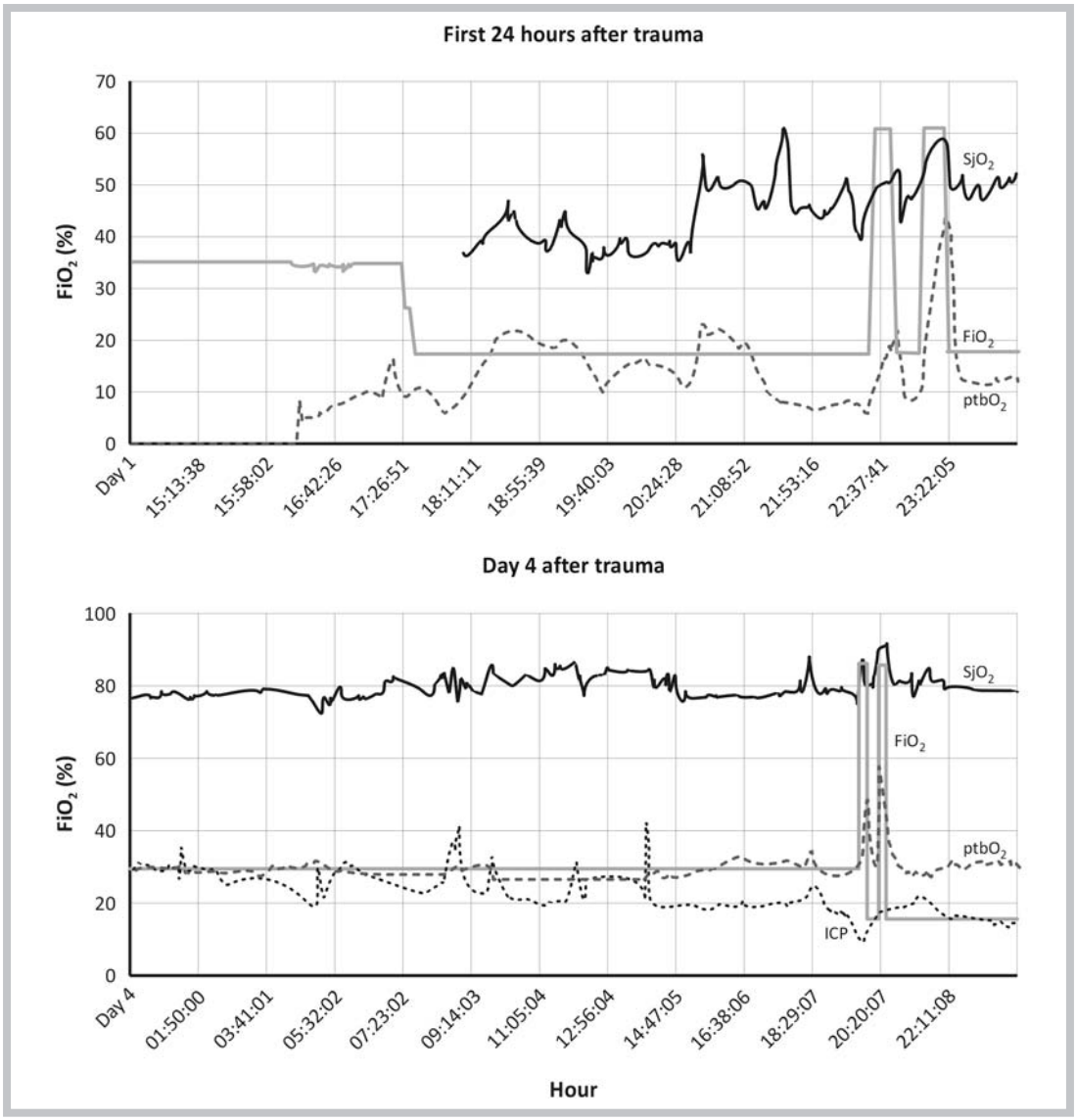


Figure 8.8. **Ischemic pattern and hyperoxia response. On the initial 24 hours after trauma the oxygen parameters SjO_2 an $ptbO_2$ shows lower values (SjO2= 55 % and $ptbO_2$= 15mmHg). From 18.11 until 22.59 abnormal lower values were observed. With hyperoxia 100 % FiO_2 both parameters increased: $ptbO_2$ reached 40 mmHg and SjO_2 60%. The main suggestion for treatment will be to find the main cause of deterioration. Ischemic pattern an hyperoxia response. On day 4 after trauma the ischemic pattern improves. ICP decreased progressively, $ptbO_2$ and SjO_2 had a better trend. With FiO_2 100 % both parameters increased, $ptbO_2$ reached 50 mmHg and SjO_2 90%, (20.20 hrs), with a hyperemia response. The appearance of hyperemia was unmasked by FiO_2 % 100 and better condition of this subdural hematoma, GCS 4, with isocoric and reactive pupils.**

The response is immediate and oxygenation can be maintained for the duration of suctioning procedures. The use of SjO_2 monitoring can therefore provide opportunities for quantifying the quality of nursing activities and permits the verification of adequate preoxygenation prior to suctioning procedures. Hyperoxemia with delivery of 100% FiO_2 as a therapeutic maneuver has been proposed by various groups [84-87]. Increasing PaO_2 has been shown to decrease tissue lactate as measured by microdialysis [88]. Its effects on metabolism appear promising, but possible oxygen toxicity should be considered [89].

8.4 Approaches to Treatment

For treating injuries from a pathophysiologic perspective, Cruz proposed three stages of altered oxygen consumption in relation to CBF and SjO_2:

- When a decrease in neuronal activity, aerobic metabolism and CO_2 production leads to a proportionate decrease in CBF, cerebral oxygen extraction remains normal. This indicates a good balance between flow and metabolism.
- When the CBF is low in relation to oxygen consumption, cerebral oxygen extraction increases to compensate for the low flow state, and this condition represents oligaemic cerebral hypoxia.
- When the CBF is relatively high in relation to oxygen consumption (defective metabolic autoregulation), cerebral oxygen extraction decreases. This condition represents relative hyperperfusion or "luxury perfusion" [90].

Treatment for elevated ICP can be differentiated according to each of the above scenarios. In hyperemic flow with decreased cerebral extraction, Cruz proposed the concept of "optimized hyperventilation", in which hyperventilation is targeted to decrease $PaCO_2$ to levels <25 mmHg or even <20 mmHg [52]. This approach remains controversial because of the high risk of cerebral ischemia in the acute phase after injury and because of the heterogeneity of CBF in different areas of the brain.

The concept of optimized hyperventilation assumes that vasodilatation and CBF are homogeneous; however, this is not necessarily the case. Caution is therefore recommended when using optimized hyperventilation under the supervision of SjO_2 and it should be used with moderation [59,60].

By contrast, optimized hyperventilation is inappropriate when the ICP is >20 mmHg and associated with increased or normal brain oxygen extraction. Cruz proposed the use of manitol, whilst other other authors recommended either hypertonic solution or barbiturate coma [52,91].

Summary of Hyperemia as Indicated by SjO_2 >75%

- High SjO_2 values are primarily caused by a low cerebral metabolic rate.
- Hyperemia as indicated by SjO_2 >75% occurs predominantly after the first 48 hours.
- Although hyperemia may be a cause of intracranial hypertension, high SjO_2 values are also found in patients with normal ICP.
- The pathophysiologic mechanisms underlying hyperemia are potentially reversible through respiratory modifications and metabolic intervention.
- Hyperemia as indicated by a high SjO_2 can be associated with severe disturbances in cerebral autoregulation.
- Prior to initiating treatment for high SjO_2 values, calibration errors should be excluded.

8.4.1 Practical Approach: Hypoperfusion due to SjO_2 <55-60%

Low SjO_2 values, which reflect increased oxygen extraction in relation to flow, are indicative of an increased risk of ischemia [50]. The therapeutic approaches in these patients should be aimed to increase oxygen delivery. In patients with raised ICP and a SjO_2 <55%, we recommend correcting hemoglobin levels as a first step if these are low. Whilst a restricted approach to transfusion is currently recommended in general trauma following the demonstration of a lower mortality, it should also be remembered that brain trauma is a different situation [93,94].

Cerebral ischemia is particularly frequent in TBI patients with anemia and cerebral hypoperfusion. Much evidence exists that cerebral ischemia is a commonly encountered

problem after TBI, particularly in the first 24 hours [50]. In this period, low CBF values and low values of jugular venous saturation (<65%) have been shown to occur frequently. Short-duration hypotensive episodes often cause SjO_2 to fall to values <65%, illustrating the deleterious effect of low blood pressure on cerebral oxygenation[95]. In their histopathology studies, Teasdale et al. demonstrated the presence of cerebral ischemia in over 90% of cases [96].

More recently, magnetic resonance imaging (MRI) studies have shown that hypotension after TBI is associated with neuronal loss in the thalamic region [97, 98]. In a study by Robertson et al. [50,95], hypotension was the leading cause of episodes of jugular venous desaturation. Insufficient cerebral oxygenation and insufficient blood flow due to hypotensive insults are an important cause of secondary brain damage after TBI.

The effects of such secondary insults may be greatest in patients with intracranial hematoma. Many patients with cerebral contusion or intracranial hematoma show secondary deterioration and often present with the clinical syndrome of "talk and deteriorate" [99]. This illustrates that outcome is not only determined by the primary lesion and serves to highlight the possibly devastating influence secondary brain damage can have. Reports from the Manchester Emergency Services highlighted poorer outcome in moderate TBI patients with associated systemic injuries [100]. The priority of preventing and treating cerebral ischemia is to target appropriate levels of blood pressure and arterial oxygenation. Critical decreases in SjO_2 <50% for 10 minutes or longer are absolute indications for instituting vigorous therapy [50]. Early therapeutic interventions aimed to avert such critical episodes are strongly recommended.

Prevention and treatment of cerebral hypoperfusion requires adequate fluid resuscitation and the combined use of vasopressors. Various authors state a preference for the use of norepinephrine [101-103], as the drug is more selective and its effects more constant (see section on regional monitoring). Rosner devised eight rules to identify the best point of perfusion level based on multimodality monitoring [104] (Table 8.3).

- The abnormal brain frequently needs more CPP
- The Cushing response to increased ICP consists of an increase in mABP. This response is produced for inadequate blood flow. The systemic hypertension results, which improves blood flow to needed levels. In chronic hypertensive patient is that these apparently extreme levels of systemic pressure are frequently maintained quite well, as long as the physician does not interfere. High blood pressure are a necessity. A similar situation exists in young children, they become quite hypertensive, this hypertension is a clear cut/guide to what their brains seem require at any given moment
- Lundberg A-waves or plateau waves indicate that CPP is inadequate. It is important to recognize the occurrence of such waves
- Artificially raising or stabilizing CPP at a constant level above the threshold will eliminate these waves.
- If CPP is above the lower limits of autoregulation, then ICP will vary inversely with CPP. With vasopressor use an increase in mABP will benefit ICP, with a lower descendent pattern; such is described in Figure 8.9.
- The pinch maneuver induce pain stimulus, which promotes transit hypertension similar, than vasopressor response. If painful stimulation promotes a decreased in ICP and increasing tendency in BP, this maneuver can be used for an evaluations of autoregulation curve that patient is functioning. In conditions of plenary sedation this maneuver is not really evaluated. In some cases the pain maneuver may associate with arousal and an increase in $CMRO_2$ and ICP, with a detrimental response
- CPP versus PVI. The PVI index (Pressure-Volume Index) measures the compliance of the brain (Marmarou Index) This parameter calculate at multiple different cerebral perfusion pressures may provide a quantitate estimate of whether a patient is on the healthy versus low side of the autoregulatory curve. If PVI is plotted at multiple CPP levels and the slope is positive then the suggestions is that patient is on the healthy side of autoregulation curve. If the patient had a poor compliance, the patient is in dangerous position
- The SjO_2 and $ptbO_2$ offers a new approach for a better optimization of CPP. This approach is discussed in $ptbO_2$ section

Table 8.3. **Rosner's rules to identify the best point of perfusion level based on multimodality monitoring.**

The optimal CPP level can vary between individual patients. Several studies suggest aiming at values of 60 to 70 mmHg [104,105] and international guidelines recommend maintaining CPP >60 mmHg [59,60], although lower levels may be considered acceptable in selected patients. When taking SjO_2 into account, it should be remembered that the detection of desaturation events requires continuous monitoring as short-duration episodes, which may be very harmful and are not detected by intermittent monitoring [106]. Desaturation events can occur in up to 40% of TBI patients.

In patients with low SjO_2 values, therapeutic modalities that may increase vasoconstriction, such as hyperventilation, should be avoided. Also, it is advisable to frequently reassess the acid-base balance, specifically with regard to $paCO_2$ and respiratory alkalosis, by means of regular blood gas analysis and continuous monitoring of end-tidal CO_2.

Following the correction and optimization of systemic parameters (anemia, hyperthermia, arterial pCO_2 and arterial blood pressure), every effort should be made to determine

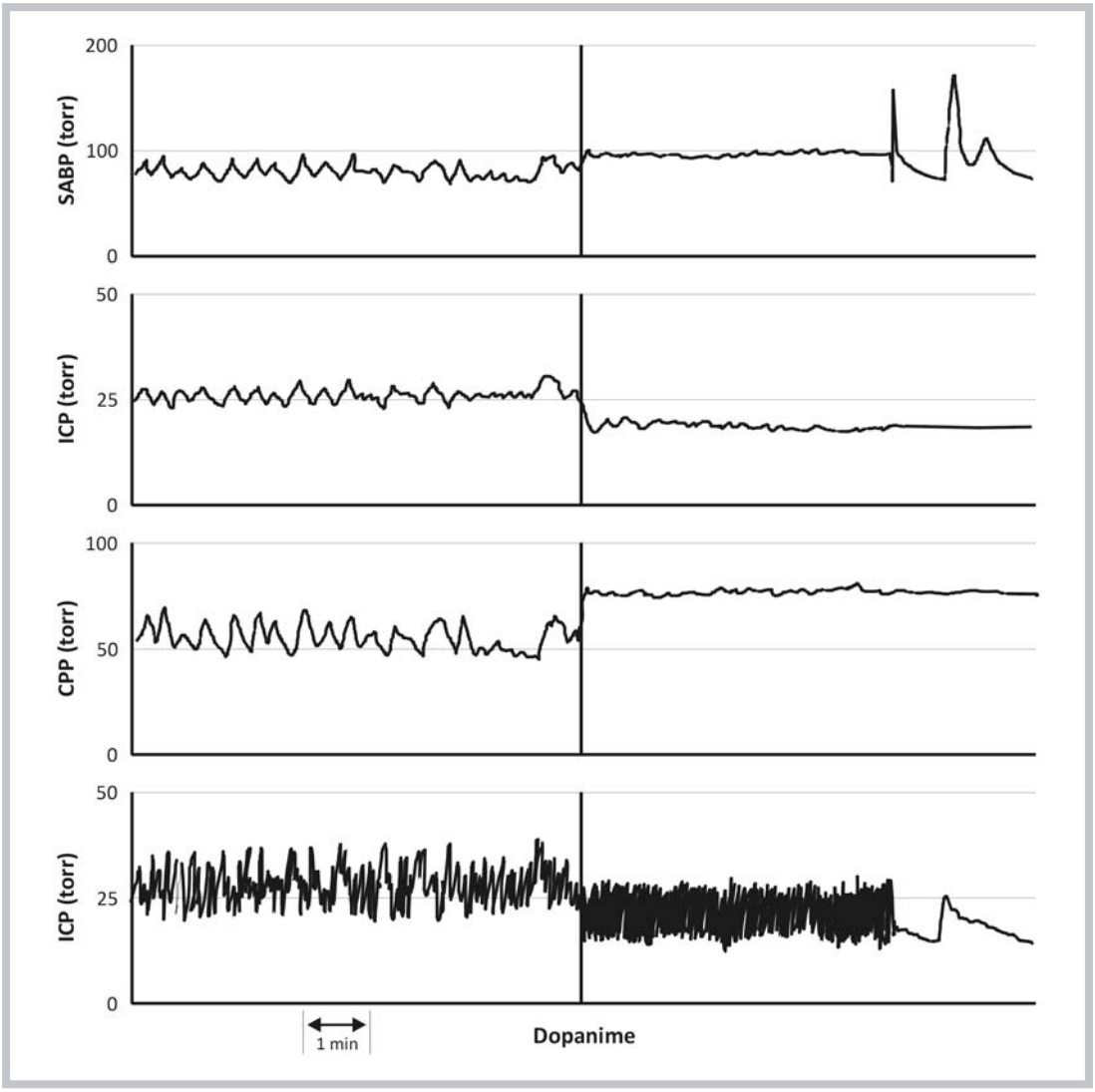


Figure 8.9. **The vasopressor effect of dopamine decreases ICP. Upper panels show sistolic arterial blood pressure (SABP), ICP, and CPP. The insufficient systolic blood pressure around 90 mmHg was not the better combination with ICP of 35 mmHg. Vasopressor effort decreased ICP to 20-25 mmHg.**

the cause of desaturation in order to target therapy more appropriately. If low blood pressure is the problem, this should be corrected; if a low CPP has resulted from increased ICP, then the management should be primarily directed at treating the raised ICP.

8.4.2 Theoretical Approach: Avoiding Risks of Hyperventilation in Patients with Hypoperfusion (SjO_2 <55%)

Lowering arterial pCO_2 by hyperventilation is a recognized and effective approach to reduce elevated ICP [107]. The mechanism of action is by reduction of cerebral blood volume owing to vasoconstriction. Experimental studies using a cranial window have clearly confirmed that vasoconstriction of the pial arteries results from hyperventilation [108]. Studies using electroencephalography (EEG), however, showed that, whilst decreasing ICP, hyperventilation also produces flattening of wave form activity on the EEG [109].

Clinical evidence also exists that hyperventilation may compromise cerebral blood flow and oxygenation. In the first 24 hours after injury, global CBF is reduced in 30-70% of patients with severe TBI. In such patients the risk of cerebral ischemia on instituting hyperventilation may be particularly high [110]. An early work by Obrist [111] demonstrated that hyperventilation to an arterial pCO_2 of 23.2±2.8 mmHg reduced CBF to 18.6±4.4 ml/100 g/min and increased arterial venous content differences by 10.5±0.7 vols. %.

Subsequent studies have shown that hyperventilation is the second most common cause of desaturation following a hypotensive episode [50,51]. Deliberate or inadvertent hyperventilation episodes may occur during the entire clinical course, extending from the injury site to the emergency room and the intensive care unit. The risk of hyperventilation is particularly high during transport [112] and is not always recognized.

In a descriptive study investigating the effects of hyperventilation in 21 patients in Mexico City, we found that in 82.6% of 97 samples the arterial pCO_2 was <30 mmHg and SjO_2 <65% in 45% of the samples [113]. These studies were performed using intermittent SjO_2 monitoring with a co-oximeter, and the real incidence of jugular desaturation was probably underestimated. A strong case can be made for implementing further education and awareness to prevent and correct the “routine” use of hyperventilation, and this approach should be supported by motivation and training.

Level II guideline recommendations advise against hyperventilation in patients without elevated ICP. This recommendation is based on a relatively small number of patients, but the real impact of hyperventilation on outcome after TBI is uncertain. We suggest that hyperventilation may be definitely deleterious in some patients, but – if monitored closely – it may be beneficial in others.

There are well-documented risks associated with the use of hyperventilation to decrease CBF, to decrease brain oxygen tension, and to cause jugular desaturation [50,59,60]. More recent studies using positron emission tomography (PET) have shown that $CMRO_2$ is unaffected by moderate hyperventilation [114]. Microdialysis studies, however, have shown that short-duration hyperventilation in the first 24 hours after injury can increase brain lactate and decrease cerebral extraction of oxygen [115]. Uncertainty exists about which patients may and which will not benefit from hyperventilation. Caution in the use of hyperventilation is advisable. The following recommendations can be made:

- Avoid hyperventilation in the first 24 hours after trauma and during transport. When applied, use hyperventilation only for short periods [59,60].
- Do not exceed a moderate level of hyperventilation ($paCO_2$ 30-35 mmHg) [59,60].
- Closely monitor and assess the end-tidal CO_2 and/or arterial blood gasses at least every 6 hours.

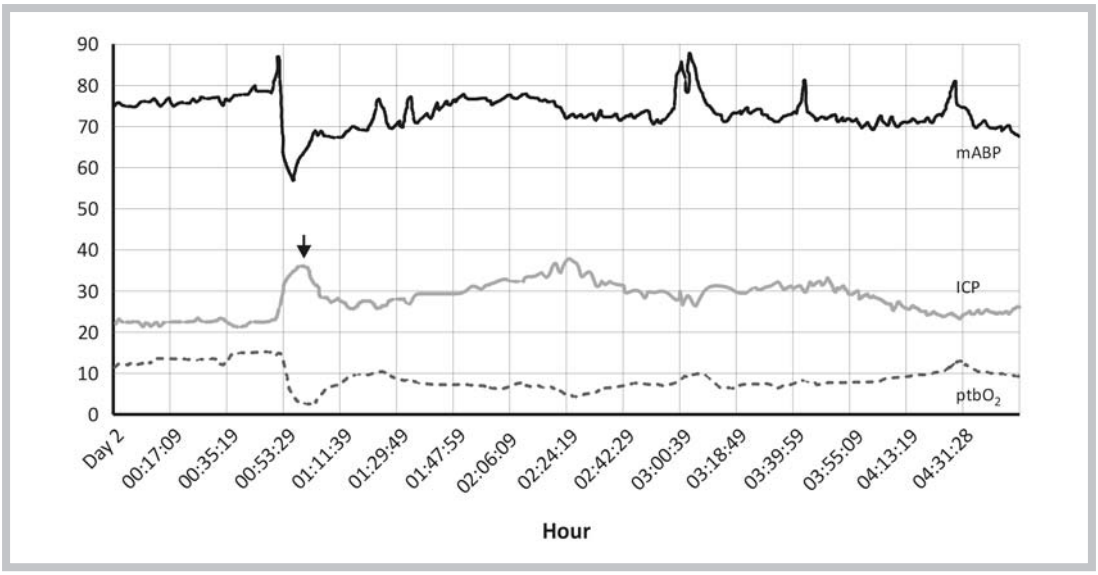


Figure 8.10. Effect of adrenergic activation in oxygen pressure tissue and ICP. A male, 15 years old, was injured by a car while riding a bicycle. The initial GCS was 8, EMV: 3, 3,2. He had a right tibia fracture and fractures of 3th and 4th left ribs, with compressed perimesecephalic cisterns in the CT scan. The ICP increased (arrow) until 35 mmHg during the bone fixation procedure, for insufficient anesthesia, $ptbO_2$ decreased (00.53 hour). The mABP rose until 90 mmHg, later decreased 60 mmHg. Probably $ptbO_2$ decreased for secondary hypovolemia associated with ICP elevation, beside initial MABP around 70 mmHg.

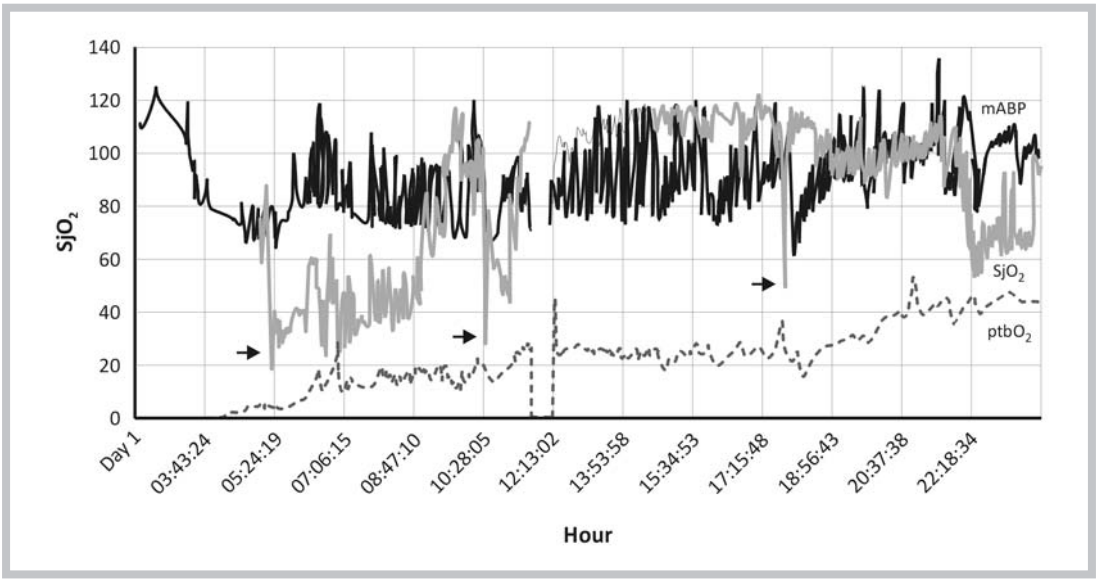


Figure 8.11. Initial correction of hypoperfusion and late hyperemia in SjO_2. 58-year-old male, GCS = 6, 3-meter fall. On the admission his pupils were reactive. The CT scan showed diffuse hemorrhagic points with left parietal contusion and a middle line deviation of no more than 5 mm. Apparently the injuries were not really severe, it seemed that ICP was below 20 mmHg on the initial 24 hours after trauma. However, from 3.34 hours until 9.30 hours the oxygenation parameters showed marked hypoperfusion. Beside, mean arterial blood pressure (mABP) was higher than 60 mmHg. Later, SjO_2 showed hyperemia (SjO_2 >75%) not correlated with normal ICP. The mean ICP was below 20 mmHg. During this stage the mABP was 80-120 mmHg. The main cause of this vascular autoregulation was probably a higher arterial blood pressure. Three months after the trauma the GOS was 4. Arrows: fiberoptic SjO_2 calibration.

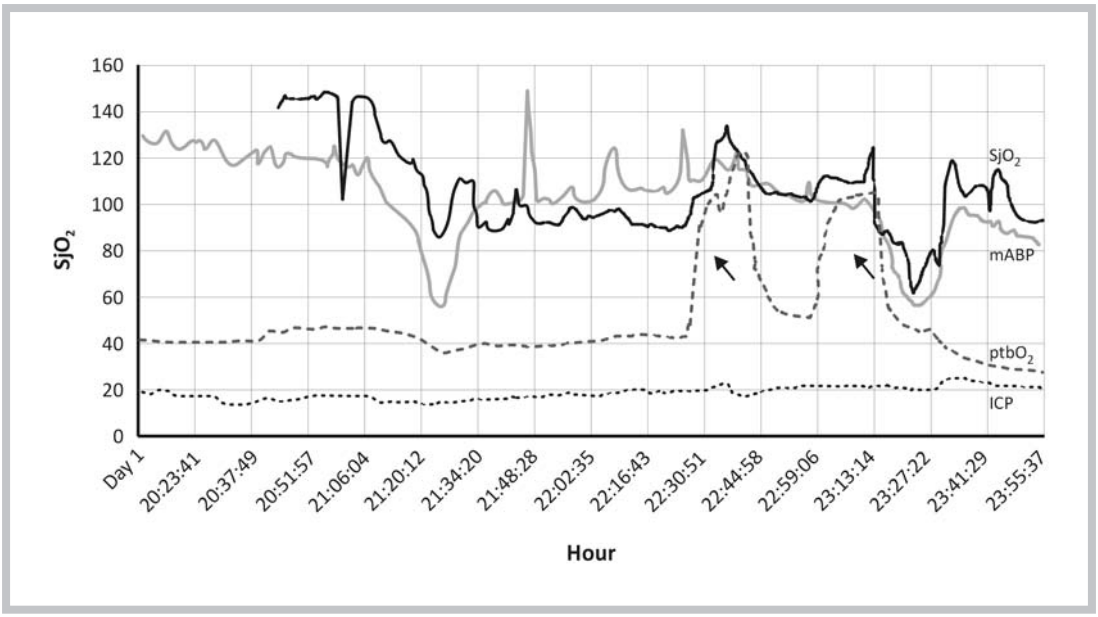


Figure 8.12. **Hypotension and hypoperfusion in a hypertensive patient with TBI. In TBI the main secondary injury factor associated with a poor outcome is hypotension. In this patient, GCS 7, with isocoric pupils (negative/positive), the mean arterial blood pressure decreased from 120 to 50 mmHg (20.00 to 21.20 hours) with associated effect in SjO_2 and $ptbO_2$. Apparently the main effect was observed in SjO_2 which persisted until the first maneuver 100 % FiO_2 (first arrow); SjO_2 increased until 80%, together with mean arterial blood pressure higher than 100 mmHg (22.44 hour). These hemodynamic changes indicate a severe affection. However, the ICP was normal. In chronic hypertension the key point for BP must be interpreted in relation with ICP, in order to test the vascular autoregulation limit. In the first initial 24 hour after trauma, sudden changes in hypotension and hypertension induce severe edema. The sudden hemodynamic change greatly increased ICP. On day 3, ICP reached 35 mmHg. Three months after trauma, GOS was 3 points.**

These considerations illustrate that an understanding of the underlying pathophysiology in TBI patients is complex and that treatment approaches may carry both benefits and risks. Current insights into pathophysiology and results from multimodality monitoring strongly support the concept of a more individualized approach, instead of standardized protocols, in managing TBI patients.

Applying personalized approaches requires a full understanding of the ongoing pathophysiology. In the absence of dedicated multimodality monitoring, we do not know whether the patients may be in an oligaemic or a hyperperfusion state. And although important, ICP monitoring only provides information on a single parameter. It should be remembered that prophylactic hyperventilation will not prevent increases in ICP [59]and that hyperventilation may decrease cerebral oxygenation, as measured by brain tissue oxygen pressure, in patients with normal and those with elevated ICP [59,60].

Further insight into the pathophysiology of individual patients can be gained from measuring both global (SjO_2) and regional (brain tissue oxygen pressure) cerebral oxygen parameters. Examples of different treatment approaches are summarized in the figures (Figures 8.10-8.12).

These examples are not evidence-based but rather represent the consensus of experts experienced in TBI treatment and with a history of participation in clinical trials and research.

8.4.3 Regional Approach: Brain Tissue Oxygen Pressure

The regional approach relies on brain tissue oxygen monitoring, commonly abbreviated as $ptbO_2$, $ptiO_2$, or $PbrO_2$. In this section we shall use the abbreviation $ptbO_2$ (partial pressure of brain oxygen tension).

8.4.4 Development of a Clark-type Electrode for Measuring Brain Tissue Oxygenation

The technology for $ptbO_2$ measurement originated from studies on photosynthesis. In 1938, Blinks and Skow used a platinum electrode as a cathode for measuring pCO_2 in plant tissue [116]. Brink, Davies and Bronk attempted this technique in human tissue, but "the metal poisoned the blood" [117]. This report prompted Clark (Figure 8.13) to cover the cathode and anode with polyethylene to "prevent intoxication" [118].

The polyethylene covering effectively reduced oxygen consumption by the electrode and facilitated the diffusion of environmental oxygen to the electrode. Since 1954 the Clark electrode has been used in the measurement of blood gases.

Although Clark attempted to monitor oxygen tension in the brain with this method, it was not until 1980 that Dr. W. Fleckenstein in Germany further refined the methodology for use in tissue measurements in experiments first on small animals and then on humans [119]. Measurement in both the brain parenchyma and the cerebrospinal fluid (CSF) showed higher levels of pO_2 in the CSF compared to the parenchyma, with a much greater and more rapid influence of arterial pO_2 on measured values. This was probably due to the rich vascularization of the choroid plexus where no blood-brain barrier is present. Reperfusion studies showed a much slower recovery of brain tissue pO_2 following global ischemia than in the CSF. It was therefore concluded that brain tissue measurements would provide greater relevance to cerebral oxygenation in clinical use [120].

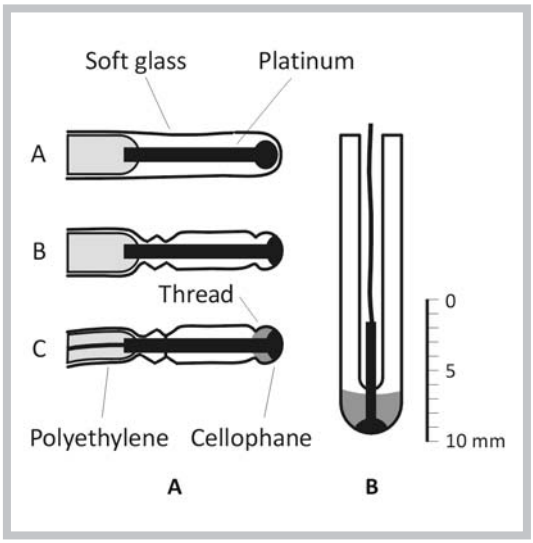


Figure 8.13. **Catheter components: A) Catheter covered by cellophane. B) Catheter distal portion. A shiny platinum cathode covered with a layer of cellophane has been found to be suitable for the direct measurement of oxygen tension in whole blood by polarographic procedures. The cellophane covering prevents the undesirable effects of the red cells which interfere with oxygen tension measurements using a bare platinum electrode, and in addition nearly abolishes the "stirring effect". A tiny cathode of this type (2 mm diameter and 8 mm long) mounted on a catheter can be passed into the major blood vessels and the chambers of the heart, for continuous recording of oxygen tension. Such cathodes are easily calibrated and are stable, reproducible and sensitive.**

The basic principle behind the Clark-type electrode is that environmental oxygen diffuses through the polyethylene covering into a chamber containing a gold or platinum electrode immersed in an electrolyte solution. In the chamber, the oxygen is converted to OH^- at the gold cathode to produce an electric potential that can be measured. Re-

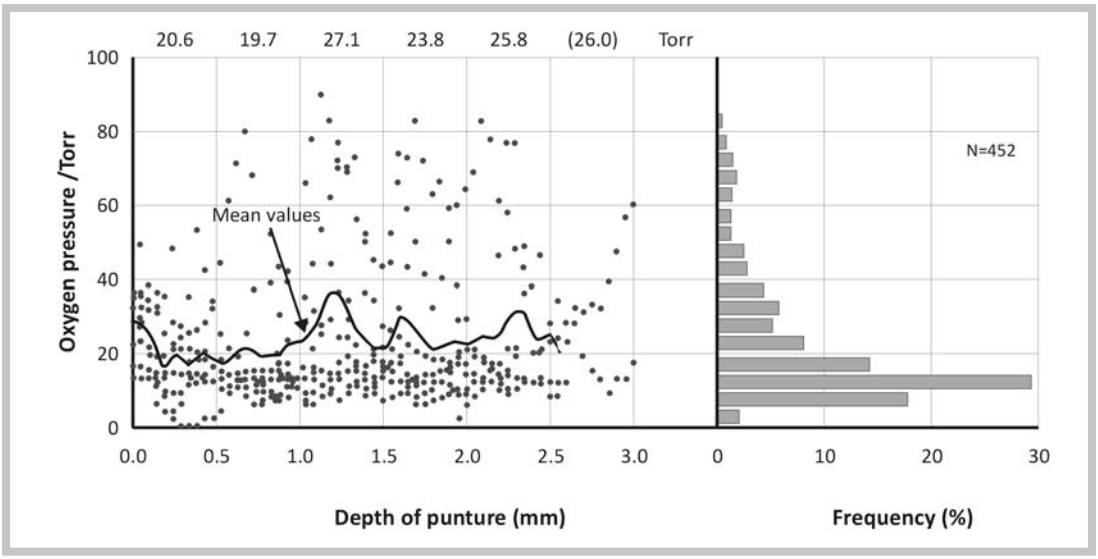


Figure 8.14. **Heterogeneity and $ptbO_2$ in experimental kidney (rat). Values of nine punctures in relation to the depth of the puncture. Significant heterogeneity for surface anesthesia. Low values coexist with values close to paO_2 pressure.**

duction of water with oxygen within this chamber is expressed according to the chemical reaction:

$$2H_2O + O_2 \rightarrow 4OH^-$$

thus providing 4 OH and generating the electric potential.

Initially, the electrodes were designed as fast-response systems to measure the electric potential very locally. This permitted study into the heterogeneity of cerebral pO_2 and related cerebrovascular distribution, which could be expressed as $ptbO_2$ histograms. The great heterogeneity of $ptbO_2$ in brain tissue, however, made this approach difficult for clinical use.

For clinical application a catheter was designed with a larger measurement area and a slower response, thus averaging local heterogeneity and providing an average oxygen tension within a specific area of the brain from which oxygen could diffuse to the catheter. The $ptbO_2$ thus measured can be considered as the average of values of thousands of capillaries surrounding the catheter, i.e., 200-10000 fields created by local diffusion. The $ptbO_2$ reflects the balance between available oxygen flowing through the tissue microvasculature and local consumption. In other words, it is the partial pressure of oxygen in the extravascular and extracellular interstitial space. It does not measure the intracellular oxygen concentration in cell bodies. Normal values of $ptbO_2$ measured with the Clark catheter technology are within the range of 20 to 40 mmHg, with an average of 25-27 mmHg at normal ICP and CPP levels [121,127,131] (Figure 8.14).

8.4.5 Factors Influencing Brain Tissue Oxygen Tension

$ptbO_2$ responds directly to oxygen tension in the blood and the number and diameter of capillaries per volume of measured tissue. More parameters are described in the following sections: FiO_2, temperature, pressure perfusion, hemoglobin, $paCO_2$, ICP, vascular autoregulation, etc. [122-131] (see Table 8.4 and Figure 8.15).

Local factors influencing $ptbO_2$	• Oxygen consumption of neurons and glia cells • Conditions of diffusion and gradients of oxygen: at capillary, venular, arteriolar of the brain tissue area • Number of perfused capillaries per volume of tissue supplied • Longitude and diameter of the capillary irrigated • Rate and microflow pattern: vascular autoregulation • Release of oxygen for the hemoglobin
Systemic factors influencing $ptbO_2$	• Arterial blood pressure, intracranial pressure, cerebral pressure perfusion • $PaCO_2$, temperature, % fraction oxygen, hemoglobin content, p50, blood • Viscosity, hematocrit, SaO_2, venous saturation

Table 8.4. **What is measured: local and systemic factors?**

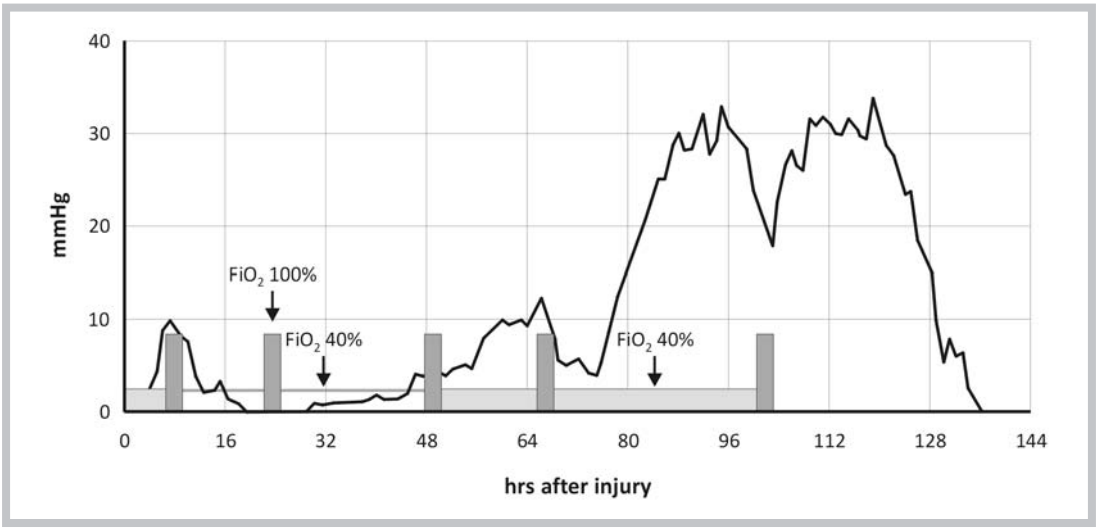


Figure 8.15. **Influence of anemia and FiO_2 100% on $ptbO_2$ in severe TBI.**

Here we report an explanatory case. In the last summer a 24-year-old male crashed with his auto into a tree. Three hours after the trauma he arrived into the hospital with a GCS 6: O1, M4, V:1. He was intubated outside the hospital due to insufficient spontaneous breathing. The paramedics reported a femoral and also a right frontal fracture. The abdominal ultrasonography did not report bleeding. The mediastinum was widened and he had no hip fractures.

The initial CT scan showed lesions in the orbit, ethmoidal and frontal sinuses. The basal cisterns were filled with blood and air. There was a small left parietal hematoma and blood in the third horn of the right ventricle and in the Sylvian fissure. The parenchyma showed diffuse hemorrhagic points in both hemispheres. The X ray chest showed a left lung contusion. The initial ICP was 20 mmHg. The pupils were dilated. He was treated with vasopressors and fluid replacement. In the second scan ofthe second day there was a large left hypodense area on the irrigation areas of the middle cerebral artery, an anterior frontal contusion, and a small left parietal subdural hematoma. Later he developed diabetes insipidus with sodium of 150 Meq. 6 days after the admision the ICP was 40 mmHg.

The initial pHa was 7.24, paO_2 180 mmHg (24.1 kPa), $paCO_2$ 47.6 mmHg (5.64 kPa) with baseline FiO_2 65%, the ventilator was programmed with 15 breaths per min and MV 10.000 ml, Hb 6.4 g. After treatment with vasopressors, mABP reached 77 mmHg, HR 142 per min., CPP 57 mmHg, SaO_2 99%, $paCO_2$ 36.7 mmHg (4.9 kPa). The initial $ptbO_2$ was 1 mmHg; 15 minutes after oxygen 100%, it increased to 3 mmHg and two hours lat-

er, with the same maneuver, it increased to 10 mmHg, with a mABP of 85 mmHg. The trend line of pHa was in correlation with $ptbO_2$, suggesting a better metabolism with poor oxygen caused by anemia. On the second day of admission the body temperature was 39°C. Due to the patient's religion (Jehovah's Witness), the family did not allow a blood transfusion until four days after admission, when doctors finally managed to persuade the family.

On the fifth day of hospitalization a SPECT was performed, and the $ptbO_2$ increased to 30 mmHg. The initial 24 hours of $ptbO_2$ monitoring suggested a global pattern, but on the last day the $ptbO_2$ of 30 mmHg indicated a local $ptbO_2$ pattern.

8.4.6 The Purpose of $PtbO_2$ Measurement: A Surrogate for Global Oxygenation or to Save the Penumbra?

The $ptbO_2$ reflects global cerebral oxygenation if the catheter tip is placed in a relatively undamaged part of the white matter; the validity of this concept has been confirmed in studies with single-photon emission computed tomography (SPECT), SjO_2, regional CBF and ΔAjO_2 [132,133]. This approach may be called *pars pro toto* in which measurements taken in a small part are representative of the global situation. Several studies have shown that this approach may even provide more accurate information than SjO_2 for the detection of ischemic events [134]. Others, however, have suggested that $ptbO_2$ may be better suited to capture events associated with hypotension and that SjO_2 may be more sensitive to the effects of hyperventilation. Ultimately, both approaches may be considered complementary.

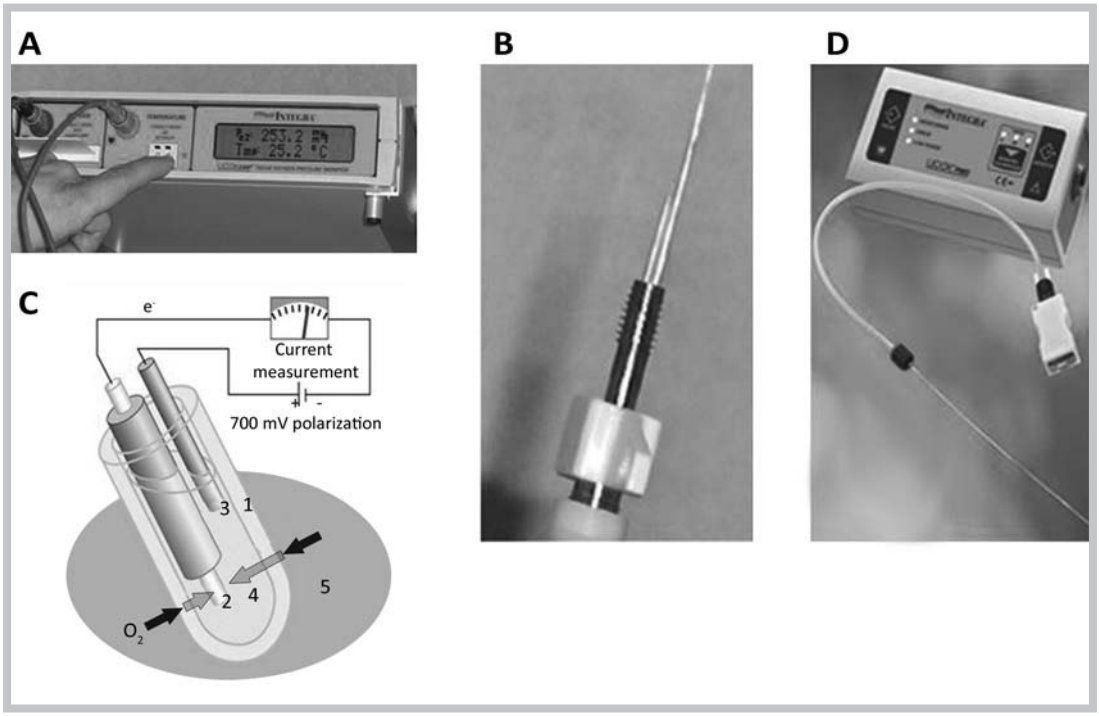


Figure 8.16. **Licox System. (A). Licox Monitor. (B). Oxygen catheter with attached ICP catheter. (C). Components of the catheter tip: 1) Polyethylene cover, 2) Cathode: gold electrode, 3) Anode: silver electrode, 4) Environment electrolyte, 5) Brain tissue environment with surrounding oxygen. (D). Monitoring module MPO and Licox oxygen catheter which is connected to the bedside monitor.**

Some authors recommend deliberate placement of the brain tissue oxygen probe in the penumbra area of a contusional or an ischemic area. The intent with this approach is to measure local values in the attempt to save valuable tissue and to prevent contusion or lesion expansion. Stocchetti et al. [123,137] successfully increased mean arterial pressure (MAP) to improve local perfusion of areas surrounding contusions. Catheter position in the penumbra area was confirmed by CT scanning. Although the benefit of this approach has not been subjected to double blind randomized studies, the concept is appealing and holds potential. Its clinical application will necessarily remain restricted to surgically treated cases, as positioning in the penumbra area is otherwise difficult.

8.4.7 Techniques for Monitoring $ptbO_2$

The most widely used technique for monitoring brain tissue oxygen tension is the Licox device, marketed by Integra. It uses a modern version of the original Clark-type electrode developed by Dr. Fleckenstein for brain tissue monitoring. A large body of clinical experience with this approach now exists, with extensive reports on its stability, safety [138], use as a monitor and as a guide to brain oxygen targeted therapy (Figure 8.16).

The only other currently available device we are aware of is that marketed by Raumedic [139], which is based on a different technology. Because it has become available only in recent years, comparison of results obtained with the Raumedic sensor and the Licox sensor are unavailable (Figure 8.16, Figure 8.17 and Table 8.5)

Until a few years ago, the Neurotrend catheter was marketed but has since been withdrawn from the market. The Neurotrend catheter provided simultaneous measurement of pH, pcO_2, $ptbO_2$, and brain temperature. There are comparative

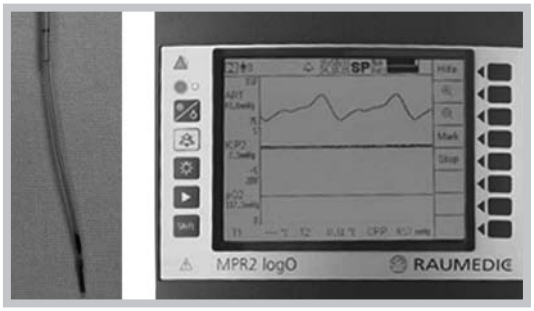


Figure 8.17. **Raumedic System. Recently introduced, it measures simultaneously ICP, brain temperature and oxygenation in a single catheter. Applying an optical technique, denominate "fluorescence", it catches the circulating cerebral oxygen. At the tip of the catheter is a luminophore, which captures the signal. After absorbing the light, with some energy the phosphor enters a state of excitement that is later modified to a state of relaxation. Relaxation involves the dissipation of energy throughout the swing and emission of a photon of lower energy and longer wavelength (fluorescence). To put it in another way, we can say that the oxygen is trapped; the oxygen saturation of the hemoglobin molecule makes the accuracy and greater magnitude of oxygen measurements.**

Characteristics	Licox	Neurovent
Storage	Refrigerator	Air ambient
Oxygen consumption	Yes	No
Electrolitic consumption	Yes	No
Monitoring time	Restricted	Without limit
ICP and temperature in the same catheter	No	Yes
Diameter	1.5/0.49 mm	5 Fr/1.65 mm
Catchment area	13 mm^2	22 mm^2
T/90-35°C	<200 s	<200 s

Table 8.5. **Comparison between Licox (Integra) and Neurovent (Raumedic) systems.**

studies between the results obtained with the Neurotrend versus the Licox catheter. In 49 Licox catheters of 42 patients, data free artefacts were obtained in 37 (88%) patients, whereas in 50 Neurotrend catheters of 35 patients, data free of artefacts were obtained in 14 (40%) patients. The incidence of catheter ruptured for the screw and malfunction was higher for Neurotrend catheter (20 and 8%, respectively) than for the Licox device (0 and 2%, respectively) [140]. The authors reported two hematomas occurring in 99 catheters but did not provide further analysis [140]. There was no difference in the safety profile of the two devices. In general, approximately 5 to 10 mmHg higher values were reported with use of the Neurotrend catheter as compared to the Licox catheter. This observation should be taken into consideration when comparing studies using the two devices.

Stability and safety of Licox catheters:

- Two iatrogenic hematomas have been reported in 2 patients, with surgical consequences (1.7%).
- No infections were reported after 6.7±3.9 days.
- The complications rate (e.g., dislocation) was 13.6%.
- The average adaptation time was 79.0±51 minutes.
- The maximum error was 1.07±2.14%, tested at temperatures between 22 and 37 C° and an oxygen pressure of 0. 44 and 150 mmHg; this number is irrelevant for everyday clinical practice.
- The zero error at the end of monitoring, tested by dipping the catheter into a solution without oxygen was 0.21±0.25 mmHg. This error is insignificant for clinical practice.
- Excluding data from the first hour, these results are reliable in 100% of cases [138].

8.4.8 Practical Aspects of Implantation

Oxygen probes can be introduced during a surgical procedure or through a dedicated burr hole. In the latter case, the intent is usually to monitor a relatively undamaged part of the brain in the right frontal region when possible. When inserted through a dedicated burr hole, fixation is best obtained with a subarachnoid screw through which the catheter can be introduced into the brain. Single lumen and multilumen screws permit the introduction of other catheters, e.g., ICP, brain temperature or CBF catheters. Since pO_2 monitoring with a Clark-type electrode is influenced by temperature (for each °C $ptbO_2$ changes by approximately 4%, temperature correction is required. To do this, one may use direct measurement of brain temperature or manually input core temperature values from the measured core temperature. Currently available pO_2 catheters ordinarily combine pO_2 sensors and a brain temperature sensor to automatically correct temperature, making the device much simpler in general clinical use (Figure 8.16).

Drilling the screw insertion hole into the skull demands meticulous technique to completely remove any bony rim and to puncture the Dura adequately. CSF output confirms good access. When using a multilumen screw, the central catheter should be inserted first. Prior to insertion, the catheter must be calibrated according to the manufacturer's specifications. Each catheter has specific settings for determining temperature, humidity, barometric pressure, oxygen content, and nitrogen level. These values are contained on a chip which comes with the catheter and which is inserted into the monitoring device. This matrix automatically sets the catheter's unique calibration values.

Following insertion and fixation, an equilibration time must elapse before the measured values can be considered reliable and representative of cerebral oxygenation. The "run-in time" can vary between patients, but stable values are generally obtained within 1 to 2 hours (Figure 8.18).

Accurate catheter functioning should be evaluated by performing an oxygen challenge test (increasing FiO_2 to 100% for 10 min). Normally, the oxygen challenge test will lead to a substantial increase in brain tissue oxygen, thus confirming adequate catheter functioning [141]. Catheter malposition or malfunction should be suspected in the absence of a catheter response to increasing FiO_2. Low values and an absence of response to an oxygen challenge test may be caused by a small local hematoma around the probe tip.

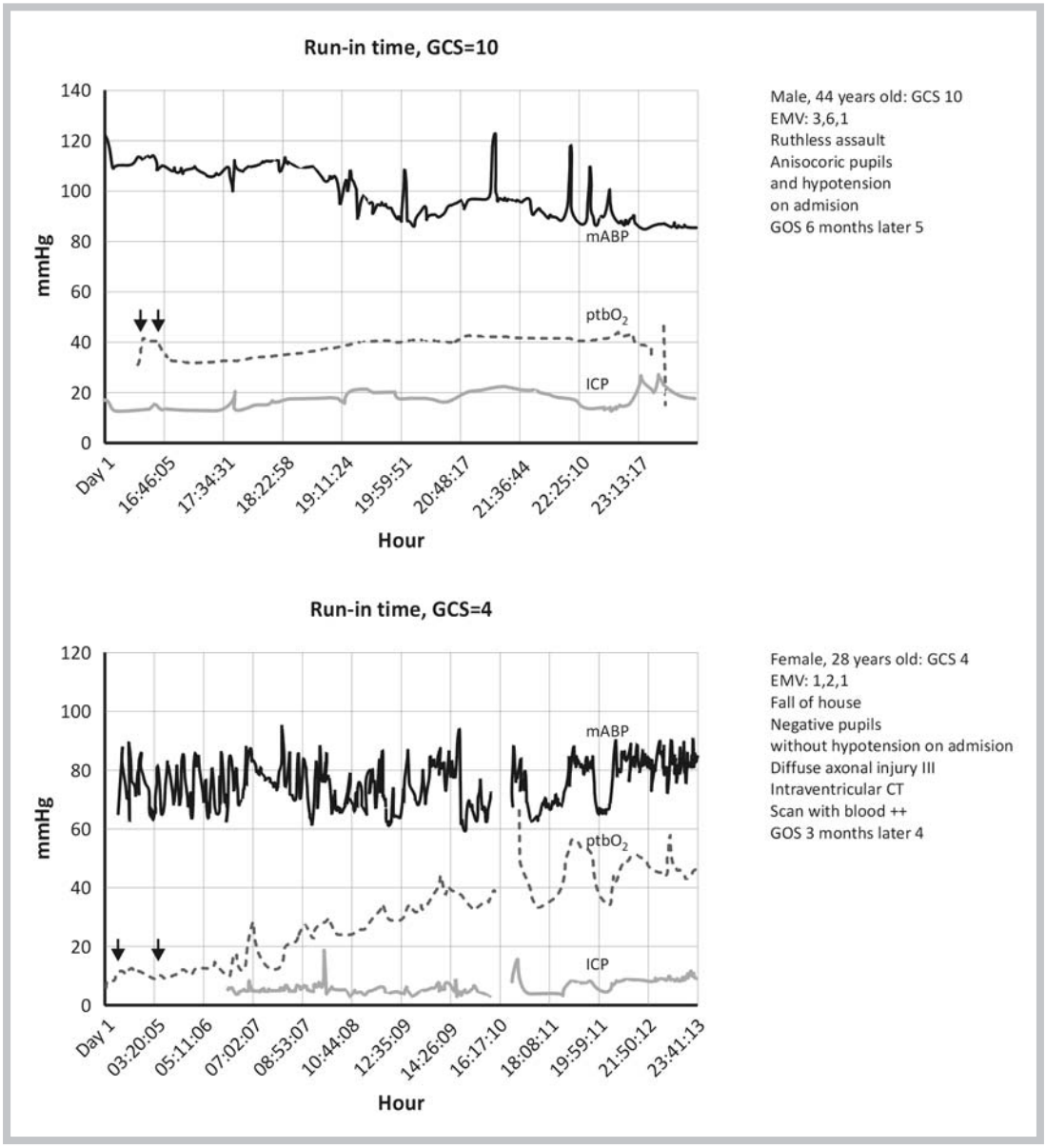


Figure 8.18. **Run-in time and GCS. The term ”run-in time” was coined by the Rotterdam group and corresponds to the effective $ptbO_2$ stabilization time after catheter insertion. This period represents the damage caused by the insertion of tissue oxygen catheter. In patients with better Glasgow Coma Scale, we have observed a lower stabilization time than in patients with less GCS score. Apparently, the run-in time is also affected by the presence of secondary injury factors. It is assumed that a longer run-in time period could be associated with hypotension and hypoxia. These two images show these associated factors. Arrows show the run-in time period.**

Alternatively, excluding technical malfunction, the probe may be positioned in non-perfused unviable tissue, otherwise CBF may be seriously compromised. The catheter position should be confirmed in all instances by routine CT follow-up.
In TBI, monitoring should be started as early as possible, as low CBF and the risk of secondary ischemia is greatest within the first 24 hours; the recommended duration of monitoring is generally the same as that required for invasive monitoring, including ICP monitoring [110].

8.4.9 Tissue Oxygenation Monitoring and Clinical Qualities

A monitoring technique is evaluated by the quality and relevance of the information that it provides. Quality parameters include accuracy, utility and reliability. Monitoring of the partial pressure of oxygen in the brain tissue is relevant for interpreting the pathophysiology of TBI and can aid in individualizing the treatment towards the needs of a given patient. The accuracy, reliability and utility of this technique have been extensively studied in the clinical setting [15,18,10,142].

8.4.10 Clinical Accuracy

To properly understand the concept of oxygen supply and consumption as studied by $ptbO_2$ monitoring, some knowledge of intracranial and extracranial pathophysiology, especially hemodynamic and cellular metabolism, is required [42,44-46,143]. The partial pressure of brain tissue oxygen is dependent on CBF and oxygen delivery and consumption. Concepts included in the SjO_2 section are also applicable. We refer to this section and the references [40,43,48,54].
In clinical practice, the indication for ICU admission and monitoring in a TBI patient is determined by the severity of the patient's condition as expressed by the GCS level, CT scan findings, pupillary reactivity, secondary insults, and the potential risks for deterioration [21,23,25,100]. In their extensive studies, the Rotterdam group found no clear association between the poststabilization of GCS scores and $ptbO_2$ in patients with severe or moderate TBI. This may be interpreted as indicating that oxygen status may be disturbed at all levels of severity. Moreover, we should remember that tissue oxygenation is heterogeneous in both normal and pathologic situations [27,29]. In TBI patients, brain tissue oxygen may be relatively normal in some regions, whilst in others there may be ischemic conditions with low $ptbO_2$ values. It should be noted that the intent of $ptbO_2$ monitoring as performed by the Rotterdam group was to monitor in a relatively undamaged part of the brain [15,144].
In contrast, the Houston group preferentially placed the catheter in close proximity to a brain contusion. With this approach, a clearer relationship was found between $ptbO_2$ and GCS, especially with regard to the motor component [136]. Moreover, they found a significant relationship between lower $ptbO_2$ values and outcome when the probe was positioned in the penumbra of (operated) mass lesions. Further studies are required to determine the pros and cons of monitoring in the penumbra versus in a relatively undamaged part of the brain where $ptbO_2$ may be considered more representative of global cerebral oxygenation.
The relationship between pupillary response and $ptbO_2$ was studied by the Rotterdam group [15,144]. They found an association between lower $ptbO_2$ values and a negative response of both pupils in the initial 24 hours after injury, suggesting an association between lower values and more severe injury. After 24 hours there was a mixed pattern and no apparent difference between lower and higher $ptbO_2$.

More recent studies have not addressed the relationship between pupillary reactivity and $ptbO_2$ in much detail. Pre-admission hypotensive episodes are closely related to poorer outcome. Although the relationship between lower blood pressure levels and poorer outcome is continuous, particular attention has been paid in the literature to episodes of systolic blood pressure ≤90 mmHg [8,100]. The relationship between pre-ad-

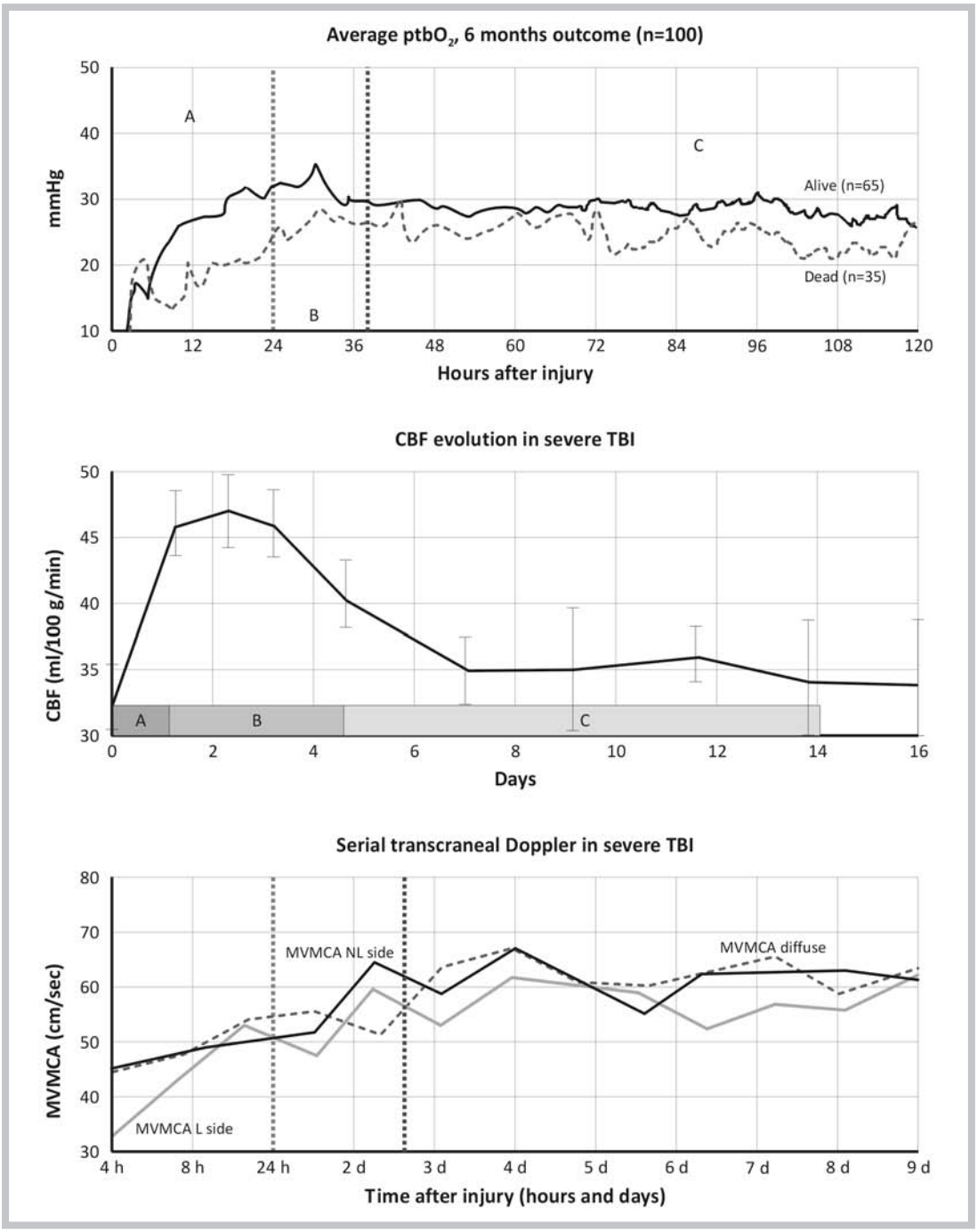


Figure 8.19. **Patterns over time of $ptbO_2$, CBF, and serial TCD.**
MVMCA = mean velocitiy middle cerebral artery non-lesion

mission hypotensive insults and $ptbO_2$ is weak. This is easily explained by the fact that hypotensive episodes may have been already corrected by the time that monitoring was initiated. Nevertheless, experimental and clinical studies have documented that $ptbO_2$ monitoring after shock trauma can be a useful guide to improve oxygen delivery.

Studies by the Rotterdam group have clearly shown lower values of $ptbO_2$ in nonsurvivors versus survivors during the first 24 hours after injury [144]. Over the next days, however, there was no clear difference in the average values between the groups. This lack of association with outcome in later phases of monitoring could be seen as poor specificity of the technique, but it further demonstrates the heterogeneous nature of TBI and highlights the evolution of changes in CBF and brain oxygen tension over time.

A 3-phase pattern in the evolution of CBF over time has been described by several authors [15,145,146]. This pattern has also been demonstrated in $ptbO_2$ monitoring by recent publications, in which the intent was to optimize oxygenation with vasopressors, fluid, and respiratory measures, as well as to improve ICP and cerebral perfusion pressure [16,20,30,147,148]. In the absence of an "optimization intention", this evolutionary picture of $ptbO_2$ may be different (Figure 8.19).

According to the Rotterdam studies, low $ptbO_2$ values are most often observed during the first 24 hours after injury. In a series of 100 patients, values <15 mmHg occurred in 57 patients, values <10 mmHg in 42, and values ≤5 mmHg in 22. It was subsequently suggested that this period can be characterized by "oxygen depression". In the 36-48-hours after injury, the average $ptbO_2$ values increased to approximately 46 mmHg. This period was therefore considered to represent an "overshoot" likely due to vasodilation secondary to the initial ischemia. Over the following days, the average tissue oxygen remained stable at around 30 mmHg and was considered as the "stabilization stage". The three phases of evolution of brain tissue oxygen over time are summarized in Table 8.6.

The evolution of $ptbO_2$ values over time corresponds to that described for CBF, Transcra¬nial Doppler and SjO_2 (Figure 8.19) [15]. Further work is needed to determine appropriate thresholds for initiating treatment to improve cerebral oxygenation. Such thresholds might conceptually be different for the three evolutionary phases described after TBI. In general, thresholds of 10-15 mmHg have been proposed [15,18,19,142,144]. Such critical levels may need to be individualized, as they can vary between patients and over time. Evolution over time is a highly relevant factor and not always recognized in studies. Many do not report the time of monitoring initiation [30], the stage of $ptbO_2$ evolution [17,30], the duration of trends or report only average values [16,17]. We have found that an individualized analysis may yield additional relevant insights.

Therefore, $ptbO_2$ monitoring in TBI ought to be interpreted on an individual basis to obtain better insight into the pathophysiological status. Noratam et al. [17] described a different pattern of $ptbO_2$evolution over 5 days of monitoring, which may be explained by the inclusion of patients with less severe conditions (GCS 13-15). They described the main abnormalities of $ptbO_2$ levels only after the initial 24 hours, unlike observations by other studies and different from several studies on CBF, TCD and other techniques [110,145-146].

The Rotterdam group found no relationship between patient age and $ptbO_2$, whereas the Robertson group did [15,136]. This difference may be explained by the fact that they preferentially placed the probe in the penumbra of a damaged area, thus introducing bias toward older patients. The Stocchetti group described lower mean $ptbO_2$ in the pericontusional tissue (19.7±2.1 mmHg) than in normal appearing tissue (25.5±1.5 mmHg; p <0.05), despite a higher cerebral perfusion pressure (73.7±2.3 versus 67.4±1.4 mmHg; p <0.05) in these pa-

<24 hours	24-36 hours	≥36 hours
Depression	Overshoot	Stabilization

Table 8.6. Evolution of $ptbO_2$ over time.

tients; therefore, probe position is an important factor in the interpretation of results and it also influences prognosis [41] (Figure 8.20).

Lower $ptbO_2$ values have also been reported in patients with compressed basal cisterns on CT examination. The prognostic value of low $ptbO_2$ values has been studied in multivariate logistic

Regression analysis. These studies confirmed an independent prognostic effect of $ptbO_2$; the probability of death increased 3.8 times (95% confidence interval [CI] 1.6-8.9; P=0.002) when the $ptbO_2$ was <10 mmHg for a total period of 30 minutes during the first 24 hours after trauma. Patients with a $ptbO_2$ >10 mmHg had a 2.8 higher chance of favourable outcome (95% CI 1.2-6.3; P=0.015).

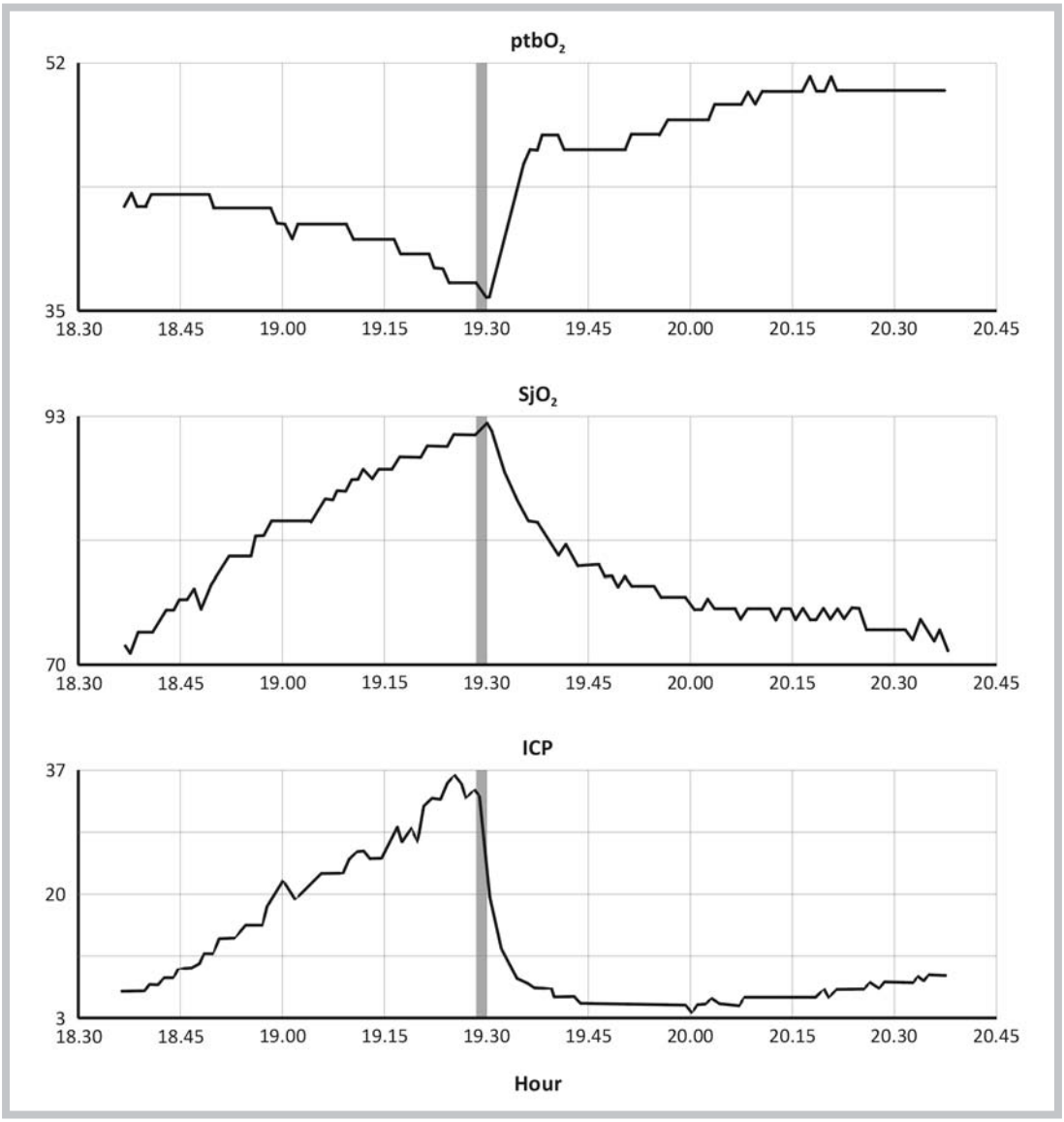


Figure 8.20. **Global and local oxygen parameters. There is a different trend for SjO_2 and $ptbO_2$. After ICP increasing until 36 mmHg (19.30 hours), also SjO_2 incrases, while $ptbO_2$pattern decreases to 36 mmHg. This response was caused by the different position of these two parameters. The local one was measured in the healthy brain, while the global parameter was positioned in the damaged brain.**

Increasing depth and longer duration of low $ptbO_2$ values are related to a higher risk of death and unfavourable outcome: a doubling of mortality was noted in patients with a $ptbO_2$ <5 mmHg for 30 minutes, in those with moderate hypoxia (<10 mmHg) after 1 hour and 45 minutes, and in those with milder tissue hypoxia (<15 mmHg) after 4 hours. Other studies have shown similar results [27,105,142].

Lower $ptbO_2$ values are also associated with poorer cognitive functioning in survivors, resulting in more problems in work re-integration [149]. These results clearly demonstrate an association between brain tissue hypoxia and increased mortality and poorer outcome in survivors [15, 142,144,150]. It is likely that this association is causal. Thus, it would seem appropriate to prevent brain tissue hypoxia from occurring, and if it does, to correct it rapidly. As a consequence, the concept of oxygen-targeted management was introduced.

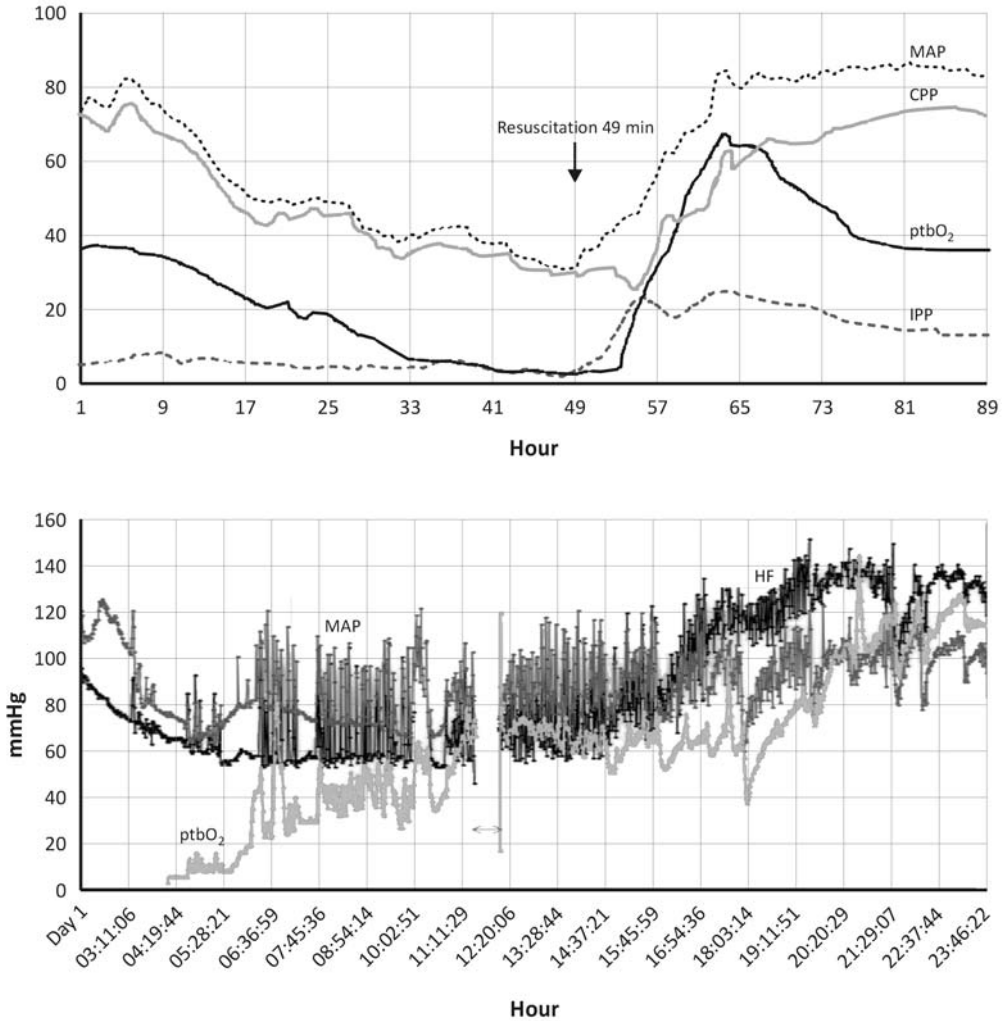


Figure 8.21. **Hypotension in experimental and clinical shock. The correlation between hypoperfusion induced by bleeding and $ptbO_2$ is very close. With the improvement in hypovolemia, tissue oxygenation improves. Lower figure: in clinical situation $ptbO_2$ follows the increasing trend of mean arterial pressure (MAP).**

8.4.11 Improving Cerebral Oxygenation

There are various different approaches to increase brain tissue pO_2:

- Increase arterial blood pressure (and cerebral perfusion pressure).
- Increase arterial oxygen content and/or partial oxygen pressure.
- Decrease metabolism.

8.4.12 Increasing Blood Pressure to Improve Oxygen Delivery

The rationale for increasing blood pressure to improve $ptbO_2$ stems from the assumption that by improving blood pressure the driving force behind cerebral perfusion will in-

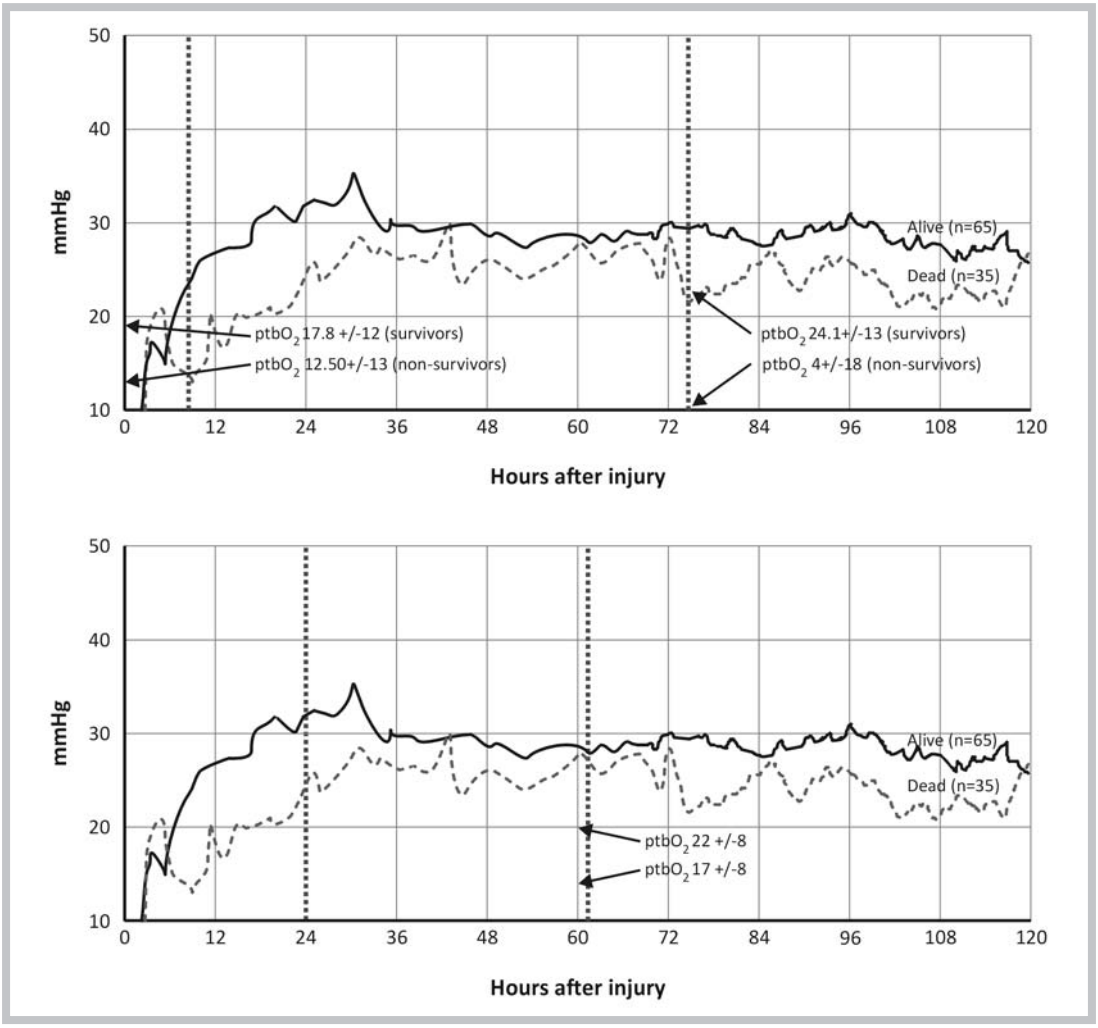


Figure 8.22. **$PtbO_2$ trend over time and vasopressor influence in severe TBI. Using the Rotterdam $ptbO_2$ trend in time, the influence of two norepinephrine trials is comparing with the natural $ptbO_2$ evolution. (A). The first trail tested the $ptbO_2$ response on the initial 24 hours in comparison with the 72 hours response. For the natural $ptbO_2$ response, the initial 6 hours response was higher than the 72 hours, and secondly it has the same evolution of CBF [30]. (B). The authors tested $ptbO_2$ response only on a mean of 62 hours over time, $ptbO_2$ increased 5 mmHg. This maneuver does not increase the $CMRO_2$ response. This maneuver should be related to the outcome. Therefore the best $ptbO_2$/CPP response with vasopressors occurred on the initial 24 hours [31].**

Author	Maneuver analysis	Over time evolution tests	Efficacy of vasopressors on $ptbO_2$ mmHg and SjO_2 %	Reference
Ang BT	Mean $ptbO_2$ comparison survivors vs. no survivors, trend over time Norepinephrine was used	Initial (6 hours) and 72 hours after trauma	$\Delta ptbO_2$ 6.22 mmHg in survivors vs. no survivors at initial 6 hours vs. 72 hours p <0.005)	*J Neurol, Neurosurg Pschiatry* 2007; 78: 298-302
Coles JP	Mean SjO_2 comparison same patients: before and after	Mean time 58 hours	ΔSjO_2 5 mmHg (p <0.005) SjO_2 72±7 vs. 77±7	*Brain* 2004; 127: 2479-90
Jhonston AJ	Mean $ptbO_2$ comparison in the same patient: before and after	Mean time	$\Delta ptbO_2$ 5.00 mmHg (p <0.001) 17±8 vs 22± 8 mmHg	*Crit Care Med* 2005; 33: 189-95
Cremer OL	Median $ptbO_2$ comparison at days 1, 2 and 3	Day 1, day 2, day 3	$\Delta ptbO_2$ 9 mmHg; comparison: initial 24 hours vs. 48 hours (p<0.005) Day 2 vs. day 3 non significant	*Anesth Analg* 2004; 99: 1211-7.
Lang E	% $ptbO_2$/%CPP Mean $ptbO_2$	From day 1 to day 10	The average $ptbO_2$ increases with CPP elevation: day 1: 0.16±0.11 (0.02-0.36) and 0.16±0.06 (0.04-0.24); day 10: $ptbO_2$ 5.8±4 (1.2-14.5) and 6.25±2.9 (1-11.5)	*Critical Care Medicine* 2003; 31: 267-71
Soehle M	Ability of the brain to maintain $ptbO_2$ despite changes in CPP. Different states of $ptbO_2$ autoregulation: present, moderate, impaired	Linear regression slope $\Delta ptbO_2/\Delta CPP$, case by case analysis	Autoregulation is present when CPP elevation is ineffective to raise $ptbO_2$. Pronounced elevation in $ptbO_2$ with CPP elevation, autoregulation is absent	*Neurological Research* 2003; 25: 411-7

Table 8.7. **Efficacy of increasing blood pressure to improve $ptbO_2$ and SjO_2 in severe TBI and SHA.**

crease and result in better tissue perfusion and oxygenation. Its practical efficacy will, however, be influenced by individual factors such as the time after injury and the degree to which autoregulation is disturbed [15,30,140,147,151]. The results from two studies illustrate the time-dependency of the effectiveness of increasing blood pressure [30,147]. Increasing blood pressure with norepinephrine during the "depression stage" after injury produced an average increase in $ptbO_2$ of 7 mmHg, with a 30% increase in mean arterial pressure and improved cerebral perfusion. No data exist that specifically describe the response of $ptbO_2$ to vasopressors during the overshoot phase. The Cambridge group described an increase of 5 mmHg after vasopressors administration at 72 hours after injury. What can be concluded is that vasopressor administration effectively increases $ptbO_2$ at any time after injury [30] (Figure 8.21, Figure 8.22 and Table 8.7).

In principle, $ptbO_2$ is considered indicative of better tissue oxygenation. This is not completely correct, however, as increasing blood pressure does not necessarily translate into a reduction in ischemia. Hypoxic regions of the brain may not be capable of extracting sufficient oxygen due to oxygen diffusion gradients resulting in a diffusion barrier [152]. Microvascular collapse and vascular edema may contribute to this diffusion barrier [153]. The efficacy of increasing blood pressure to improve $ptbO_2$ will also depend on the degree to which autoregulation is intact or disturbed [154]. In patients with disturbed autoregulation, increasing blood pressure may increase ICP and edema, thus impeding the diffusion barrier to oxygen. In patients with more intact autoregulation, increasing blood pressure will decrease ICP and improve oxygenation.

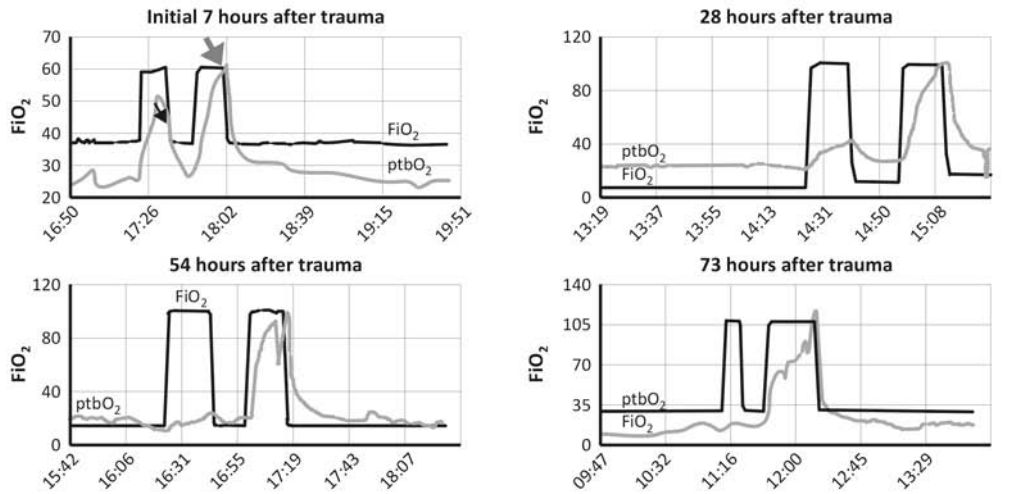
Careful interpretation of monitoring can aid in the identification of patients who may benefit from the use of vasopressors to improve oxygenation [152] (Figure 8.22). Unfortunately, few cases have been studied during the critical period of the first 24 hours. Further studies are needed to identify which patient subgroups are at particular risk of ischemia and may likely respond to this treatment modality. PET studies can demonstrate response to vasopressor therapy and have demonstrated a decreased volume of ischemia [152]. In a select series of 53 TBI patients, 25 historical controls were treated with ICP monitoring and 28 additionally received monitoring and treatment for tissue oxygenation. The ICP and CPP levels were comparable between the two groups. The outcome was different, with a mortality rate of 44% for the first group and 25% for the second. This study reported a significantly better outcome ($P < 0.05$) in the monitored group. Despite the relatively small sample size and the lack of a randomized design, the study results support the concept of oxygen-targeted management [155].

When considering whether to increase blood pressure in order to improve brain perfusion and oxygenation, attention should be given to the choice of vasopressors. One study has shown that CPP increased after norepinephrine administration but not with dopamine. With norepinephrine a significant reduction was observed in oxygen extraction (37±11 versus 33±12 ml/l) and a significant increase in tissue pO_2 (19.5±2.5 versus 23.3±8.3 mmHg). Response to the challenge test with dopamine was more variable than with norepinephrine [101,103).

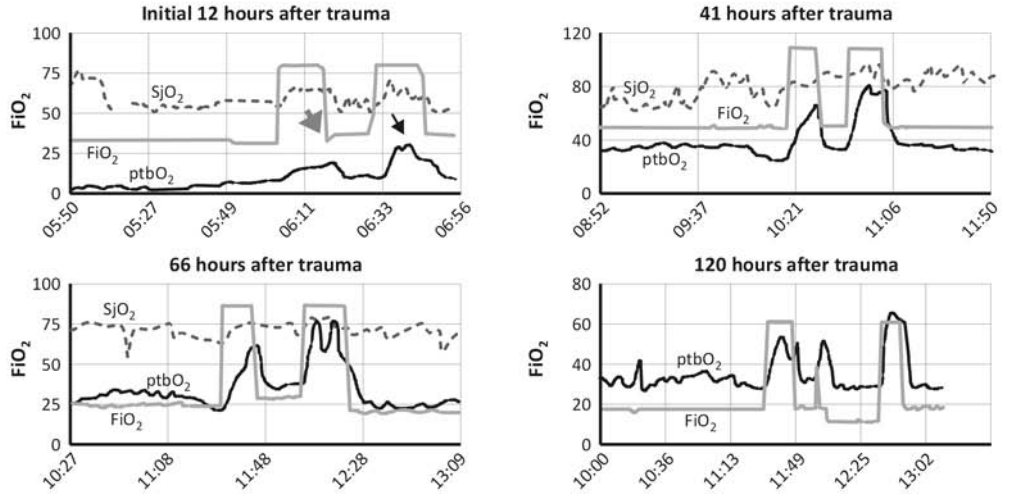
Mannitol is effective in reducing ICP, and it also improves microcirculation by decreasing blood viscosity. One would expect that the decrease in ICP and improved microcirculation could potentially improve $ptbO_2$, but this has not been confirmed in clinical studies [15,156]. However, the use of hypertonic saline in hypotensive patients improves arterial blood pressure and oxygenation, with a reduction of 45% in ICP that persists for 6 hours [157]. The important clinical conclusion from such observations is that oxygen monitoring should be used in addition to ICP monitoring, as the two modalities provide different types of information.

8.4.13 Increasing Arterial Oxygen Pressure and/or Content to Improve Cerebral Oxygenation

Increasing the fraction of inspired oxygen (FiO_2) is highly effective in increasing the partial tissue oxygen pressure. The response to the increase is immediate. We investigated the response to oxygen in 41 TBI patients with a GCS ≤8 by means of a standardised approach: FiO_2 was increased for 15 minutes and the observed changes quantified. The response was expressed as oxygen reactivity and related to outcome at 6 months. In a total of 145 tests, the baseline $ptbO_2$ ranged between 4 and 15 mmHg and the arterial paO_2 between 73 and 237 mmHg. After 15 minutes of 100% FiO_2 administration, the $ptbO_2$ increased to a minimum of 9.1 and the maximum 200 mmHg and the arterial pO_2 from 196 to 499 mmHg. We observed three different patterns of response: response type A was characterized by a sharp increase in $ptbO_2$, reaching a plateau within several minutes; pattern B by the lack of a plateau; and pattern C by a short-duration plateau, followed by a subsequent increase. Patterns characterized by a plateau (type A) were considered to have more stable regulatory mechanisms. This pattern observed in the first 24 hours after injury was associated with a more favourable outcome ($P=0.06$). Patients with high oxygen reactivity (1.03±0.6) during the first 24 hours had a poorer outcome compared to those with lower reactivity (0.61±0.51; $P=0.02$). The association between higher O_2 reactivity and poorer outcome may reflect more severe disturbances of autoregulatory mechanisms [126].



28-year-old female, fallen from a horse, GCS 4. CT scan with diffuse axonal injury; normal middle line structures; intraventricular blood in the right side; subarachnoid hemorrhage in the convexity; mesenceph. cisterns present. The four figures show a progressive increasing pattern in $ptbO_2$ (gray arrow). The initial (7 hours after trauma) ptO_2 was 60 mmHg; in the following days reached 100 and 120 mmHg. These responses were produced with a FiO_2 100% during 15 minutes without pharmacological relaxation. The 4th graph shows a sequence of spontaneous hyperventilation. The initial wave (black arrow) was produced with 100% oxygen plus hyperventilation during 15 minutes (20% more of tidal volume). The sequence describes a decreasing trend in ptO_2, from 60 to 20 mmHg. Apparently hyperventilation test induced a tremendous tissues response, which was unmasked by FiO_2 100%.
The hyperventilation reactivity is unpredictable. The GOS 6 months after trauma was 4. These reactivity tests can be used as therapeutic tools to prevent damage, baceuse hyperventilation has particular reactivity in some cases.



59-year-old male, fallen from a roof (three meters high). CT scan with bilateral temporal subdural hematomas, with midline structures deviation right to left, mesenceph cistern absent. The initial ptO_2 and SjO_2 show an ischemic pattern; with FiO_2 80%, ptO_2 reached 30 mmHg and SjO_2 70%; in the last days ptO_2 and SjO_2 were in normal range. On day 5, SjO_2 was removed incidentally. Some publications suggest hyperoxia as a treatment during the initial 24 hours after trauma. In this patient an initial global ischemic pattern is evident. Hyperoxia increased in both tests: hyperventilation test plus FiO_2 80% (gray arrow) and hyperoxia test without hyperventilation (black arrow), therefore hyperventilation it is not an acceptable tool especially in the initial 24 fours after trauma. Hyperventilation plus FiO_2 is a better protection maneuver. The patient was alive after 6 months of trauma.

Figure 8.23. **Hyperoxia and $ptbO_2$ response in TBI: two examples. Hyperoxia in TBI is not completely understood. Two possible scenarios are have been suggested. In one case, hyperoxia is a good treatment since it decreases the toxic metabolites and promotes oxide reduction. In the other, it gives no benefit and probably can cause damage. Neither of these hypotheses have been proved. Regardless of the absence of approved therapeutic guidelines, hyperoxia is used such as a "helmet" for brain protection, especially in the initial 24 hours after trauma under $ptbO_2$ monitoring.**

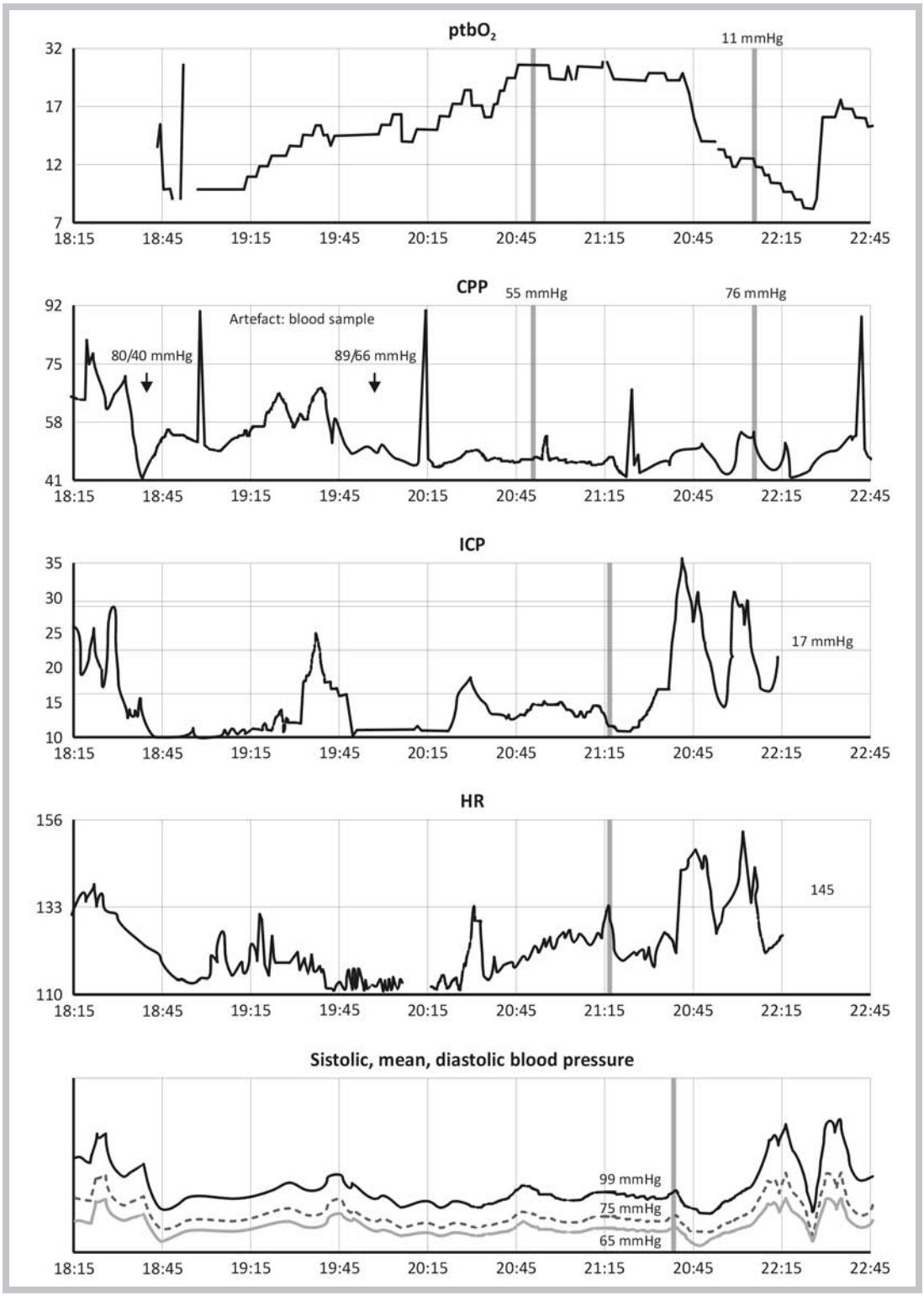


Figure 8.24. 31-year-old male, on admission: bronchoaspiration. For four hours, $ptbO_2$ <20 mmHg, with peaks <10 mmHg for 15 minutes. Hypotension contributed to a low PPC. Hypertension (180/110 mmHg) caused an increase in ICP, suggesting vascular autoregulation. The response was a decrease in ptO_2.

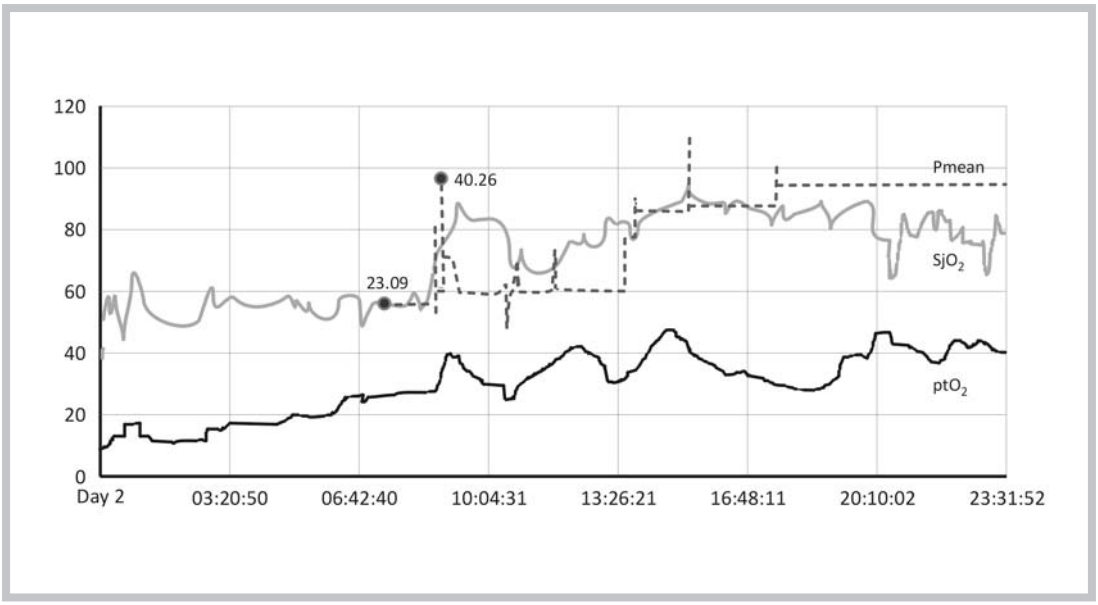


Figure 8.25. **Alveolar recruitment maneuver monitored by SjO_2 and $ptbO_2$. Poor initial respiratory response to ventilatory treatment, with impairment in global and regional cerebral oxygenation, and with improvement after alveolar recruitment. Pmean was increased to 23 mmHg and 40 mmHg progressively, oxygenation response was satisfactory: SjO_2 from 43 to 85% and $ptbO_2$ from 8 to 40 mmHg. Later Pmean decreased (both regional and global parameters). A more stable oxygenation was obtained with Pmean = 40 mmHg. An integrated monitoring, including ICP, is essential to avoid serious risks.**

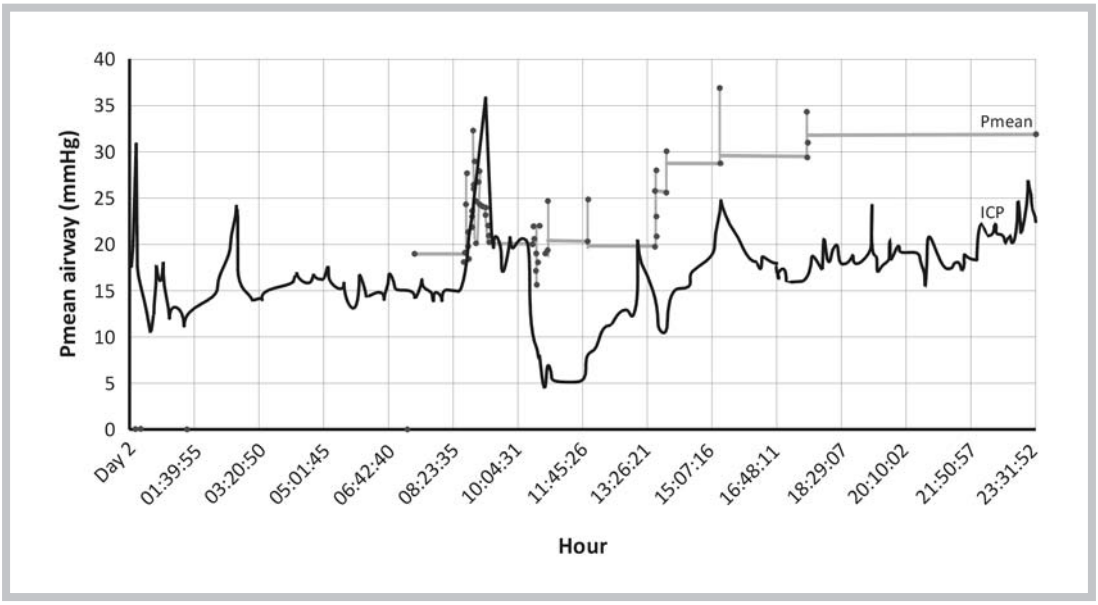


Figure 8.26. **ICP response to the increase in intrathoracic pressure consecutive to increased Pmean can be deleterious. If there is no integrated monitoring of regional and global tissue oxygenation, continuous end-tidal CO_2, MAP, ICP and frequent blood gas controls is not possible to observe the effects of mechanical ventilation on cerebral oxygenation and the spatial dynamics of the brain. In this case (severe TBI and bronchoaspiration), with alveolar recruitment ICP reached 35 mmHg, then after 5 minutes decreased to 5 mmHg with consequent hyperventilation; subsequently remained <25 mmHg. Alveolar recruitment is needed to improve cerebral oxygenation.**

The clinical efficacy of hyperoxia in the treatment of TBI is still under study [158-160] (Figure 8.23). We recommend short periods (15-20 min) of hyperoxia (FiO_2 100%) during resuscitation and as treatment for unexplained tissue hypoxia [59]. The concept of using hyperoxia to increase cerebral oxygenation is controversial. Advocates refer to studies by Bullock et al. that showed a decrease in lactate in the extracellular fluid as measured by microdialysis after 1 hour of FiO_2 100%. This suggests that the increase in FiO_2 produces increments in mitochondrial oxygen, improves oxygen diffusion, and increases $CMRO_2$ [159,161].

Others, however, state that hyperoxia does not increase the oxygen content of blood, which is considered a critical parameter for oxygen delivery. Arterial oxygen content (CaO_2) is determined by the sum of oxygen bound to hemoglobin (Hgb x O_2 saturation) and the oxygen dissolved in the plasma (arterial oxygen tension [PaO_2] x 0.003). At a normal hematocrit and oxygen tension, CaO_2 values are approximately 15 vol %. Under physiological O_2 tension, the amount of oxygen dissolved in plasma is negligible, however, normobaric hyperoxia may increase the amount of dissolved oxygen by approximately 0.5-1 vol >%, whilst hyperbaric oxygen can increase the oxygen content more substantially [162-163].

Therefore, doubts exist whether the improvement of $ptbO_2$ seen with hyperoxia really translates into improved oxygen delivery. In a recent study comparing the impact of 24 hours of breathing 100% oxygen in 52 patients with severe TBI versus historical controls, the groups were well matched for age, sex, postresuscitation GCS, and ICP during the first 12 hours after injury. Both groups were monitored with microdialysis and brain tissue O_2 sensors. In the hyperoxia-treated group, ICP was lower, dialysate glucose levels higher, and lactate and lactate-pyruvate ratios lower. The magnitude of the difference in ICP was not clinically significant (12 vs. 15 mmHg) and the implications of the biochemical changes are unknown. At 6 months after injury, the mean GCS score in the hyperoxia-treated patients was higher than in the control group (3.2 versus 2.8) but these differences were not statistically significant. Studies with hyperbaric oxygen show encouraging results [161]. Controversies persist on the user of hyperoxia, however.

Alveolar recruitment maneuvers may be more effective in improving cerebral oxygenation. Recruitment maneuvers favour increased tissue oxygenation not simply as a result of the increased fraction of inspired oxygen, but more particularly as PEEP can improve oxygen transfer over the lungs. The use of PEEP has been described in patients without intracranial hypertension [164-166]. Increasing PEEP from 5 to 15 cmH_2O increased SpO_2 from 95.5±2.1 to 98.6±1.2% (P=0.0001) and $PtbO_2$ from 27.8±6.5 to 33.9±6.7 mmHg (P=0.0001), without a significant effect on ICP and CPP (8.3±4.4 to 8.7±4.4 mmHg; P=0.14 and 94.8±8.2 to 94.6±8.0 mmHg; P=0.78), respectively [33]. In patients with intracranial hypertension, however, the risk of increasing ICP and decreasing CPP cannot be excluded. In such patients, multiparameter monitoring, including ICP and $ptbO_2$ is recommended; this may help prevent secondary complications due to elevations in ICP potentially produced by alveolar recruitment maneuvers (Figure 8.25, Figure 8.26).

The oxygen-carrying capacity of blood can be improved by blood transfusion. However, $ptbO_2$ can diminish rather than increase, especially after the transfusion of blood older than 19 days [167]. The baseline $ptbO_2$ level may be relevant to the response after blood transfusion. Murillo Cabezas et al. reported that blood transfusions produced an increase in $ptbO_2$ in all patients with a baseline <15 mmHg, whilst an increase was only observed in 75% of patients with a baseline $ptbO_2$ >15 mmHg (P <0.01). The relative increment in $ptbO_2$ after 3 hours was correlated with the baseline $ptbO_2$ (r^2 0.17; P=0.001) [168].

8.4.14 Reducing Metabolism to Protect the Brain From Ischemia

Cerebral metabolism may be reduced by sedatives (barbiturates, propofol) or by hypothermia. Both approaches are effective in reducing oxygen demand and ICP. Conflicting results are reported for $ptbO_2$. One small study on the effect of barbiturates on patients with refractory intracranial hypertension claimed improvement in cerebral oxygenation in 6 out of 8 patients [169.170]. Others, however, reported a significant decrease in tissue oxygenation after barbiturate administration; a possible explanation for this is the increased occurrence of pneumonia in patients treated with barbiturates and myocardial depression. Propofol given in a dose to induce EEG burst suppression does not appear to affect tissue oxygenation [171].
Results on the effect on $ptbO_2$ of hypothermia are conflicting. A study of hypothermia in 30 trial patients reported that $ptbO_2$ decreased with hypothermia, with greater intensity at <35°C. In another study the effect of moderate hypothermia (34-36°C) was studied in 33 patients with raised ICP (≥20 mmHg). In these patients hypothermia led to a decrease in $ptbO_2$from 33±24 to 30±22 mmHg. Conversely, in a study involving 72 TBI patients which focused on the occurrence of hyperthermia, it was reported that "hyperthermia does not appear to reduce $ptbO_2$ or to increase tissue episodes of hypoxia". This provides evidence for the conclusion that "hyperthermia may worsen the prognosis of TBI through mechanisms that do not involve oxygen" [172-174]. The ostensibly adverse effect of hypothermia on brain tissue oxygenation can be explained by a decreased perfusion during hypothermia due to pulmonary and cardiac effects. This emphasizes the importance of monitoring also to detect adverse consequences and complications of instituted treatments.

8.5 Early Detection and Treatment of Ischemia

Ischemia is one of the main factors involved in the development of secondary damage after TBI. Cerebral ischemia may result from systemic insults (e.g., hypoxia and hypotension) and intrinsic pathophysiologic mechanisms. Excessive hyperventilation is a major cause of ischemia due to vasoconstriction. Although it often occurs inadvertently, it may also be deliberate as treatment to reduce ICP. Monitoring $ptbO_2$ when using hyperventilation is recommended to safeguard against cerebral ischemia (Figure 8.27, Figure 8.28). We investigated the effect on $ptbO_2$ by reducing $paCO_2$ under standardized approaches: in patients ventilated because of severe TBI, increasing the tidal volume by 20% reduced $paCO_2$ by an average of 3.8±1.7 mmHg from a baseline of 32.3±3.5 mmHg. On the first day after injury, reactivity was low (0.8±2.3 mmHg) and increased over subsequent days; on day 5 the change was 61±4.4 mmHg. Higher reactivity was correlated with poorer outcome [175]. The lower reactivity in the earlier phases after injury can be explained by the more prominent arteriolar narrowing during the first 24 hours, indicative of metabolic depression or pathologic vasoconstriction and possibly caused by the swelling of podocytes of astrocytes. In such a state of vasoconstriction, the range of hyperventilation on day 1 was unable to induce any greater vasoconstriction. With time, however, the vessel diameter increased and the effects could be seen more clearly.
Although from a clinical perspective, the risk of moderate hyperventilation seems to be greatest in the first 24 hours after injury, we found that in 15% of the patients, hyperventilation induced a paradoxical response by increasing $ptbO_2$.This paradoxical response would seem to indicate a redistribution of CBF following hyperventilation [175-177]. This phenomenon likely represents the steal mechanism and has consequently

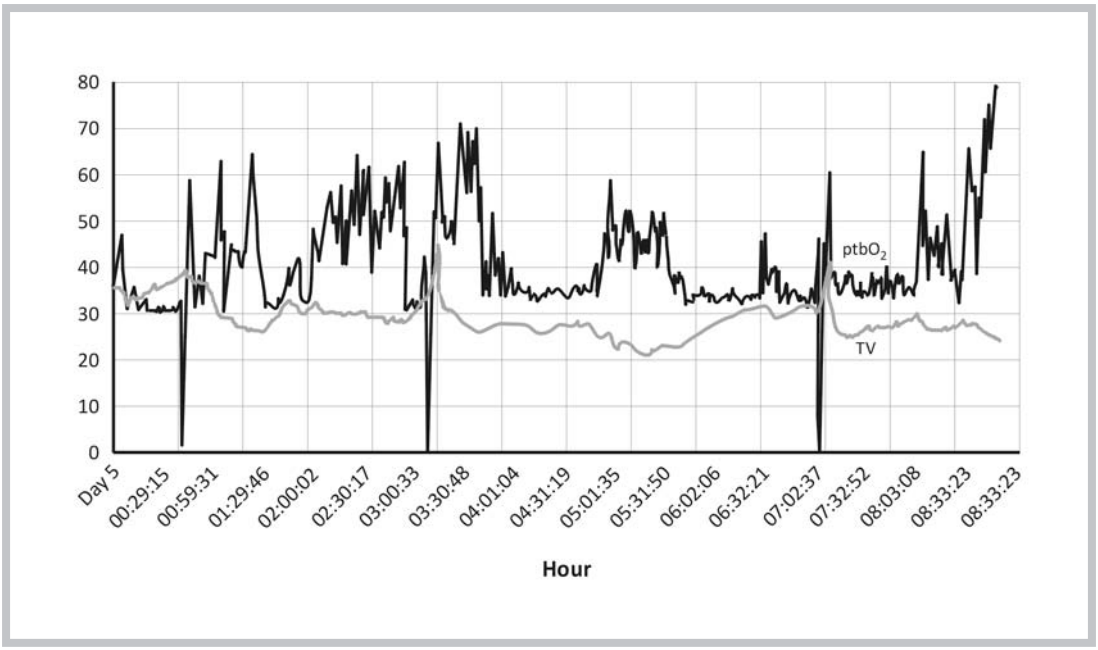


Figure 8.27. **TBI patient in pressure support 5 days after trauma. The prognosis in TBI is influenced by several secondary factors; one of the most important but less studied is hyperventilation. Patients in pressure support frequently show periods of ischemia induced by hyperventilation. In this case the patient was in the weaning period after 5 days of ventilation. Around 4.46 hours the TV increased until 550 ml, with a consequence decreased $ptbO_2$. With a continuous monitoring of TV and $ptbO_2$ it is possible to understand the real influence of hyperventilation.**

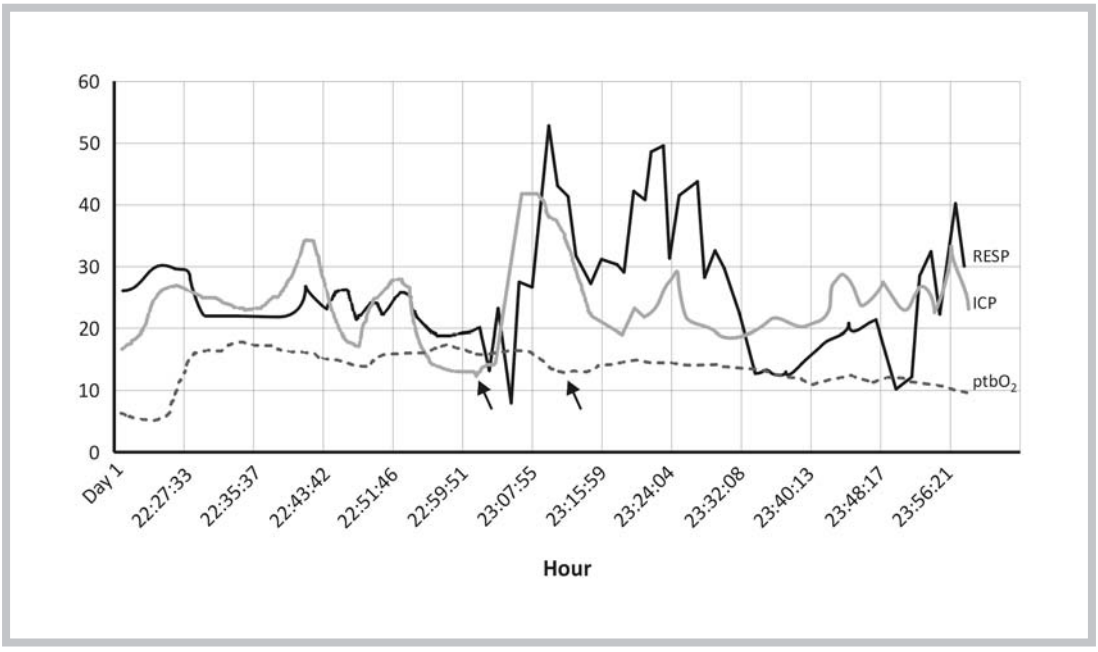


Figure 8.28. **Several events of ischemia induced by hyperventilation. Continuous recording of $ptbO_2$, RESP, and ICP shows multiples episodes of hyperventilation with the potentially damage in brain metabolism. In this Figure it is evident the absence of $eTCO_2$ monitoring in order to avoid more damage. The ICP response induced by hyperventilation always shows a decreasing pattern with a sacrificed $ptbO_2$.**

been called the “Robin Hood phenomenon”, which might be considered a warning sign (Figure 8.24)

Interpretation of response to hyperventilation is complex and requires insight into brain metabolism and vascular autoregulation. Studies with PET and combined EEG and evoked potential monitoring have shown the adverse effects of hyperventilation [107,109,110,178]. The reduction in CBF and $CMRO_2$ resulting from hyperventilation poses challenges in the care of trauma patients, and this would seem to indicate exhaustion of physiologic reserves and a compromise of oxidative metabolism. Whilst recognising the complexity of interpreting the effect of hyperventilation on $ptbO_2$, we consider $ptbO_2$ monitoring indicated in patients treated with hyperventilation.

8.5.1 Relationship between SjO_2 and $ptbO_2$

Prior to the implementation of $ptbO_2$ monitoring, SjO_2 monitoring was routinely employed in neurointensive care. This technique was prone to many artefacts, primarily due to light errors subsequent to catheter malposition, which made multiple calibrations necessary. Almost 65% of the data suffered from artefacts. Such problems do not occur with $ptbO_2$ monitoring. Both techniques offer complementary information in neurocritical care. $PtbO_2$ is a local technique for monitoring in areas considered at risk, whilst SjO_2 monitoring offers a more global approach. In combination, these techniques facilitate monitoring and targeted intervention against ischemia.

In our experience with 45 patients monitored with both parameters, we began monitoring on average at 7.5 hours (range, 2.5-12) after injury. The average recording time was 110 hours (range, 15.8-144). The SjO_2 catheter was calibrated *in vivo* every 8 hours.

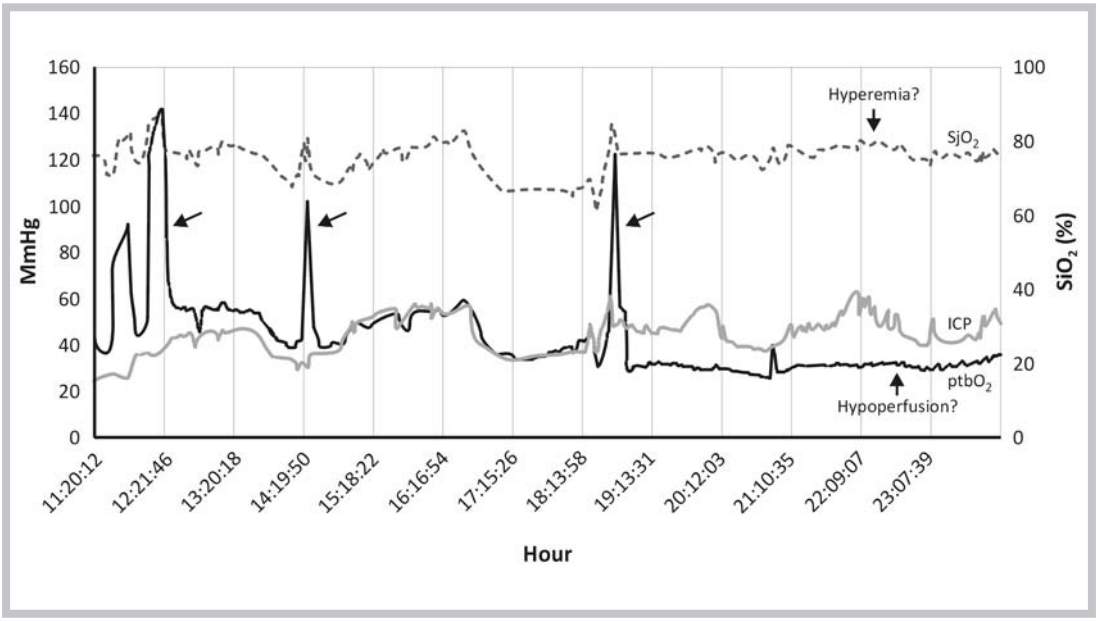


Figure 8.29. **Synchronic correlation between $ptbO_2$ and SjO_2 directed by ICP. 37-year-old female, anisocoric pupils: pos/neg and poor outcome. The initial evolution shows a similar pattern, with an increasing and decreasing trend in ICP, SjO_2 and $ptbO_2$, even in hypotension moments, hyperoxia, hyperventilation until 20.04 hours, later the highest ICP of 60 mmHg (22.02 hours induced in SjO_2 a possible hyperemia event, but but hypoperfusion in $ptbO_2$. This ambiguous pattern is due to the regional and global monitoring of both parameters and the severity of the TBI.**

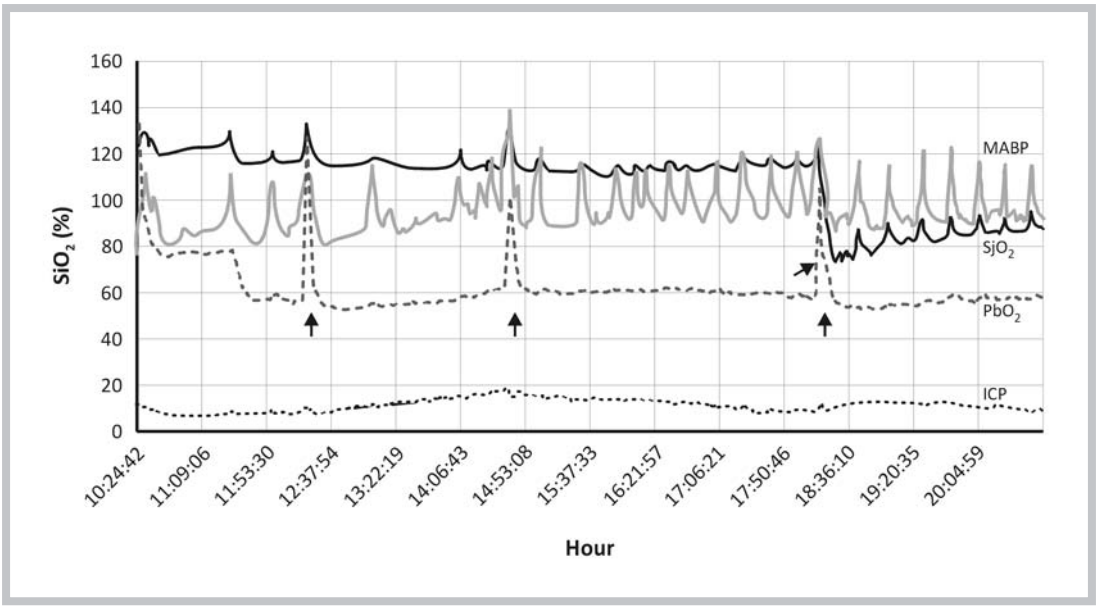


Figure 8.30. **SjO_2 oscillations dependent of blood pressure, with small changes in $ptbO_2$. TBI patient, GCS 13 on the admission, not completely sedated, with poor outcome. The oscillated mean blood pressure (mABP), with several fluctuations between 80-120 mmHg, induced normal fluctuations in SjO_2. At 18.13 a desaturation event occurred, with small $ptbO_2$ repercussion. Arrows show preoxygenation FiO_2 100% maneuvers.**

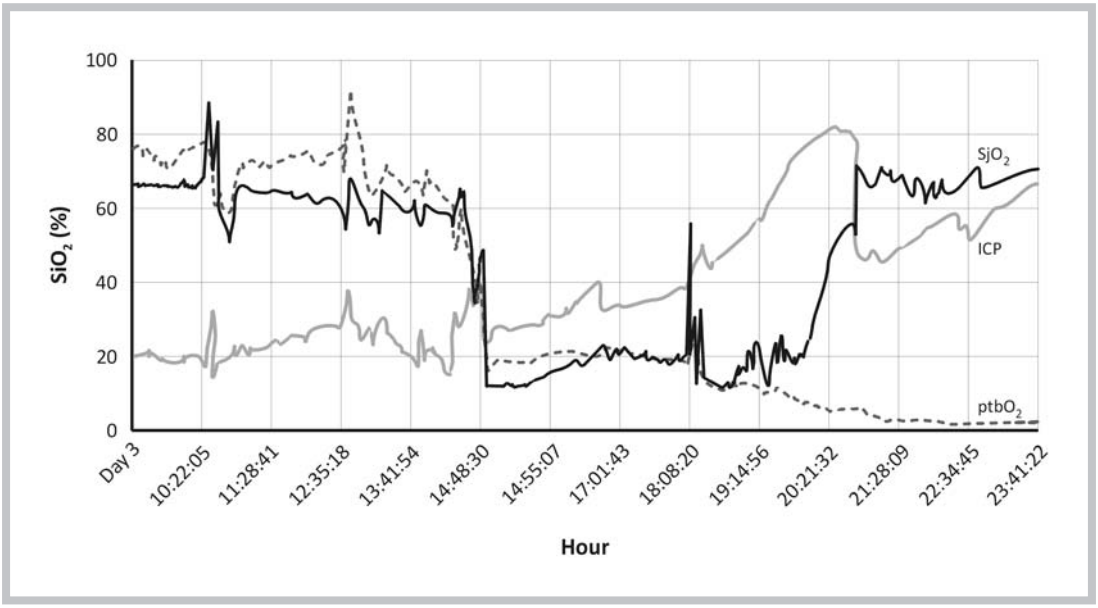


Figure 8.31. **Dramatic evolution of TBI patient with GCS 13. 83-year-old male, fallen during a sport race. GCS 13: E:3; M:5; V:5. With anisocoric pupils: post/neg. On the CT scan the perimesencephalic cisterns was compressed, with subarachnoid hemorrhage in the convexity and cisterns; frontotemporal contusion in the left side, without midline shift. The ICP on day 3 showed several spikes: 30 mmHg, progressively increased until 40 mmHg (14.51 hours), and later 50 mmHg (20.21 hour). A tremendous high $ptbO_2$ of 91.7 mmHg with a decline SjO_2 70%, showed the heterogeneity pattern of this injury. In a decline trend SjO_2 and $ptbO_2$ the patient shows a new ICP wave (14.48 hours) which produced a severe ischemic event. Later there was dissociation between SjO_2 and $ptbO_2$ in herniation moment. The $ptbO_2$ was in the frontal lobe of the lobe of the same temporal contusion.**

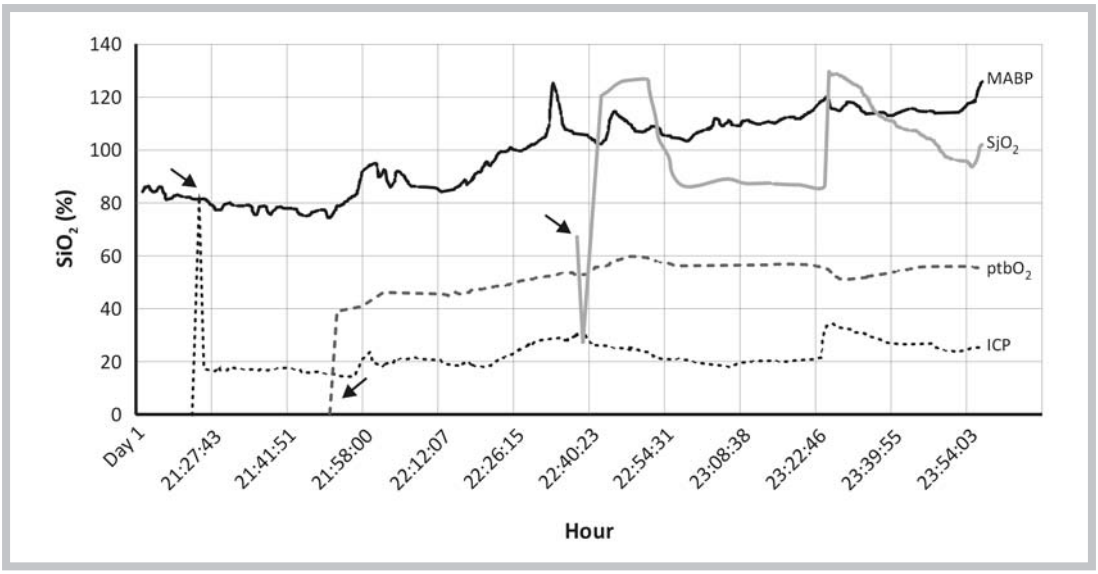


Figure 8.32. **Validity of $ptbO_2$ values and run-in time. In this case: a short and high run-in time. The $ptbO_2$ calibration test postinsercion had a good correlation with solution calibration. These tests show the substantial validity of the high $ptbO_2$. Arrows indicate the insertion technique of $ptbO_2$, ICP and SjO_2. The influence of chronic hypertension and ICP peaks (22.40 hour and 23.32 hour) influenced $ptbO_2$ and SjO_2 values.**

Substantial readjustment of the settings of more than 10% was required in 25% of all calibrations. The evolution pattern of SjO_2 in the first 24 hours after trauma was similar to that observed with $ptbO_2$ monitoring. The SjO_2 was approximately 65% in the initial 24 hours after trauma, increasing to 80% after 60 hours. The correlation between both techniques was 0.30±0.25 (range 0.13-0.72). The highest correlation between the

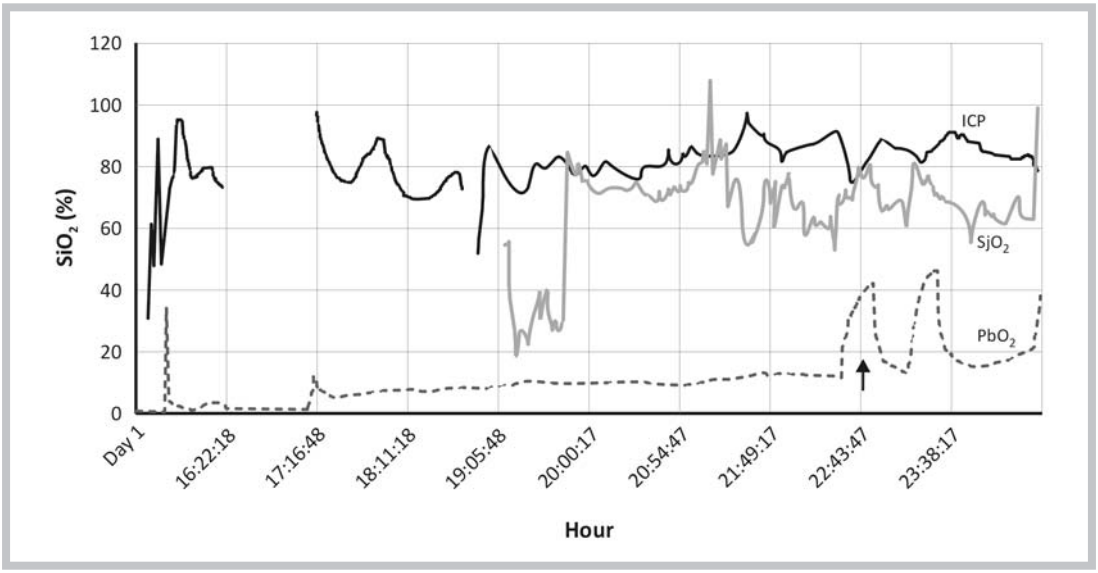


Figure 8.33. **$ptbO_2$ and SjO_2 trend in case of high ICP: there is no doubt about the predictive value of both parameters. $ptbO_2$ had a long run-in time and also a longer period <15 mmHg, with a high oxygen reactivity in test 100 % FiO_2, even during low $ptbO_2$ (arrow) (22.16-23.11 hour). $ptbO_2$ increased up to 95 mmHg. It was evident that CPP had a strong correlation with $ptbO_2$, instead of SjO_2. The high oxygen reactivity associated with low values means that cerebral oxygen consumption is decreasing.**

techniques occurred during periods of hyperoxemia and hyperventilation. Low SjO_2 values were not always accompanied by low $ptbO_2$ values, and an inverse relationship was sometimes noted [15]. When the $ptbO_2$ catheter was implanted in a relatively undamaged part of the brain, discordant values between the techniques were common. Discrepancies between the two techniques were also noted in the diagnosis of brain death, brain herniation, psychomotor excitation, sudden episodes of raised ICP. Figures 8.29, 8.30, 8.31, and 8.32 show some examples.

Both techniques are recommended for monitoring the risk of ischemia. The interpretation of hyperemia by $ptbO_2$ monitoring is not fully explored and is confounded by effects of high FiO_2. Therefore, it is necessary to exclude the effects of FiO_2 when a possible hyperemic state is suspected. In our experience, monitoring does not adequately capture hyperemia. Hyperemic status, as evidenced by high SjO_2 and small $AVDO_2$, often has normal $ptbO_2$ values, but in some special cases when the vascular autoregulation is affected the $ptbO_2$ it may be high (Figure 8.33).

In conclusion, the interpretation of hyperemia must be based on global CBF values and not on the results of $ptbO_2$ monitoring. The parameter of oxygen partial pressure in the tissue is composed of three elements: arterial paO_2; venous oxygen pressure; and tissue oxygen. It does not reflect only CBF. Tissue hypoxia may occur with global hyperemia (SjO_2 >75% or $AVDO_2$ <3). SjO_2 values do not differentiate between situations of hyperemia or extensive tissue infarction. If the $ptbO_2$ catheter is inserted into an infarcted area, with no or very limited oxygen consumption, low values may occur, whilst high SjO_2 values can be observed. Sahuquillo, describing 244 simultaneous jugular and $ptbO_2$ measurements, reported 31 episodes of tissue hypoxia <15 mmHg (12.7% of episodes) in a presumed hyperemic state. We conclude that both techniques offer complementary information [179].

8.6 Suggestions and Limitations

In the last sections we compared the early publications on $ptbO_2$ monitoring (Rotterdam group) with the more recent literature, described new applications of $ptbO_2$, and briefly discussed some aspects of SjO_2.

Traumatic brain ischemia is an important target for therapy as it can worsen the primary injury and lead to poorer outcome. A Clark-type electrode inserted into a relatively undamaged part of the brain can be employed to monitor for ischemia and to optimize treatment. When the electrode is placed in the penumbra of a damaged area, therapy can be aimed to protect tissue at risk. Initial studies suggested lower mortality in patients without impairment of brain oxygenation. With the new technological advances in the Clark catheter – produced 10 years later –the measured area has been augmented, the random uncertainty reduced, and the reliability of this technique further improved. There are, however, no randomized clinical trials to confirm a clinical benefit of $ptbO_2$, ICP and other hemodynamic monitoring techniques. Centres using these techniques report decreased mortality, improved oxygen delivery and/or a better balance between intake and oxygen consumption [15,18,19]. Perhaps the greatest benefit is that, when combined, these monitoring techniques afford greater insight into the on going pathophysiology and the understanding of the complex pattern of brain injury, thus offering opportunities for more individualized and targeted management.

To obtain more definitive results, collaboration between researchers for database integration and cooperative multicentre studies are needed. In other words, sharing goals, with acceptable patient groups to achieve representative samples. In the absence of co-

operative studies, results will remain dispersed and it will be impossible to adequately face the challenges of personalizing treatment based on a monitoring strategy. At most, 20 groups around the world are actively involved in this area of research, and we strongly encourage collaboration.

In comparison to cardiology, sample sizes in studies on $ptbO_2$ monitoring are relatively small and few have a randomized design. Recent interest has focused on monitoring at later periods after injury, whilst results already obtained in the 1980s have demonstrated that the initial 24 hours after trauma are critical and that low brain tissue oxygen values are particularly prevalent in this period [15,24]. Standardization of terminology is also required. In the Ovid database, 938 manuscripts were identified by the English abbreviation "$ptiO_2$", whilst a search utilizing the search term "brain tissue oxygen monitoring" yielded almost 10,000 reports.

Despite initial publications describing the prognostic value of $ptbO_2$ monitoring and the association between clinical and monitoring values, relatively few studies since then have focused on these relevant aspects. Much work is needed to define specific ptO_2 thresholds for treatment and how these may differ between white and grey matter and according the time elapsed since injury. The debate remains open as to whether monitoring should be performed preferentially in a relatively undamaged part of the brain, and be taken as representative of more global cerebral oxygenation, or in the penumbra of a lesion, with the intent to preserve this tissue at increased risk.

Our knowledge of the pathophysiologic mechanisms underlying the results of $ptbO_2$ measurement is still relatively incomplete and the heterogeneity and variability of brain tissue oxygen distribution may confound their interpretation. We should further recognize that also with the more recently produced catheter, a certain equilibration time, often termed the "run-in time", is required, thus limiting its use immediately after insertion. Although from a theoretical perspective the use of multiple catheters placed in different regions might be preferred, this is pragmatically impossible and would pose too high a risk to patients. Nevertheless, we feel that the current status of $ptbO_2$ monitoring has advanced to a level that it can be considered part of routine clinical monitoring.

To gain optimal benefit, however, education and learning are prerequisite to creating a team with knowledge of oxygen supply and consumption. Appropriate implementation of the technology requires much more than a simple working group composed of a doctor and a nurse plugging in the connection between monitor and equipment. Multidisciplinary collaboration and involvement of Intensive therapy experts for advanced data integration and analysis should be encouraged.

8.7 Conclusions

$PtbO_2$ monitoring reflects overall oxygenation after TBI if the probe is positioned in a relatively undamaged part of the brain. In these situations, initially low values within the first 24 hours after injury are common, reflecting a decrease in CBF possibly due to increased vascular resistance or decreased metabolism. Low initial values in this period are independently associated with poorer outcome at 6 months. In pragmatic terms, $ptbO_2$ monitoring is easier to perform and less prone to artefacts than SjO_2 monitoring. Both techniques, however, yield potentially different information and should be considered complementary.

The use of $ptbO_2$ monitoring to safeguard against ischemia in the use of hyperventilation to treat raised ICP is now widely recognized. The adverse effects of even small decreases in blood pressure or changes in arterial oxygenation can now be monitored

more closely and accurately. Furthermore, evaluating changes in brain tissue oxygen subsequent to changes in blood pressure or ventilation status offers insights into autoregulation and CO_2 reactivity. We recommend that it should be used only in units experienced in ICP monitoring and where potential complications can be treated neurosurgically [15,33-36].

Monitoring $ptbO_2$ cannot replace ICP monitoring; instead, it should be seen as an addition that provides more insight into the ongoing pathophysiology in a given patient. We consider the benefits of cerebral oxygenation monitoring to greatly outweigh the risks. Multidisciplinary and international collaboration between study groups is strongly encouraged to advance our standards of care and to facilitate personalised management.

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9 Monitoring Cerebral Blood Flow and Cerebral Autoregulation: Basic Principles, Techniques, Common Patterns and Interpretation of Results

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9.1 Introduction

The successful management of patients with brain injury requires an understanding of the physiological principles of cerebral blood flow (CBF). Ignoring these principles can lead to deleterious events in the neurocritically-ill patient [1,2]. Two examples suffice to illustrate this point: 1) a patient presents with an acute ischemic stroke and a systolic blood pressure of 180 mmHg which is aggressively lowered to 120 mmHg, resulting in extension of the stroke; and 2) a patient with subarachnoid hemorrhage has a mean arterial blood pressure of 125 mmHg which is aggressively lowered to 100 mmHg on the seventh day of hospitalization, leading to diffuse cerebral ischemia. It is important to realize that CBF is closely linked to brain metabolism in most circumstances and that the treatments initiated by clinicians have to maintain a balance between the systemic events and the normal delivery of oxygen to the brain.

9.2 Physiology of Cerebral Circulation

The brain of a human adult weighs approximately 1200-1400 g which accounts for only 2-3% of the total body weight. Despite this the brain receives about 20% of the total cardiac output. This is mainly due to the fact that the cerebral metabolic rate for oxygen ($CMRO_2$) is high and that the brain utilizes glucose as the major substrate to meet its energy needs. Neurons are very active and consume most of the available energy, while the glial cells utilize only 10% although they make up 50% of brain weight [3]. The average CBF is approximately 50 ml/100 g brain tissue per minute. The cerebral ischemia threshold value is <20 ml/100 g/min. Irreversible brain damage or stroke occurs when the CBF falls to <10-15 ml/100 g/min. From this it follows that between levels of 15 and 20 ml/100 g/min the changes are reversible. This area has been called the penumbra. In other words, in situations of severe ischemia there is a central area or core, which represents infarction, and a peripheral area which represents ischemia without neuronal death. This concept is very important because the primary goal of therapeutic interventions in the neurocritical care unit is to preserve the periphery or penumbra while trying to lessen the core.

Because the brain has no energy reserves, its function relies almost exclusively on the delivery of oxygen and glucose, which implies that CBF, $CMRO_2$ and cerebral oxygen extraction are coupled under normal physiological conditions. These factors have been implicated in the Fick principle devised by Adolf Fick in 1870 [4]. Based on the principle of conservation of mass, the equation provides a simple way to determine that the amount of a substance detected by an organ per unit of time is equal to the organ blood flow multiplied by the difference between arterial and venous concentration. Applied to the brain, Fick's equation is derived as follows:

$CMRO_2 = CBF \times AVDO_2$, where $AVDO_2$ is the difference in arterio-venous oxygen.

How does the brain keep the coupling of these parts intact in normal situations?
To compensate for the metabolic rate, fluctuations in cerebral perfusion pressure (CPP) and changes in blood viscosity, the diameter of the cerebral blood vessels changes to maintain a constant $AVDO_2$, which has been termed autoregulation of CBF (Figure 9.1) [5]. Although the exact mechanisms underlying such autoregulation have not been fully elucidated, the two most accepted are myogenic and metabolic in origin. According to the former, pressure changes through the vascular wall lead to changes in arteriole diameter. The latter is based on the hypothesis that changes in the microenvironment alter vasomotor response. These changes are mediated by $PaCO_2$, PaO_2, and tissue temperature. There is also evidence that sympathetic nerve activity, blood rheology, and chronic hypertension have an important effect on CBF autoregulation (Table 9.1). It is important to take these factors into account when the patient enters the neurocritical care unit. Specific situations include:

- Cerebral edema in patients with increased $PaCO_2$ and body temperature can trigger an increase in intracranial pressure (ICP).
- In patients with hypertensive encephalopathy, there is most certainly maximum vasoconstriction in the arterioles. A rapid decrease in the MAP to normal levels can cause global cerebral ischemia.

Factors	Changes in CBF
CPP	CPP increase (usually >25 mmHg) or significant decrease in mean arterial pressure (<60 mmHg) leads to decreased CBF
$PaCO_2$	$PaCO_2$-arteriolar response mediated by changes in extracellular pH. CBF changes 3-4% for every 1% change in $PaCO_2$. The relationship is almost linear up to 100-120 mmHg $PaCO_2$
PaO_2	CBF increases dramatically when PaO_2 falls to <50 mmHg
Brain temperature	Tissue temperature increases $CMRO_2$ 6-7% per degree C rise in temperature. Hypothermia decreases $CMRO_2$
Innervation-sympathetic nervous system	Sympathetic nerve activation of the sympathetic alpha adrenergic nerves shifts the autoregulation curve to the right (more vasoconstriction), while denervation shifts it to the left
Chronic hypertension	Chronic hemodynamic changes lead to changes in the structure of arterioles. The self-regulatory curve is shifted to the right. There is greater tolerance to increases in blood pressure but lower tolerance to decreases
Blood viscosity	In normotensive conditions, a fall in hematocrit from 35 to 25% leads to an increase of 30% in CBF. Falling pressure leads to a loss of the relationship. Compensatory vasodilation mechanisms are lost when hematocrit is decreased by 19%

Table 9.1. **Physiological and pathological factors affecting CBF autoregulation.**

- A decrease in the MAP can cause irreversible damage, leading to cerebral ischemia in patients with lesions with mass effect.

After this introduction and review of the physiology of the cerebral vasculature, let's now explore the different methods at our disposal to determine CBF in our patients in the neurocritical care unit.

9.3 Techniques to Measure Cerebral Blood Flow

Practical and efficient measurement of CBF is difficult. Such impediment limits the information needed to determine the evolution of deleterious factors which may affect neuronal viability. One potential adverse events of this would be a delay in therapeutic interventions that could

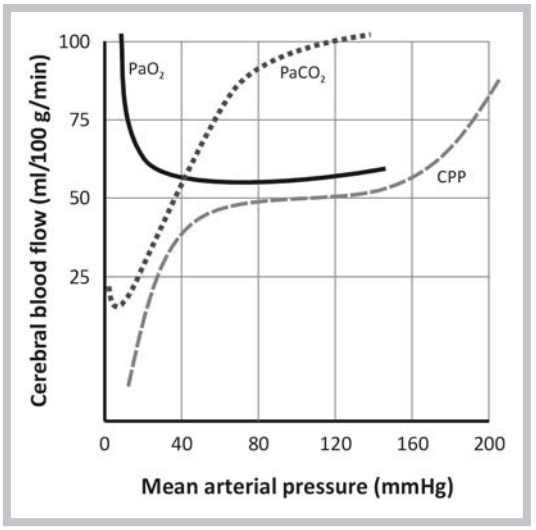

Figure 9.1. **Under physiological conditions, the brain maintains CBF within normal limits through autoregulation when the CPP is between 40 and 140 mmHg. Other factors that independently affect CBF are the PaO_2 and $PaCO_2$. This diagram, drawn by the author, is based on a figure taken from [5].**

Method	Advantages	Disadvantages
Neurologic examination	May be repeated as needed	Cannot detect early changes in CBF
CPP	Can be measured continuously	Needs ICP catheter insertion and depends on the CVR
EEG	Not invasive and can be continuously measured	Interference may be an issue and costly equipment is needed for data analysis
Fick's Principle	Allows direct measurement of CBF and is considered the gold standard	Invasive, determines global CBF and requires manual sampling
$Xenon^{133}$	May be repeated as needed	Poor resolution and does not allow proper evaluation of CBF in subcortical structures
Xenon-enhanced CT	Measures regional CBF and may be repeated as needed	Expensive, technically difficult, and has the anesthetic effects of xenon
PET	Allows measurement of cerebral blood volume, tissue oxygen extraction, and $CMRO_2$	Expensive, not readily accessible; requires skilled personnel and patient transport out of the neurocritical unit
MRI and perfusion CT	Measures CBF and cerebral blood volume	Allows qualitative measurement; depends on comparison of data from the two cerebral hemispheres
TCD	Portable, inexpensive, and allows continuous measurement	Measures the speed of blood flow but not CBF; is operator-dependent and acoustic windows; allows only study of the basal arteries of the circle of Willis
Thermal diffusion flowmetry	Allows continuous and quantitative real-time CBF measurement in the area of interest	Requires insertion of a catheter and allows only measurement of local CBF

Table 9.2. **Comparison of different methods of measuring CBF in a neurocritical care unit.**

$CMRO_2$ = cerebral metabolic rate for oxygen
CPP = cerebral perfusion pressure
CVR = cerebral vascular resistance
CT = computed tomography
EEG = electroencephalography
ICP = intracranial pressure
PET = positron emission tomography
MRI = magnetic resonance imaging
TCD = transcranial doppler sonography

potentially reverse or prevent ischemic insults. AAn ideal technique of CBF measurement must meet the following requisites: portable, repeatable, and inexpensive. Since no currently available technology meets all these requirements, we are forced to use methods that are not always optimal (Table 9.2).

The neurologic examination can reveal altered level of consciousness or changes indicating that CBF is below acceptable thresholds for normal neuronal function. Early assessment is vital because when clinical changes are evident, irreversible changes have probably already occurred [2].

Measurement of CPP has been used as a substitute for evaluating CBF as this is directly related to CPP and inversely related to cerebral vascular resistance (CVR) according to the following equation:

$$CBF = CPP / CVR$$

From a practical standpoint, CVR is not easy to determine. Therefore, the CPP is derived from the difference between mean arterial pressure (MAP) and ICP:

$$CPP = MAP – ICP$$

Normal CPP values are between 55 and 70 mmHg [6]. It should be noted that a normal CPP can be used as a surrogate marker of normal CBF as long as the CVR is also normal. For example, if the CVR is high, as occurs in cerebral vasospasm, then a normal CPP may be associated with cerebral ischemia. Similarly, if the CVR is low, a normal CPP could lead to cerebral hyperemia.

Continuous electroencephalography (EEG) monitoring can furnish data complementary to neurological findings to detect early changes in CBF. Because CBF changes in a predictable manner in situations of cerebral ischemia, such alterations may prompt the neurointensivist to intervene early [7,8]. At CBF levels between 16 and 22 ml/100 g/min there is a predominance of slow waves, followed by a decrease in the amplitude when the CBF is 11-19 ml/100 g/min which can reach an almost total reduction on the EEG tracing when levels are <10 ml/100 g/min.

The first technique for the quantitative measurement of CBF, as devised by Kety and Schmidt, was based on the Fick method described above and used nitrous oxide as a marker as this gas is metabolically inert and diffuses quickly in the brain [9]. The gas is inhaled and blood samples are obtained from an artery or a jugular vein. The technique relies on two conditions: a continuous CBF and freedom from contamination of jugular samples with extracerebral blood. Inhaled or intravenous administration of xenon^{133} has also been used for similar measurements. The advantage of this technique is that you have a small portable unit, but the disadvantage is that the partition coefficient of the blood-brain barrier for this material is abnormal in pathological conditions.

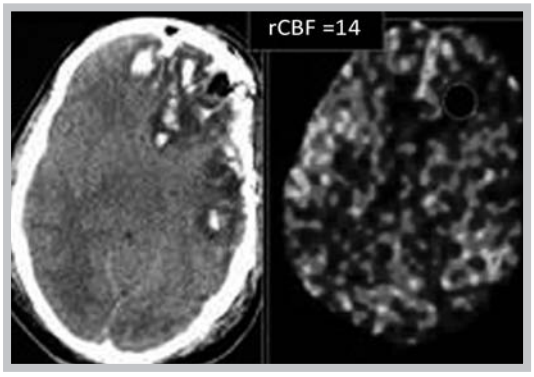

Figure 9.2. **Xenon-enhanced CT scan in a patient with severe traumatic brain injury. Note the significant decrease in CBF in the left frontal region which, if not corrected, can lead to cerebral ischemia with subsequent infarction. Courtesy of Dr. Claudia Robertson, Ben Taub Hospital, Houston, Texas.**

Xenon-enhanced computed tomography (CT) offers the advantages that once the gas is inhaled it acts as a contrast medium

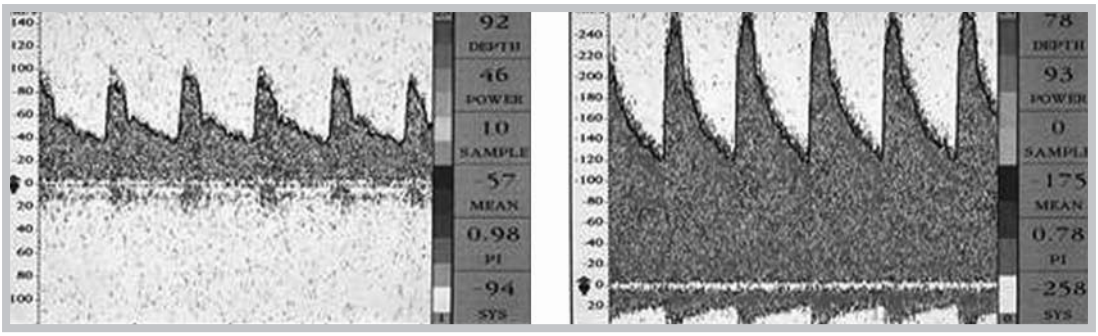

Figure 9.3. **Transcranial Doppler of a patient with a subarachnoid hemorrhage. The left panel shows the tracing on day 3 and the right panel the tracing on day 7 when the patient was in a confusional state, with double vision and tetraparesis. The right panel shows a basilar artery vasospasm.**

for cerebral CT and it has a higher spatial resolution, so that regional CBF can be measured [10] (Figure 9.2).

Other advances in diagnostic imaging have allowed us to use positron emission tomography (PET) and magnetic resonance imaging (MRI). Although advances in these techniques continue, there remain limitations to their use (Table 9.2).

The last two CBF measurement tools we will mention are transcranial Doppler ultrasound (TCD) and thermal diffusion flowmetry [11-16]. TD measures CBF velocity, from which CBF can be estimated if the amount of blood flow through the cerebral vessels is measured simultaneously. However, the cerebral blood flow velocity rate is used in clinical practice. A detailed analysis of blood flow velocity, the pulsatility index are obtained to detect cerebral vasopasm in patients with subarachnoid hemorrhage (Figure 9.3), the pattern of collateral circulation in the circle of Willis in patients with vascular stenosis, arterial reperfusion status after thrombolysis in patients with acute ischemic stroke, and progression to cerebral circulatory arrest.

Thermal diffusion flowmetry allows us to calculate an index of cortical blood flow by measuring the dispersion of heat delivered through a catheter per unit of time. The major advantage of this technique is that it can continuously determine CBF based on a very simple principle (Table 9.2).

9.4 CBF in Pathological Conditions

Secondary injury resulting from a decrease in CBF to a critical level can lead to poorer clinical outcomes. The following paragraphs present the data from studies in which CBF was measured in such common brain diseases as severe traumatic brain injury, seizures, subarachnoid hemorrhage, acute ischemic stroke, and stroke or intracerebral hemorrhage. Importantly, there is considerable controversy regarding the use of data from the CBF measurement methods discussed above. For instance, there have been reports of important variability in the methodology and the definition of CBF thresholds for the diagnosis of cerebral ischemia in several clinical conditions such as severe traumatic brain injury and acute ischemic stroke [17,18].

In the initial phase of severe traumatic brain injury, there is a decrease in CBF in 50-60% of patients [19]. However, this does not always indicate that the patient is suffering from cerebral ischemia. To determine this, $AVDO_2$ data are also needed, which show that in approximately 27% of cases the delivery does not meet the demand. It has also been shown that in the first days after trauma, some patients have hyperemia, i.e., in-

creased CBF beyond the metabolic requirement [20]. Both ischemia and hyperemia may increase ICP, leading to disastrous results for the patient. It follows that proper management of CBF is essential, and most researchers agree that a CPP of 55-70 mmHg is sufficient to maintain brain function.

In patients with subarachnoid hemorrhage and altered level of consciousness there is a greater decrease in CBF than in those who arrive alert. This reduction can occur in the first two days after the initial event and may gradually continue for the first weeks. The critical point in the management and monitoring of CBF in these patients is during cerebral vasospasm. The most commonly used method, as discussed above, is TCD which demonstrated increases in flow rate (usually >200 cm/sec). The absolute value is not necessarily the best indication of vasospasm but instead the changes with increases >50 cm/sec over a 24-hour period. The usual management of vasospasm includes hypertensive therapy according to the hypothesis that it will increase CBF. However, we must emphasize that the autoregulation mechanism is altered, and, whether global or focal, it is difficult from a clinical perspective to determine if the therapy causes an increase or a decrease in CBF steal from areas with normal vasoreactivity [11,12].

PET studies in patients with acute stroke [21] have shown that CBF can follow various patterns:

- Increased cerebral blood volume to maintain normal CBF (normal or autoregulation).
- Increased oxygen extraction in response to a decrease in CBF to maintain $CMRO_2$ (oligohemia).
- Increased oxygen extraction to compensate for a decrease in CBF and $CMRO_2$ (ischemia).
- CBF and $CMRO_2$ with very low oxygen extraction (irreversible ischemic injury).

There is a growing body of evidence that supports the concept of a penumbra surrounding a central area of infarction. This means that the peripheral area is still viable and that all efforts should be undertaken to preserve it with thrombolytic therapy or to increase MAP.

In patients with intracerebral hemorrhage, it is uncertain whether there is cerebral ischemia around the hematoma. Several studies have shown that CBF and $CMRO_2$ decrease in proportion to each other, which has been called a brain in “hibernation” [22]. As hypertension is common during the acute period, it was postulated that aggressive treatment can lead to cerebral ischemia and poor clinical outcome. However, this has not been demonstrated and, indeed, there is evidence showing that a greater decrease in MAP improved clinical outcomes most likely due to a lower proportion of cerebral rebleeding [23].

Finally, we shall look at CBF during seizures, which has been studied since the 1930s following the discovery by Penfield that they alter the local environment [24]. Later it was found that CBF decreases during the interictal period in the affected temporal lobe or the entire ipsilateral hemisphere, with significant increases during the seizure, followed by a decrease in the postictal period [25]. There are very few studies to date that have correlated the coupling of delivery and demand, but preliminary studies indicate that it may occur or that there may be a decoupling.

9.5 Key Concepts

The brain autoregulates CBF to maintain a constant supply of glucose and oxygen in response to changes in the brain’s microenvironment. The major factors in this process are $PaCO_2$, PaO_2, tissue temperature, ICP, and CPP. They must be standardized or controlled

to prevent CBF from falling to critical levels which potentially lead to irreversible brain injury. Furthermore, in patients with chronic hypertension the autoregulation curve is shifted to the right, which means that "normal" CPP can result in ischemia in such patients. There are several methods to measure CBF in the neurocritical care unit. The most common are physical examination, CPP, EEG, xenon-enhanced CT, MRI, TCD, and thermal diffusion flowmetry. All these techniques have advantages and disadvantages, and there are no definitive data on their predictive value with respect to the diagnosis of cerebral ischemia and their impact on clinical outcomes.

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10 The Current Role of Transcranial Doppler in the Intensive Care Unit. Indications, Bases for Its Correct Interpretation, Most Frequent Applications and Patterns

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10.1 CBF Monitoring at the Bedside. Transcranial Doppler Ultrasound

In the mid-nineteenth century, Christian Andreas Doppler described the effect that bears his name. He showed that it is possible to measure the velocity of a moving object based on the measurement of the variation in the frequency (Doppler shift or Doppler frequency shift) and wavelength (light, sound, electromagnetic) that experiences a wave on reflection from the object.

Spencer and Reid used and popularized the Doppler effect to obtain information from the circulation in different blood vessels using ultrasound. Cerebral circulation was not possible to assess at an earlier stage because it was interpreted that the ultrasound could not pass through the skull. In 1982, Aaslid and colleagues introduced transcranial Doppler (TCD) in clinical practice to evaluate cerebral hemodynamics using ultrasound waves of 2 MHz, the smallest frequency used in medicine to that date. They were able to show that it is possible to measure the velocity and direction of cerebral blood flow (CBF) in several intracranial blood vessels through an intact skull and noninvasively [2-4]:

- The proximal segments of the arteries which make up the circle of Willis.
- The arteries that give rise to them (carotids and vertebral arteries).
- Their major branches.
- The major cerebral veins and venous sinuses.

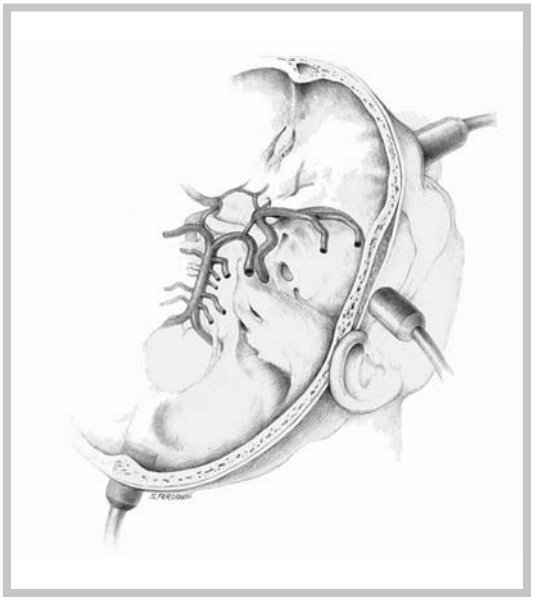

Figure 10.1. Insonation bone windows through which the arteries giving rise to the circle of Willis and its major branches can be studied: transforaminal, transtemporal and transorbital insonation windows.

IThe vessels that can be studied with TCD are:

- Proximal segments of the arteries making up the circle of Willlis.
- The arteries that gives them rise(carotids and vertebral arteries).
- Their major branches.
- It also allows blood flow circulation at major cerebral veins and venous sinuses to be assessed.

In experienced hands, this tool provides considerable amount of information in "real time" (excellent temporal resolution). It is also fast, simple, non-invasive, reproducible and feasible to perform at the bedside as often as the patient condition requires it, or even in a continuous way. All these features make the technique extremely valuable in the critical care setting. It is the only non-invasive technology available today that allows neurointensive care physicians or neuro-emergencists to monitor the intracranial hemodynamic characteristics at the patient´s bedside, without transfers (avoiding associated risks), in real time, noninvasively, through the intact skull. In this way the functional/dynamic information provided by this technique complements very well the static data provided by a CT or MRI.

What variable does TCD measure? As anticipated above, TCD measures Cerebral Blood Flow Velocity (FV) and its direction in the large basal cerebral arteries (Willis circle and main branches). In order to simplify the evaluation of FV a "spectral envelope" corresponding to the maximum flow velocity throughout the pulse cycle is created. Three specific points can be recognized in this envelope: peak systolic, end diastolic and mean flow velocity. The relationships between these velocities define indices (pulsatility and resistance index). Mean flow velocities and their relationships with velocities obtained from respective extra-cranial segments of carotid and vertebral arteries define different cerebral hemodynamic patterns. More information about ultrasound physics and specific characteristics of the technique are attached at the end of the chapter (see Appendix).

It is essential to note that FV as measured by TCD, is not synonymous with cerebral blood flow (CBF). CBF represents a flow (in mL/sec, and FV represents a velocity, in cm/sec. Although absolute values of CBF cannot be measured with TCD, changes in FV during continuous monitoring reflect proportional changes in CBF. This means that during continuous monitoring, if FV doubles, CBF has doubled, if the FV decreases by half means that the CBF has halved. However, we cannot know the absolute numeric value of these flows.

When studying cerebral hemodynamics in critically ill patients, it is important to assess the results in light of the systemic hemodynamics (arterial pressure), the presence of drugs (sedation, analgesics, vasopressors) or pathophysiological changes which act on the cerebral circulation (temperature, hemoglobin). It is also desirable to perform multiple neuromonitoring. This allows the simultaneous assessment of several variables. The parameters thus obtained allow a deeper evaluation of existing alterations. Other – invasive- variables which complement the information provided by TCD ultrasonography are ICP, cerebral oxygenation (global, by JSO_2, and local, by $PtiO_2$), continuous or intermittent EEG, etc.

Increase in velocity	Decrease in velocity
• Hyperflow • Vasospasm • Seizures • Anemia • Hypertension associated with loss of autoregulation • Fever • Arteriovenous malformation • Preeclampsia • Younger age • Decompressive craniectomy	• Intracranial hypertension • Decreased perfusion pressure • Hypocapnia • Drugs (indomethacin) • Hypotension associated with loss of autoregulation • Hypoxia • Cerebral circulatory arrest • Hypothermia • Older age

Table 10.1. **Factors causing an increase or a decrease in CBFV.**

10.2 Flow Velocity and Pulsatility Index. Normal Range and its Variations

Normal flow velocities vary in different vessels. In addition, they vary with age, systemic and/or cerebral hemodynamics, physicochemical characteristics of blood (viscosity), etc. FV oscillates between 30 and 80 cm/s, approximately. For example, in the adult group, FV in the middle cerebral artery (MCA) is 58±12 cm/s. FV in the basilar artery is 36±12 cm/s.

Side to side (right to left) variations has been detected in normal individuals, but differences above 15% should not be interpreted as normal. A daily variation is also possible but should be assumed as normal only if it is lower than 10 cm/s.

10.3 Clinical Applications of Transcranial Doppler in Intensive Care Medicine

TCD is an important non-invasive diagnostic tool in evaluating patients with cerebrovascular disease. In Intensive Care its use is particularly aimed to detection and monitoring of changes in cerebral hemodynamic in subarachnoid hemorrhage (SAH), ischemic and hemorrhagic stroke, traumatic brain injury (TBI) and other diseases not so frequent but equally serious, such as meningitis and encephalitis, severe vasculitis, etc. The most frequent disturbances of cerebral hemodynamic in these patients are secondary to increased intracranial pressure and the possible development of cerebral circulatory arrest (CCA), cerebral vasospasm, hyperemia, and impaired cerebrovascular reactivity (autoregulation and CO_2 reactivity). In the intensive care unit there are many technical difficulties, related to: 1) the multiple monitoring systems which surround the patients, with wires and catheters, respirators; 2) the difficulties of positioning non collaborating patients. The fundamental interest in the neurocritical care patient is often to evaluate the alterations of cerebral hemodynamic globally, or to search for assimetries. To diagnose these alterations it is enough to insonate middle cerebral arteries bilaterally, and the basilar artery in the posterior sector. However, if the main interest is the study of a localized disturbance, such as vasospasm, the evaluation should be detailed along each vessel.

TCD has a broad spectrum of clinical applications. In neurocritical patients, its major applications are:

- To confirm or exclude the existence of intracranial hypertension (ICH) in many clinical scenarios, assisting in the decision making process on the indication of invasive monitoring of ICP [5-14].
- To diagnose cerebral circulatory arrest (CCA) [15-21] (with very high specificity), avoiding invasive procedures or transfers, thus helping in the diagnosis of brain death.
- To help in the diagnosis and monitoring of cerebral vasospasm. Vasospasm is one of the main SAH neurological complications and appears quite frequently in the course of this disease, but is also important to remember that vasospasm has been demonstrated in the evolution of TBI and CNS infections [26-30].
- In the stroke patient, the TCD can provide immediate information about the status of cerebral hemodynamics, evidence if there is vascular stenosis (partial occlusion) or complete occlusion, can monitor the time course of recanalization when performing thrombolytics, and even enhance the action of these drugs. In addition it can pro-

vide information regarding the pathophysiological mechanism of stroke, such as the existence of microemboli and detect the presence of right-left shunt in cryptogenic stroke. Finally, it is also possible to evaluate the cerebral circulatory reserve and the status of cerebral autoregulation, thus helping the clinician in the management, monitoring of treatment and prognostic assessment.

In the ICU is common that many of the variables which are able to influence the intracranial hemodynamic are altered, so that the probable influence on the founded FV should be taken into account. But the most important factor, given its hazard, which should always be thought as a cause of a low FV is the rise in intracranial pressure.

10.3.1 Pulsatility Index and Resistance Index

From the FV waveform systolic, diastolic and mean velocities can be calculated. Analysing the relationship of these velocities various indices of cerebrovascular resistance can be calculated. Pulsatility index (PI) and resistance index (RI) are widely used and complement the characterization of sonographic patterns.

The IP is calculated using the following formula:

$$PI = (FV_s - FV_d) / FV_m$$

TCD ultrasound software usually calculates PI and time-averaged mean velocities for each sonogram and displays them on the screen.

RI is calculated using the following formula:

$$RI = (FV_s - FV_d) / FV_s$$

These indices are very helpful when assessing a particular patient, especially in intensive care medicine. Intracranial hypertension slows the flow velocity, preventing the normal flow of blood through the cerebral vascular bed. Velocities are affected and decrease mainly in diastole, which is the period of the cardiac cycle in which blood enters into the brain circuit with less power. This leads to a relatively greater increase in the FV_s ($FV_s - FV_d$) and explains that the PI or RI indices increase when ICP is going up. There are other factors able to descend the FV in the absence of intracranial hypertension, which are factors that act directly on the arteriolar resistance (diameter). Therefore, when either of these two indices is above the normal value the physician should act promptly searching for the presence of any factor that could be affecting the normal blood flow circulation, such as:

- Intracranial hypertension leading to a decrease in the cerebral perfusion pressure (CPP).
- Increased cerebrovascular resistance from another source, such as the presence of a cerebral circulation vasoconstrictor (ie, hypocapnia, indomethacin).
- Bradycardia. In this situation, the time between heartbeats is greater, so that the diastolic velocity decreases for a longer period, until it reaches the new wave pulse, increasing the velocity-gap ($FV_s - FV_d$).
- Vascular stiffness (rigidity); in the absence of energy absorption by the arterial wall, the FV_s goes up while the FV_d goes down.

The most widely used of the two indices is the PI. Its normal value varies between 0.60 and 1.20. Although the normal maximum value is 1.20, clinically is reasonable to suspect the presence of significant intracranial pressure increase and seek their cause when the index is above 1.00. The PI findings during the acute phase of TBI have been corre-

lated with the prognosis. An increase in PI, mainly when is associated with a decrease in FV_d, indicates a poor CPP. Several clinical studies in adults and children who have suffered head injury (different degrees of severity) have shown worse outcomes associated with low flow velocities (less than 25 cm/s in children) and raised PI (above 1.3 or 1.5) [34-36].

The pathological process triggered by the acute and severe CNS disease can affect the cerebral circulation in many and complex different ways. Under certain conditions specific changes prevail. For example, vasospasm is known as a frequent complication of SAH, but that does not mean that there is no vasospasm in other neurological diseases, or that vasospasm is the only cerebral hemodynamic complication of SAH. On the other hand, different alterations often coexist and the physician should have them in mind, knowing that in many circumstances different alterations act in an opposite directions leading to a ¨pseudonormal ultrasound pattern¨ (also called mixed pattern).

Doppler pathological patterns are not related to specific diseases, but to its pathophysiological impact on cerebral circulation. Therefore, the impact of the most frequent alterations: intracranial hypertension and vasospasm, on FV and PI will be first described. Finally, some reference to different acute neurological conditions (SAH, TBI, stroke) will be added, with a schematic analysis of the hemodynamic changes that may be encountered during their course.

10.4 Transcranial Ultrasonographic Abnormalities in Neurocritical Patients

TCD ultrasonography provides valuable information about the effect on cerebral circulation of the pathophysiological changes produced by neurological injuries. It detects abnormal modifications consistent with increased intracranial pressure, cerebral circulatory arrest, vasospasm, hyperemia and impaired cerebrovascular reactivity.

The different patterns to be analyzed are:

- High-velocity pattern.
- Low-velocity pattern.
- High-resistance pattern.
- Cerebral Circulatory Arrest (CCA) pattern.

10.4.1 High-velocity Patterns

Both hyperemia and vasospasm are evident in TCD sonogram as an increase in flow velocity.

Vasospasm Vasospasm of cerebral arteries may be focal or diffuse. Its first hemodynamic consequence is a decrease in the pressure loss through the stenotic segment. If the cerebrovascular autoregulatory mechanism works, local CBF can be maintained at the expense of a dilatation of distal small autoregulatory vessels. The same amount of blood (per unit time) passes through an arterial segment whose lumen has fallen. Therefore, the blood must pass more rapidly (compensatory response). This velocity augmentation occurs, therefore, in the stenotic segment. If we measure CBF rather than flow velocity, we would find it preserved if autoregulation is working properly, or decreased if autoregulation is defective/impaired or if it is maintained but not enough to compensate a very severe spasm. It must be **emphasized that in the case of vasospasm, CBF is not increased.**

Hyperemia. In this case **CBF is increased**, regardless of whether the cause is (greater brain metabolic demand or ¨luxury perfusion¨), more blood than in normal conditions is passing through a normal/increased vessel calibre. Therefore, it circulates faster.

High Velocity Differential Diagnosis

As it has been mentioned before, an increased FV may correspond to vasospasm or hyperemia. Is it possible to distinguish them? Lindegaard [37] proposed to study the relationship between the FV in the intracranial affected vessel and the velocity in the extracranial vessel supplying blood to it. As vasospasm is an alteration of the intracranial arteries which have been in contact with subrachnoid blood, flow velocity increases in the compromised intracranial artery, but not in the extracranial one, therefore the rate between the two velocities increases. On the other hand, if the velocity increase is due to hyperemia, the increase in FV is seen in both, the intracranial and extracranial vessels. Therefore, the relationship between these velocities remains normal. These concepts are the basis of Soustiel [38] and Lindegaard indexes, for the anterior and posterior sectors, respectively.

Anterior circulation: Mean FV in the middle cerebral artery (MCA FV_m) is compared with the corresponding value in the ipsilateral extracranial internal carotid artery (ICA) at the entrance of the skull base (ICA FV_m). This relationship MCA / ICA is known as Lindegaard Index (LI), or hemispheric index. An LI >3 indicates vasospasm and if >6 severe vasospasm. Values <2 (normal) indicate hyperemia.

Posterior circulation: FV in the basilar artery (BA) is compared with corresponding value in the extracranial vertebral arteries (EVA) that supplies it, known as BA / EVA index or Soustiel index. The cut-off value is 2**.**

Time Course of Vasospasm and CBFV-related Changes

Vasospasm, which occurs in several pathological conditions (SAH, TEC, meningitis, etc.), is an abnormal and dynamic process. In SAH it begins around the 4th day after bleeding, has a maximum between the 7th and 10th day, and disappears around the end of the third week after the bleeding. It may progress to a mild degree and then improve, or increase to a point where regional cerebral autoregulation cannot compensate for the decrease in regional perfusion pressure, and consequently CBF decreases in the area irrigated by the affected artery eventually resulting in clinical signs of ischemia, depending on the extent, topography and collateral circulation. During the phase in which CBF is maintained, vessel lumen reduction is accompanied by a compensatory increase in flow velocity (see appendix). When vasospasm further increases, flow starts to decrease due to the inability of the regional autoregulatory mechanism to compensate for the higher drop in regional CPP. This point is known as **critical vasospasm**. High velocity starts to decrease (**could be interpreted as improving vasospasm**) and in some cases flow ceases. It is important to note here the importance of performing a daily monitoring of these patients, since at this stage a normal flow velocity (in just one study) should not be interpreted as vasospasm absence. At this stage, a third factor also plays a crucial role: blood flow through the narrowed vessel. Additionally, it should be noticed that the rise of the arterial blood pressure in a patient whose regional perfusion pressure has decreased below the lower limit of autoregulation may increase flow through the stenotic segment, increasing FV again. This increase does not signify a worsening but an improvement of the situation. In summary, not always an initial FV decrease has to be interpreted as an indicator of vasospasm improvement, nor an increase in CBF as vasospasm worsening, but the values must be interpreted in light of the clinical and therapeutic maneuvers, taking always into account the values of patient's arterial blood pressure, and ICP-CPP if available [39].

TCD in Subarachnoid Hemorrhage

TCD is widely used for screening and monitoring vasospasm in SAH due to its simplicity, lack of invasiveness and the possibility of being performed at bedside. In patients with good clinical grade, the usefulness of TCD is most often the diagnosis and follow-up of cerebral arteries vasospasm. This technique has an excellent diagnostic specificity and an acceptable sensitivity for cerebral vasospasm. It allows an early diagnosis before clinical neurological deficit occurs. This study should be performed daily (or every two days) during the first week (after bleeding) to be able to demonstrate vasospasm onset and monitor its progress and clinical impact. As it has been previously mentioned, the typical diagnostic vasospasm pattern is characterized by an increased cerebral blood flow velocity (FV). This increase begins between days 3 and 10, reaches its maximum between days 11 and 20, and finally returns to normal within 4 weeks [40].

Many studies in SAH patients have found diagnostic velocities at different arteries.

Middle Cerebral Artery (MCA)

Aaslid and colleagues initially described three degrees of vasospasm in SAH: mild, moderate and severe with velocity limits of 120 and 200 cm/s. At the same time he emphasized Lindegaard index as an essential complement of these values. LI limits described by this author were 3 and 6 to distinguish between the three grades of vasospasm [41]. According to Vora et al., FV greater than 200 cm/s is an index of severe vasospasm, and FV lower than 120 cm/s is an index of mild vasospasm, or absence of vasospasm [19,42]. Another related study investigated velocity values associated with angiographic or clinical vasospasm, finding a threshold of 100 cm/s when angiographic vasospasm was evident (sensitivity and specificity of 1.00 and 0.75 respectively), and of 160 cm/s when clinical vasospasm was detected (sensitivity and specificity of 100%) [43].

Other studies have evaluated the percentage of velocity change comparing to a control TCD assessment (ICU admission) [44].

Other Vessels Insonated Through the Temporal Window

Anterior cerebral artery (ACA) and posterior cerebral artery (PCA): considering as a cut-off value 110 cm/s for the PCA and 130 cm/s for the ACA, specificity is very good (93% and 100%, respectively). However, the sensitivity, due to a number of anatomical and technical factors, is not reliable. This means that if TCD results are normal vasospasm can not be excluded. Since often ACA vasospasm does not associate MCA compromise, especially after an anterior communicating aneurysm rupture, great caution should be given to make treatment decisions based only on a negative test for vasospasm diagnosis [45].

Other Vessels Insonated Through the Posterior Window

n this sector FV ≥ 60 cm/s is indicative of vasospasm in both arteries (vertebral and basilar), with low sensitivity and high specificity for the vertebral artery [46]. For the basilar artery, a value of 85 cm/s has 90% specificity and 50% sensitivity. When considering a limit of 80 cm/s for the diagnosis of vertebral artery vasospasm and 95 cm/s for the basilar artery, the specificity and positive predictive value goes up to 100% [47,48].

It is important to remember that in SAH patients very often multiple changes in cerebral hemodynamic coexist (including vasospasm), mainly in those with greater clinical severity (poor grade SAH). Intracranial hypertension, frequently associated with hydrocephalus or brain swelling, vasospasm, hyperemia triggered by non-convulsive epileptic activity or impaired cerebral autoregulation, systemic disorders (spontaneous or generated by our treatment) like fever, sepsis, hyponatremia, anemia, hypercapnia, hypocapnia, hypovolemia, hypervolemia, hypertension, hypoxemia. All these variables may cause intracranial hemodynamic changes and make TCD interpretation a real challenge for doctors. For example, the frequent association between a) **vasospasm** (typically increases FV and reduces the PI) and b) **intracranial hypertension** (decreases FV and increases PI) re-

sults in a tricky "**pseudo normal pattern**". It is also common that these patients have severe systemic complications, including sepsis, which may be accompanied by an hyperdynamic state with cerebral hyperemia. Hence, it is crucial to use the mentioned indices (PI and/or RI) in order to be able to detect how greatly all these systemic disturbances are affecting (or not) the TCD pattern. These indices significantly improve the specificity of the high-velocity pattern in the diagnosis of vasospasm. It is also necessary to evaluate the TCD results in the light of the patient clinical and systemic neuromonitoring (ICP, CPP, PtO_2 if available) situation.

High-velocity Pattern in Traumatic Brain Injury

Although the main cause of poor outcome in severe TBI is high ICP (especially refractory ICH), which is not responsible for high velocity pattern, this pattern has often been reported in this context. TBI is an extremely heterogeneous disease in which the risk of simplifying a complex and dynamic pathological process is always present and physicians should keep this in mind. However, in everyday practice, it is useful to recognize the intracranial hemodynamic changes described by Martin et al. They found, in a large group of TBI patients, three consecutive ultrasonographic patterns: hypoperfusion, hyperemia and vasospasm (Figure 10.2).

Other Causes of High-velocity Patterns

Inflammatory and infectious disorders, such as cerebral vasculitis, encephalitis and meningitis, often present high-velocity patterns caused by focal (at different topography) or diffuse artery narrowing. Vasospasm is also possible in these scenarios.

Cerebral arteriovenous malformations (AVM) show a high velocity pattern explained by the existence of multiple arterio-venous low resistance shunts.

Arterial blood flow selectively passes with high velocity through these dilated veins, creating a chronically hypoperfused brain area where small arterioles and precapillary sphincters dilate as a compensatory mechanism, to maximise blood entrance and to offset chronic hypoperfusion.

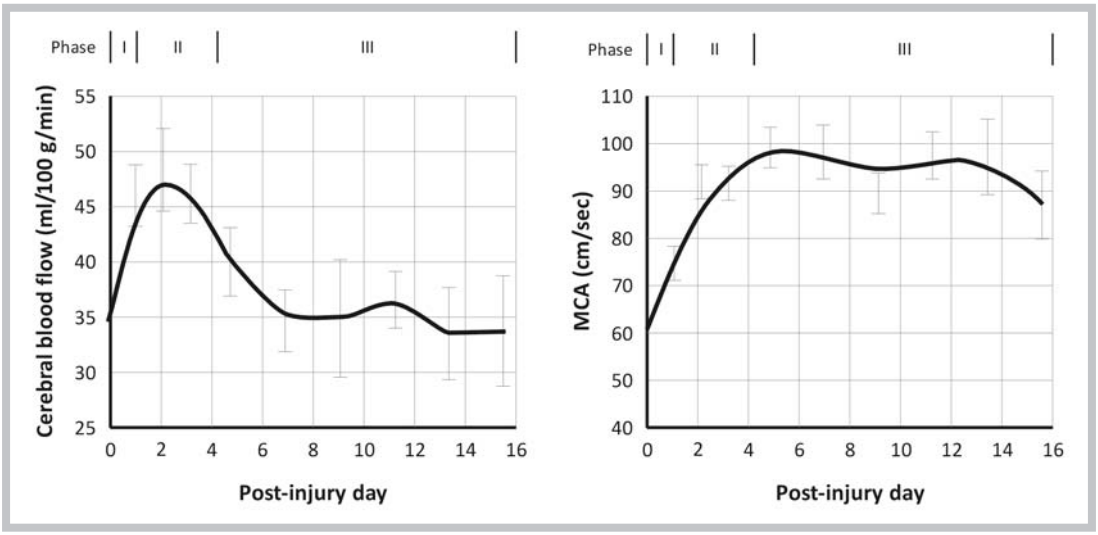

Figure 10.2. **Phases found in cerebral hemodynamics in a group of severe TBI patients. Phase I, first 24 hours, hypoperfusion with low velocity. Phase II, high velocity and CBF: hyperemia stage. Phase III, high velocity, but low CBF: vasospasm stage. Note how a high velocity in the TCD does not make a diagnosis of vasospasm by itself.**

During the postoperative period, after AVM excision, when chronic hypoperfusion is corrected, special attention should be paid to systemic hypertension. A severe hyperperfusion syndrome (high sonographic velocity pattern with a LI <2) followed by brain edema and hemorrhage can be triggered by high or even normal blood pressure levels. This situation is known as circulatory "breakthrough". It can eventually lead to brain edema and intracranial hypertension. The same complications can appear whenever a correction of a chronic hypoperfusion state is performed, as after carotid endarterectomy.

Low-velocity Pattern: Intracranial Hypertension

ICH may complicate the course of many acute neurological diseases. In relation to pressure, according to the following formula, an ICP increase leads to a CPP decrease:

$$CPP = MAP – ICP$$

Thus, when the ICP equals the diastolic blood pressure, brain perfusion stops in diastole, and when the ICP equals the systolic blood pressure, perfusion stops completely. It should be emphasised that TCD measures FV and can indirectly estimate relative changes of the cerebral blood flow. Broadly speaking, the fundamental concept is that an ICP increase impairs the inflow of blood into the brain. Therefore, FV decreases. The first portion of the sonogram which is affected is the end diastolic velocity. Velocity is slowed in this part because it is the portion of the pulse wave during which the blood flows with lower energy. Initially peak systolic velocity increases due to cardiac compensation. As the CVR indices (PI and RI) depend on the differential velocity ($FV_s – FV_d$) they go up. When ICP increases more, all velocities decrease, but the principally affected one is always the diastolic velocity, leading to a progressive increase of the PI. This pattern of low velocity with increased PI is called **high-resistance pattern**. Although it can have several causes, when detected in a neurocritical patient, the treating physician **should always suspect the presence of intracranial hypertension and act accordingly.** An example is provided in Figure 10.3.

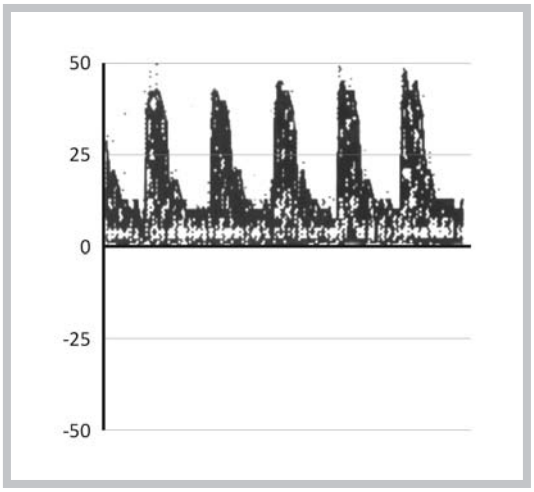

Figure 10.3. **Example of a high resistance sonogram in the MCA in a 66 y.o female, after removal of a parasagittal meningioma complicated by a hematoma in the surgical site. GCS 3 under thiopental. Note the low FV (24 cm/s) and the increased PI (1.58). This study raises suspicion about the presence of ICH, and rule out the cerebral circulatory arrest diagnosis in a patient without the possibility of being clinically evaluated for being under the influence of thiopental.**

Other Causes of a Low-velocity Pattern

In intensive care medicine, a low velocity pattern may be due, in addition to ICH, to:

- Arterial hypotension below the buffering capacity of the autoregulatory mechanism (severe shock of any etiology or relative hypotension in a chronic hypertensive patient with the inferior autoregulatory threshold shifted to the right). If this is the only factor causing the low velocity, the PI can be normal or decreased.
- Presence of small resistance vessels vasoconstrictor mechanisms or drugs (hypocapnia, indomethacin). It is accompanied by increased IP.

- In the first stage of TBI (24hs, see Martin´s diagram, hypoperfusion phase) there is a cerebral flow velocity reduction. The underlying mechanisms are still unclear. Some investigators have interpreted it as a cause of cerebral ischemia, but modern theories attribute it to a decreased demand by the injured brain.

10.5 Extreme Expression of Intracranial Hypertension: Cerebral Circulatory Arrest

Increases in ICP are accompanied by a decrease in all flow velocities. This phenomenon affects the diastolic phase earlier and more intensely, soon resulting in the cessation of diastolic flow (systolic peaks). A reverberating diastolic flow can then be seen (the flow that entered in systole is turned back during diastole). In the next stage there is a minimal movement of blood, only at the beginning of systole, which is known as systolic spikes. Subsequently, the flow ceases completely (the ultrasound beam cannot detect anyt blood movement). Reverberating flow and systolic spikes patterns correspond to what is accepted as “cerebral circulatory arrest” (Figure 10.3). When this pattern is found bilaterally in the anterior circulation and in the posterior sector and these alterations persist for at least 30 minutes (is not a transitory state), it can be used to support the diagnosis of brain death.

10.6 TCD as a Complementary (Auxiliary) Diagnostic Technique in Determining Brain Death

Most patients who progress to brain death have suffered severe intracranial hypertension with a concomitant decrease in cerebral perfusion pressure. This generates a glob-

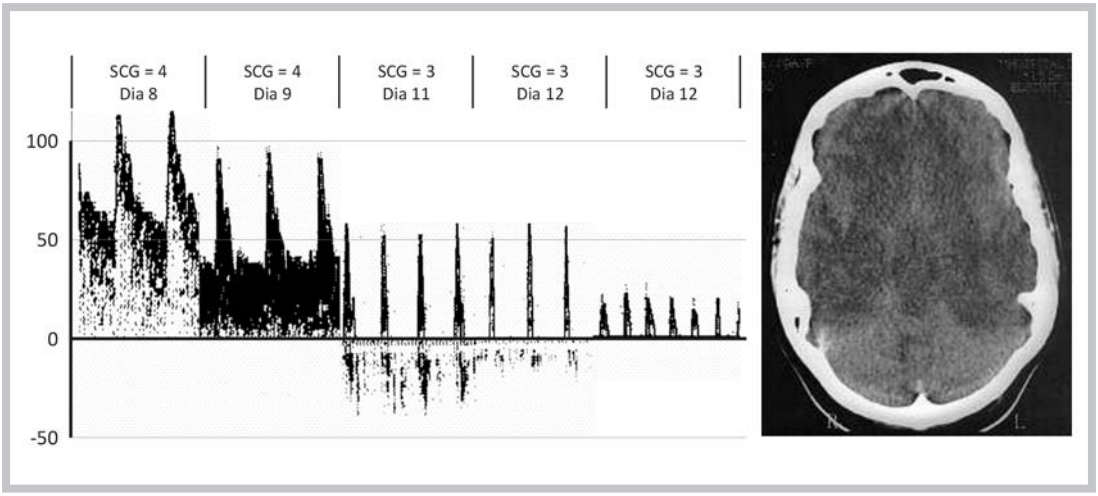

Figure 10.4. **Typical TCD alterations ending in a cerebral circulatory arrest pattern in a 17-year-old girl with asthma after successful resuscitation from a hypoxic cardiac circulatory arrest. She eventually progressed to brain death (clinical diagnosis) on the 12th day. The first sonogram (left) is normal. The second shows the high-resistance pattern followed by the reverberating pattern. Finally, the third sonogram shows the systolic spikes pattern. An anoxic-ischemic brain injury may take weeks to evolve, to crebral circulatory arrest, as seen in this example. The head CT shows a white cerebellum with diffuse swelling (images from our archives).**

al brain ischemia and ends in the irreversible loss of life-sustaining functions. The time course of the blood flow changes can be followed with TCD until a cerebral circulatory arrest pattern can ultimately be identified. An example of typical TCD alterations is provided in Figure 10.4.

10.7 Summary of Changes in Cerebral Hemodynamics: Muñoz Chard

The classification scheme of Muñoz [49], presented in Figure 10.5, classifies alterations of cerebral hemodynamics into three different categories corresponding to pathological PI values (increased or decreased), pathological CBFV values (high or decreased), and normal values.
The diagram is helpful for interpreting the results of a transcranial ultrasound. It highlights five main patterns:

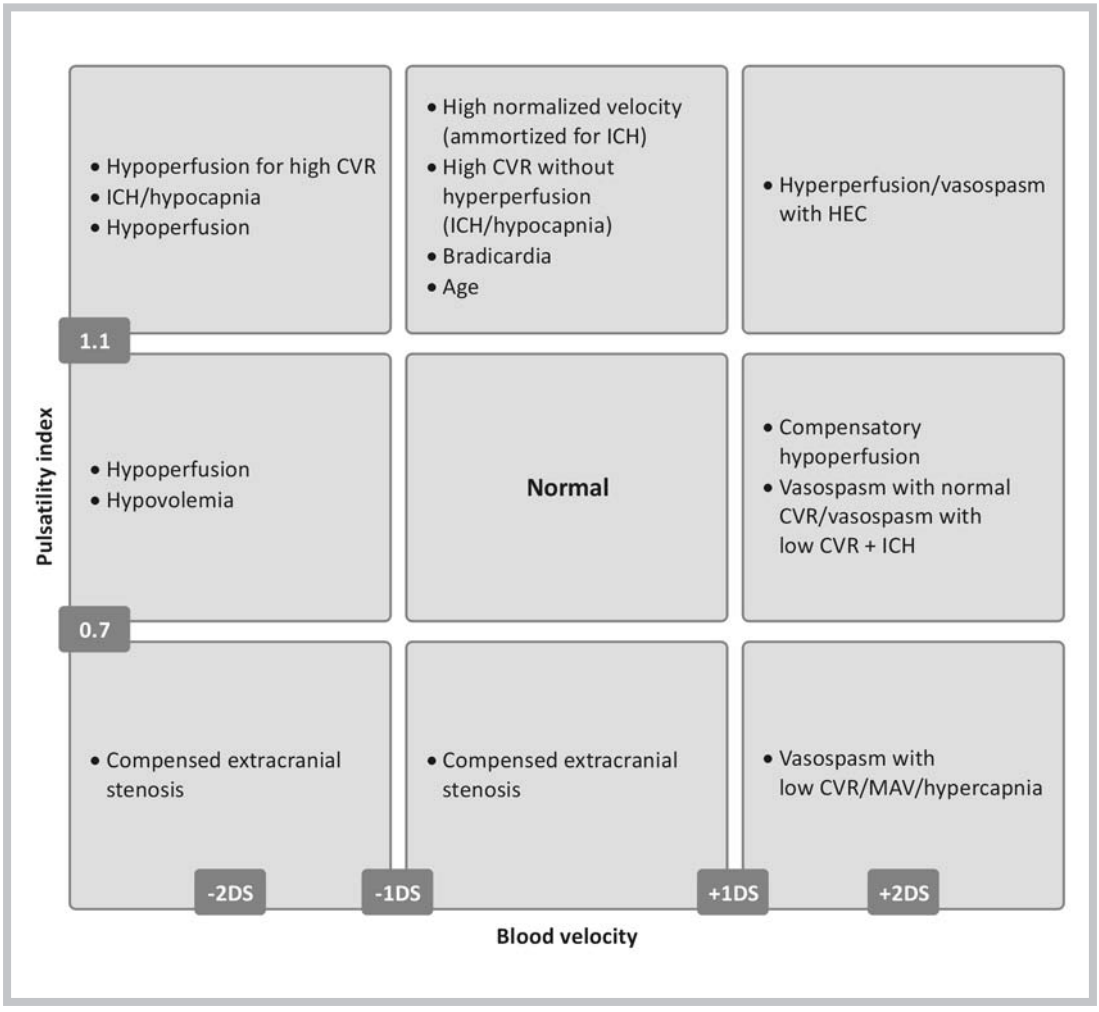

Figure 10.5. The classification scheme of Muñoz [49].

- Normal or pseudonormal pattern (FV_m and PI normal for patient age and the insonated vessel).
- Low velocity pattern (FV_m lower than 1 SD of the normal velocity value of the insonated vessel at the patient´s age). It Implies a reduction of cerebral blood flow (CBF) coupled or not to brain metabolism. The decrease in CBF may depend on many factors, both systemic (hypotension, hypothermia, etc.) or intracranial ones (intracranial hypertension, etc.).
- High-velocity pattern (FV_m greater than 1 SD of the normal velocity value of the insonated vessel at the patient´s age). It does not necessarily imply an increase in CBF. Two situations can be distinguished: hyperemia (a real increase in CBF) and vasospasm (CBF constant or low).
- High-pulsatility pattern (high PI) is caused by an increase in cerebrovascular resistance (CVR) distal to the insonated point. The increase in CVR may be active (vasoconstriction) or passive (vascular bed compression due to intracranial hypertension). Its extreme expression is the cerebral circulatory arrest pattern.
- Low-pulsatility pattern (low PI) is caused by a reduction in CVR distal to the insonated point. The reduced CVR may be related to a low-resistance vascular bed of anatomic origin (arteriovenous malformations) or a state of vasodilation induced by different etiologies (ischemia, drugs, hypercapnia, etc.).

The patterns are considered as symmetrical or asymmetrical depending on whether they are detected bilaterally or unilaterally, respectively.

10.8 Assessment of Cerebrovascular Reactivity

Under normal conditions, cerebral blood flow resistance in the vascular bed is low in the conductance vessels (large arteries and their main branches) and in the venous sector. The main areas that generate resistance to flow are the arteriolar sector, the leptomeningeal arterioles and the precapillary sphincters, where a pressure drop of 80% normally occurs. This area of the vascular bed also has the property to vary small vessel resistance by vasoconstriction or vasodilation (potentially), leading or not to changes in CBF depending on the stimulus the vessels are responding to. Owing to its vascular reactive properties, it is referred to as the “area of cerebrovascular resistance”.

Cerebrovascular reactivity is defined as the ability of the arteriolar bed to respond to different stimuli with changes in cerebrovascular resistance. Depending on the stimulus, four types of cerebrovascular reactivity can be distinguished:

- CO_2 reactivity.
- Metabolic reactivity.
- Reactivity to drugs.
- Cerebral autoregulation (CA).

In the first three types, changes in cerebrovascular resistance lead to higher or lower CBF, either regionally or globally, according to the stimulus and where it acts. In contrast, in cerebral autoregulation, the resistance modifications tend to keep the CBF constant while the stimulus (blood pressure) changes. Vascular reactivity can be manipulated clinically to generate changes in cerebral blood volume (CBV), CBF, and intracranial pressure. Therefore, its assessment is often useful to gain an idea of how the CVR area is going to respond to different therapeutic options (maneuvers or drugs) widely used in this clinical scenario. Its evaluation also has prognostic value. The more severe the injury, the more impaired the reactivity, the worse the patient outcome.

10.8.1 Autoregulation

Cerebral autoregulation (CA) or pressor cerebrovascular reactivity is the capacity of the vascular bed to maintain, by vasoactive responses, cerebral blood flow (CBF) constant between two CPP "thresholds", the upper and lower limits of CA, where:

$$CBF = CPP/CVR$$

and, if ICP is normal:

$$CBF = MAP/CVR$$

The last equation clearly shows that CA requires that changes in CVR be proportional to changes in mean arterial pressure (MAP) to maintain CBF constant (see appendix).

Cerebral Autoregulation

There are two main ways to assess cerebral autoregulation:

- "Static" CA takes into account the magnitude of the CBF response in relation to the degree of CPP variation, without considering relevant the time course of this response.
- "Dynamic" CA takes into account the time course of the CBF response to sudden changes in CPP (**the time the cerebral vessels need to dilate and return the CBF to baseline**).

In summary, to evaluate CA, changes in CPP or MAP (if ICP monitoring is not available) have to be simultaneously compared with changes in CBF. Changes in flow velocity are proportional to changes in CBF, provided that the cross sectional area of the insonated artery does not change during the study. This has been demonstrated by several researchers, including Giller.

Static Autoregulation

Static autoregulation refers to CBF changes independent of time, as described by Lassen's classical curve. To study this type of autoregulation, it is necessary to generate a slow change in MAP and evaluate the response of CBF. MAP can be increased (approximately 20 mmHg) by infusing a vasopressor agent without direct action on the central nervous system (CNS), preferably phenylephrine (PE) or noradrenaline (NA). Several values of CPP (or MAP) and the corresponding values of FV for a period of approximately 20-30 minutes are recorded. Maintaining ta stable PCO_2 during the study is crucial. Sedation should be used. Other variables which may influence the cerebrovascular response should also be monitored (i.e., temperature, SO_2). The expected response of the cerebral circulation, which tends to maintain CBF constant while MAP is rising, is accomplished by the contraction of the small vessels, arterioles and precapillary sphincters, leading to augmentation of CVR.

There are different ways to express the change in flow relative to the change in pressure:

- The **slope of the best fit line between both variables**. In this case, a change in CBF (as a percentage of baseline CBF) is calculated per mmHg of CPP increase.
- The **correlation coefficient between both variables.** Positive values tending to 1 indicate impaired autoregulation (pressure-flow passive relationship). In contrast, values close to zero or negative ones indicate good autoregulation or active vessel response (pressure-flow independent relationship).
- The **cerebrovascular resistance behaviour** (instead that the change in flow) in relation to the change in CPP or MAP. In this case, the results should be interpreted in

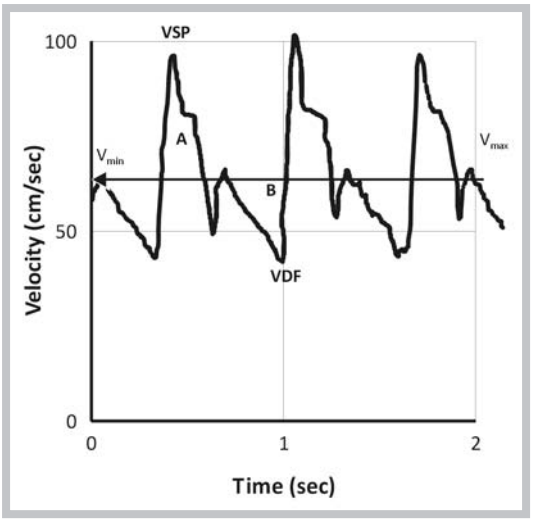

Figure 10.6. **Autoregulation as expressed by the velocity slope.**

reverse: the more the resistance increases (while MAP is rising), the better the autoregulation.

Figure 10.6 shows autoregulation as expressed by the velocity slope.

Three ranges have been defined: slope variation <0.4% per mmHg of change in CPP corresponds to preservation of autoregulation; an intermediate group (0.4-0.9%); and a third range with a slope >0.9% corresponding to impaired/abolished autoregulation. The lack of consensus on the way investigators evaluate CA makes it difficult to compare results across different studies. For example, a velocity slope of nearly zero expresses an excellent static autoregulation (as in the above example). However, if the same result is shown as a change in CVR (rather than a change in flow velocity), the same response would be expressed as a resistance index (i.e.RoR, rate of regulation).

$$RoR = [\%\ \text{change in CVR} / \%\ \text{change BP}] \times 100$$

If CA is preserved, a direct proportional change in CVR (1% increase in resistance for every 1% increase in BP) would be expected (RoR = 100 means excellent CA), since flow stability is due to the increase in CVR when AP increases.

There are excellent reviews of methods for measuring CA by R. Panerai (Leicester University, UK).

Dynamic Autoregulation

Dynamic CA evaluates the time-course and extent of CBF changes elicited by sudden and sharp CPP changes. We emphasize that TCD, thanks to its excellent time-resolution, is the ideal method for this assessment, displaying the changes in FV while the CPP change is taking place. Since it is the first method, and practically the only one so far, that allows this "on line" assessment, the concept of dynamic CAR (DCA) and the methods for its evaluation has emerged almost simultaneously with the rise of TCD. The change in the CPP can be generated by a change of ICP or BP. In clinical research, for ethical reasons, only BP manipulation is used. Therefore, DCA in critically ill patients has been evaluated through the temporal course of CBF changes caused by a sudden and provoked drop in BP. Recently (last decade), spontaneous BP oscillations have gained considerable research and clinical importance.

Some of the methods used to evaluate DCA are: Giller's test or transient hyperemic response test, Aaslid transient hypotension, and continuous monitoring of spontaneous changes using a moving correlation index of cerebral perfusion pressure and middle cerebral artery flow velocity.

The Transient Carotid Compression Test or Giller's Maneuver [50] (Transient hyperemic response test [TRHT])

This method is based on a short (5 sec) and sharp compression of the extracranial internal carotid artery (at the base of the neck) while evaluating the change in the FV in the ipsilateral MCA (carotid terminal branch). Carotid compression reduces the flow in the

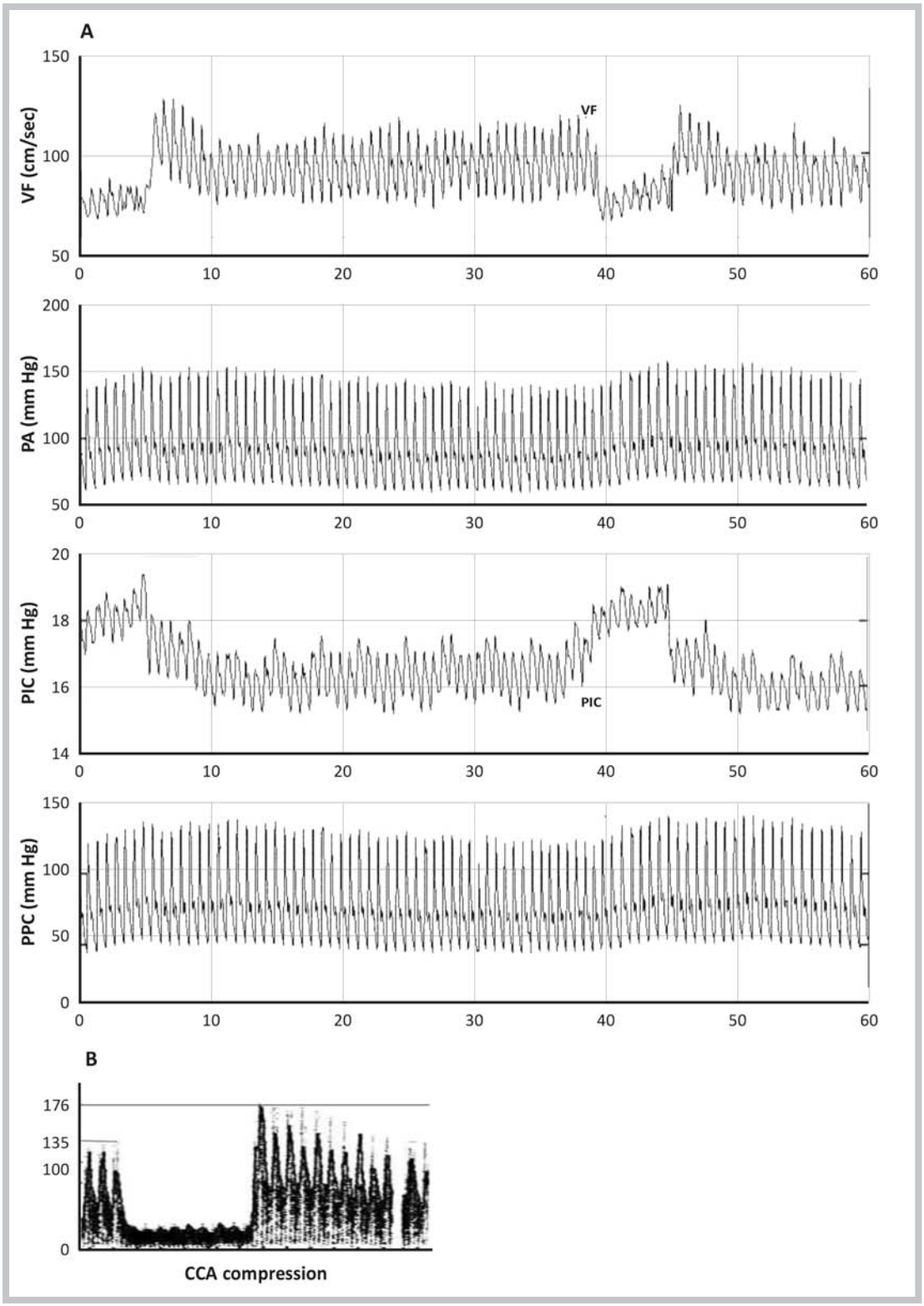

Figure 10.7. **(A). Giller test result recorded by our in-house acquisition data software (CONTINE). (B). Changes in the velocity as seen on the TCD screen (15 s).**

Figure 10.8. **Aaslid's maneuver in a volunteer.**

MCA territory, thereby reducing the CPP in the territory supplied by the artery. If DCA is intact, a rapid vasodilation response of small blood vessels occurs which tends to maintain CBF constant. Sudden release of compression produces a transient hyperemic response as the CPP normalizes and acts on a dilated vascular bed. This hyperemic response is detected by TCD as an increased flow velocity at the insonated ipsilateral MCA. If DCA is impaired, then compensatory vasodilation is minimal or absent. Accepted indicators of preserved DCA are values ≥1.1 according to the formula: FV post-compression/FV pre-compression.

Compression is applied to the base of the neck to avoid compressing the carotid bulb or the carotid bifurcation. The Giller test is one of the easiest tests to assess DCA. It has been widely used [51-54] and its results are reproducible, provided that the duration of compression is at least 5 seconds.

The figure on the left shows a Giller test recorded by our acquisition data software (CONTINE). In this example, a good DCA exists. A rapid increase in ICP is observed (lower arrow). This ICP increment can be explained by the vasodilation of the small arteriolar resistance vessels, leading to an increase in cerebral blood volume. Since compression is applied to the ICA and the blood pressure is recorded in the radial artery, the **regional change in blood pressure** is not detected. However, a change in the CPP due to the ICP-related change is visible.

The right figure shows the changes in the FV (15 s). It is another example of good DCA.

Aaslid Test or Cuff Deflation Test

In this case, systolic blood pressure manipulation is done using the thigh cuffs method. Two cuffs are inflated bilaterally at the proximal thighs, above the patient's systolic pressure, keeping them inflated for 3 minutes and releasing them suddenly. This maneuver elicites a reactive hyperemia in the legs vascular bed so that after releasing the compression the venous return decreases by "pooling" blood at the lower limbs and a sudden systolic blood pressure fall follows immediately after the compression is released. The magnitude of the drop in BP is usually around 20 mmHg. A drop exceeding 10 mmHg is considered a sufficient stimulus. FV in the insonated MCA (proportional to the CBF) also

drops. In healthy volunteers, with intact DCA, FV recovers within 15 seconds, while blood pressure takes more than twice to return to baseline. It is clear that normal CA responds immediately to preserve CBF regardless of systemic blood pressure regulatory mechanisms.

Figure 10.8 shows Aaslid's maneuver in a volunteer. The thigh cuffs remain inflated for 3 min and a fixed transducer records FV in the MCA. Wide Velcro ® fasteners are used to permit rapid cuff release. (there are also specially designed cuffs with a greater diameter and wide connectors that allow faster deflation). Clamps are placed to maintain the cuff fully inflated during the 3 min.

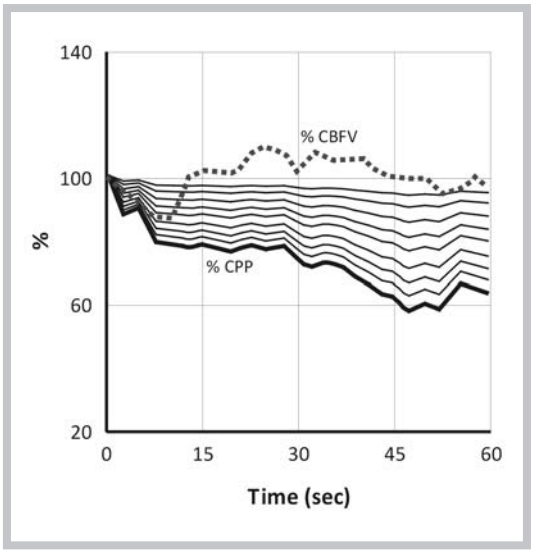

Figure 10.9. **Ten hypothetical curves and two real FV and CPP curves in a patient with intact DCA, ARI = 9 [57]. Real FV curve = dotted line % CBFV; real CPP curve = black line % CPP.**

Test limitations:

- Continuous blood pressure monitoring is required, which is not a problem in critically ill patients but it could be outside the ICU. For patients without arterial catheterization (invasive blood pressure monitoring not available), continuous monitoring can be performed using noninvasive devices based on plethysmography (Finapres).
- Inability to induce a significant drop in blood pressure, particularly in patients with peripheral vascular disease.
- It is contraindicated in patients with lower limb pathologies (i.e., fractures or deep venous thrombosis [DVT]).

The results are evaluated in different ways. Aaslid, who coined the term "dynamic autoregulation", initially measured the resistance recovery slope [55]. Tiecks and coworkers, from the same gropu, later described a comparison between the pressure drop and the immediate CVR response (first initial seconds), making a comparison between responses, rather than an absolute assessment of flow velocity behaviour [56]. Our group has also compared the CPP-FV response based on the Tiecks concept but using a slower variable sampling, CPP and FV recorded every 2.5 seconds (maximum allowed by our monitors), over a 1 minute-period (Figure 10.9). We also graduated the response in 10 levels, dynamic autoregulation index (ARI) from zero to a maximum of 9 [57].

In patients with impaired CA (ARI <5), MCA FV takes longer to recover, and it passively follows the systemic BP recovery when DCA is completely lost (ARI = 0).

Monitoring the Response to Spontaneous Pressure Changes

Researchers from Cambridge University have created a method by which the CBF response to oscillations in spontaneous blood pressure is evaluated by calculating Pearson's correlation coefficient between FV and CPP every 4 minutes (Pearson correlation coefficient varies between 1 and -1, wherein zero or negative values mean independence of FV from CPI and positive values indicate CPP-FV passive behaviour). In each 4-minute period, several CPP and FV pairs (40-50) are correlated (Figure 10.10).

If the correlation coefficient is close to 1, this means that the FV varies passively and directly following CPP oscillation CA is impaired. In contrast, zero or negative correlation

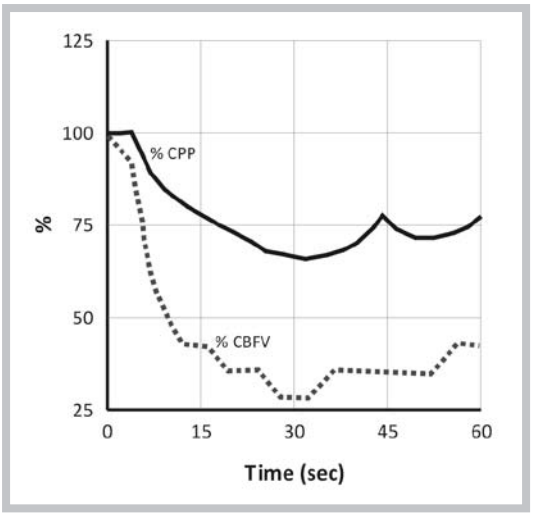

Figure 10.10. **Ten hypothetical curves and two real FV and CPP curves in a patient with intact DCA, ARI=9 [57].**

coefficients indicate an active response or good/intact CA (FV is independent of CPP changes). Each 4-minute interval overlaps to the following one every 4 seconds (sequentially) along the entire period of monitoring (around 1 hour). The final average result (including all 4-minute interval averages) is taken as representative of the patient's DCA status. To calculate optimal CPP, each 4-minute interval coefficient is plotted in relation to CPP intervals of 5 mmHg. The CPP interval corresponding to the lowest correlation coefficient identifies the patient's optimal/best CPP (range of CPP within the lower and upper limit of autoregulation or CBF plateau phase). This method has gained growing interest from neurointensivists, since it can potentially guide CPP therapy and individualize treatment.

10.8.2 CO_2 Reactivity

Arterial pCO_2 is a strong stimulus of the CVR (mentioned above). On the one hand, hypercapnia dilates small resistance vessels in the cerebral circulatory bed, resulting in hyperemia and augmentation of CBV. On the other, hypocapnia constricts small resistance vessels, thus slowing (decreasing) CBF. Under normal conditions, CBF varies 5% per mmHg increase or decrease of the pCO_2. In severe TBI patients, impaired CO_2 reactivity has been demonstrated to be associated with poor outcome.

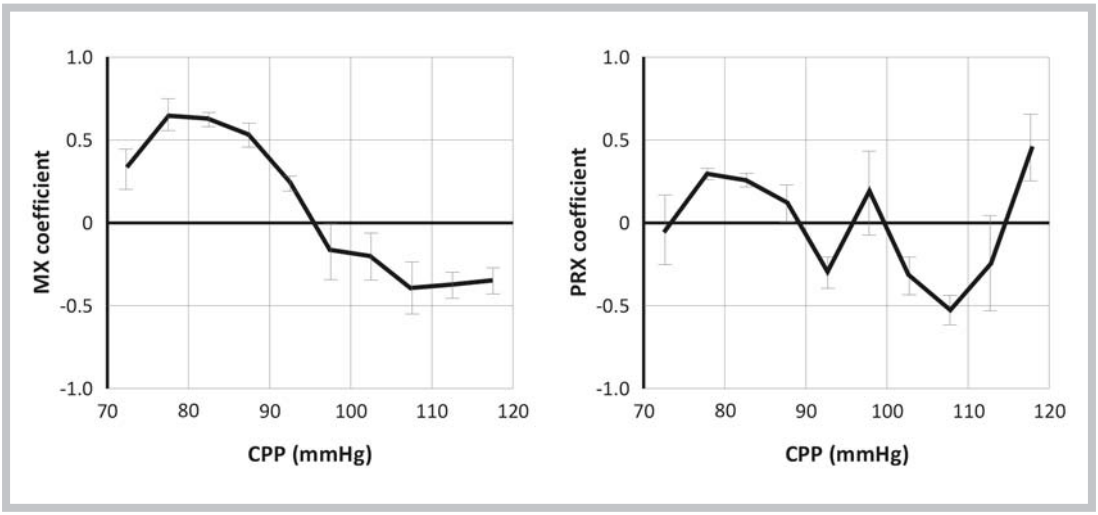

Figure 10.11. **In this case the graph shows that the lowest correlation coefficients (best CA) are located in the right part of the register where the pressure is higher. However, note that in the PRx register (bottom) the recorded higher pressure levels deteriorates the index indicating that at this point the AR threshold has been exceeded.**

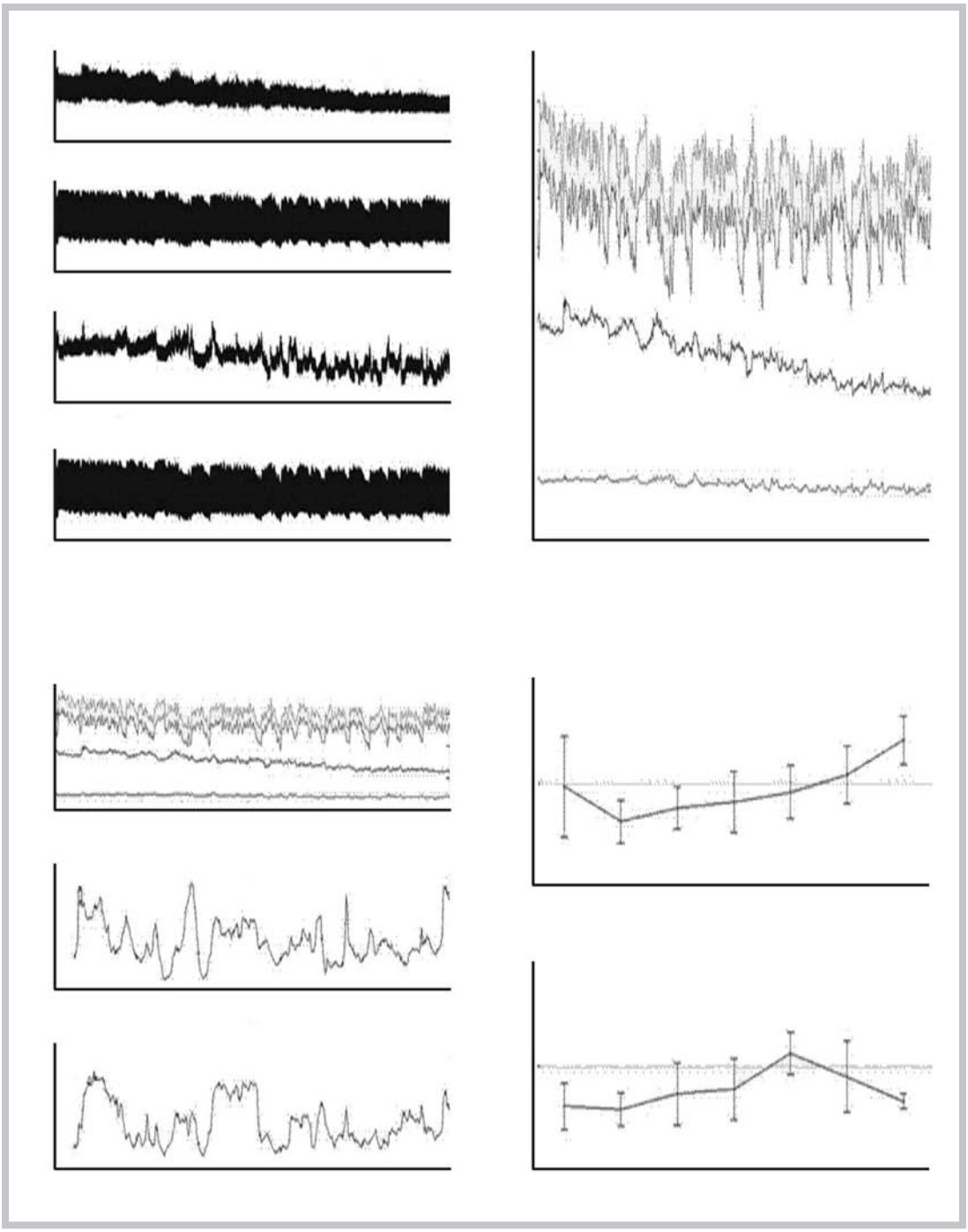

Figure 10.12. Optimal CPP calculated by our in-house software. A 47-year-old woman, Hunt-Hess 3, Fisher 3 SAH; MCA aneurysm clipping and decompression. One hour continuous monitoring of CAR. (A) Acquired variables (from the top): CBFV, BP, ICP and CPP (MAP – ICP). Spontaneous oscillations of the 3 variables can be seen. (B) Average values of the previous variables (from the top): MAP, CPP, $CBFV_m$ and ICP. (C) Above: the four variables together. Middle: Mx (moving correlation coefficient between CBFV and CPP). Bottom: PRx (moving correlation coefficient between ICP and MAP). (D) Optimal CPP; correlation coefficients on the y axis: Mx (top) and PRx (bottom), and blood pressure on the x axis. In this patient, the best CAR (corresponding to the lowest indices) was found when CPP and MAP values were low (see text).

In normal subjects, the percentage of flow velocity variation in the MCA to changes in $ETCO_2$ closely approximates the changes in CBF, indicating that vasomotor response is limited to the small arterioles, without alteration in the insonated artery diameter. FV changes elicited by pCO_2 manipulation (minute ventilation modifications) are used to calculate the CO_2 reactivity index [58]. CO_2 manipulation should be applied with extreme caution in patients with severe brain injury since even small pCO_2 changes can have deleterious effects on cerebral hemodynamics. Hypoventilation in the context of impaired cerebral compliance can cause an increase in CBV, leading to severe ICH. Conversely, hyperventilation, which can decrease CBV and ICP, always carries the risk of cerebral ischemia. These facts highlight multimodal neuromonitoring importance in this complex clinical scenario.

10.8.3 Reactivity to Drugs

Some drugs exert direct action on CVR while others act first on brain metabolism and secondarily on CVR. Indomethacin (member of the former group), a non-steroidal anti-inflammatory drug, exerts its action, at least partially, through inhibition of cyclo-oxygenase enzyme [59]. It causes vasoconstriction in the CVR area, thus leading to CBF and CBV reduction and potentially ICP drop too. In our experience, indomethacin caused a 28% decrease in FV in severe TBI patients. In addition, ICP was reduced and DCA improved significantly [60].

10.9 Appendix

In order to properly perform and interpret a TCD examination, the operator must have a thorough understanding of the:

- Physical basis of ultrasound in medicine.
- Cerebral basal artery anatomy (Willis polygon) and physiology.
- Possible pathophysiological disturbances in this particular area.

10.9.1 Physical Basis of TCD: the Doppler Effect

The Doppler Effect is the wave frequency shift (sound, light, etc.) when reflected by a moving object. This frequency change is called the “Doppler shift” or “Doppler frequency shift.” From this change in frequency it is possible to measure in real time the velocity of blood particles circulating in blood vessels.

Waves. Ultrasound

A wave is a disturbance or oscillation that travels through spacetime, accompanied by a transfer of energy. It is characterized by its frequency, wavelength and amplitude. The frequency is inversely proportional to the wavelength, and is expressed in Hertz (Hz). 1 Hz = one wave per second. Amplitude is the magnitude of the wave – how high it goes on the y axis. Doppler techniques in medical diagnosis **use ultrasound waves**. Ultrasound refers to the sound whose frequency is higher than the frequency of the sound audible by the human ear. The frequency of ultrasound waves used in medicine is on the order of megahertzs (MHz), i.e., one million waves per second, often between 2 and 8 MHz. TCD is based on the lowest ultrasound frequency waves among those used in medicine to date: 2 MHz. The higher the frequency (used), the better the spatial resolution

(of the method). In TCD the low frequency waves make bone penetration possible, but at the same time negatively affect the spatial resolution of the technique.

Angle of Insonation

If the direction of the ultrasonic beam is not exactly the same as the direction of the blood flow velocity, the measured velocity is lower than the real velocity. This is due to the **angle of insonation** between both vectors. The measured velocity should be divided by the **cosine of the angle of insonation** to determine the real velocity. If the angle is 0°, the error is nonexistent (cosine of zero ° = 1); the larger the angle, the greater the difference between the real and the measured velocity (**at an angle of 15° the cosine remains more than 0, 96; error <4%**). If the angle is 90°, the cosine is 0, and blood flow cannot be detected by the operator. According to the most frequent anatomic conditions between the acoustic windows and the insonated cerebral vessel, the angle of insonation is usually <30°, which results in an acceptable low error. In clinical practice, this error can be minimized by changing the angle of insonation until the highest possible velocity at each insonated point is detected (Figure 10.13). This higher velocity corresponds to the lower angle of insonation and therefore is the closest to the real velocity. Finally, while recognizing the importance of these theoretical disquisitions, what really matters at the patient bedside is not the exact (absolute) flow velocity value, but the relative changes that may take place over time. Likewise, it is important to know that the angle of insonation does not alter the relationship between the different velocities (FV_s, FV_d, FV_m) but **impacts on them equally**, without altering the value of PI and/or the RI. These are the main reasons why this issue is far from being clinically important.

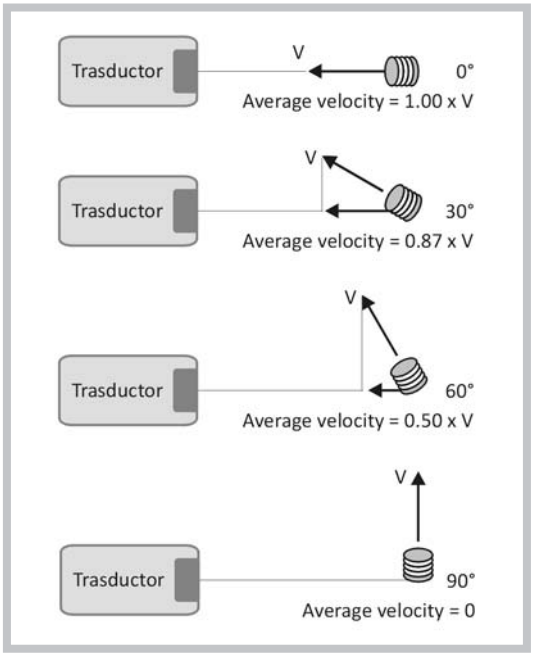

Figure 10.13. **Angle of insonation: angle between the emitted ultrasound beam and the blood flow velocity vector. Note that between 0° and 30° the influence of the angle is low or minimal.**

10.9.2 Basic TCD Recording

The basic TCD study of an intracranial artery shows a flow velocity waveform in relation to time. By convention, if blood flow moves toward the transducer, a positive signal (wave) is recorded, while if it moves away from the transducer, a negative signal is seen on the screen. Since blood particles (mainly red blood cells) travel at dif-

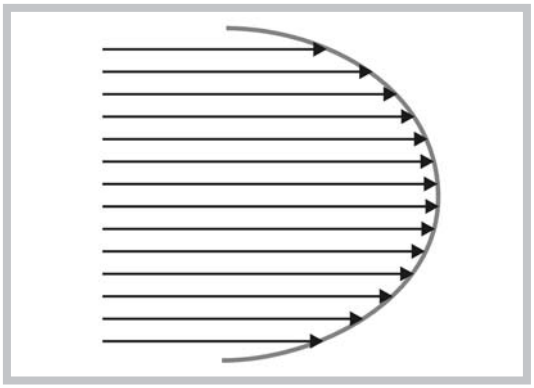

Figure 10.14. **Red blood cells travelling at different velocitys in laminar flow through a vessel. Note how the erythrocytes in the centre of the vessel move faster (higher velocity).**

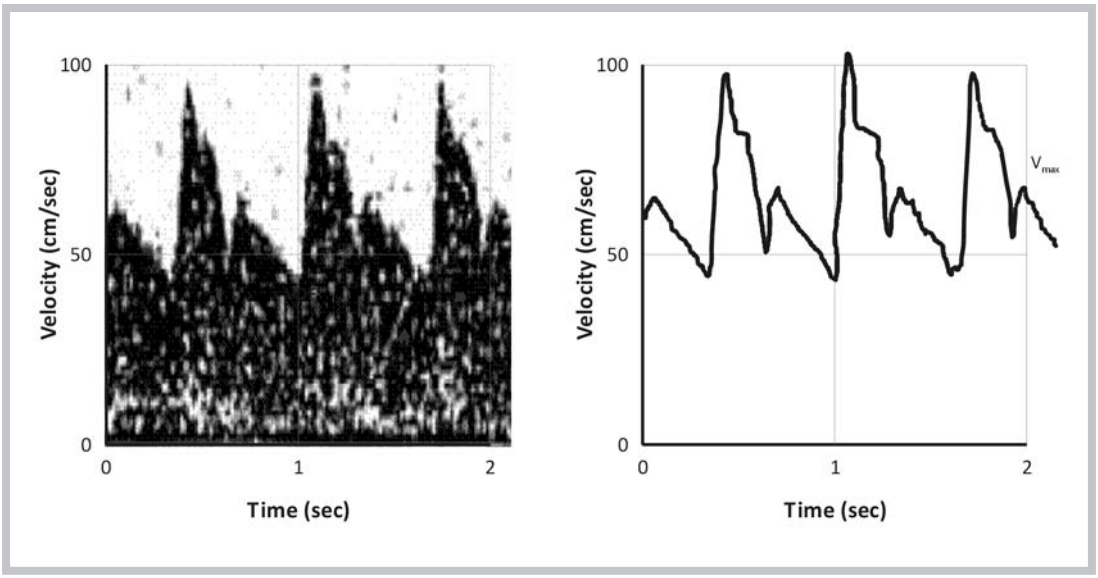

Figure 10.15. An example of a MCA sonogram.

ferent velocities, a single line cannot be displayed, so that a "velocity spectrum" is shown (mixture of many frequency components). To simplify the evaluation of this sonogram, the spectral envelope corresponding to the maximum velocity during the cardiac cycle is created, indicating the velocity of the fastest blood particles which, in laminar flow conditions, are those circulating in the centre of the blood flow through the vessel (Figure 10.14).

The obtained envelope curve begins and ends without decreasing to zero velocity at any point in the cardiac cycle. This means that cerebral blood flow at the major cerebral arteries is continuous, not stopping at any moment under normal conditions. Various different velocities are measured to calculate the indices: peak systolic blood flow velocity (FV_s); end-diastolic blood flow velocity (FV_d); mean blood flow velocity (FV_m). TCD is used to study blood flow velocity in the main cerebral arteries at the base of the brain (MCA, ACA, PCA, vertebral artery [VA] and basilarl artery [BA]), the communicating arteries, and the main branches (collateral circulation) of the all these arteries.

The vessels are insonated through acoustic windows which are areas of the skull where the bone is thinner (temporal and occipital windows) and/or where there are natural cranial openings (fontanelle and orbital windows) that allow the passage of ultrasound waves. The transducer emits a beam of ultrasound waves and receives the waves returning after reflection from the moving particles at a certain depth, analyzes the changes, and displays the results on a screen that shows veloci ties (y axis) in relation to time (x axis) (see Appendix for a detailed explanation). The ultrasound beam is directed to a target vessel and the beam angle and depth are adjusted to detect and analyze the target vascular segment of a particular cerebral artery. Figure 10.15 gives an example of a MCA sonogram. The spectral envelope is detailed. The flow velocity increases rapidly in the systolic phase where it reaches a maximum, after which it begins to decrease, falling more slowly in the diastolic phase, until it rises again, pushed forward by a new wave pulse.

From each envelope certain points of interest are recognized that characterize the flow pattern: peak systolic velocity (FV_s); end-diastolic velocity (FV_d); and mean velocity (FV_m) (Figure 10.16).

The key features of a normal TCD sonogram are: velocities are always positive and the flow velocity (envelope) never reaches 0, or, in other words, the flow velocity does not stop (cease) or reverberate under normal conditions. As the resistance in the brain vasculature is lower than in the systemic (extracranial) vasculature, the end-diastolic velocity in the former is greater than in the latter (peripheral arteries), the PI and RI values are lower (check indices formulas). Arterial bifurcations are easily recognized because two flow velocity signals (waveforms) seen on the screen travel in opposite directions (towards and away from the transducer or positive and negative signal respectively).
Since TCD ultrasound is pulsed, it allows to study the target vessels at different depths along their course.
Each cerebral artery can be recognized according to different complementary factors

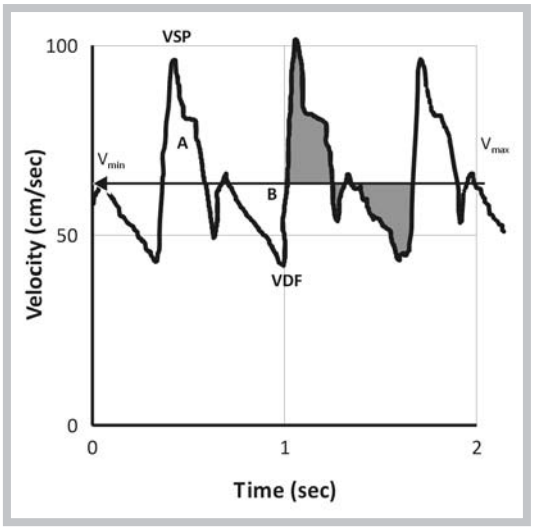

Figure 10.16. **Spectral contour points defining the peak systolic velocity (FV_s), end diastolic velocity (FV_d), and mean velocity (FV_m). he average velocity is the one which divides the surfaces in two similar areas (colored in gray).**

- The **acoustic window** in use.
- The ultrasonic **beam direction** to find the FV signal.
- The **depth** at which the Doppler signal appears.
- The response to compression (ICA) or vibration **maneuvers.**
- The relation with **vascular bifurcations.**

Normal velocitys vary from one cerebral artery to another and with certain physiological variables as well. velocities change with age, being higher in childhood and then declining with age. Normal values in healthy adults for three age groups are shown in Table 10.2.

Artery (depth in mm)	FV_s (cm/s)	FV_d (cm/s)	FV_m (cm/s)	Age (years)
MCA (50 mm)	95±14	46±7	58±8	<40
	91±17	44±10	58±12	40-60
	78±15	32±9	45±11	>60
ACA (70 mm)	76±17	36±9	47±14	<40
	86±20	41±7	53±11	40-60
	73±20	34±9	45±14	>60
PCA (60 mm)	53±11	26±7	34±8	<40
	60±21	29±8	37±10	40-60
	51±12	22±7	30±9	>60
VA/BA (75 mm)	56±8	27±5	35±8	<40
	60±17	29±8	36±12	40-60
	51±19	21±9	31±12	>60

Table 10.2. **Normal values in healthy adults for three age groups [61].**

Other important variables that influence blood flow velocity in the cerebral arteries are the blood pressure, pCO_2, pCO_2, temperature, heart rate, viscosity (its major determinant is the hematocrit), etc.

Peak systolic velocity is the velocity that corresponds to the highest point in the upward sector of the envelope curve. It is related to the force of systolic contraction. End-diastolic velocity is the lowest point of the downward sector of the envelope curve, before starting a new systolic phase (or cardiac cycle). This velocity is related to CVR and represents the outflow velocity from the intracranial circuit. Compared with flow velocity in extracranial vessels, the velocity (FV_d) in the intracranial circuit is higher, indicating that cerebral circulation is a system of lower vascular resistance. Under normal conditions, FV_d never reaches 0. Summarizing, the normal blood flow in the intracranial arteries travels in one direction, does not have any reverse or stopping point during a cardiac cycle, and the end-diastolic velocity is high compared with the arteries of the rest of the circulatory system.

The FV_m is calculated mathematically as the time average FV of the envelope. It can also be calculated graphically in the Doppler sonogram.

The Gosling pulsatility index (PI) is given by the formula $PI = (FV_s – FV_d)/FV_m$. It is related to CVR. PI increase can be triggered by multiple factors among which are: increased CVR, ICH, hyperventilation, bradycardia, increased blood viscosity, vascular stiffness and age.

10.10 TCD in Evaluating Hemodynamics

10.10.1 Difference Between Flow Velocity and Flow

It is essential to note that every Doppler technique measures flow velocity. In the case of TCD, it measures cerebral blood flow velocity (FV). **FV and CBF are two different entities**. FV is measured in cm/s and CBF is measured in ml x min^{-1} x 100 g^{-1} (i.e., 60 cm seg speed ACM^{-1} and FSC^{-1} x 100 g = 50 ml x min^{-1}). **Although the absolute values of CBF cannot be measured with TCD, changes in flow velocity reflect proportional changes in blood flow**. This statement is true provided that the vessel diameter (at the insonated point) and the angle of insonation remain unchanged. If both conditions are met, a change from a velocity of 40 cm/s to 80 cm/s indicates that CBF has doubled (although the absolute flow value is unknown).

To be able to correctly interpret changes in intracranial hemodynamics using TCD, it is important to keep the concept in mind that TCD assesses flow velocity (distance/time), measured in cm/s, but not flow (volume/time). Unfortunately, TCD technology does not have enough spatial resolution to accurately measure the diameter. If this technical limitations could be overcome, the product (FV x sectional area of the insonated vessel) would easily calculate CBF.

There is another hemodynamical important concept: Based on the equation CBF = FV. area, where: FV = CBF/area, it can be inferred that whenever the insonated artery diameter (and therefore the cross-sectional area of the vessel) remains constant, changes in CBF are equivalent to proportional changes in flow velocity. This concept is useful to assess relative changes in flow during the study of cerebrovascular reactivity. To study this extraordinary ability of cerebral vessels, different stimuli are applied to the small vessels that regulate CVR (resistance vessels), which open or close the “tap” that facilitates or impedes the passage of blood through the insonated vessel (conductance vessel). However, because the diameter of the insonated artery remains constant, the velocity changes in the insonated artery segment indicate changes in the CBF that passes through it.

Transcranial Doppler

- Measures CBF velocity in the large vessels of the circle of Willis and its branches.
- Estimates relative changes in CBF as long as no changes in cross sectional area of the insonated vessel.
- Differentiate when referring to:
  - CVR, represented mainly by small arterioles and precapillary sphincters. These small vessels represent more than 80% of the total resistance to blood flow through cerebral vascular tree. They constrict or dialte rapidly when exposed to differentl stimuli (blood pressure, CO_2, indomethacin, seizures, etc.).. When these small blood vessels constrict resistance increases and the passes more slowly through the large insonated vessel, whose cross-sectional area has not changed. TCD shows low circulatory velocities with high PI. In these cases the change in velocity is proportional to the change in flow.
  - The insonated vessel (large vessel of the base of the brain) generates minimum resistance to the passage of blood and its diameter changes slowly, usually over days, in response to inflammatory processes, eg. inflammation caused by blood contact with the adventitial surface of vessels during SAH. When vasospasm starts, large vessel diameter decreases, and consequently distal small vessels dilate to maintain the flow, ie CVR. Therefore, flow passes faster through the insonated spastic vessel, because distal resistance decreases (the sluice is opened). That's why, during vasospasm, while there's no ICH, an increase in flow velocity is accompanied by a decreased IP. In this case a flow velocity increase does not imply increased flow, but rather its maintenance.

Conversely, while the CBF passing through a given conductance vessel remains constant, the reduction in the cross-sectional area of the vessel (i.e., SAH vasospasm or atherosclerotic/vasculitic intracranial stenosis) is accompanied by an increase in velocity at the insonated segment (explained by the principle of continuity):

$$F = V_1 \times A_1 = V_2 \times A_2$$

Since flow is equal to velocity multiplied by the cross-sectional area of the vessel, if the flow does not change, a decrease in vessel diameter is accompanied by an increase in velocity, and vice versa.

A reduction in arterial diameter produces a pressure drop between both ends of the narrowed (stenotic or constricted) segment, leading to a fall in perfusion pressure in the distribution territory of that vessel. The difference in pressure (ΔP) between these two points, rather than absolute pressure, determines the flow. But resistance also plays a critical role. The resistance factors are the conditions that hamper the blood flow: viscosity (n), length of the narrowed segment (l) and **vessel radius** (r). Resistance (R) to flow exerted by the spastic (narrowed) segment is expressed by **Poiseuille's law** [62,63]:

$$R = 8 \times n \times l / \pi \times r^4$$

Flow is directly proportional to the pressure difference between the two end points of the narrowed vessel and inversely proportional to the resistance created by the narrowed segment.

$$F = \Delta P / R$$

and substituting R:

$$F = \Delta P \times \pi \times r^4 / 8 \times n \times l$$

where

$$\Delta P = F\ 8 \times n \times l / \pi \times r^4$$

That is, for a given blood viscosity, if $CBF_{regional}$ remains constant, the pressure drop generated by a spastic segment would be proportional to the length of the spastic segment and inversely proportional to the fourth power of the radius. This pressure drop is (potentially) counterbalanced by the $AR_{regional}$ (cerebrovascular reactivity pressure). If there is good $AR_{regional}$, an active vascular response (with vasodilator capacity) of the small arterioles will be seen. Such vasodilation tends to maintain $CBF_{regional}$ relatively constant. If vasospasm continues to rise and/or the $AR_{regional}$ is impaired, the $CPP_{regional}$ drop exceeds the lower limit of AR and resistance cannot drop more the $CBF_{regional}$ begins to descend. From this point onward, since both CBF and arterial diameter are no longer constant, TCD interpretation becomes more difficult. Figure 10.17 [64] shows the evolution of the V_{max} and CBF as the arterial diameter decreases (from right to left). The lower curve of each panel shows the changes for a MAP of 100 mmHg, and the upper curve for an induced MAP of 140 mmHg (induced hypertension). Initially, as the diameter decreases, the CBFregional remains constant owing to active autoregulatory compensation (pressure reactivity [CAR]), so that the velocity increases (simultaneously). Once the autoregulatory compensation is outweighed by the pressure drop caused by a more severe stenosis, CBF begins to fall (point known as critical vasospasm) and the velocity remains almost unchanged but then also begins to decline. If at that time the doctor increases the patient's BP, a CBF increase is likely to occur since the fact of being situated below the lower limit of AR allows the CBF to passively and rapidly increase with increasing the BP. It is important to understand and remember this concept, since the increase in flow velocity does not represent a worsening of vasospasm in this case, but rather an improvement in CBF.

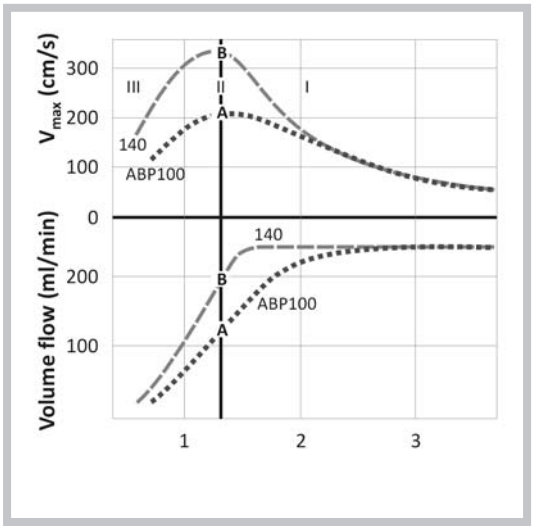

Figure 10.17. **Evolution of the V_{max} and CBF as the arterial diameter decreases (from right to left).**

10.11 Relationship Between CBF and CPP

The relationship between CBF and CPP is given by Ohm's law of hemodynamics:

$$CBF = CPP / CVR$$

where CVR is the cerebrovascular resistance mainly determined by the arteriolar resistance.

Given that:

$$CPP = MAP – ICP$$

the CBF can also be expressed as:

$$CBF = (MAP – ICP) / CVR$$

Under conditions where ICP and cerebrovascular compliance are both normal, this term can be omitted, so that:

$$CBF = MAP / CVR$$

10.11.1 Limitations of the Technique

As with any diagnostic technique, TCD has certain limitations that we can minimize by understanding the physical basis of the method:

- It is **operator-dependent**, so that an adequate interpretation of the findings and the time needed to conduct the study depend on the expertise of the examiner.
- In a low percentage of cases the temporal acoustic window is impermeable to the ultrasound beam due to the the skull physical characteristics bone. This usually occurs in 5-15% of patients and **varies with the experience and patience of the operator**. The acoustic window becomes more impermeable in women over 60 years of age. In some cases, this can be partially solved by insonating through other windows.
- In inexperienced hands, the common anatomic variations of the circle of Willis may result in errors in the correct identification of cerebral vessels.
- Disturbances (noise interferences) caused by monitoring devices are minimal (or insignificant). In our experience, we have had some difficulties only in pediatric patients while trying to demonstrate a CCA pattern, in which the ventilator (cycle) can interfere with the identification of very small systolic spikes, which can be detected only in the expiratory phase, making it sometimes necessary to disconnect the patient (for just a few seconds) to identify the pattern.
- When studying a non-intubated patient with mild depression of consciousness who does not cooperate (involuntary/voluntary movements and/or involuntary breathing sounds, etc.) trying to find an appropriate acoustic window can also be more difficult.

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11 Neurophysiologic Monitoring in Neurointensive Care: EEG, EMG, and Evoked Potentials

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11.1 Introduction

Electrophysiological tests (electroencephalography [EEG] and evoked potentials [EP]) provide a functional evaluation of the central nervous system [CNS], support the clinical evaluation, and are complementary to imaging tests (computed tomography [CT], and magnetic resonance imaging [MRI]). In a comatose patient, neurophysiological alterations may occur without evidence of structural injury: there are CNS lesions which are left out of neurophysiological investigation [1].

In the context of neurophysiological methods used in the ICU, this chapter will describe evoked potentials and EEG, which, in our opinion, provide most information, and we will describe their usefulness for diagnosis, prognosis and monitoring. In addition we will discuss the use of electromyography/electroneurography (EMG/ENG) to diagnose generalized hyposthenia arising during the ICU stay. The International Federation of Clinical Neurophysiology Guidelines [1] indicate the standards for the use of EEG and evoked potentials during coma and in unresponsive states. One of the most recent guidelines on clinical neurophysiology in the ICU [2] recommends that some tests (EEG, short and long latency EP, EMG) should not be used as standard tests, but rather selected on the basis of evidence.

11.2 Electroencephalography

EEG measures cortical bioelectric activity. It is generated from the spatial and temporal summation of excitatory and inhibitory postsynaptic potentials of the superficial cortical layers (mainly the pyramidal cells of layers III and V) and is modulated by thalamocortical transmission. EEG involves placing electrodes on the scalp according to the international 10-20 system to explore the greatest areas of the cerebral hemispheres [3].

Rationale for the use of EEG in the ICU is related to the following considerations:

- It is closely related to brain metabolism.
- It is sensitive to the most common causes of brain damage (hypoxia/ischemia).
- It detects brain dysfunction already at an irreversible stage.
- It relates to brain topography.
- It is the best available method to record critical epileptic activity and for differential diagnosis with many non-epileptic motor manifestations.
- It is the only method to diagnose non-convulsive seizures.

The intensive care unit poses many technical difficulties for EEG acquisition; therefore it is important to descrive some technical details about EEG recording. The technician who

performs the EEG should be an expert not only in EEG testing, but also in the laboratory diagnosis of neurological diseases.
There are no specific electrodes for EEG recording in the ICU: they are chosen according to the duration of the recording, the conditions of the scalp, and the alertness of the patient.
EEG skull caps can have an array of electrodes or needle electrodes incorporated. Positioning a skull cap fitted with electrodes is not normally problematic, but it requires skin integrity. A cap with needles is recommended in patients undergoing craniotomy or for monitoring brain activity. In this case, the EEG assembly will include at least 8 electrodes, F-C-T-O (or P if there is significant orthostatic edema of the scalp) suited to the presence of obstacles (injuries, craniotomies, drainages, monitoring probes). It is advisable to apply a fixed recording and stimulation protocol. An example of an EEG registration protocol in the ICU is: duration of at least 30 minutes, 5 minutes of initial recording without stimulation, followed by the evaluation of reactivity to different types of stimuli: acoustic, nociceptive, and passive eye opening. Each type of stimulus should be administered at least twice and the recording should last at least 5 minutes after stimulus end. In the differential diagnosis of motor manifestations, a video-polygraph is required. If there are critical manifestations of EEG or unexpected clinical features (e.g., non-convulsive status epilepticus), the recording will last longer than 30 minutes and any observed motor manifestation will be recorded. Finally, correct test interpretation will rely on: cause of coma, time elapsed since the beginning of coma, Glasgow Coma Scale (GCS) score, neuroimaging, and ongoing sedation.

11.3 Evoked Potential

Evoked potential (EP) is defined as a change in the electrical potential in a sensory organ along the peripheral afferent pathway and at the intracerebral level in response to a transient stimulus quantified in physical parameters (intensity, duration, frequency). There are several types of evoked potential for sensory, somatosensory, acoustic and visual modalities. In general, the evoked potential width is lower than the spontaneous EEG activity, so that mathematical averaging methods are needed to extract these signals from background noise (not only biological, but also environmental EEG-EMG) and render them easily identifiable in their wave shape, made by several subsequent components with negative-positive polarity.
Evoked potentials can be classified as exogenous or obligatory when they depend mainly on the physical characteristics of the stimulus, or endogenous or event-related when they rely on the stimulus processing by the subject (stimulus categorization, discrimination between several stimuli, storage, decision-making task). Exogenous evoked potentials originate mainly from specific primary and periprimary cortical areas, while obligatory potentials are generated in parietal and frontal polymodal association areas.
The classification of evoked potential according to a latency criterion is extremely useful because it defines the components according to different anatomical topography (peripheral, subcortical, intracortical in primary and secondary areas) and a different sensitivity to sedatives and anesthetics. In general, components are classified as short, medium and long-latency (within 10 ms, 10-50 ms, and over 100 ms, respectively), but such time limits may differ slightly depending on the sensory modality.
The early components of evoked potential are used during the acute phase of brain damage when, because of sedation, curarization, or the severity of coma itself, clinical assessment is difficult. Such components are substantially resistant to sedation, which

facilitates the recording because muscle and movement artefacts can be removed. The long latency and cognitive components are more applicable in a postacute phase, since they are extremely sensitive to neurosedation and require clinical optimization to be recordable (remission of any pharmacological effect, resolution of septic-dysmetabolic abnormalities).

The short-latency evoked potential most frequently used in the ICU is short-latency somatosensory evoked potentials (SEPs) and brainstem auditory evoked potentials (BAEPs): SEPs afford the advantage of having peripheral, spinal, brainstem and, intracortical components which are easily identifiable in all subjects and permit exploration of the transmission of a large tract of the CNS. BAEPs explore a small portion of the acoustic transmission at the bulbopontine level; the identification of peripheral afference, wave I in particular, can often be problematic. Another limitation is that primary cortical responses are difficult to identify. In fact, the generators of these components reside in the depth of the Sylvian fissure (Brodmann areas 41 and 42) and so are unlikely to be recorded with surface electrodes, unlike the early cortical SEPs, whose generators lie on the convexity of the postcentral gyrus (area 2 b in particular). In addition, acoustic myogenic reflexes, which cannot be eliminated by averaging methods, have latencies similar to those of early cortical acoustic components and can therefore mask them.

Despite such problems, the most commonly used EP in the ICU in recent years, and for which there is a greater evidence of their clinical usefulness, are short-latency SEPs in stimulation of the upper limb. Short-latency SEPs are sensitive to both traumatic structural damage and hypoxic-ischemic damage, and are able to indicate lesion topography. But beyond that, in the absence of severe lesions along the somatosensory afferent pathways, from which an index of the "global" brain function can be extrapolated at the brainstem, thalamocortical and intracortical transmission level of both hemispheres (Figure 11.1).

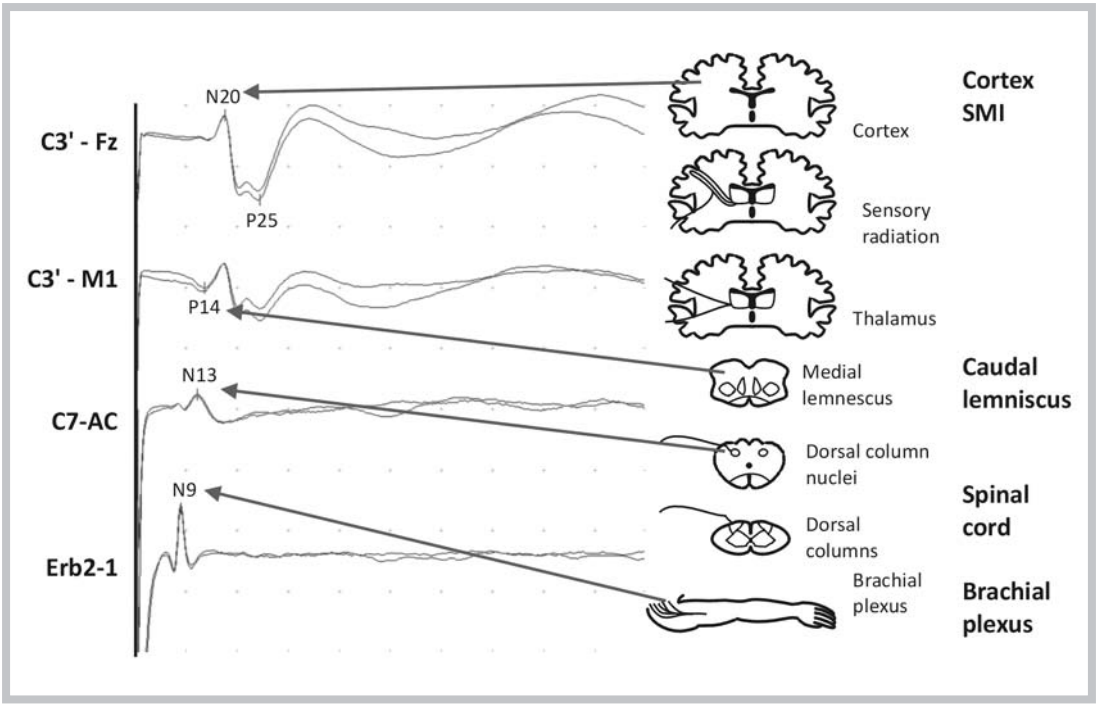

Figure 11.1. **Extracranial (brachial plexus, N9, and cervical spinal, N13, potentials), intracranial lemniscus (P14), and intracortical (N20-P25) SEP components.**

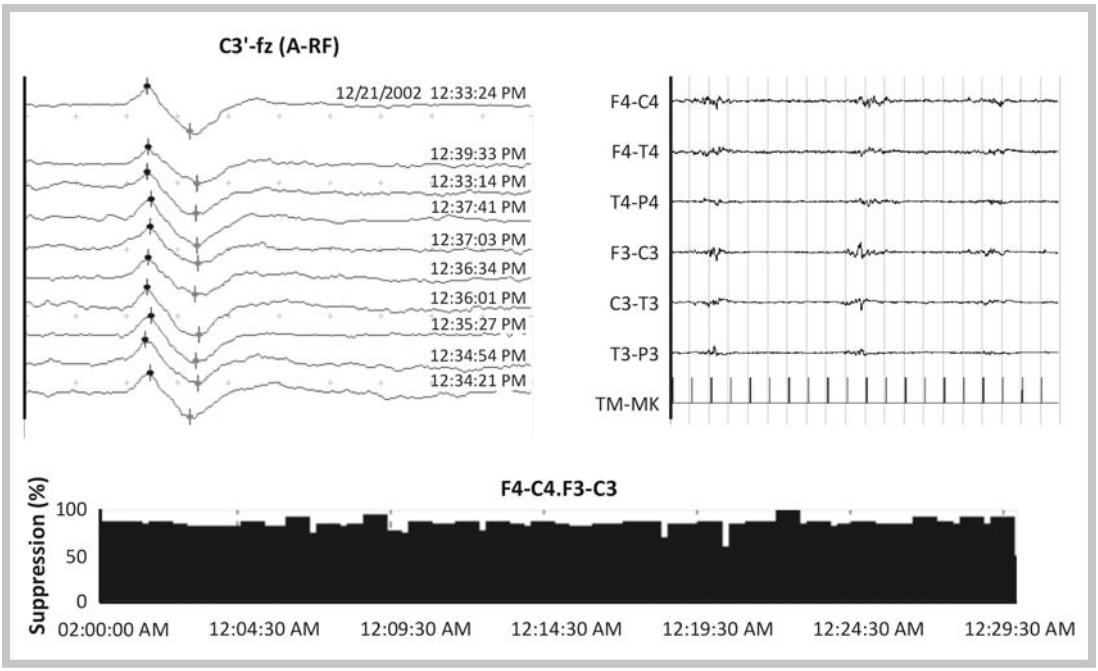

Figure 11.2. **During a continuous infusion of thiopental sodium (TPS), with a suppression of about 90%, which precludes EEG evaluation for clinical purposes, the early components of SEPs are well measurable in their latency and amplitude parameters.**

This information is very useful in the neurocritical patient, who is often poorly clinically evaluable because of pharmacological sedation, curarization, or the severity of coma itself. SEPs have the additional advantage of being resistant to anesthetics, having a waveform easily interpretable and comparable at subsequent tests (Figure 11.2).

Because we believe that a reason for the underuse of SEPs in the ICU is due to major technical difficulties of recording in that environment and the perceived lower reliability of the test result, more precise technical information is necessary about their recording.

First, it is necessary that the neuropathophysiology technician and the neurophysiologist have experience in recording and interpretation of evoked potentials in the laboratory for neurological diagnosis, in addition to specific training in the intensive care field.

It is also necessary that the technician communicates the problems encountered during the examination: obstacles to stimulation in conventional locations; excessive environmental artifacts or patient-related artifacts; and the need to perform sedation or curarization to optimize the recording.

Intradermal needle electrodes or silver chloride cup electrodes are used, possibly braided to reduce artifacts.

The recording apparatus for SEPs should have at least 2 channels (4 recommended). For full specifications on amplifiers and averaging and electrical safety, please refer to the guidelines reported in Suppl. 8 of *Muscle and Nerve*, 1999 (S123-138).

We want to stress the importance of some methodological aspects:

- Stimulus frequency: 3-5 Hz; analysis time: 50 or 100 ms (with the lowest frequency of stimulation and the greater analysis time also intermediate-latency intracortical components subsequent to N20-P25 are more identifiable; analysis time of 100 ms is therefore necessary to determine the absence of any cortical response).
- Number of mediated responses: 200-400, depending on recording conditions (signal-to-noise ratio) and identifiable components. At least two sets of repeatable responses

must be obtained. It is advisable to obtain a larger number of repeatable series when altered patterns of clinical relevance are detected (absence of cortical SEP).

- Stimulus intensity: in cases of curarization the evaluation of response width from Erb's point or cortical allows to verify that the stimulus intensity is supramaximal.

To record SEPs with median nerve stimulation the electrodes are placed at Erb's point (contralateral Erb), at the spinous process Cv7 (referred to antecollis) and C3'-C4' (referring to Fz and the ipsilateral mastoid) (Figure 11.3). A non-cephalic reference can be used, but this creates more artifacts. We also suggest the use of the Fz reference because, even though the latter produces a greater variability of interindividual width, it prevents the influence of subcortical potentials and reduces the interference contamination. In addition, the Fz reference allows the recognition of cortical responses even when their presence is questionable considering only the tracks with mastoid reference. It is also important to establish the criteria for SEPs abnormality (Figure 11.3):

- Absence of mandatory components (N9 in an ipsicontralateral derivation from Erb's point, N20 in a derivation with Fz reference, P14 in a derivation with auricular or mastoid reference, N13 in a derivation with AC reference) (Figure 11.3C). This criterion implies that there must be adequate technical conditions to identify a component

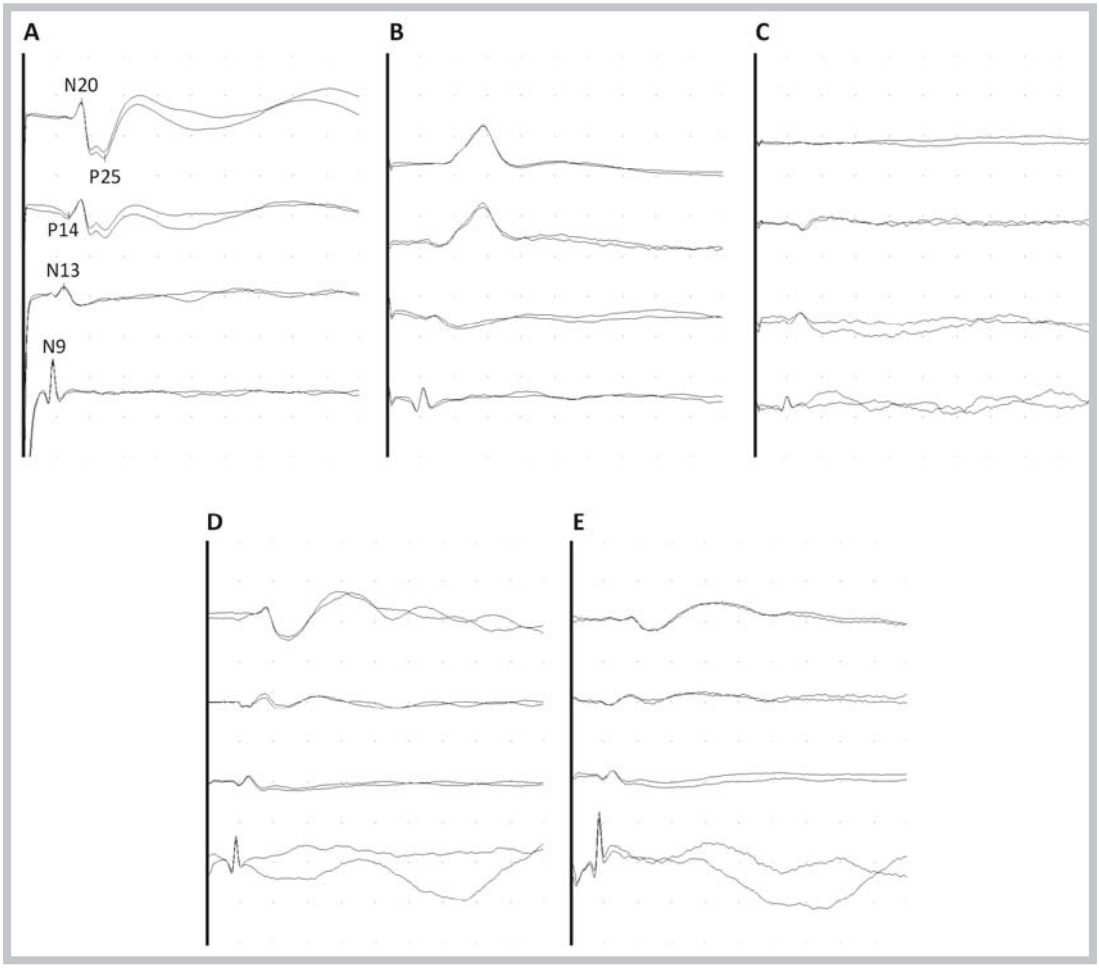

Figure 11.3. **Example of SEP classification. (A). Normal SEP. (B). Pathological SEP because of an increase in the transmission time. (C). Absent cortical SEP, considering both Fz and mastoid reference. (D) and (E). Pathological width asymmetry (>50%) of the cortical SEP between the two hemispheres with normal transmission time [4].**

if present. Sometimes not being able to replicate some of the responses (especially spinal and subcortical) in the presence of excessive artifacts is a technical limitation rather than an abnormality of the patient.

- Extension of interpeak latencies (N9-N13, N13-N20 and P14-N20). Generally, reference is made to the limits of 2.5-3.0 standard deviation (SD) of average values for each laboratory (Figure 11.3B). The problem of not having homogeneous normative data for patients in the ICU must be considered. In addition, many non-pathological factors can interfere with the interpeak latencies (temperature, therapy, etc.).
- Asymmetries. In the absence of a change in latency, a variation in the width should be viewed with caution, given the high variability in normal subjects for both absolute values and the interside asymmetry itself (Figure 11.3D-E). However, we consider it useful for the N20 cortical component to accept as pathological a reduction in width of more than 50% of the contralateral.

The EEG and the EPs can be used for both diagnosis/prognosis and monitoring the evolution of brain damage or the occurrence of secondary damage. Discontinuous evaluation is sufficient for the former, while continuous neurophysiological evaluation is required for the latter in oder to obtain more detailed clinical data.

11.3.1 Using EEG and EP for Diagnostic and Prognostic Purposes

Diagnosis

Although EEG is underused in coma [5], its diagnostic utility is confirmed in clinical practice for differential diagnosis at the bedside (metabolic, infectious, drug, and epileptic causes).

EEG is the best available method to diagnose epileptic activity: the increased use of EEG and continuous EEG (CEEG) in the ICU has revealed a surprisingly high incidence (8-28%) of non-convulsive seizures and non-convulsive status epilepticus in patients with acute brain damage [6]. EEG is the only method available to diagnose such conditions and to guide their treatment. Young [5] proposed the most commonly followed primary and secondary diagnostic criteria. These criteria have been recently reviewed by Chong and Hirsch [7].

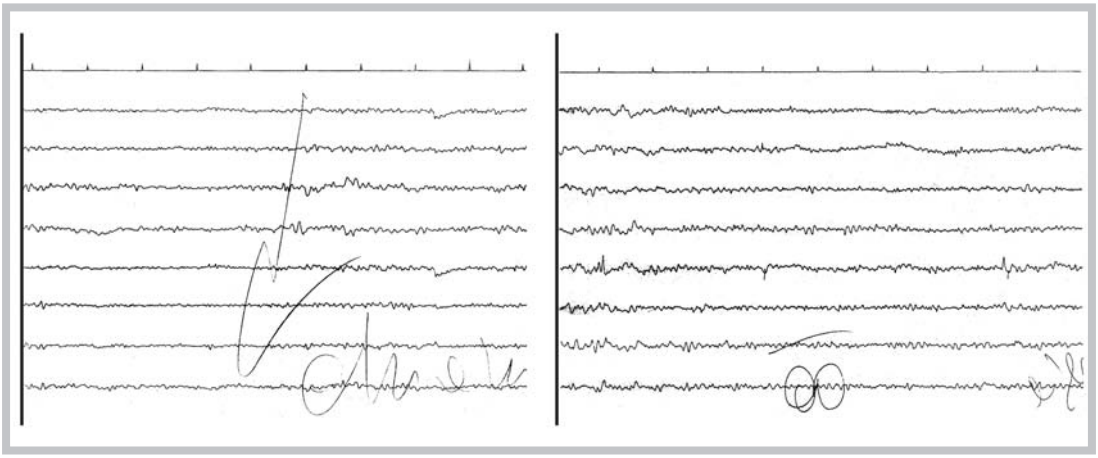

Figure 11.4. **Locked-in due to a ventral pons-midbrain ischemic lesion. The left tracing shows passive eye opening with a slight desynchronization of alpha rhythm. The right tracing shows how the acoustic stimulus generates a "paradoxical" alpha rhythm. The presence of a reactive alpha rhythm confirms the diagnosis of locked-in.**

EEG is useful for the differential diagnosis of motor manifestations in ICU patients who may have a wide variety of non-epileptic involuntary and semi-voluntary movements such as tremors, spasms, tetanic spasms, septic rigor, stiffness due to neuroleptics, extrapyramidal movements, ischemic tremors, tonic head and eye deviations, and abnormal posturing.

Besides providing indications on the etiopathogenesis of coma (when it is not known), EEG findings may also be diagnostic of the effective state of consciousness. Its contribution is decisive in determining the depth of coma beyond the clinical evidence and highlighting the discrepancy between the apparent clinical status and the effective depth of the consciousness disturbance in particular conditions (traumatic and vascular locked-in states, neuromyopathy in critically ill patients, frontal syndrome or associations thereof).

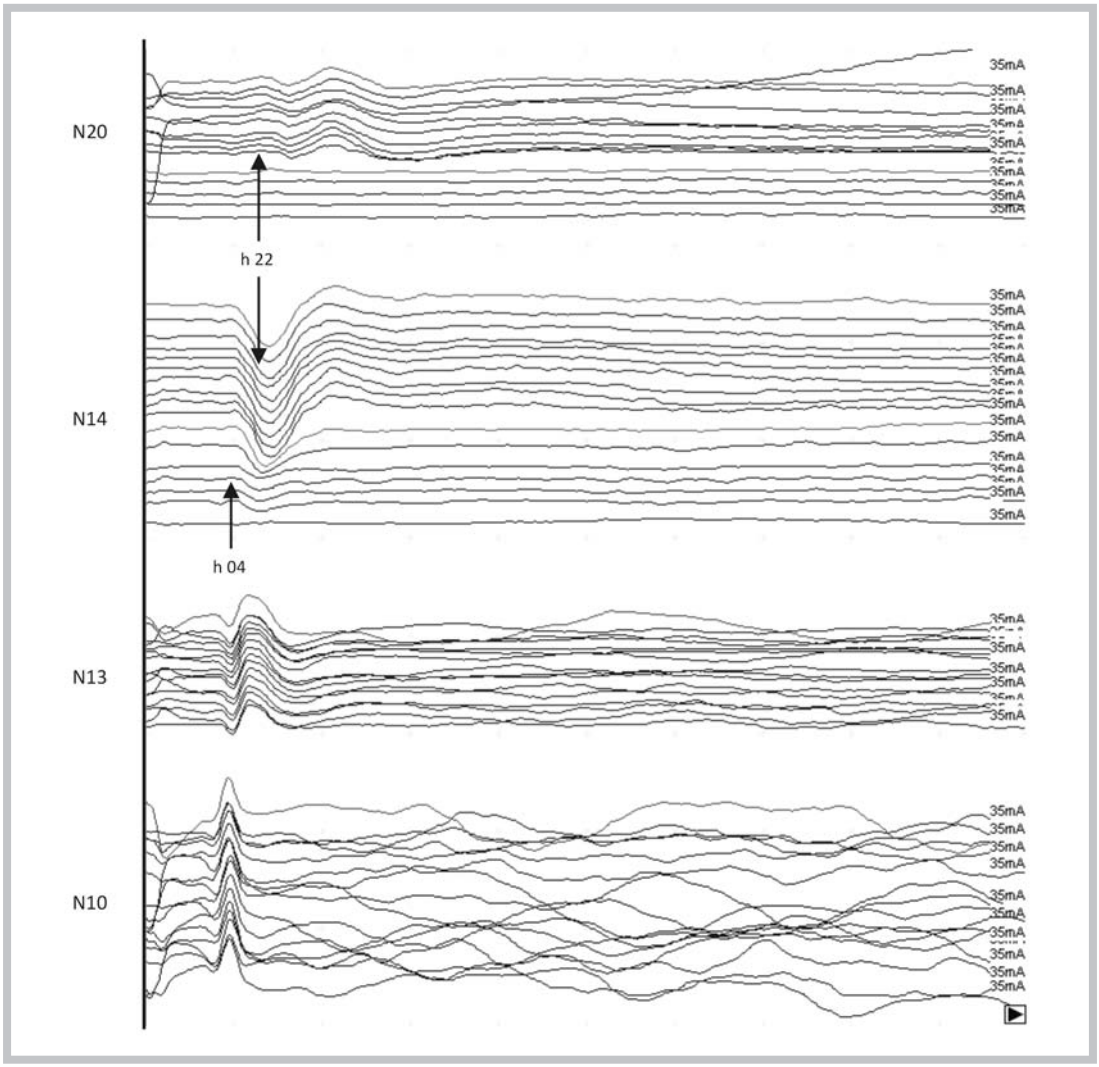

Figure 11.5. **Post-traumatic coma: rostrocaudal deterioration in a patient who could not be evaluated clinically or by EEG because he/she was under profound neurosedation (thiopental sodium infusion) until the night before. At 22 h the N20 intracortical component disappeared; 6 hours later, with the disappearance of the P14 bulbar component, the SEP pattern of brain death (extracranial components unchanged) is evident. Transcranial Doppler (TCD) performed 2 hours later confirmed the absence of intracranial blood flow.**

Considering only the motor responses, in the absence of an EEG, it is very difficult to determine the real consciousness disturbance in these conditions [1,8]. Logically, the EEG data must be integrated with neuroimaging and other neurophysiological tests. The presence and/or duration of coma may be overestimated considering the clinical evaluation alone (Figure 11.4).

Furthermore, EEG is one of the tests to confirm the diagnosis of brain death in some countries [9]. It is should be noted that the short-latency EP, and SEPs in particular, are considered by some authors to be very useful for the diagnosis of brain death when "confounding" factors are present, as in drug neurosedation, which invalidate and render the clinical criteria alone and EEG insufficient.

Changes in SEPs reliably reflect the rostrocaudal deterioration of brain damage until brain death, with loss, first, of intracortical components, and then of the caudal lemniscus component (P14), which reflects bulbar generator activity. The loss of all intracranial components (N20 and P14), when first recorded, associated with conservation of extracranial components (N13, N10) is the SEPs pattern of brain death (Figure 11.5).

As indicated in European guidelines [2], the short latency EP improve the timeliness, safety and the reliability of the diagnosis of brain death, especially when this cannot be made using conventional criteria.

Prognosis

A systematic review of EEG scales for the classification of coma severity [5,10,11,12,13,14] is beyond the scope of this chapter. Suffice it to state that all these classifications are based on the assessment of the background activity, the presence of reactivity and variability, and the detection of special patterns.

The Synek's classification (1988, 1990) [13,15] divides into three categories with different prognostic significance (favourable, uncertain, unfavourable) the EEG patterns most frequently found in post-traumatic coma and hypoxic-ischemic coma (Table 11.1).

It is useful to briefly mention the epidemiology of the two different types of coma. The first generally has a poor prognosis on awakening, as 70-80% of patients experience death or a vegetative state. In the second type about 60% of patients awaken, with 30% mortality (the latter mostly early). Therefore, in the first type the early prognosis of unfavourable outcome will be more important, while in the second, in addition to the recovery of a state of consciousness, the early prognosis of residual disability will be very useful.

Favourable significance	Uncertain significance	Unfavourable significance
Grade 1	Grade 2, non-reactive	Low amplitude, grade 3
Grade 2, reactive	Grade 3, diffuse delta non-reactive/(reactive)	Burst-suppression, grade 4
		Epileptiform discharges, grade 4
		Low output, grade 4
		Isoelectric, grade 5
Spindle pattern coma, grade 3	Epileptiform discharges, grade 3	Alpha pattern coma, non-reactive
Frontal rhythmic delta reactive/non-reactive	Alpha coma, reactive	Theta pattern coma
		BIPLEDs, PEDs

Table 11.1. **Synek's classification of prognostic categories of EEG patterns in post-traumatic and hypoxic-ischemic coma. [13].**

11.3.2 Hypoxic-ischemic Coma

It should be noted that EEG is more useful in the prognosis of hypoxic-ischemic coma, as the frequency of special or low voltage patterns falling in the category with a poor prognosis is very high for this type of coma. It proves less useful in the post-traumatic phase, when the most frequent EEG pattern is characterized by irregular, often non-reactive dominant medium voltage delta, belonging to the class of uncertain prognostic significance (Figure 11.6).

When preparing to make an early prognosis of hypoxic-ischemic coma, we must consider at least six meta-analyses on the evidence of the usefulness of short-latency EP and in particular of SEPs [16,17,18,19]. All studies agree in indicating that the bilateral ab-

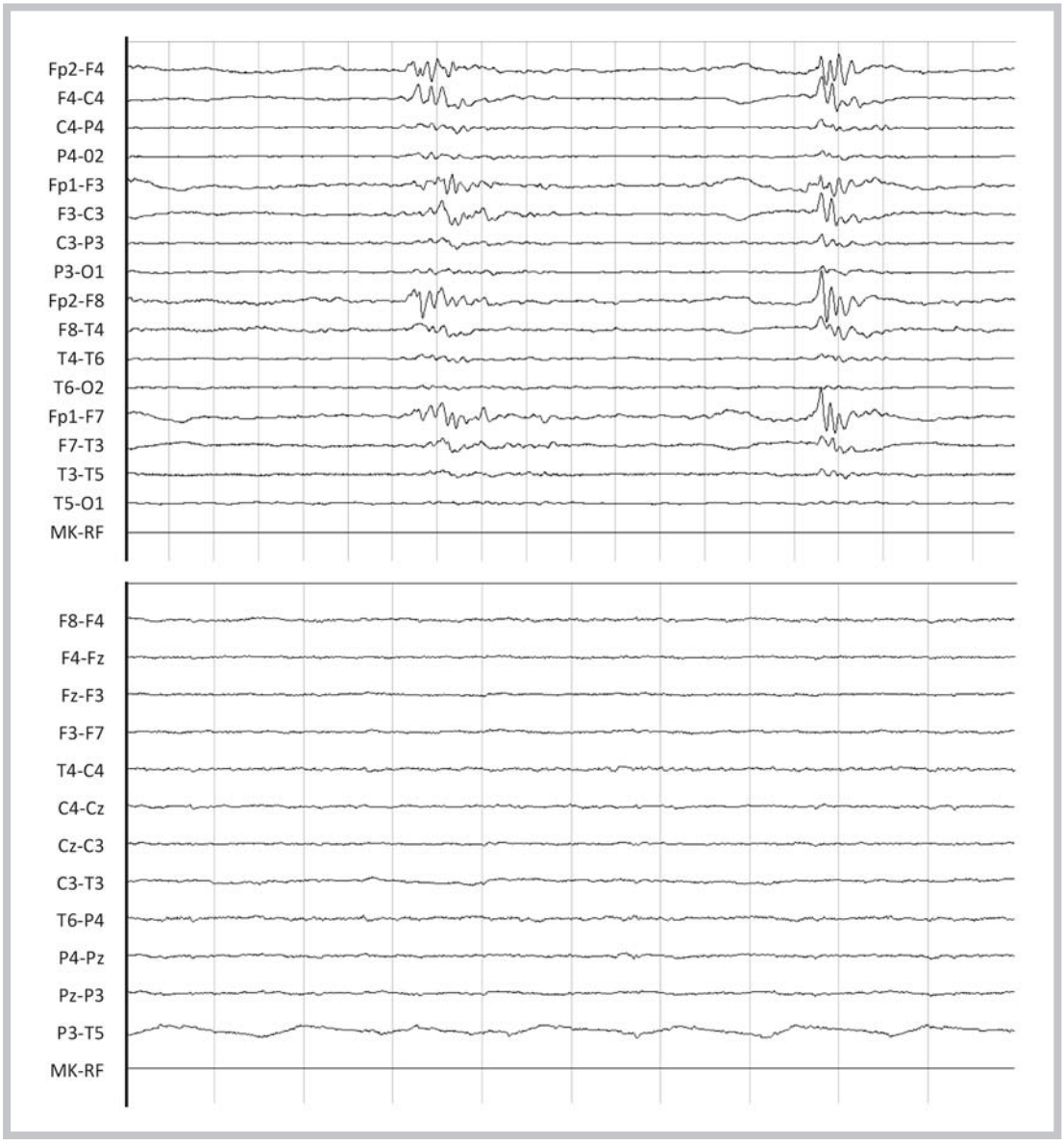

Figure 11.6. **EEG burst suppression pattern (left tracing) at 24 hours in hypoxic-ischemic coma (Glasgow Coma Scale score [GCS] = 4), which at 48 hours is transformed into low voltage pattern (right tracing).**

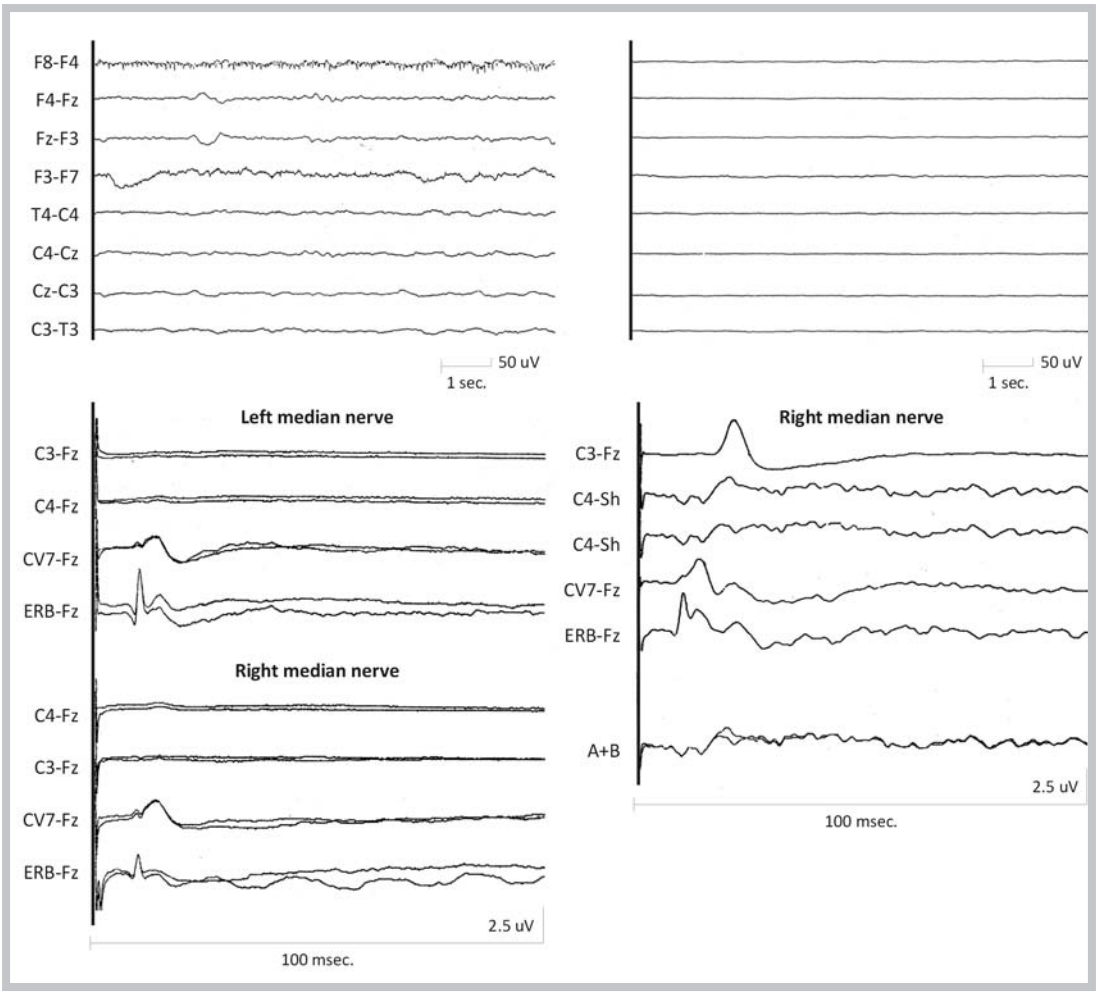

Figure 11.7. **(A). EEG recording of theta delta non-reactive activity and a SEP pattern absent in both hemispheres. (B). Low-voltage EEG/absence of cortical electrical activity and SEPs bilaterally present, albeit simplified.**

sence of cortical SEP has 100% adverse prognostic significance (all patients die or remain in a vegetative state). Zandbergen et al. [16] proposed "clinical" guidelines for the prognosis of unfavourable outcome of hypoxic-ischemic coma, postponing the prognostic assessment to 72 hours and limiting SEPs recording in patients with absent photomotor or with M 1-3/GCS. A proposal for European guidelines on the use of neurophysiological tests in the ICU recommends an evaluation already at 24 hours [2]. A report by the American Academy of Neurology found the SEPs among the most reliable prognostic tests in hypoxic-ischemic coma [20], but does not include EEG for which there is less evidence in the literature. We believe instead that the two tests complement each other, and albeit infrequently, EEG can provide information on unfavourable outcome not obtainable with SEPs alone (Figure 11.7).

In our hospital we have implemented an EEG-SEP protocol agreed upon with interventional cardiologists and the general intensive care unit for the early prognosis of hypoxic-ischemic coma. The protocol includes an EEG-SEP recording at 24 hours in a patient with a motor GCS ≤3: in EEG-SEP patterns unfavourable for the recovery of consciousness (bilateral absence of SEPs, severe EEG abnormalities), given the clinical importance of this finding, we perform a confirmatory test at 48-72 hours.

The clinical usefulness of early prognosis is, in case of negative patterns, that it discourages aggressive interventions for hemodynamics in severely unstable patients, informs the family early on outcome and refers patients to low-intensity rehabilitation facilities after discharge from the ICU.

11.3.3 Post-traumatic Coma

As mentioned, EEG and GCS itself are less reliable as early prognostic indicators in post-traumatic coma compared with hypoxic-ischemic coma [21]. Neurosedation in the early stage hinders clinical evaluation of the patient and makes the underlying EEG activity and reactivity less interpretable. Early SEPs do not have these limitations and are sensitive only to structural damage. A meta-analysis by Robinson et al [18] not only confirms the highly unfavourable prognostic value of absent SEP patterns in post-traumatic coma (90-95% of non-"awakening" in bilateral absence of SEPs) but also highlights the favourable prognostic significance of the normal pattern SEP (over 90% of "awakening" in bilaterally normal SEPs).

By classifying the pattern of SEP alterations in both hemispheres (Figure 11.3) it is possible to group the changes into three categories with different prognostic significance: Grade 1 [(NN, NP): normal] with favourable prognosis; Grade 3 [(AA): absent] with poor prognosis; and Grade 2 [(NA, PP, AA): preserved] with uncertain prognosis. It should be noted that grades 1 and 3 allow correct classification in 65-70% of patients with severe post-traumatic coma. In addition, the normal pattern (grade 1) in our series has a positive predictive index of "awakening" of more than 90% and good functional recovery according to the Glasgow Outcome Scale (GOS) of more than 80% [4].

In our series, a severe disability according to the GOS is associated, in nearly 100% of cases, with absent mono- or bilateral SEPs. Thus, a SEP performed already at 24-48 hours after severe head injury can predict two very divergent paths according to the length of stay in the ICU and subsequent rehabilitation processes in patients with normal SEP and absent or severely hypovolted SEP.

Finally, a comparative meta-analysis examined which was the best single early indicator of prognosis from among SEP, computed tomography (CT), EEG and GCS and photomotor reflex in post-traumatic and hypoxic-ischemic coma [22]. The work selected 26 comparable studies including over 800 patients and concluded that SEP is the best single prognostic indicator. Based on this evidence SEPs should always be associated with clinical tests for determining early prognosis of coma due to acute brain damage.

11.4 Continuous Neurophysiological Monitoring (EEG-SEP) in the ICU

As mentioned at the beginning of this chapter, continuous neurophysiological monitoring is required to establish clinical and therapeutic strategies in the comatose patient. Its purpose is to identify early the evolution of primary brain damage or the possible occurrence of secondary complications.

The demand for a greater use of such monitoring has several reasons:

- The growing interest and neurological involvement in neuroresuscitation.
- The widespread application of neurophysiological methods in intraoperative monitoring.
- Technological innovation and the benefits provided by digital EEG (processing by analysis of quantitative EEG signal, ease of storage and network transmission).

11.4.1 EEG Monitoring

The diagnosis and treatment of status epilepticus have been verified as indications for the use of continuous EEG in the ICU. The incidence of seizures (NCS, non-convulsive seizures) and non-convulsive status epilepticus (NCSE) in the ICU is very high (Table 11.2) and is certainly underestimated in the absence of prolonged or continuous EEG recordings.

Drislane et al. [30] reported the high incidence of NCSE in medical and surgical ICUs (heart surgery in particular) and the delay in EEG diagnosis, even in the presence of a previous clinical crisis.

The diagnosis of NCS and NCSE is made by conventional EEG interpretation (see Young criteria, reviewed by Chong, discussed above), but quantitative EEG (QEEG) may provide a useful tool for even inexperienced personnel to monitor the therapy effectiveness (Figure 11.8).

- 11-51% NCS patients in ICU [23]
- 34% NCS and 3/4 NCSE in acute brain damage [24]
- 12% NCS or NCSE in severe head injury [25]
- 22, 8 and 28% NCS, respectively, in head injury, ischemic stroke, and intracranial hemorrhage [26]
- 8% NCSE in comatose patients in the absence of critical clinical manifestations [27]
- 12-53% NCSE after treatment of a GCSE sometimes with considerable delay in diagnosis [28,29]

Table 11.2. Frequency of crisis and non-convulsive status epilepticus in the ICU.

GCSE = generalized convulsive status epilepticus
NCS = non-convulsive seizures
NCSE = non-convulsive status epilepticus

For the diagnosis of refractory status epilepticus it is necessary to look for a persistent NCSE. Continuous EEG monitoring can be useful to assess the effectiveness of therapy and establish the duration of treatment and methods of reduction and withdrawal of therapy.

Recently, the use of CEEG has found an indication, still potential, in the evaluation of stroke and diagnosis of vasospasm and delayed cerebral ischemia in SAH. Diffuse attenuation of all frequencies without an increase in delta is considered a high risk EEG pattern in extensive ischemic lesions for the occurrence of malignant brain edema [31]. According to Vespa et al. [32], the trend of alpha relative variation can predict the onset of vasospasm by even more than 2 days before diagnosis with transcranial doppler (TCD) and angiography. In addition, various QEEG parameters in SAH have been considered possible indicators of vasospasm and ischemia, such as total power (1-30 Hz), alpha ratio (6-14/1-20 Hz) and alpha/delta ratio (8-13/1-4 Hz) [26,32,33].

Jordan [31] reported the clinical impact of CEEG in 200 randomized patients monitored in the ICU on three clinical decisions such as starting or changing anti-epileptic therapy, transporting patients for CT or magnetic resonance imaging (MRI) and interventions on hemodynamics in order to optimize cerebral perfusion pressure. This impact was decisive in 51%, complementary 31%, and irrelevant in 18% of cases.

Concerning the indications for the usefulness of continuous EEG in the ICU (conventional and QEEG), there is sufficient evidence for the diagnosis and treatment of NCS and NCSE, there are pilot studies on its usefulness for the diagnosis of acute ischemia, while data are very limited on its usefulness for prognosis and absent for monitoring of the evolution of acute brain injury [34].

Despite the extensive use of SEPs in intraoperative monitoring, and the demonstrated prognostic utility of SEP in acute brain injury (close correlation between changes in SEPs in early phase and brain damage, which then affects the prognosis) there are very few studies on continuous monitoring of SEP in the ICU [35,36]. This is even more surprising considering that for the most common monitoring in acute severe brain injury, intracranial pressure (ICP), there is insufficient evidence for a close causal relationship between ICP increases and neurological damage [37].

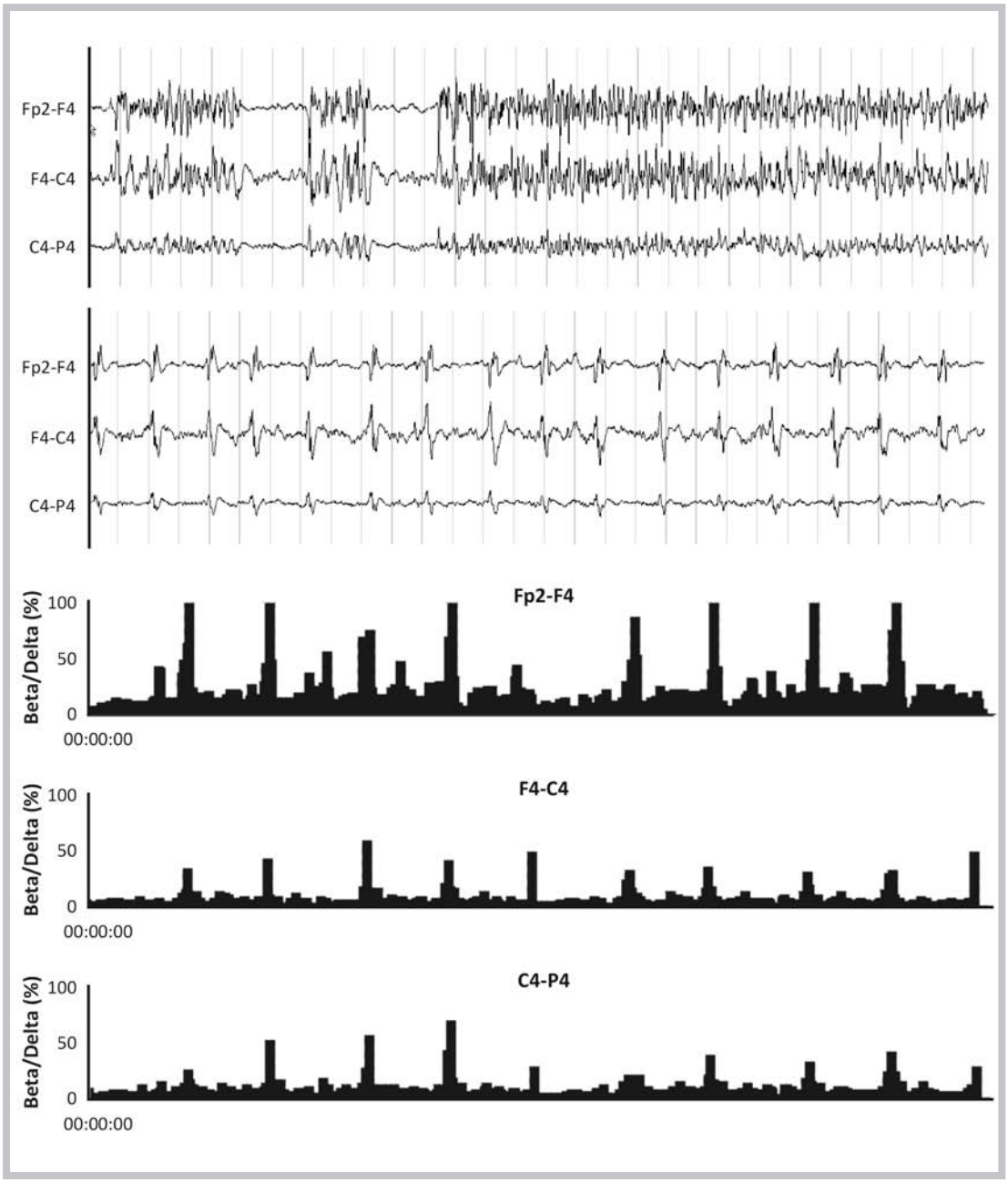

Figure 11.8. **NCSE in a patient with subarachnoid hemorrhage (SAH) due to rupture of an anterior communicating artery aneurysm. Conventional EEG tracings showing both critical (multiple-spike discharge) and intercritical ([PLED] periodic lateralized eileptiform discharges) activities in fronto-central areas (right panel). (Lower panels) QEEG with trending bar visualization of seizures (each bar is made up of a power ratio with the fastest critical frequencies in the numerator and the slowest frequencies of intercritical activities in the denominator. For every crisis there is a power peak up). The QEEG represents 1 hour of compressed EEG.**

In addition to the aforementioned clinical rationale, the "technical" rational for continuous SEP monitoring in the ICU is to couple the high sensitivity and variability of EEG with the stability of SEPs, with the advantage of their easy translatability in quantitative trends of latency and amplitude, easily assessed even by unskilled personnel. This could

facilitate timely clinical interpretation of the high-risk pattern for the onset of an acute or progressive neurological deterioration.

Based on this rationale, in our hospital we perform continuous EEG-SEP monitoring in comatose patients (GCS <9) admitted to the neuroresuscitation department for head trauma and intracranial bleeding and monitored for ICP [38,39]. The registration protocol provides for the performance of alternating cycles of EEG and SEPs, with alternate stimulation of the left and right median nerve, and the monitoring of both hemispheres (latency trends and amplitude for the SEPs with alarms, which can be set).

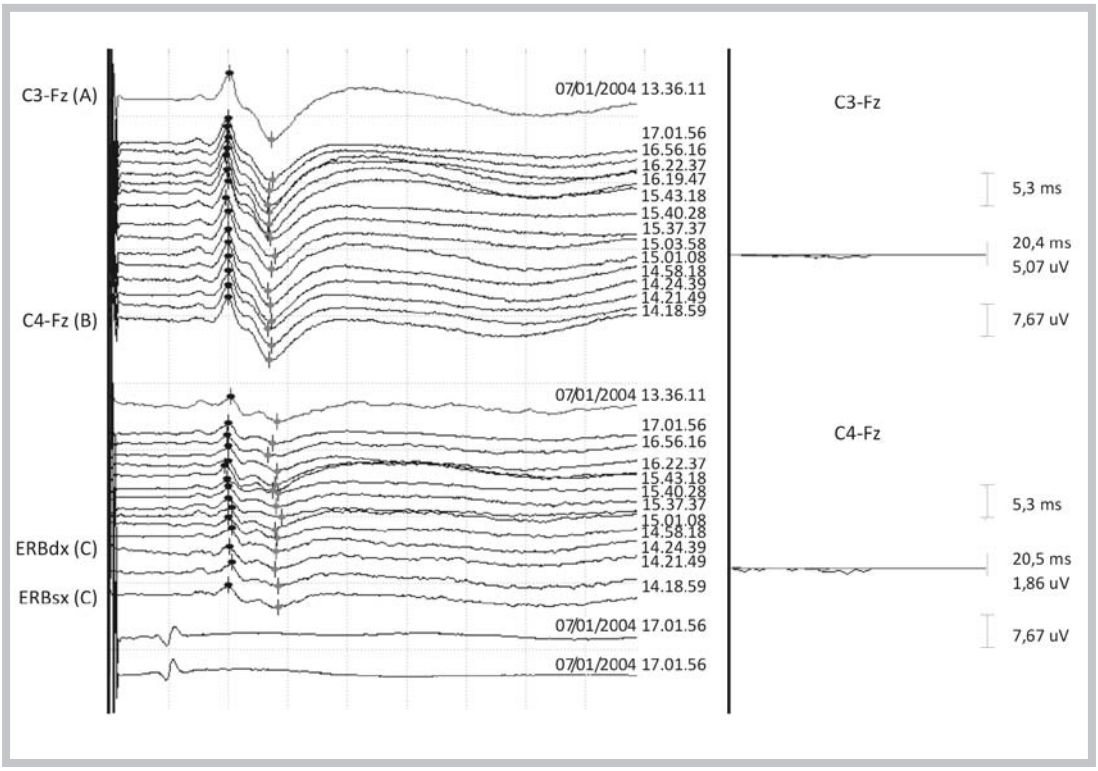

Figure 11.9. **Stable SEP monitoring on both hemispheres in a patient in coma after a SAH with favourable evolution (right side: quantitative trends of latency and amplitude of cortical response).**

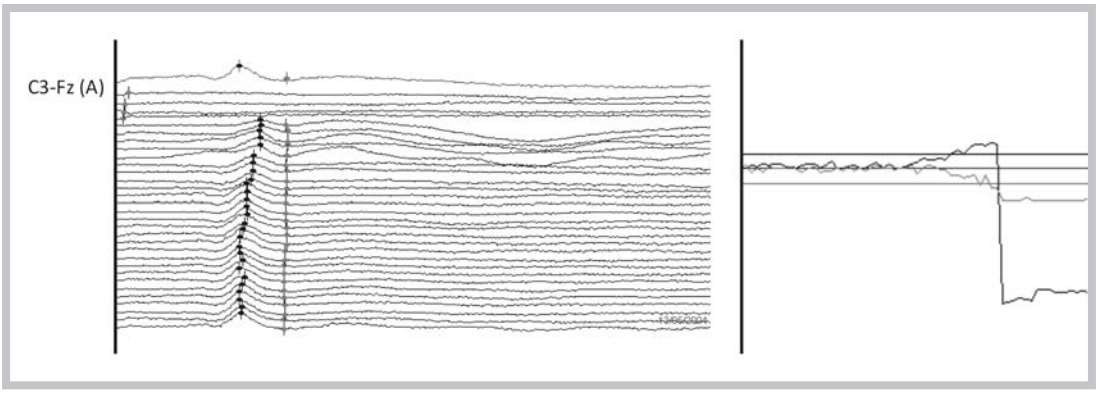

Figure 11.10. **SEP tracing of the left hemisphere in a patient in a coma due to head trauma. Note the progressive reduction in amplitude and increased latency until the disappearance of the cortical response due to the gradual onset of severe intracranial pressure due to increasing cerebral edema.**

In over continuously monitored 80 patients we observed that all patients resulted clinically stable (assessed by serial CT and GCS) and that the SEPs did showed no significant change in latency and amplitude except those induced by neurosedation (Figure 11.9). Conversely, whenever clinical deterioration occurred (18%), the SEPs showed significant changes in latency and amplitude (Figure 11.10), with different patterns such as sudden disappearance or progressive decrease in the amplitude of cortical SEPs.

When we evaluated the correlation between changes in SEPs and trend values of ICP, we found that the changes in SEP may precede or follow an increase in ICP, likely depending on the different pathogenic mechanism underlying the onset of neurological deterioration. In addition, confirming the ominous prognostic significance of an absent SEP pattern, 12 out of 13 patients who could not be monitored owing to the bilateral absence of SEPs in the basic recording died in the ICU and one remained in a vegetative state at 6 months after discharge.

We also observed that while the SEPs (stable or deteriorating) correlated with the outcomes of our patients in the acute phase (stability or progression of primary damage and/or onset of secondary complications), the trend of the ICP values, calculated as average values of maximum daily ICP, presented a lower correlation with the outcome.

This experience leads us to believe that neurophysiological monitoring is an ideal complement to other physiological parameters monitored in the ICU: while ICP is merely an index of blood pressure (from which a hemodynamic concept of cerebral perfusion is extrapolated), CEEG-SEP monitoring reflects, ultimately, the ability of neurons to extract oxygen and, therefore, the extent to which the brain parenchyma remains metabolically active during acute cerebral damage. The association of neurophysiological monitoring with ICP and TCD monitoring may help to optimize the choice and timing of treatment in individual patients.

11.5 EMG in the ICU

The causes of overall muscle weakness most commonly found in the ICU can be divided into pre-existing and arising during hospitalization itself. Many neuromuscular diseases can lead to ICU admission (Guillain-Barré syndrome, myasthenia gravis, amyotrophic lateral sclerosis, etc.). But in this chapter we will deal only with overall muscle weaknesses associated with respiratory muscle weakness which arise during the ICU stay. Some neuromuscular disorders may be revealed (myasthenia) or precipitated (rhabdomyolysis) by infections or drugs used in the ICU [40]. Other causes of weakness are post-surgical complications (e.g., spinal cord ischemia after aortic surgery). Critical illness polyneuromyopathy (CIPM) is still the most important cause of ICU-acquired weakness [41]. This condition was initially described as critical illness polyneuropathy (CIP), but a predominant muscle involvement was later reported (CIM, critical illness myopathy). Today, they are considered as a single nosological entity (CIPM). The onset of muscle weakness is often not detected because of the severity of critical illness (concurrent septic encephalopathy) and because of sedation. Often, overall hypotonia and poor or absent motor responses of the limbs are present but with conservation, in most cases, of facial expression and head movement. Moreover, central motor deficits can coexist in the same patient (e.g., brain damage with lesions of the pyramidal tract).

Neuromyopathy develops during sepsis or multiorgan failure (MOF) in up to 70% of critically ill patients. Pre-existing diseases (asthma, chronic obstructive pulmonary disease [COPD], diabetes, renal failure) may favour its onset. Laboratory tests are not very informative; CPK values are frequently normal. Invasive investigations such as muscle biop-

sy to look for peculiar histological alterations (selective loss of thick myosin filaments, selective atrophy of type II fibres, acute necrotizing myopathy) are rarely feasible in ICU patients.

CIM types in the initial phase with purely functional alterations in the absence of structural changes have also been described [42].

In this context, EMG is essential to confirm the presence of neuromuscular disease and differential diagnosis with other causes of neuromuscular weakness.

ENG/EMG extended to the upper and lower limbs for the exploration of motor, sensory and mixed nerves is necessary: external popliteal sciatic nerve (EPS nerve), internal popliteal sciatic nerve (IPS nerve), sural nerve at the lower limbs, ulnar nerve, median motor and sensory nerve. Repetitive stimulation may be useful in doubtful cases of the persistence of the effect of neuromuscular blocking agents. Moreover, direct muscle stimulation (DMS) can be used, easily executable only for the derivation of the tibialis anterior muscle to identify primary impairment of the muscle [43]. The needle EMG examination must include the exploration of at least one muscle distal and proximal to a lower and upper limb.

Key findings for the diagnosis of CIPM. Conduction velocities are normal or only slightly reduced. The distal latencies are usually normal. The characteristic finding is a reduction in the compound muscle action potential (CMAP) amplitude with increased duration (Figure 11.11).

In addition, the increased duration of CMAP without changes in distal and proximal stimulation, defined as "synchronous dispersion", is considered a typical neurophysiological finding and is attributed to the decrease in conduction velocity of muscle fibres [44]. Unlike CMAP, the action potentials of sensory nerves may be of normal size [45].

This figure is considered a useful criterion for distinguishing types with motor involvement only (CIM) from motor and sensory types (CIP). However, the sensory nerve action potential may be reduced owing to tissue edema generally higher in the lower limbs (sural nerve). A reduction in sensory action potential (SAP) in the upper limbs (ulnar and median nerves) is, instead, a sure sign of sensory involvement.

Thus, CMAP is the most reliable finding, but its reduction can be due to axonal injury and primary muscle involvement. In view of the limitations of traditional neuronographic findings, the direct muscle stimulation technique has been proposed in order to distinguish between CIP and CIM. It assesses the ratio between the amplitude of CMAP after stimulation of the nerve (neCMAP) and that of CMAP after direct stimulation of the muscle (dmCMAP). In primitive muscle involvement, CMAP will be reduced by both stimulation of the nerve and direct stimulation of the muscle, with a ratio of 0.5 to 1 (Figure 11.12).

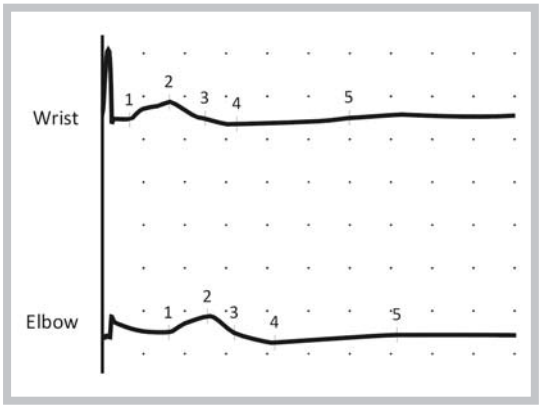

Figure 11.11. **CMAP derived from the abductor digiti minimi muscle (ADM muscle). Note the reduction in amplitude and the increase in duration. The increased duration of CMAP is of equal magnitude for distal and proximal stimulation.**

On EMG examination, spontaneous activity is a variable finding for magnitude and onset timing [46,47], so it isn't an essential criterion for diagnosis. In the CIPM individual, motor unit potential (MUP) can be short-lasting, with low amplitude and polyphasic morphology. But it is often impossible to obtain the patient's collaboration for the analysis of voluntary activity.

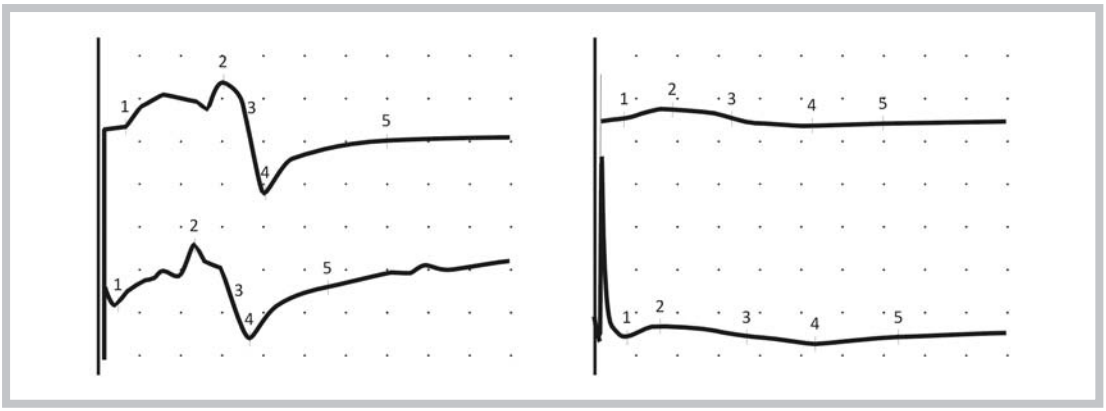

Figure 11.12. **Direct muscle stimulation in a normal subject (left panel) and in a patient with CIPM (right panel). Note the reduction in amplitude due to both nerve stimulation and stimulation of the muscle.**

Hence, the most reliable EMG parameters for diagnosis are essentially neuronographic, and in particular:

- Reduction in amplitude associated with increased duration of CMAP with synchronous dispersion pattern.
- Reduction in CMAP amplitude due to direct muscle stimulation with a neCMAP/dmCMAP ratio >0.5.

In our experience, "myopathic" involvement has been consistently detected, both with motor involvement only and with motor and sensory involvement. This myopathic component was confirmed by direct muscle stimulation.

In the alteration of muscle excitability, characteristic neuronographic findings of longer-lasting CMAPs are also present. This finding, typically impaired in patients with neuromyopathy, is also easier to obtain than DMS.

The above finding is attributed to hypoexcitability of the muscle responsible for weakness, and it is consistent with the inexcitability of the muscle membrane due to inactivation of Na^+ channels, according to data Rich and Pinter [48] obtained in an experimental animal model of acute myopathy.

The findings of reduced muscle excitability and increased duration of CMAP may have a common basis, supporting the pathogenic hypothesis that considers the neuromyopathy related to an alteration of transmembrane ion currents secondary to changes in the expression of isoforms of voltage-gated channels. These functional changes may also affect other tissues in septic patients (heart tissue, CNS), thus explaining the observed systemic abnormalities (ECG amplitude reduction, slowing down and reduction in the amplitude of EEG traces).

The neuromuscular impairment may be an additional "plug", being a part of a broader systemic framework of "multiple organ failure" secondary to the "syndrome of generalized loss of electrical excitability in septic patients" according to a term coined by Teener and Rich in 2006 [49], which would allow a common vision of changes detected in septic patients and would unify nerve, muscle, myocardium and cortical neuron involvement.

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12 Monitoring Brain Chemistry by Microdialysis During Neurointensive Care

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12.1 Introduction

This chapter focuses on the use of microdialysis during neurointensive care. The emphasis is on the use and interpretation of bedside microdialysis in clinical practice. We apologize for leaving out several excellent articles on clinical findings not yet applicable in routine intensive care.

We have attempted to highlight those areas where there is unanimous agreement on findings and their interpretation. We hope to present knowledge that may be useful for preventing and relieving secondary insults, predicting outcome and guiding therapy during neurointensive care.

12.2 The Microdialysis Technique

Microdialysis, a technique for sampling the chemistry of the interstitial fluid of tissues and organs, started as an animal research technique but has gradually been applied to humans and animals [1]. Minimally invasive and simple to perform in a clinical setting, it has become a standard technique in physiological and pharmacological investigations on animals, with thousands of papers published to date. During the last 10 years it has developed into a clinically useful technique, with about 1000 papers published on its use in brain and peripheral tissues.

The idea of inserting a dialysis catheter into the tissue where a continuous flow of physiological fluid inside the catheter equilibrates with the interstitial fluid outside was conceived of more than 30 years ago by Delgado et al. and Ungerstedt et al. [2,3] using slightly different technical approaches. Today, the Ungerstedt approach of using a “hollow fibre” has become the standard technique. In its simplicity it forms a “biosensor”, where samples of the tissue chemistry are transported out of the body for analysis, in contrast to the traditional biosensor, where the analysis takes place inside the body. The availability of modern analytical techniques has made microdialysis a “universal” biosensor capable of monitoring essentially every small and medium sized molecular compound in the interstitial fluid of endogenous and exogenous origin. Today, there are CE-labelled and FDA-approved microdialysis catheters (Figure 12.1) and bedside chemical analyzers available for human use on the world market (CMA Microdialysis, Stockholm).

The dialysis membrane at the distal end of a microdialysis catheter functions like a blood capillary. Chemical substances from the interstitial fluid diffuse across the membrane

into the perfusion fluid inside the catheter. The recovery of a particular substance is defined as the concentration in the dialysate expressed as a percent of the concentration in the interstitial fluid.

A low perfusion flow and a long dialysis membrane yield a high recovery. If the membrane is long enough and the flow slow enough, the concentration in the dialysate will approach the concentration in the interstitial fluid, i.e., recovery will be close to 100%. In the human brain the perfusion flow is ordinarily 0.3 µl/min and the length of the membrane is usually 10 mm (allowing exact positioning in relation to a lesion). Under these conditions, the recovery has been estimated to be approximately 70% [4]. By using a longer membrane, e.g., 30 mm, and the same perfusion flow, it is possible to reach 100% recovery in the human brain.

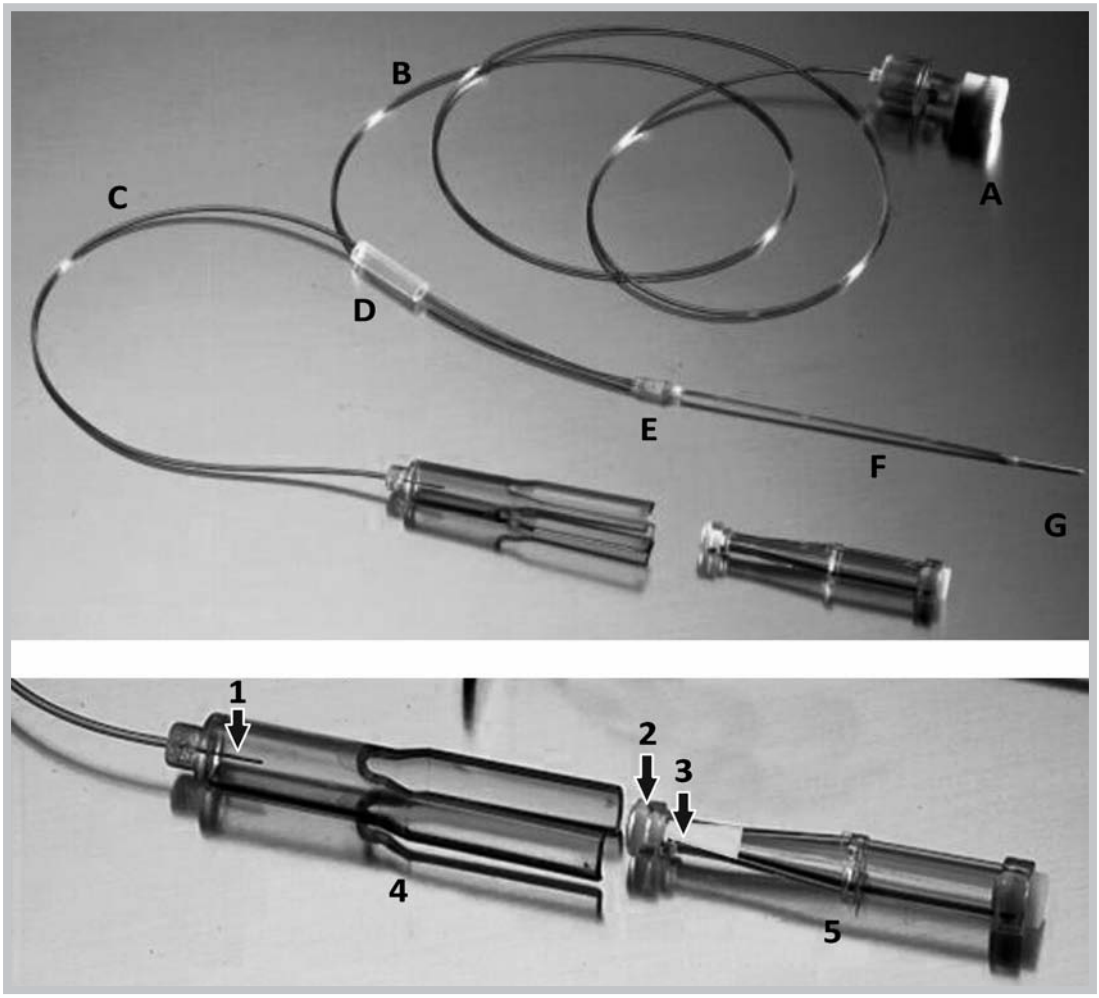

Figure 12.1. **The CMA70 brain catheter. The Luer (A) connects to the CMA106 syringe. The inflow (B) and outflow (C) tubes are surrounded by a sliding cuff (D) which is used to suture the catheter to the skin of the scalp. The two tubes join in the cylindrical "liquid cross" (E) which connects to the shaft (F) and the dialysis membrane (G) with a gold tip. The protective tube is not shown. The vial holder and the microvial are shown in the lower panel. The holder needle penetrates the membrane of the microvial when the vial is pushed into the holder. The sample is collected in the neck of the bottle just under the membrane.**

1 = Needle
2 = Membrane
3 = Sample
4 = Vial holder
5 = Microvial

It is important to realize that the concentration in the dialysate depends not only upon the flow and the length of the membrane but also upon the supply of substances from the blood capillaries, as well as from uptake and release from cells. For example, the supply of glucose to the microdialysis catheter may decrease due to a decrease in the capillary blood flow or due to an increase in the cellular uptake of glucose.

The high recovery of substances that can be achieved in the human brain makes it possible to analyze most neurotransmitters and energy metabolites but also cytokines [5] and small proteins by using catheters with a high cut off (100,000 Dalton). The priority of most investigators of the human brain has been to arrive at a clinically useful application of microdialysis. Therefore, the majority of studies have been done on patients with severe brain trauma or hemorrhage, where analysis of the brain energy state is of direct clinical importance and where such knowledge may improve patient outcome. In this chapter, we have concentrated on the use of microdialysis for the detection and monitoring of ischemia and energy breakdown.

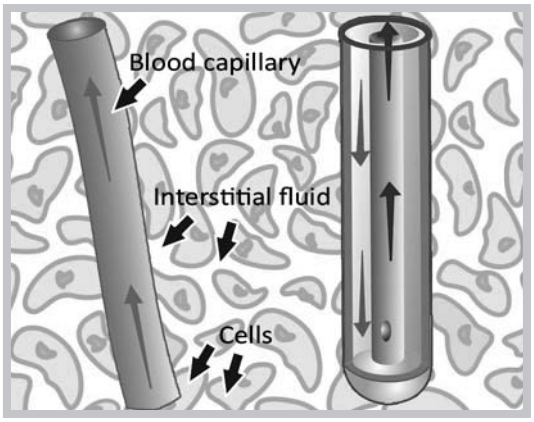

Figure 12.2. **The microdialysis catheter takes up substances delivered by the blood, e.g., glucose and drugs, but also substances released from the cells, e.g., cellular metabolism markers.**

12.3 Biochemical Markers of Ischemia and Cell Damage

The interstitial fluid is the "crossroads" of all substances passing between cells and blood capillaries. By monitoring this compartment in the brain, it is possible to obtain crucial information about the biochemistry of neurons and glia and how seriously the brain cells are affected by ischemia, hyperemia, trauma, hemorrhage, vasospasm, for example, as well as various physiological, pharmacological and surgical interventions during intensive care.

Although microdialysis samples essentially all small molecular substances present in the interstitial fluid, the use of microdialysis in neurointensive care has focused on markers of ischemia and cell damage. The reason is that they are of obvious importance for tissue survival, well understood from a biochemical point of view and easy to interpret in the clinical setting of intensive care.

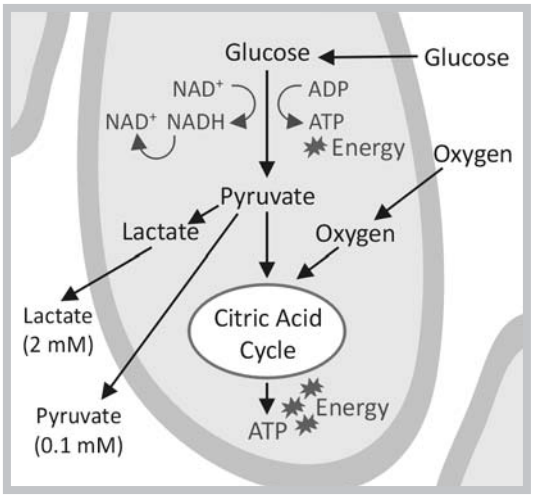

Figure 12.3. **A cell surrounded by interstitial fluid. Anaerobic glycolysis leads to the production of lactate and pyruvate that enter the surrounding fluid where they can be taken up by the microdialysis catheter. The aerobic part of glycolysis utilizes the citric acid cycle to produce the bulk of energy in the form of ATP.**

Microdialysis tells us how cells react to an increase or decrease in the supply of oxygen and glucose. However, while normal brain tissue may not suffer when exposed to a moderate decrease in oxygen and glucose, vulnerable cells in the pericontusional penumbra may simply not survive. Subsequently, severe secondary damage to brain tissue may pass unnoticed if microdialysis is not performed in the most vulnerable tissue of the brain (see below).

12.4 Lactate/Pyruvate Ratio

The lactate/pyruvate ratio is a well-known marker of changes in the redox state of cells caused by ischemia and mitochondrial dysfunction [6]. Pyruvate is formed from glucose in the anaerobic part of glycolysis to generate two molecules of ATP. It enters the citric acid cycle provided that oxygen is available. The citric acid cycle is the dominant producer of energy and yields 32 molecules of ATP. If the tissue is exposed to ischemia (a decrease in blood flow causing an inadequate supply of oxygen and glucose), the production of ATP from the citric acid cycle decreases.

The cells attempt to compensate for the decrease in ATP production by increasing the turnover of glucose in the anaerobic part of glycolysis. During this process it is necessary to regenerate NAD^+ from NADH by converting pyruvate to lactate, which causes an increase in lactate and the lactate/pyruvate ratio (Figure 12.3).

The decrease in glucose delivery from the blood capillaries causes a fall in glucose concentration in the interstitial fluid. This leads to a decreased production of pyruvate due to a lack of glucose. In the dialysate this is seen as a fall in pyruvate and a further increase in the lactate/pyruvate ratio, i.e., a worsening of the ischemia. In a recent study, Vespa et al. [7] compared the lactate/pyruvate ratio by means of positron emission tomography (PET) to investigate the metabolism of glucose and oxygen; they concluded that an increase in the lactate/pyruvate ratio is a sign of a metabolic crisis, which is not necessarily synonymous with ischemic cell damage. This emphasizes the importance of using glycerol as a marker of cell membrane decomposition and cell damage (see below) in addition to the lactate/pyruvate ratio.

The use of a ratio between the two analytes has the advantage of abolishing the influence of changes in catheter recovery, as such a change will similarly influence both lactate and pyruvate. Therefore, the lactate/pyruvate ratio may be used to compare the redox state of different tissues in one individual, as well as in different individuals. The ratio is essentially the same in all tissues, i.e., about 20. We consider a ratio >25 as a sign of beginning tissue ischemia.

Lactate alone is a less good marker of the redox state of cells, as an increase in lactate may be due to hypoxia, ischemia as well as hypermetabolism [8].

12.5 Glycerol

Glycerol is an integral component of the cell membrane. Loss of energy due to ischemia leads to an influx of calcium into the cells, activation of phospholipases, and eventually cell membrane decomposition which liberates glycerol into the interstitial fluid [9].

Considering the fast changes in glycerol concentration in vulnerable pericontusional brain tissue, which are often related to changes in the cerebral perfusion pressure (CPP),

it seems likely that the cells may react by "leaking" more or less glycerol according to the severity of the ischemia. The normal glycerol concentration in the dialysate from the brain when using a 10 mm dialysis membrane and a perfusion flow of 0.3 µl/min is approximately 50-100 µM [10].
In subcutaneous adipose tissue, on the other hand, glycerol originates from the splitting of fat (triglycerides) into free fatty acids and glycerol. This process is controlled mainly by the local sympathetic noradrenalin nerve terminals. Glycerol in the subcutaneous tissue is therefore an indirect marker of sympathetic tone in the dermatome where the catheter is inserted [11].
During intensive care a subcutaneous catheter may be inserted in the periumbilical region to monitor glycerol as an indicator of sympathetic "stress" and glucose as an indicator of systemic blood glucose levels [12]. The normal glycerol concentration in the dialysate from the subcutaneous tissue of a sedated patient when using a microdialysis catheter with a 30 mm dialysis membrane and a perfusion flow of 0.3 µl/min is approximately 200 µM.

12.6 Glutamate

During ischemia there is an increased release of glutamate, which may open neuronal calcium channels and initiate a pathological influx of calcium that causes cell damage. An increasing level of glutamate in the dialysate from the human brain is an indirect marker of cell damage. However, it is difficult to interpret changes in brain glutamate because glutamate release from neurons is mixed with a metabolic pool of glutamate.
The normal glutamate concentration in the dialysate from the brain of a sedated patient when using a 10 mm dialysis membrane and a perfusion flow of 0.3µl/min is approximately 10 µM and somewhat higher in a non-sedated patient [10].

12.7 Glucose

As the primary source of energy to the brain, glucose is an important marker of changes in brain metabolism. Glucose levels in the dialysate from the human brain may, however, change for several reasons:

- Ischemia – an insufficient capillary blood flow. Less glucose is delivered to the microdialysis catheter and the concentration in the dialysate **decreases**.
- Hyperemia – an increase in capillary blood flow. More glucose is delivered to the microdialysis catheter and the concentration in the dialysate **increases**.
- Hyperglycemia – increased blood glucose concentration due to metabolic stress, insulin resistance or intravenous infusion of glucose. More glucose is delivered to the microdialysis catheter and the concentration in the dialysate **increases**.
- Hypermetabolism or hypometabolism – increased or decreased uptake of glucose into the cells, e.g., a shift from aerobic to anaerobic metabolism. This will affect the amount of glucose in the tissue available to the microdialysis catheter, causing a **decreased** or **increased** concentration in the dialysate.

The fact that the glucose concentration in the dialysate may change for several reasons makes it difficult to interpret glucose levels unless glucose is compared to other markers. A subcutaneous microdialysis catheter implanted in the periumbilical region of the abdomen is of great value, as it will reveal changes in systemic blood glucose. If a change

in the brain is parallel to a change in subcutaneous glucose, the change is in all probability due to a variation in systemic blood glucose.
If the change in brain glucose is not parallel to a change in systemic blood glucose, it is probably due to altered brain capillary perfusion, e.g., hyperemia or hyper- or hypometabolism, which causes a simultaneous increase or decrease in both lactate and pyruvate.
On the other hand, if a decrease in brain dialysate glucose coincides with an increase in lactate and a decrease in pyruvate, it is in all probability due to ischemia. By observing the changes in lactate and pyruvate it is possible to interpret the changes in glucose.

12.8 Implanting and Positioning of Microdialysis Catheters

Microdialysis monitors the local chemistry of an area of the brain roughly corresponding to the length of the catheter membrane and a diameter of a few mm. The interpretation of microdialysis data will therefore depend upon the position of the catheter in relation to the existing pathology. The first clinical microdialysis catheters to appear on the market were not visible on computed tomography (CT) scans. Several clinical studies in the literature are difficult to interpret, as we do not know if the microdialysis catheters ended up in normal tissue or penumbra tissue surrounding a contusion or in damaged or dead tissue.
Today's catheters have a gold tip which renders them visible on CT scans. For the interpretation of bedside microdialysis data it is of great importance that the position of a catheter in the brain is can be visualized by CT [13]. Only then can microdialysis data be effectively used to provide an early warning of secondary insults and to evaluate the result of various clinical interventions aimed at improving the condition of brain tissue during neurointensive care.
It is important to adopt a consistent strategy of where to place catheters: in the penumbra surrounding a mass lesion; in the region most likely to be affected by vasospasm after subarachnoid hemorrhage; and/or in "normal" brain tissue. The general principles of where to place catheters in different categories of patients have been agreed upon

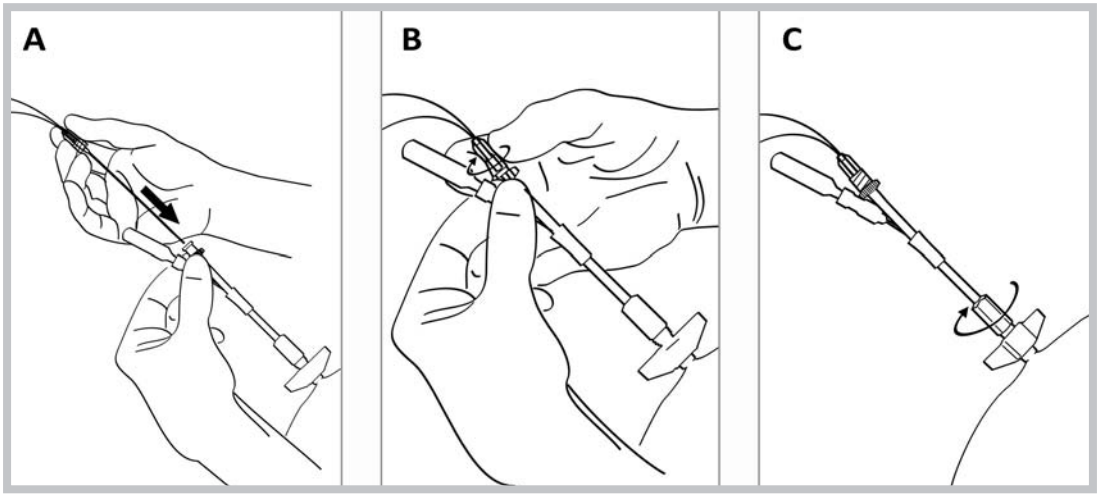

Figure 12.4. **(A). After fixing the bolt to the skull bone, the CMA 70 microdialysis bolt catheter is passed through the entrance tube. (B). The Luer lock connector of the catheter is fixed to the tube connector. (C). The tube channels are sealed by tightening the expansion nut.**

in a consensus paper authored by experienced users of microdialysis in neurointensive care [14].

In the intensive care unit (ICU) it is often convenient to place catheters through cranial bolts, thus obviating the need to bring the patient into the operating room. However, it is difficult to position the catheter in a selected region of the brain when using bolts, as there is no provision for changing catheter depth or angle. In the ICU, catheters are therefore often tunnellated and placed through burr holes to better aim for a predefined region of the brain [15].

In craniotomy, it is easy to place the catheter under visual inspection into the pericontusional penumbra of a lesion or in the territory of the parent vessel of an aneurysm. The catheter is tunnelated under the scalp and a small incision is made through the dura, subarachnoidea and pia. The dialysis membrane is positioned in the penumbra, usually 1 cm from the border of the lesion or in the region most likely to be affected by vasospasm after hemorrhage. In our experience, we have seen no consistent difference in the chemistry whether the catheter is placed in the white or the gray matter. However, it is to be expected that the levels of neurotransmitters may vary depending upon the

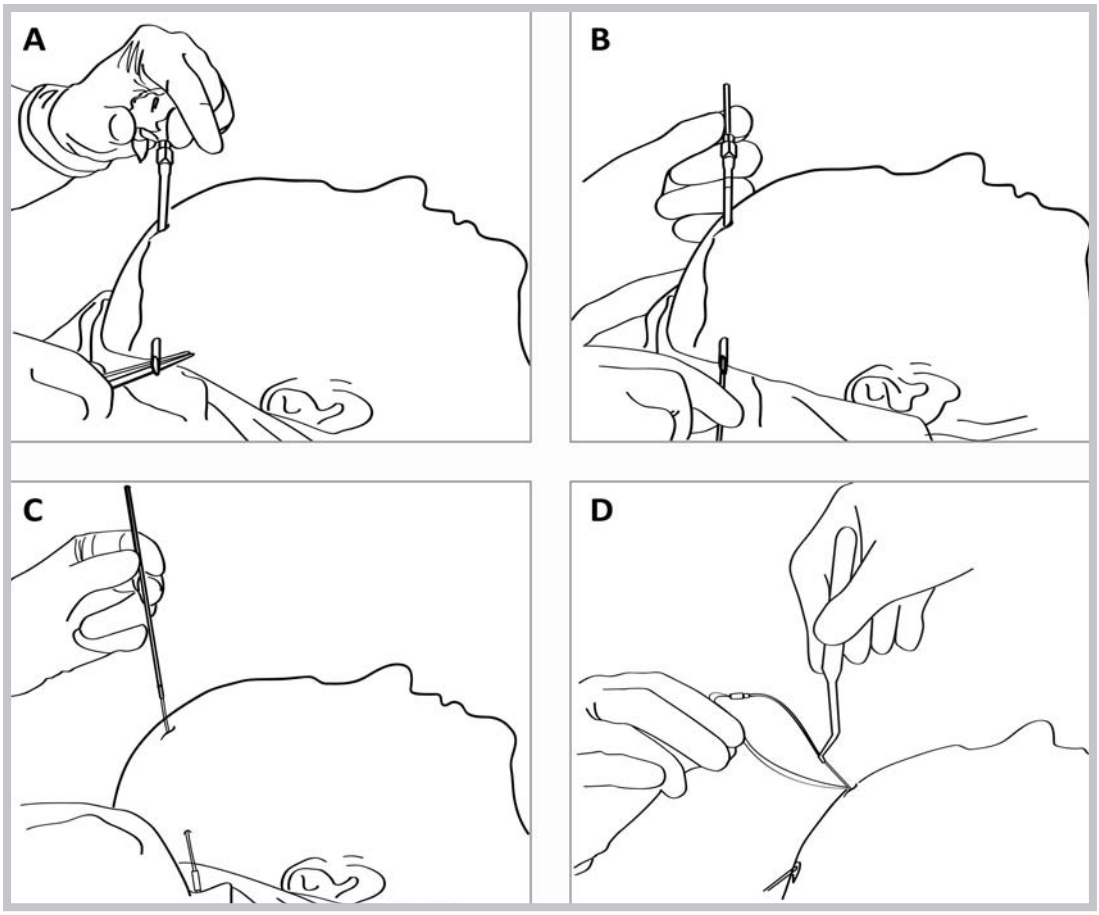

Figure 12.5. **(A). After drilling a hole in the skull bone and opening the dura, a tunnelator is passed under the scalp. (B). The CMA 70 microdialysis catheter is passed through the tunnelator and the tunnelator is then retracted. (C). The protection tube is removed from the catheter by turning it counter-clockwise. (D) The catheter is held firmly at the shaft (without touching the membrane) by a forceps or by hand and passed into the brain through the hole in the dura. The inlet and outlet tubings are stretched and the fixation cuff is sutured to the skin (see Figure 12.6).**

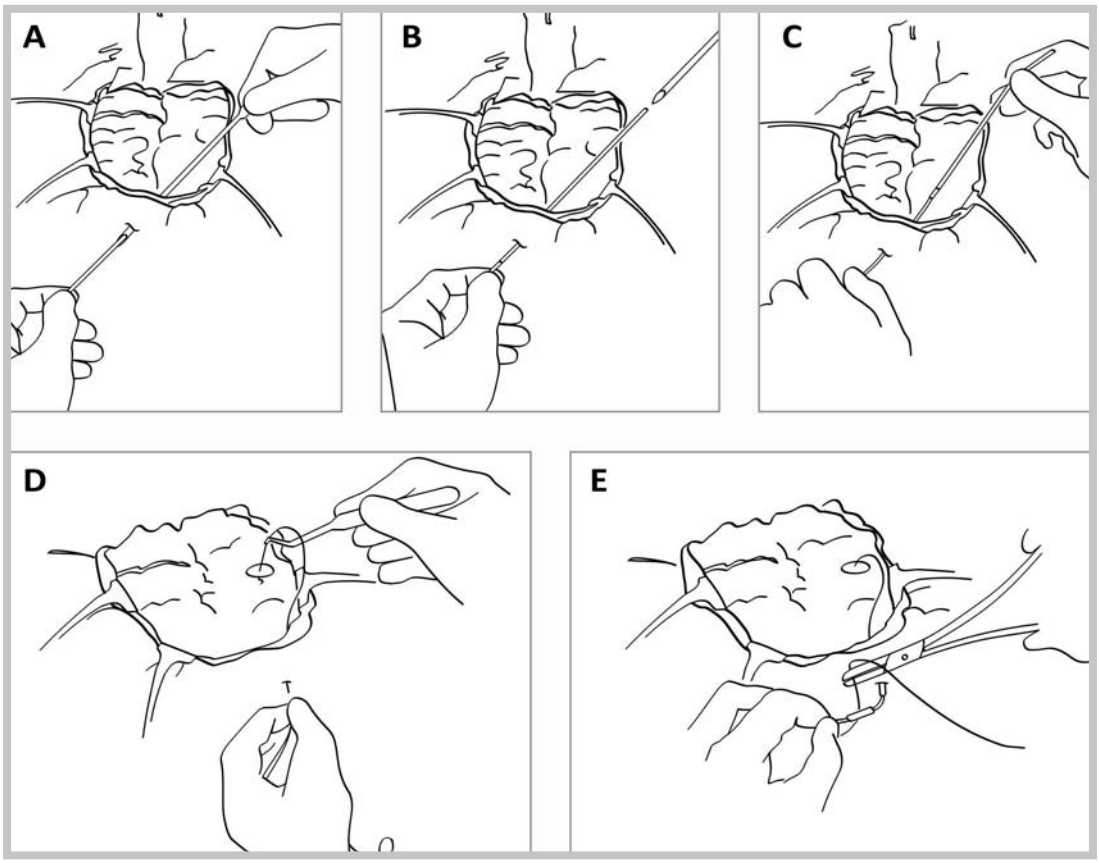

Figure 12.6. (A). During open surgery the dura is repositioned. A hole is cut in the dura where the catheter will be inserted. A tunnelator is passed under the scalp. The CMA 70 microdialysis catheter is passed through the tunnelator. (B). The tunnelator is retracted. (C). The protection tube is removed by turning it counter-clockwise. (D). The catheter is held firmly at the shaft (without touching the membrane) by a forceps or by hand and passed into the brain through the hole in the dura. (E). The inlet and outlet tubings are stretched and the fixation cuff is sutured to the skin.

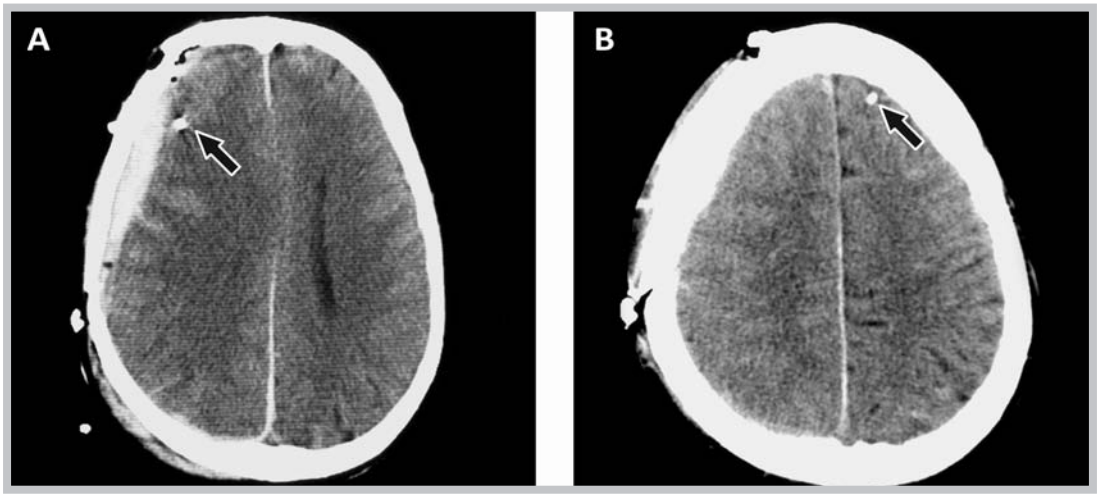

Figure 12.7. (A). Epidural hematoma. The arrow points to the gold tip which is easily seen on the CT scan. (B). Contralateral side showing the visible gold tip.

position. The cuff, which slides over the inflow and outflow tubing, is sutured tightly to the skin so that the catheter cannot be pulled out if, for example, the attached microdialysis pump drops out of the patient's bed.
Irrespective of how the catheter is introduced into the brain, it is important to locate the gold tip of the catheter on the first CT scan performed after implantation. The catheter location will determine how relevant the biochemical data are for the interpretation of brain pathology and the early warning of a secondary insult.

12.9 Selecting Perfusion Flow

The flow of a standard, commercially available microdialysis pump is 0.3 µl/min, which yields approximately 70% recovery when using a 10 mm dialysis membrane [16,17]. Catheters with a 20 or 30 mm membrane will give nearly 100% recovery in the brain. There may be situations where a higher perfusion flow is necessary, for example, when sampling is frequent and the 0.3 µl/min flow rate does not provide enough sample volume to permit analysis. Such may be the case during intraoperative microdialysis when samples are changed every minute in order to monitor ischemia during temporary clipping, for example. A flow rate of 1 µl/min will yield a recovery of approximately 30% using a 10 mm membrane [17].
Another reason to use a high perfusion flow is to reduce the time delay that occurs when the dialysate flows from the brain to the microvial. The delay is in the range of 20 min when the perfusion flow rate is 0.3 µl/min, but it can be reduced to close to 1 min if the flow is increased to 5 µl/min. In this way, it is possible to react to changes in brain chemistry during surgical procedures, for example, ischemia resulting from brain retraction [18]. During neurointensive care, however, because chemical changes usually take place over several hours, a 20-min delay is of minimal consequence.
During normal intensive care it is highly advisable to use the standard flow and standard catheter so that the data between patients in the same or different clinical departments can be compared over time.

12.10 Multimodal Monitoring

In order to make effective use of microdialysis data it is essential to relate them to other data collected at the bedside. This may be done using software which allows for integrating data from the microdialysis analyzer, the ICU monitor displaying intracranial pressure (ICP) and cerebral perfusion pressure (CPP), a tissue oxygen analyzer, the ventilator, the infusion pumps, or other machines.
This "multimodal monitoring" allows for the display of all data as trend curves on one computer screen. It creates the framework for individualizing therapy on the basis of clinical status, brain tissue chemistry and the effect of therapeutical interventions.

12.11 Interpreting Microdialysis Data

During intensive care, brain chemistry often changes profoundly in the patient. At our present state of knowledge, it is impossible to interpret every change; however, major

pathological states manifest themselves as dramatic increases or decreases in biochemical markers.
The first hours of microdialysis data give an indication of how severely the brain tissue is affected in the pericontusional penumbra. This information gives a reference value for determining whether tissue physiology is improving or deteriorating.
The implantation of a microdialysis catheter inflicts a certain amount of trauma to the brain tissue. This is well known from animal studies and it usually takes an hour or more before baseline values are reached after an implantation. In the human brain this is particularly evident for glutamate and sometimes for glycerol. In a clinical setting, however, the time between catheter implantation and the actual use of microdialysis data is often longer than 1 hour due to the various different procedures taking place around the patient.
The range from normal to pathological levels of different analytes are well known from normal brain tissue in patients with posterior fossa tumours [10] and from damaged as well as "normal" brain tissue in patients with traumatic brain injury (TBI) or subarachnoid hemorrhage (SAH). Normal levels differ strongly from pathological levels in severe brain trauma (see below).

12.12 Clinical Studies

The following is a brief account of studies where microdialysis was applied to neurosurgery and neurointensive care. The purpose is to present a selection of papers that describe biochemical findings of particular relevance for the early detection of secondary damage and the evaluation of therapeutic interventions during surgery and neurointensive care.
Microdialysis of the human brain was first performed in 1987 at the Karolinska Institute to alleviate tremor in a Parkinson patient with a thalamic lesion [19]. The catheter was introduced stereotaxically and samples were collected every 10 min and analyzed for a vast array of neurotransmitters and metabolites. We found that baseline levels of the various analytes in the dialysate were much higher than in animals due to the possibility of using a much larger dialysis membrane. Even more importantly, baseline levels were reached much faster probably due to the small implantation trauma in relation to the size of the human brain.
We performed the first study on brain ischemia in Uppsala by monitoring the brain chemistry in tissue which was resected during tumour surgery [20]. This led to a study of microdialysis during neurointensive care of TBI and SAH, in which changes especially in lactate, pyruvate and glutamate were described [21].
The experience from Karolinska and Uppsala prompted us, in cooperation with neurosurgery in Lund, to develop flexible catheters more suitable for implantation in the human brain and a microdialysis analyzer (CMA Microdialysis, Stockholm) designed for bedside use.

12.12.1 Subarachnoid Hemorrhage

Microdialysis has been used extensively for monitoring ischemia in SAH patients. Hamberger et al. and Runnerstam et al. found that the level of consciousness in the postoperative phase was inversely related to the total amino acid concentration in the neuronal environment adjacent to a SAH [22,23].

Persson et al. found that severe ischemia, e.g., temporary clipping, severe hypoxemia or infarct development within or close to the probe area resulted in a clearly detectable increase in the lactate/pyruvate ratio [8]. In many instances this was followed by an increase in glutamate when the lactate/pyruvate ratio reached values of approximately 25 or above. The lactate/pyruvate ratio appeared to be a more reliable marker compared to lactate alone. As opposed to lactate T, there was a statistically significant correlation between the lactate/pyruvate ratio and clinical outcome during days 0-4.

In a study combining microdialysis and PET, Enblad et al. concluded that the energy-related metabolites (lactate, lactate/pyruvate ratio and hypoxanthine) may be used as extracellular markers of ischemia [24].

Säveland et al. found that increased levels of glutamate correlate well with clinical course and neurological symptoms [25]. However, a rise of glutamate in one region did not necessarily parallel to the rise in the other regions. Nilsson et al. described the detailed biochemistry of vasospasm and concluded that lactate and glutamate may be the most sensitive and early markers for incipient ischemia, followed by the lactate/pyruvate ratio and glycerol, during manifest ischemia and cell degeneration [26]. They found that metabolic changes preceded the increase in blood flow velocity as recorded by transcranial Doppler (TCD).

In a series of studies, Unterberg and co-workers placed microdialysis catheters 25 to 35 mm into the parenchyma of the vascular territory most likely to be affected by vasospasm [27,28] concluded that microdialysis "can be carried out routinely in the ICU setting to detect and monitor patterns of metabolic impairment. Compared to TCD, it has a remarkable specificity, making it a well-suited method to monitor delayed ischemic neurological deficits following aneurysmal hemorrhage".

Sarrafzadeh et al. found that lactate and glutamate are early markers of clinical vasospasm, followed by lactate/pyruvate ratio and glycerol, during manifest vasospasm in patients with SAH [29] They stated that bedside cerebral microdialysis is a safe technique for the indication of acute and delayed ischemic neurological deficits in SAH patients when the catheter is inserted into the region of interest. They went on to suggest that "early detection of metabolic changes might also allow optimization of standard intensive care treatments, such as triple-H therapy". Skjøth-Rasmussen et al. found that the ischemic pattern after SAH preceded the occurrence of delayed ischemic neurological deficits by a mean interval of 11 hours [30].

12.12.2 Traumatic Brain Injury

Persson and Hillered (1992) conducted the first microdialysis studies of the human brain after traumatic brain injury (TBI). They found that microdialysis can be used for long-term studies of energy-related metabolites and amino acids, e.g., glutamate, and that the fluctuation of these substances corresponded to various clinical events "presumably involving hypoxia/ischemia". They used the lactate/pyruvate ratio as a marker for energy disturbance in the brain. This ratio is known to reflect the redox potential of the tissue and thereby the severity of ischemia.

They presented several arguments for the reliability of the lactate/pyruvate ratio in comparison to the use of the absolute concentration of other substances in the dialysate:

- Due to the structural similarity of lactate and pyruvate, any change in *in vivo* diffusion conditions during a pathological state could be expected to affect both metabolites similarly
- Being a ratio, it is independent of probe characteristics

- On the basis of a review of 13 papers in the literature describing the normal brain lactate/pyruvate ratio in different species, they concluded that the basal level of the lactate/pyruvate ratio is <20.

This fits with the basal lactate/pyruvate ratio of 23 that we found in the normal brains of patients operated for posterior fossa tumours [10].

Bullock, Zauner and co-workers made the important observation that when placing the microdialysis catheter next to a cerebral contusion, sustained cerebral blood flow reductions caused a massive release of excitatory amino acids, whereas in patients without secondary ischemic, complications or focal contusions, posttraumatic glutamate release appears to be only transient [31]. They conclude that sustained high ICP and poor outcome were significantly correlated with high levels of glutamate (>20 μM) [32].

In 1995 CE-labelled microdialysis catheters intended for human use and an instrument for bedside analysis of glucose, lactate, pyruvate, glycerol and glutamate came onto the market (CMA Microdialysis, Stockholm). This enabled us to start routine monitoring of all patients with severe head injuries in Lund and a few years later in Stockholm. In our first report on normal brain, we established baseline values for energy-related metabolites (see below) [10].

In view of previous findings, we routinely placed one catheter in the pericontusional, penumbra tissue and a second catheter in normal tissue, usually through a second burr hole in front of the intraventricular ICP catheter. We found that microdialysis could be performed on a routine basis by the regular staff in an ICU and that the data could be used for detecting global and local complications [33].

Our most important observations were:

- The metabolites measured give information that is of direct clinical importance regarding substrate availability (glucose), redox state of the tissue (lactate/pyruvate ratio), degradation of glycerophospholipids in cell membranes (glycerol), and extracellular concentration of excitatory amino acids (glutamate).
- There was a marked difference in the energy metabolism of the pericontusional tissue as compared to normal tissue in the same patients.
- The biochemical consequences of severe anaemic hypoxia were observed several hours before the deterioration was detected by conventional methods (ICP-CPP).

We were able to compare the mean levels of the various markers in the pericontusional area of a patient with a fatal traumatic lesion [33] versus the values obtained during wakefulness in the normal human brain [10]:

- Glucose: 0.1 (fatal); 1.7 (normal).
- Lactate: 8.9 (fatal); 2.9 (normal).
- Pyruvate: 31 (fatal); 166 (normal).
- Lactate/pyruvate ratio: 458 (fatal); 23 (normal).
- Glycerol: 573 (fatal); 82 (normal).
- Glutamate: 381 (fatal); 16 (normal).

In a study of 27 patients treated according to the Lund concept, we documented the brain chemistry in patients with favourable outcome [33] in contrast to the previous study of fatal outcome. Our intention was that such data may serve as reference data for bedside prediction of outcome in the individual patient.

The introduction of microdialysis catheters with a gold tip visible on CT marked a quantum leap in the use of microdialysis in routine monitoring during neurointensive care. It became possible to visualize the catheter position in relation to the contusion or hemorrhage and thereby determine the relevance of the microdialysis data. In our first study where the catheter position was verified, we received further proof of the pronounced difference in sensitivity to secondary insults between normal brain and the tissue of the pericontusional penumbra [13].

Several papers have substantiated the ability of intracerebral microdialysis to predict outcome after ischemia and metabolic crisis [34] and its usefulness in managing neurointensive care patients, e.g., the management of systemic glucose in relation to intracerebral glucose levels [35].

12.12.3 Intraoperative Microdialysis

Mendelowitsch, Landholt and co-workers introduced microdialysis as a technique of perioperative monitoring during neurosurgery [36]. In patients undergoing extra-intracranial bypass operations, they placed a catheter 1-1.5 cm from the bypass site immediately after craniotomy. pH was measured online by a flow-through sensor, while glucose and lactate were determined colourimetrically and fluorometrically, respectively. During the first four bypass operations there were no marked changes in any of the measured parameters, while in the fifth patient the last temporary clipping caused glucose to fall to unmeasurable values, with an increase in lactate and a slight reduction in pH over 20 min. In a subsequent study of 10 patients, they added the analysis of glutamate and found three patients with a significant increase in intraoperative glutamate, two of which awoke with hemiparesis [37].

They also monitored the brain during aneurysm surgery by means of a catheter inserted into the cortex frontally in the region where retractor compression was expected. Online pH was reduced and lactate increased during retraction and glucose was decreased in most but not all patients [36]. They concluded that microdialysis is a sensitive method for detecting intraoperative changes in cerebral metabolism and they emphasized that glutamate is an excellent marker of neuronal damage.

The tissue damage caused by brain retraction was also evaluated by Xu et al. in a study of patients operated on subfrontally for pituitary adenoma [18]. The catheters were placed in the cerebral cortex beneath the brain retractor. Glucose remained within the normal range, whereas the lactate/pyruvate ratio, glutamate and glycerol were all considerably above the normal range. This was interpreted as an incomplete ischemia which, however, seemed to cause tissue damage as indicated by the high glutamate and glycerol levels.

Hutchinson et al. demonstrated how combined microdialysis and tissue oxygen monitoring was able to assist in decision making in a patient undergoing aneurysm surgery where the level of oxygen, glucose and pyruvate decreased while lactate and glutamate increased during intraoperative ischemia, as well as postoperative hydrocephalus [16].

12.12.4 Middle Cerebral Artery Infarction

Severe hemispheric stroke carries a high mortality because of the formation of fatal brain edema. Berger et al. reported a case of fatal middle cerebral artery (MCA) infarction where the neurochemical alterations contralateral to the infarction preceded the clinical signs of herniation for several hours [38].

Schneweis et al. used ICP and microdialysis in the ipsilateral frontal lobe in an attempt to identify at-risk MCA patients and to aid in selecting invasive therapy, e.g., decompressive hemicraniectomy or hypothermia [39]. They found that chemical changes varied in accordance with clinical course, size of infarction and brain edema. Stable ICP and chemistry was found in patients without progressive space-occupying infarcts, whereas an increase in ICP, glutamate and the lactate/pyruvate ratio was followed by massive edema and large infarcts.

Berger et al. assessed the effect of therapeutic moderate hypothermia with microdialysis and were able to characterize three different brain regions with different reactions to hypothermia [40]:

- Noninfarcted tissue with stable chemistry and a moderate lowering of glutamate, lactate and pyruvate during hypothermia.
- Peri-infarct tissue where hypothermia caused a pronounced lowering of glutamate, glycerol, lactate and pyruvate.
- Irreversibly damaged tissue, with excessive increases of glutamate, glycerol and lactate and lowering of pyruvate.

They concluded that microdialysis is a safe and feasible neurochemical monitoring method to differentiate normal brain tissue, salvageable tissue and irreversibly damaged tissue and to estimate the effect of hypothermia on these different compartments. Therefore, future treatment strategies for life-threatening stroke should be guided by close neurochemical monitoring.

12.12.5 Drug Distribution

Microdialysis monitors the concentration of endogenous and exogenous substances in the interstitial fluid of the brain. This offers a unique window on the distribution and the free fraction of drugs in the brain and on the changes in endogenous substances that reflect a drug's effect on brain neurotransmission and metabolism.

In a neurointensive care setting it is clearly of interest to determine the penetration of anti-infective agents across the blood-brain barrier into the interstitial fluid where the drug becomes available to brain cells. Mindermann et al. published the first study on the penetration of antibiotics into the human brain [41]. They determined the absolute concentration of free rifampin in the interstitial fluid by equilibrium dialysis (no-net-flux method) in patients receiving a standard dose of rifampin before resection of primary brain tumours. Rifampin concentration was highest within tumours, followed by perifocal regions and normal brain tissue.

Another important aspect of drug penetration into the brain during neurointensive care is the possibility that drugs may penetrate more effectively into areas where the blood-brain barrier function is disrupted due trauma or stroke. Bouw et al. found that there was an increase in morphine levels near a trauma site, i.e., the pericontusional penumbra, when compared to uninjured brain tissue [42]. This is very likely because damage to the barrier in the penumbra region allows drugs to penetrate more freely. This also means that the vulnerable penumbra cells, which are most prone to suffer secondary damage, are exposed to unknown doses of drugs. While this may offer an opportunity to target drug treatment to the vulnerable cells, it carries the risk of unknowingly impairing their function, making them more susceptible to secondary damage.

12.13 Conclusions

Today, microdialysis is a well-established technique for monitoring brain tissue during neurointensive care. Numerous studies have described the chemistry of ischemia during SAH, TBI and stroke. These studies have identified markers to assess the extent of tissue pathology, its change over time. and its relationship with variables such as ICP and CPP monitored at the bedside.

The discovery that the pericontusional penumbra tissue has an increased sensitivity to secondary insults is well documented [12,43,44], providing the clinician with a unique opportunity to identify changes in chemistry which may develop into secondary damage before it has manifested itself in clinical signs. Most important, it gives the clinician the possibility to determine the effect of a therapeutic intervention aimed at correcting brain chemistry and avoiding secondary damage, e.g., by individualizing the CPP, provided that the catheters are located in the vulnerable pericontusional tissue [45]. The implications of microdialysis data obtained in clinical studies have been discussed in a recent consensus paper on microdialysis procedures in patients with SAH and TBI [14].

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Section 3.
General Support

13 Fluid Therapy in Acute Brain Injury

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13.1 Introduction

The management of intravenous fluids in neurocritical patients plays an important role in the evolution and prognosis of acute brain injury. There is no clear consensus on what type of solution or at what stage of neurological disease fluid therapy should be initiated. Parameters extrapolated from studies on less neurocritical conditions provide only an approximation to the pathophysiology of acute brain injury.

This chapter develops general concepts in the management of water and electrolyte metabolism in the central nervous system, describes parenteral solutions commonly used in neurocritical care, and assesses their respective strengths and weaknesses.

The infusion of parenteral solutions may influence the development of cerebral edema [1], and the infusion of hypotonic fluids is reported to decrease plasma osmolarity, with the subsequent development of cerebral edema. Insofar as these observations may have been accurate, there was the widely held misconception that we should "restrict fluid intake" in the acute neurological patient to prevent intracranial hypertension [2]; however, fluid restriction also carries the risk of hypovolemia, hypotension and decreased cerebral perfusion pressure, a triad which favours the development of cerebral ischemia [3-6].

Water is the most abundant component of the body and accounts for 60-80% of body weight depending on age, sex, and body fat content. About half (50-60%) is distributed as intracellular water, the rest as extracellular water (38-45%), with the remaining small fraction as transcellular water.

With few exceptions, the cell membrane is permeable to the passage of water through an osmotic gradient. Osmolarity refers to the concentration of solutes in a solution; the osmotic gradient is the pressure difference between two solutions, wherein a solvent will move from a solution of lower to a solution of higher osmolar concentration, bringing it, the water in this example, to a higher osmolarity equal on both sides of the gradient.

Intracellular anions are macromolecules which do not diffuse across membranes; they attract large numbers of cations, the main one being potassium (K^+). Conversely, extracellular anions are small, and the major cation is sodium (Na^+). Cellular homeostasis is maintained by Na/K AT pumps that prevent cells from bursting. The other factor regulating cell volume is the osmolarity of the extracellular space [7].

The brain is highly sensitive to changes in homeostasis. A state of hyponatremia leads to an increase in cell volume, resulting in cerebral edema, whereas hypernatremia leads to cellular dehydration, with shrinkage of the brain parenchyma [8].

Importantly, some molecules are ineffective osmoles (ethanol, urea): they can increase the concentration of solutes in the extracellular space but do not cause water movement across a membrane. In contrast, effective osmoles such as hypertonic saline solutions attract water from the intracellular to the extracellular space by increasing the osmolarity [9]. For this reason, we use the term "tone" when referring to the effective osmolarity of a solution.

Tone is important in evaluating hyponatremic states which can be classified as: isotonic when the loss of Na^+ equals that of water; hypotonic when the loss of Na^+ is greater than that of water; and hypertonic when the loss of water is greater.
Control of osmoregulation is important because it involves the interaction between the kidney and the thirst mechanism through the antidiuretic hormone (ADH). This system is so sensitive that changes in serum osmolality of 1-2% can activate or inhibit it, while larger volume changes (8-10%) are required to activate the thirst mechanism and the release of ADH [10,11].
Fluid administration in neurocritical patients presents major challenges, including maintaining adequate cerebral perfusion pressure (CPP), while avoid hyperglycemia and controlling body temperature.
Preservation of CPP requires the maintenance of normovolemia without adversely affecting intracranial pressure [12]. Several physiological principles must be considered: in the peripheral tissues the capillaries of the membranes are highly permeable to water, ions and other low-molecular-weight molecules, but limit the movement of high-molecular-weight substances such as albumin. In these tissues, the distribution of fluid between plasma and interstitial fluid volume is regulated by oncotic pressure gradients. In contrast to the systemic capillary membranes, the brain capillary membranes constituting the brain blood-barrier (BBB) are impervious to most hydrophobic solutes, including sodium [13]. Acute changes in plasma sodium, however small, generate a significant osmotic pressure gradient of water movement that can bring about changes in the brain, with important clinical manifestations [14].

13.2 Fluids Commonly Used in Neurocritical Care

Fluids commonly used in neurocritical care can be grouped into crystalloids (isotonic crystalloids, and hypertonic crystalloids) and colloids (natural colloids (albumin), and artificial colloids (gelatins, dextrans and starches).

13.2.1 Crystalloids

Isotonic crystalloid solutions (0.9% saline solution, Lactated Ringer) are inexpensive, nontoxic, safe and non-reactive (Table 13.1). Usually, in conditions where vascular permeability is involved, only one third of the administered volume remains in the intravascular space, significantly increasing the interstitial fluid; therefore, large volumes are required to overcome a particular hemodynamic situation, which can lead to a state of shock or poor progression of resuscitation [15,16]. In patients with impaired capillary permeability, a volume ratio from 1/7 to 1/10 per liter can be administered (of which only 100 ml remain in the intravascular space). Other negative effects associated with isotonic crystalloids are the development of tissue edema, acute renal failure and abdominal compartment syndrome (ACS), as may occur with aggressive resuscitation with large volumes [17-19].
Large volumes of saline (0.9% saline) may cause hyperchloremic acidosis; large volumes of Lactated Ringer's solution can cause plasma hypotonicity, leading to hyperlactatemia without acidosis. Several studies have reported a pro-inflammatory effect of Lactated Ringer's solution (caused by the structure of the D-isomer) [20,21].
Hypertonic crystalloid solutions (3%, 7.5%, 23%) have a high sodium concentration and exert a great effect as volume expanders. They expand the extracellular space very effectively, reducing the tissue water; they also have a slightly positive inotropic effect and

Composition per liter	Plasma	Saline solution 0.9%	Lactated ringer	Observation
Osmolarity	290	308	273	Isotonic?
Sodium (mEq)	140	150	132	Physiological?
Chlorine (mEq)	100	150	109	
Potassium (mEq)	4	0	4	
Calcium (mEq)	4.6	0	3	
Lactate (mMol)	1	0	28	

Table 13.1. **Isotonic crystalloid solutions.**

decrease peripheral resistance [3,20,22,23]. The interest of these solutions in neurocritical care lies in their effects on cerebral hemodynamics by improving cerebral blood flow (CBF) and decreasing intracranial pressure (ICP). The mechanisms of action for these solutions are described in Table 13.2.

Their importance resides in their ability to expand with a small volume, but their effects are transient: increased diuresis and natriuresis, reduced cell swelling, including endothelial, and improved microcirculation [24].

However, their use can lead to hyperosmolarity, hyperchloremic acidosis, volume overload, renal failure, cerebral hemorrhage, pontine myelinolysis, hypernatremia and hypokalemia [25].

They can be given as a continuous infusion or bolus. A concentration of 2% can be given by the peripheral route; however, solutions with a concentration ≥3% may cause local irritation and local tissue damage.

Practical aspects in the administration of hypertonic crystalloids are the following:

- The rate of complications is low with close monitoring of serum sodium. (Keep Na^+ 145-155 mEq/l, serum osmolarity <320 mOsm/l).
- They are given with an infusion pump. Caution is warranted since they are not compatible with all medications, including some that are compatible with 0.9% saline. Avoid administering medications and transfusions with hypertonic saline (SSH).
- General care: control the hydration status and assess the infusion according to age (greater risk of complications in the elderly).
- Laboratory monitoring: Check serum sodium every 6 h. In patients with Na^+ levels <160 mmol/l there is a higher risk of renal failure, pulmonary edema and heart failure. The problem is greater if the levels remain elevated for

Mechanism of action	Effect
Osmotic	• Reduces brain water content • Reduces the mass effect • Prevents or treats elevated ICP
Hemodynamic	• Increases TAM and CPP • Improves organ perfusion
Vasoregulation	• Optimizes cerebral perfusion • Prevents or treats elevated ICP
Immunomodulation	• Modulates inflammatory response • Reduces secondary injury
Neurochemical	• Normalizes neuronal membrane potentials • Limits neurochemical changes secondary to injury
Hypernatremic	• Prevents and treats hyponatremia

Table 13.2. **Mechanisms of action of hypertonic crystalloid solutions.**

CPP = Cerebral perfusion pressure
ICP = Intracranial pressure

Composition per liter	Plasma	SSH 3%	SSH 7.5%	23%
Osmolarity	290	1016	**2586**	7790
Sodium (mEq)	140	513	1293	3933

Table 13.3. **Mechanisms of action of hypertonic crystalloid solutions.**

more than 48 h. Levels >160 mmol/l increase the risk of seizures. Monitor plasma osmolarity.

Discontinuation of therapy with SSH:

- It is difficult to establish the time when therapy should be discontinued. In general one must take into account the presence of intracranial hypertension and the risk of hyponatremia.
- When considering completion of SSH therapy, leakage can be reduced by half every 6 h as it takes <20 ml/h to complete. During discontinuation of SSH therapy, serum sodium should be monitored every 12 h. If levels increase or decrease more than expected, they should be checked more frequently.
- General management depends on the state of hydration, electrolyte levels and the patient's clinical condition. After completing SSH therapy, serum sodium monitoring should not be different than in other critically ill patients [26,27].

13.2.2 Colloids

Colloid solutions produce higher plasma expansion and remain in the intravascular space longer than crystalloids, with increased oncotic pressure and availability of oxygen to the tissues. Animal studies have shown that some of these solutions improve microcirculation rheology. The goals of resuscitation are achieved in less time and with less volume [28-30].

Albumin (natural colloid) is produced by the liver and is responsible for 80% of plasma oncotic pressure, but remains intravascular for 24 hours; the volemic effect should not last more than 4 hours. Albumin's ability to hold water is determined by both its quantity and the plasma volume loss that has occurred. One gram of albumin increases plasma volume approximately 18 ml, and 100 ml of 25% albumin increases plasma volume about 47 ml on average.

Undesirable effects have been described:

- Occurrence of hypocalcemia.
- Altered coagulation and inhibited platelet function.
- Presents pro-inflammatory properties.
- Facilitates the formation of edema if capillary leakage is present.
- Possibility of anaphylactic reactions (0.01%).

Its use in resuscitation is controversial and a large (SAFE) trial showed no differences with crystalloids in the resuscitation of critically ill patients [31]. In a post hoc analysis based on patients with severe traumatic brain injury who had entered into the SAFE study, resuscitation with albumin was associated with higher mortality than resuscitation with saline (41.8 versus 22.2%, respectively) [32].

Dextrans are monoquaternary polysaccharides which are seldom used because of their side effects: mainly altered coagulation (reduced factor VIII); altered blood group typing has been described; risk of obstructive nephropathy; possible anaphylactic reactions (0.27%) [29,30,33].

Gels (polygeline, modified oxypolygeline, melted gelatin). Derived from bovine collagen, they are iso-oncotic and have less expansion power, which is why they are being

	HES 70/0.5	HES 130/0.4	HES 200/0.5	HES 200/0.5 (Pentastarch)	HES 450/0.7 (Hetastarch)
Concentration (%)	6	6	6	10	6
Volemic effect (h)	1-2	3-4	3-4	3-4	5–6
MW (average) Daltons	70,000	130,000	200,000	200,000	450,000
Maximum dose (ml/kg)	33	30-50	33	20	20

Table 13.4. **Characteristics of hydroxyethyl starch (HES).**

abandoned. Brief expanding effect (2-3 h). Do not alter blood grouping or coagulation or platelet adhesiveness. Do not accumulate in the body and do not affect the kidney. Anaphylactic reactions (0.34%) [29].

Hydroxyethyl starch (HES) is currently the most widely used synthetic colloid. Derived from ethoxylated amylopectin from corn, this molecule is similar to glycogen, lending it interesting features since the body does not recognize it as foreign matter. According to their molecular weight and degree of hydroxiethylation, they vary in lifetime and volemic effect (Table 13.4). The most recent have minimal side effects. Large volumes can be used to achieve enhanced expandability; retention in the intravascular space is 4-6 hours. Improve blood rheology and microcirculation, do not have pro-inflammatory properties, and effects on coagulation are negligible. Low incidence of anaphylactic reactions (0.05%). Produce less edema than crystalloids and remain longer in the intravascular space [20,24,34,35].

The most important considerations when using a specific colloid are: the probability of anaphylactoid reactions; the tendency to increase bleeding; the development of tissue edema; renal involvement; and how the colloid affects immune response. Accordingly, starches between 100-200 MW would be the most suitable colloids [36].

13.2.3 Mannitol

Mannitol, a six-carbon sugar, has been used for over half a century and is a mainstay in medical treatment for cerebral edema and reducing intracranial pressure. Solutions are available in 20 and 25%, with an osmolarity of 1098 and 1375 mOsm/l, respectively. It is not metabolized and is excreted unchanged in urine [37]. Under normal conditions, mannitol cannot cross the intact BBB, but when the BBB is impaired or with repeated doses, it may accumulate in the interstitium and the normal blood-brain gradient is reversed, thus worsening cerebral edema [38]. Mannitol reduces ICP by the following mechanisms:

- Produces expansion of plasma, decreasing blood viscosity and hematocrit, thus increasing cerebral blood flow and delivery O_2. This action is more marked when the CPP is <60 mmHg [39-41].
- The osmotic effect facilitates the drainage of cerebral edema. This effect starts about 15-30 min after administration and lasts for at least 1.5-6 h depending on the clinical condition. This effect persists but needs an intact barrier.
- Improves cerebral perfusion by improving blood rheology [42].
- Normal cerebral blood flow is maintained despite the reduction in vessel diameter (reflex vasoconstriction). There is a decrease in cerebral blood volume and therefore ICP decreases. For this mechanism to work properly, the autoregulation mechanism must be intact.
- Mannitol also has antioxidant effects, but the contribution of this mechanism is not clear.

Side effects associated with the use of mannitol include pulmonary edema, cardiac failure, headache, nausea, vomiting, dehydration, rebound edema, electrolyte disorder and acute tubular necrosis [38,41].

13.3 Use of Fluids in Neurocritical Care

13.3.1 Hemodynamic Management

Initial Resuscitation

In the early care of neurocritical patients, a set of general measures should be initiated to achieve hemodynamic stability and an adequate oxygen supply with the aim to limit or prevent secondary brain injury. Cerebral ischemia is considered the central mechanism of secondary damage. Clinical studies have shown that hypoxia and hypotension are associated with poor prognosis [12,23,43,44]. The choice of fluid for maintaining normovolemia plays a role in the treatment of acute brain injury.

Normal blood pressure should be achieved or maintained as soon as possible, based on fluid administration and eventually with vasopressors. We recommend the administration of fluids to prevent or limit the time the patient is hypotensive [43]. Most prehospital crystalloid solutions are isotonic hypertonic solutions, which have been used in some smaller studies with or without the association of colloids [45].

The initial objectives of water management should be: maintenance of adequate circulating blood volume, a slightly decreased cerebral interstitial volume, and a tendency to serum hyperosmolarity [46].

The administration of glucose solutions in these patients is not recommended, unless there is a risk of hypoglycemia because hyperglycemia may exacerbate ischemic injury [47,48].

PPC Management

The reduction in ICP in patients with acute severe traumatic brain injury was originally the only parameter considered in the management of HEC and the prevention of secondary ischemia. Later, clinical observations focused on CPP, a variable derived by subtracting the value of ICP from mean arterial pressure [5,6,12]. While recent studies have shifted the focus to CPP management, it is clear that current clinical practice and guideline recommendations advise increasing blood pressure to maintain a CPP above a “critical threshold” in the treatment of patients with acute brain injury [49-51].

A CPP of 60 mmHg appears sufficient to limit secondary injury, but it is not devoid of the risk of regional cerebral ischemia. Hypo-osmolality and hypovolemia are harmful and patients should be kept normovolemic by avoiding the use of hypotonic fluids [52]. Initially saline 0.9% it can be used, but concentrations of SSH may vary according to each individual case.

Management of Vasospasm

Volume expansion in subarachnoid hemorrhage (SAH) has two major functions: to prevent clinical vasospasm and in acute intervention when clinical symptoms of vasospasm manifest [53]. The clinical effectiveness of volume expansion and improvement of hemodynamics in the treatment of cerebral vasospasm has been explained physiologically by increased CBF in response to increased CPP [54].

SSH	Mannitol
• Prehospital? • Patients with inadequate resuscitation, hypovolemia • Need to use small volumes • CPP/TAM low at the expense of low • hyponatremia • Need for continuous osmotic infusion therapy • Refractory to manitol	• Diffuse injury • Euvolemic patient with adequate volume resuscitation • Osmolarity <320 mOsm/l • CPP low at the expense of elevated ICP • Intact autoregulation • Bolus continuous infusion useful

Table 13.5. **Uses of SSH and mannitol.**

CPP = Cerebral perfusion pressure
ICP = Intracranial pressure
TAM = ?

Overload-induced hypertension was one of the first therapies used for treatment of vasospasm in patients with SAH. Subsequently, improved neurologic outcomes were reported in patients treated with volume expansion, hemodilution and induced hypertension (triple-H therapy) [55,56].

13.3.2 Osmolar Therapy in the Management of Cerebral Edema

The proper treatment of cerebral edema, and hence of increased ICP, improves cerebral perfusion and reduces mechanical damage caused by tissue compression. The goal of therapy is the reduction of osmolar brain water and limiting secondary brain injury. In the management of cerebral edema secondary to cerebral hypertension, the appropriate use of intravenous solutions and monitoring the internal environment are mainstays in the treatment and prognosis of brain injury, because it is important to know the benefits and likely side effects of the solutions commonly used in the treatment of this disease.

Initial water resuscitation with crystalloid solutions should be performed while strictly monitoring the plasma concentrations of sodium since hyponatremia is associated with worsening of brain edema. The use of hypotonic fluids is contraindicated, as is the use of dextrose solutions given the risk of hyperglycemia and its deleterious effects on the injured brain [47,48].

Many studies have compared mannitol with SSH. The reality is that we understand there are differences between the two substances that make them useful in different stages of brain injury. Table 13.5 compares the best use of both these substances [57-60].

13.3.3 Changes in Na^+ and Body Water

Patients usually present neurocritical water balance disorders; this is particularly but not exclusively the case in patients with SAH. The incidence of hyponatremia depends on the threshold for diagnosis (Na^+ <135 mmol/l) is common in neurological patients and is particularly associated with SAH, severe head trauma and meningitis. The causes of hyponatremia are numerous, but the syndrome of inappropriate of antidiuretic hormone (SIADH) secretion or the cerebral salt-wasting syndrome (CSW) occurs more frequently in neurocritical patients [61,62]. In addition, administration of hypotonic fluids is a common cause of iatrogenic hyponatremia [63]. The close monitoring of urine output, levels of nitric oxide in blood and urine and intravascular volume are of vital importance to the most appropriate choice of fluid for every situation.

Hypernatremia is defined as a serum sodium concentration >145 mmol/l; it is common in critically patients and is often an indicator of disease severity or underlying process. Hypernatremia is usually associated with water deficit, due to either inadequate fluid intake or excessive loss.

13.3.4 Therapeutic Hypothermia

The therapeutic use of hypothermia in neurocritical patients as a neuroprotective therapy has gained interest in recent years after the encouraging results found in post-cardiac arrest patients [64,65]. Owing to the complexities of neurocritical patients, the promising results obtained experimentally have not been seen in clinical practice; nonetheless, hypothermia is used by many neurological intensive care facilities.
Intravenous infusion of large cold volumes (4 °C) is one of the more conventional techniques for inducing hypothermia. This method has been successfully used in studies of patients with sudden death. Although it rapidly decreases body temperature, the method has several contraindications associated with the massive infusion of fluids [66]. The most commonly used fluids are 0.9% saline or lactated Ringer's solution, calculated at a dose of 30-40 ml/kg.

13.4 Conclusions

Proper patient care is based on neurocritical assessment of neurological symptoms and neuromonitoring findings coupled with close monitoring of hemodynamic status in order to minimize secondary neuronal injury.
Currently, there is no magic bullet in the management of fluids in the critically patient, and it seems unlikely that a protocol will meet all requirements for all patients and different levels of resuscitation.
Fluid resuscitation with either crystalloids or colloids is generally safe and effective in critically patients, but these agents may be potentially beneficial (e.g., sepsis) or potentially harmful (e.g., head injury) in certain patient populations. Modern fluid resuscitation protocols should be designed to minimize complications and secondary insults related to water therapy. Management of the neurological patient volume (as in all critically patients) should be based on a triad note:

- Fluid management.
- Type of patient.
- Goals and objectives.

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14 The Metabolism of Sodium and Its Effect on the Brain

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14.1 Introduction

The brain is a complex and delicate structure that is highly sensitive to abrupt changes in the internal environment, where the water-electrolyte balance plays a role in regulating body processes. In this context, sodium balance is essential for the proper functioning of nerve tissue, considering that nerve cell excitability depends largely on this cation. Its passage through the cell membrane can generate action potentials, which spread to adjacent neurons, and modulate activities in specific areas of the nervous system essential for its functioning.

Sodium is a cation predominantly found in the extracellular space, whereas the potassium cation is mainly concentrated inside the cells. The estimated percentage of sodium in the extracellular space is about 90%, or about 50 g in an adult weighing 70 kg.

Sodium channels are tubular structures that span the cell membrane. Under certain circumstances, they can open to allow sodium passage, thus changing the membrane voltage at a critical point that triggers action potentials, whose morphology, amplitude and duration depend essentially on its physical and chemical properties.

Physiologically, sodium plays an essential role in maintaining homeostasis. Imbalance in the sodium/water rate can lead to serious disorders which, unless corrected promptly, can be life-threatening for the patient.

To maintain this balance, the body has various mechanisms that interact to cope with different types of insults. Thirst, for example, is a central mechanism to counteract the increased concentration of sodium in the blood.

In the kidney, the renin-angiotensin system is highly efficient in detecting voltage drops. It reduces the concentration of sodium, indirectly stimulating the production of aldosterone, a hormone that acts in the reabsorption of sodium, which, in turn, in order to reach certain concentrations, stimulates the secretion of antidiuretic hormone (ADH) by the posterior pituitary (arginine vasopressin system). The most important function of the antidiuretic hormone is to inhibit the renal excretion of water, causing its retention and a subsequent decrease in sodium concentration. Another mechanism opposed to positive sodium balance and to an increase of volume caused by fluid retention, is the auricular receptors that are sensitive to distension caused by hypervolemia, resulting in the secretion of atrial natriuretic factor (ANF) which inhibits the renal uptake of sodium and water, restoring the osmotic balance in open antagonism to renin-angiotensin and ADH.

This complex of functionally juxtaposed systems moves in physiological oscillations within certain limits, ensuring an adequate water sodium balance in the body. However, several processes can concur to impair the body ability to maintain this balance, giving rise to natriuretic imbalances whose most common expression is hyponatremia.

14.2 Hyponatremia

14.2.1 Definition

Hyponatremia refers to a sodium concentration <135 mmol/l. The management of patients with hyponatremia depends on proper identification, including its possible etiologic causes, and timely treatment.

14.2.2 Clinical Aspects and Diagnostic Difficulties

Hyponatremia affects men and women equally. It is more prevalent in the elderly and children because of the difficulties of both infants and the elderly to express thirst and freely manage their demand for liquids. The clinical manifestations of hyponatremia depend on its onset. The chronic form is fairly well tolerated by patients and most are asymptomatic, given the body ability to prevent cerebral edema which, in rigid matter such as the skull, would imply a considerable insult. In this case, the output of solutes and other substances, including proteins from the intracellular space, averts this severe threat, and levels as low as 112 mmol/l are tolerated with minimal symptoms for long periods of time. In contrast, a decrease occurring within less than 48 hours would result in a constellation of symptoms from lethargy to seizures; these effects can be life-threatening and require prompt correction of the sodium deficit.
The severity of the disease is directly related to the degree of hyponatremia and the rapidity of its onset; with explicit symptoms starting from 120mm/l, starting from concen-

Hypovolemic hyponatremia	Simultaneous loss of fluid and sodium, the latter at a higher rate, and poor replacement infusion of hypotonic water: • Marathoners (ascites, intestinal obstruction, peritonitis, burns), diarrhea, CSW in patients with trauma, SAH • Post-resection intracranial tumour. Must be distinguished from SIADH secretion (different management) • Acute or chronic renal insufficiency, salt-losing nephritis • Diuretics: thiazides, carbonic anhydrase inhibitors
Euvolemic hyponatremia	Increased body fluid (no edema), with normal sodium reserve: • Psychogenic polydipsia • Infusion of hypotonic instead of isotonic solutions in postoperative and hospitalized children • SIADH. Differentiate from CSW (different management) • Hypothyroidism • Thiazides
Hypervolemic hyponatremia	Content of water and sodium increases simultaneously, but the water increases at a higher rate: hyponatremia and edema: • Renal impairment: inability to excrete ingested sodium • Nephrotic syndrome • Congestive heart failure • Hypothyroidism • Adrenal insufficiency • Recreational drugs (e.g., ecstasy) • Cirrhosis

Table 14.1. **Causes of hyponatremia.**
SAH = subarachnoidal hemorrhage
CSW = cerebral salt wasting
SIADH = syndrome of inappropriate antidiuretic hormone

trations of 120 mmol/l. In chronic cases, this level may be much lower, with almost imperceptible manifestations. Symptoms will depend on the type of hyponatremia and its underlying cause (Table 14.1).

Hyponatremia should not be confused with pseudohyponatremia, which is almost always due to sodium masking by certain substances such as triglycerides, proteins or excess glucose without altering plasma osmolarity, in which water from the body is redistributed into the extracellular space, creating false hyponatremia; therefore, one should try to correct these anomalies. Transureteral postresection prostatic syndrome should be considered in the differential diagnosis. This is caused by the absorption of litres of hypotonic solutions given during the procedure, causing a hyponatremia with normal plasma osmolarity.

Plasma osmolarity refers to the concentration of solids in a kilogram of plasma and is expressed in millimoles per litre. The formula for calculating plasmatic osmolarity is:

$$\text{mmol/l} = 2\,(\text{sodium}) + (\text{urea}) + (\text{glucose})$$

The normal range of plasma osmolarity is 280 to 300 mmol/l.

14.2.3 Types of Hyponatremia

There are three types of hyponatremia:

1. Hypovolemic.
2. Euvolemic.
3. Hypervolemic.

Hypovolemic hyponatremia manifests in patients as a simultaneous loss of fluid and sodium, but the latter at a higher rate. Among the most frequent causes are the use of diuretics, salt-losing nephritis, adrenal insufficiency, and salt-losing encephalopathies. Among the most important extrarenal causes are burns, diarrhea, excessive sweating (marathon runners), and the third space (bowel obstruction).

In euvolemic hyponatremia, body fluids increase (no edema), with normal sodium reserve, as occurs in psychogenic polydipsia, the administration of hypotonic solutions for isotonic maintenance in hospitalized patients, hypothyroidism and the syndrome of inappropriate antidiuretic hormone (SIADH). From a strictly clinical point of view, it can sometimes be very difficult to differentiate hypovolemic from euvolemic hyponatremia, so the most practical way would be to measure plasma osmolarity and urinary sodium concentration. The latter would help to more accurately identify patients with low plasma osmolarity.

In hypervolemic hyponatremia, water and sodium content increase simultaneously, but the water increases at a higher rate, thus causing hyponatremia and edema. This, in turn, can cause congestive heart failure, liver cirrhosis and various renal diseases such as the nephrotic syndrome that reduces plasma osmotic pressure by triggering the renin-angiotensin-aldosterone system involving the reabsorption of sodium and water.

There are other classifications of hyponatremia. One is based on plasma osmolarity and hyponatremia. It describes hypotonic, isotonic and hypertonic hyponatremia, thus creating some confusion with the one just described, which implicitly relates the volume with osmolarity. Hypotonic hyponatremia, which some incorrectly refer to as “true” hyponatremia, also known as dilutional hyponatremia, refers to an excess of water in the internal environment with normal or high osmolarity. Hypertonic hyponatremia involves an excess of solute in the extracellular space; in this case, the water moves from inside the cells to the extracellular space, as occurs with hyperglycemia or mannitol.

In isotonic hyponatremia there is normal osmolarity, the excess of certain triglycerides, normal or abnormal protein concentration, as in Waldeström's disease or multiple myeloma. Moreover, glucose itself can cause water to move from the intracellular space, which is known as pseudohyponatremia.

14.2.4 Clinical Management

As explained, it is essential to properly treat hyponatremia to establish whether it's acute or chronic, and also to identify the underlying condition or comorbidities that may facilitate its occurrence. Many drugs (Table 14.2) may cause it, such as diuretics, especially thiazides, but also acetazolamide, anticonvulsants such as carbamazepine, gabapentin, zonisamide, various immunomodulators (sirolimus), selective serotonin reuptake inhibitors (SSRIs) antidepressants, non-steroidal inflammatory drugs (NSAIDs) such as indomethacin, etc. The immediate suspension of such drugs helps to reverse the disorder, which is often chronic and should be corrected gradually with infusion of solutions never higher than 8 mmol/l over 24 hours. Sometimes, the mere suspension of the offending agent is sufficient.

Some recreational drugs such as ecstasy (MDMA) can also produce hyponatremia. It is obvious that they should be suspended immediately.

Many comorbidities may lead to hyponatremia, which are mostly chronic and oligosymptomatic, even at sodium levels as low as 110 mmol/l. However, there are sudden events that can lead to lower levels where compensatory mechanisms are insufficient and the symptoms can be noted in direct proportion to the amount of sodium reduction and the rapidity of the decline below critical levels. At this point, the clinician's expertise is critical because the disease should be differentiated from acute hyponatremia. This is less frequent and sometimes present with less extreme sodium levels and can be treated in postoperative patients who have recently received excessive volumes of hypotonic solutions, or people with mental disorders and compulsive polydipsia, or marathoners who, during a run, sweat profusely and ingest significant amounts of liquids, where osmolarity does not replace sodium losses, so quick replacement in such cases is an immediate urgency.

Antiepileptics	Carbamazepine, gabapentin, oxcarbazepine, levetiracetam, zonisamide
Others	Chlorpropamide, clofibrate, cyclophosphamide, indapamide, amiodarone, aripiprazole, amiloride, amphotericin B, basiliximab, sirolimus, thiazides, acetazolamide, NSAIDs, ARBs, bromocriptine, blockers of angiotensin II, desmopressin, interferon, SSRIs, mirtazipine, nicotine, tricyclic antidepressants, phenothiazines, prostaglandins, oxytocin, theophylline, opiates, sulfonylureas, vincristine

Table 14.2. **Drugs that can cause hyponatremia.**
ACE = angiotensin converting enzyme
ARBs = angiotensin II receptor blockers
NSAIDs = non-steroidal inflammotry drugs
SSRIs = selective serotonin reuptake inhibitors

The clinical manifestations of acute hyponatremia can vary from impaired mental status to coma and seizures. Therefore, it must be corrected immediately, as cerebral edema could lead to transtentorial herniation and distortion of the brainstem with catastrophic implications. The benefit of aggressive correction far outweighs the risk of extrapontine and pontine myelinolysis. Some authors recommend corrections of no more than 8 mmol/day, without achieving levels >125 mmol/l in such a short period of treatment, especially if starting at levels <105 mmol/l. It must be emphasized that when treating the underlying causes and in patients with endocrine diseases such as diabetes, excess glucose must be managed with insulin and infusion of isotonic solution because it is a

hypertonic hyponatremia. In adrenal insufficiency, hormone restoration is also the rule, and 120 mg of hydrocortisone administered over 24 to 48 hours is very beneficial. Sometimes it is difficult to demarcate the boundaries between acute and chronic hyponatrema. The context in which symptoms develop can help in decision making; in cases

	Syndrome of inappropriate antidiuretic hormone secretion	Cerebral salt-wasting syndrome
Causes	• CNS disorders: stroke, subdural hematoma, SAH, intracranial tumours, cerebral contusion, meningitis-encephalitis • Extracerebral: small cell lung carcinoma • Other cancers: colon adenocarcinoma, pancreatic cancer, lymphoma • Drugs: NSAIDs, thiazide diuretics, aminoglycosides	• CNS disorders: SAH, tuberculous meningitis with involvement of the base structure (hypothalamus), natriuretic peptides, concussion, meningitis carcinomatosis • Extracerebral: Exaggerated action of natriuretic peptides
Pathophysiology (Both disorders have low plasma sodium and urine osmolality increased. **Volume** is the fundamental difference)	Excessive ADH action: sodium retention, and to a lesser extent, euvolemic hyponatremia, urine osmolarity > serum osmolarity	Exaggerated action of natriuretic peptides in urine osmolarity hypovolemic hyponatremia > serum osmolarity
Main differences	• No signs of dehydration, no orthostatic hypotension (euvolemia) • Normal hematocrit, potassium, BUN • Normal or elevated pulmonary capillary wedge pressure and central venous pressure • Low urine volume + high sodium • Clinical presentation depends on the degree of hyponatremia and speed of onset	• Dry mucous membranes, lack of sweating, tachycardia • Orthostatic hypotension, negative fluid balance (hypovolemia) • High potassium, BUN, elevated hematocrit • Decreased pulmonary capillary wedge pressure (<8 mmHg) • Low central venous pressure (<5 mmHg) • Increased urine output + high sodium • Clinical measures depend on degree of hyponatremia and speed of onset
Treatment	• Try to remove the cause • Fluid restriction (≥1.5 l/24 h) • Thiazides have the advantage that they stimulate excretion of more water than sodium • Diet high in salt and protein • Infusion of hypertonic solutions if not resolved with hyponatremia • Correct hyponatremia with caution: no more than 0.5 mmol/l/h (<8 mmol/l/24h)	• Try to remove the cause • Volume replacement with hypertonic solutions to achieve a positive sodium balance, range no greater than 0.5 mmol/l (avoid myelinolysis) • Fludrocortisone 0.2 mg IV 10 days (check hypertension and hypocalcemia)

Table 14.3. **Differences between syndrome of inappropriate antidiuretic hormone secretion and cerebral salt-wasting syndrome.**

ADH = antidiuretic hormone
BUN = blood urea nitrogen
CNS = central nervous system
SAH = subarachnoid hemorrhage
NSAIDs = nonsteroidal anti-inflammatory drugs

with minimal symptoms, fluid restriction alone may be enough. However, this is very delicate and in some chronic cases has caused myelinolysis. The golden rule in the management of chronic hyponatremia is to eliminate the underlying cause. In the absence of hypovolemia, logic says that fluid restriction is the first step, with close monitoring of osmolarity. If, despite this, sodium does not reach normal levels and the patient is euvolemic, a malfunction of ADH should be suspected. In this case, the antibiotic demeclocycline (Declomycin(R)) should be administered, which, with its unique "nephrotoxic" effect (epiphenomenon), water reabsorption is decreased, thus achieving normal sodium concentration. Recommended doses are between 600 and 1200 mg daily.

The SIADH secretion is a common cause of hyponatremia and an expression of several diseases, of which the most important are meningitis, intracranial tumours, subdural hematoma, cerebral contusion, subarachnoid hemorrhage (SAH), as well as extracerebral diseases such as cancer, and small cell lung carcinoma in particular, along with infections such as pneumonia. In SIADH, the subsequent hyponatremia, if not identified and treated promptly, significantly worsens the evolution of processes such as SAH, and can lead to complications such as vasospasm, and refractory cerebral edema. Therefore, its diagnosis should be suspected in neurosurgical patients who develop hyponatremia.

The antidiuretic hormone vasopressin is a nonapeptide produced by the posterior pituitary or neurohypophysis, specifically in the gigantocellular area of the supraoptic nucleus. One of its functions is to inhibit the renal excretion of water and sodium, which means small and concentrated urine volumes, hence, the term "antidiuretic." In addition, it has a significant vasoconstrictor effect. It has several other important features and is involved in complex processes such as the maintenance of circadian rhythms and the development of adaptive responses based on learning processes mediated by multisynaptic reflexes involved mainly in short and medium-term memory formation.

In neurosurgical patients, it is essential to differentiate SIADH from cerebral salt-wasting (CSW), because the treatments are different and misdiagnosis can cause serious consequences (Table 14.3). One example of this problem is SAH, where hyponatremia is common and is related to CSW in most cases and to a lesser extent to SIADH.

In fact, vasopressin's mechanism of action is well described and its inhibitory action on renal excretion of water and on increasing osmolarity is universally accepted. However, its proposed mechanism in CSW is less clear and may involve the excessive action of natriuretic peptides in the eventual failure of the renin-angiotensin-aldosterone system, with consequent sodium loss and hyponatremia.

In SIADH there is fluid retention with fluid overload, the opposite of CSW, where there is loss of sodium and hypovolemia. Hematocrit, potassium, and plasma proteins have normal values in SIADH, whereas they are increased in CSW, except for potassium which is within normal limits in CSW. Central venous pressure and pulmonary capillary resistance tend to be normal or elevated in SIADH, whereas both are decreased in CSW. With these elements clearly specified, the differential diagnosis can be established, identifying each entity and initiating treatment accordingly.

Treatment of the Syndrome of Inappropriate Antidiuretic Hormone

The core management of SIADH entails fluid restriction and the use of hypertonic solutions. Because of the frequent inability of the kidney to absorb sodium in the same proportion of water, there is a negative balance of the cation in the extracellular fluid and increased in urine. In severe brain insults and severe symptoms such as coma and seizures, treatment should be individualized. Anticonvulsants should be administered, together with monitoring of vital signs, while maintaining oxygenation and check-

ing the sodium concentration in the blood: once minimum values are reached under which seizures are controlled, the infusion rate should be slowed, so that hypertonic status should not exceed 8 mmol/l in 24 h. It is worth noting that in SAH and other injuries, such as extensive infarctions or severe contusion, fluid restriction has resulted in worsening of symptoms, hence the importance of diagnostic accuracy.
An emerging and promising method for treating SIADH is with vasopresin receptor antagonists that inhibit vasopressin binding at the level of the nephron, with subsequent renal excretion of free water and decrease in extravascular fluid.

Management of the Cerebral Salt-wasting Syndrome

The most important thing to do is initiate fluid replacement, preferably with hypertonic solutions that have proven to be safe in non-controlled studies, where the index of cardiac, metabolic and myelinolytic complications was minimal. This requires strict control of infusions of no more than 0.5 mmol/l/time to avert the occurrence of myelinolysis. The administration of fludrocortisone at rate of 0.2 mg IV twice daily for 10 days, a mineralocorticoid with a not fully understood mechanism of action, diminishes the loss of salt by the kidney eliminate at a rate with very encouraging results.

14.2.5 Complications of Hyponatremia

We have explained that the symptoms resulting from hyponatremia depend on the speed of its onset and the levels of sodium. Its expression is variable and the range of symptoms includes subtle mood changes, poor concentration, irritability, drowsiness, anorexia, malaise, unexplained headache, deteriorating level of consciousness, coma and seizures. These symptoms are very difficult to manage if sodium levels are not increased reasonably.
Although it is quite uncommon, rhabdomyolysis should be suspected in hyponatramic patients with muscle aches and spasms. Hyponatremia alone can affect the integrity of the muscle membrane. The low concentration of extracellular sodium affects the sodium-calcium cation exchange, with a net increase in intracellular calcium that triggers the activation of apoptotic systems that involve the selective death of myocytes. The damaged membrane facilitates the discharge into the bloodstream of substances with a high toxic potential such as myoglobin, whose degradation products (globin and the iron pigment within it) precipitate in the renal tubules, significantly affecting their function, and the body homeostatic mechanisms. The presence of elevated creatinphosphokynase (CPK) levels is the most important indicator to confirm the diagnosis.
Myoglobin also has to be consistently high. Rhabdomyolysis, if not diagnosed promptly, can cause kidney damage and complicate patient management; therefore, controlling the patient's metabolic status is necessary. Treatment consists of two parts: correction of hyponatremia and relief of muscle spasms by the administration of baclofen, preferably in a continuous infusion pump, up to 200 mg IV daily in severe cases. If the desired improvement is not achieved, midazolam IV can also be administered, intermittently, as needed. Muscle enzymes should be tested routinely in patients with hyponatremia and some degree of hypertonia.
Extrapontine and pontine myelinolysis as a complication of hypercorrection of hyponatremia is a concern for those who have to deal with these patients. As we have repeated throughout this chapter, the aggressive correction of hyponatremia, especially in chronic cases, is the most important factor to trigger myelinolysis.
The gradual restructuring of the internal environment through the exchange of ions and other higher molecular weight substances that travel through the extracellular

space increase long-term tolerability. However, patients are more susceptible to complications such as myelinolysis related to the massive influx of sodium into the extracellular space. The subsequent exit of fluid from oligodendrocytes to the interstitial and intravascular compartments involved in their degradation is not inflammatory demyelination, which is often not confined to the pons, as was described in the first case, which is due to various causes such as alcoholism, malnutrition and cirrhosis. Diagnosis will be based on findings from neuroimaging studies because FLAIR and T2 sequences best identify demyelinating lesions that are displayed as hyperintensities, usually symmetrical, in the pons, striatum, thalamus, or even in the cortex brain (Figures 14.1 and 14.2). Symptoms are variable and often occur several days after osmotic insult. Virtually asymptomatic cases are described meanwhile others with delirium, locked-in syndrome, coma, and death. Pyramidal or extrapyramidal elements may also be present. There is no precise correlation between symptoms, the degree of extension of lesions and their intensity on magnetic resonance imaging scans. Unfortunately, there is no effective treatment once the injury occurs, hence the importance of correcting hyponatremia rationally.

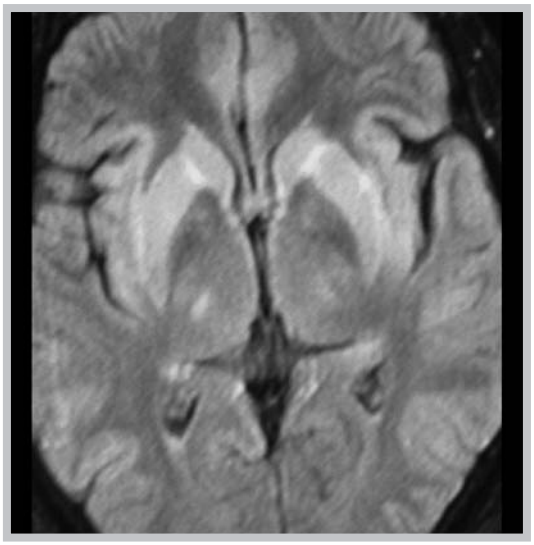

Figure 14.1. **Bilateral hyperintensity in the striatum, with FLAIR sequence, in a patient with chronic hyponatremia which worsened after 3 weeks, not promptly corrected, corresponding to extrapontine myelinolysis.**

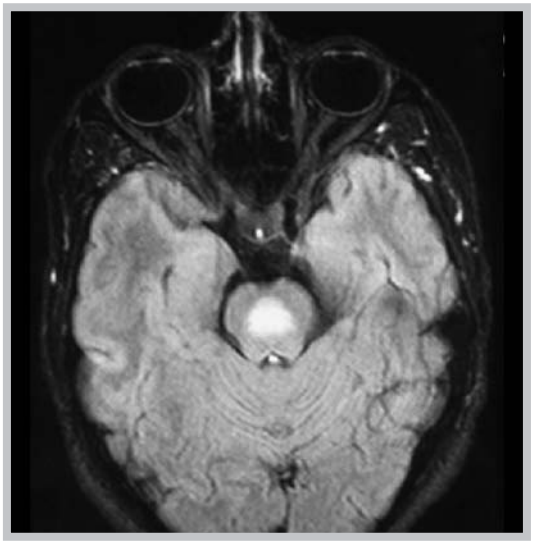

Figure 14.2. **Marked hyperintensity in the pons of the same patient, with FLAIR sequence, corresponding to pontine myelinolysis.**

14.2.6 Conclusions

Hyponatremia is a condition that can be identified and properly managed if the underlying causes are identified and possibly eliminated. On the basis of the patient's symptoms, hyponatremia should be corrected, taking into account whether it is acute or chronic and whether it constitutes an emergency or not.

In acute and life-threatening cases, the aggressive correction of sodium levels is beneficial, and the occurrence of myelinolysis is unlikely. In chronic cases, the suspension of the cause and the delicacy of the sodium correction are key to recovery without sequelae. The broad symptomatic spectrum and the presence of other comorbidities difficult to the management of hyponatremia which requires clinical expertise to finally beat it.

14.3 Hypernatremia

14.3.1 Definition, Epidemiology, and Risk factors

Hypernatremia is defined as a blood sodium concentration >145 mEq/l. It is the direct result of water loss or gain of sodium, so there is a positive balance of the cation in the extracellular space, resulting in a response to counter it by thirst, water outflow from the intracellular space or by increasing the renal sodium excretion. It is a less common alteration than hyponatremia (5% of total electrolyte disorders) and equally affects both sexes. It has a higher incidence in the elderly and children, because of the difficulty of these groups to have free access to liquids or because misaligned in the thirst mechanism in older people. Patients with psychogenic hypodipsia, children and elderly or those mismanaged with inappropriate infusions (iatrogenic) have an increased risk of hypernatremia.

The mechanisms that produce hypernatremia can be summarized as follows:

- **Loss of fluid** due to insufficient vasopressin function (decreased secretion or inadequate renal response to normal secretion). Extrarenal loss: diarrhea, profuse sweating. Decreased fluid intake (central or psychogenic adipsia, unavailability of water). The most serious consequence of this loss is cellular dehydration.
- **Increase of sodium in the extracellular space** caused by fluid losses, with positive balance of the cation, which also contributes to hormonal imbalances such as primary hyperaldosteronism and Cushing's syndrome. Further poor management of infusions (sodium bicarbonate, parenteral nutrition) and dialytic hypertonic solutions contribute to an iatrogenic increase in the sodium balance.

One of the major causes of hypernatremia is **diabetes insipidus (DI)**, both central and nephrogenic. The cardinal symptom is polyuria, which can reach more than 15 litres per day. Central DI is caused by the insufficient production and subsequent secretion of vasopressin or antidiuretic hormone by the neurohypophysis, which implies that the kidney is unable to concentrate urine. Consequently, blood sodium is increased, triggering the thirst mechanism. There are multiple root causes: ablation surgery, pituitary tumours, trauma (skull base fracture), intracranial infections, and congenital malformations. The cause is unknown in about 30% of cases. Renal or nephrogenic DI is clinically indistinguishable from central DI; however, the simple infusion of exogenous ADH (desmopressin) and the change in urine osmolarity can help in making the diagnosis: it is central if there is an increase in osmolarity and nephrogenic if urine is diluted.

In renal DI, the kidney is insensitive to adequate concentrations of ADH in the blood, and starts concentrating the urine, creating a noticeable increase of sodium in the extracellular fluid. The causes are the use of aminoglycosides, rifampicin, lithium salts, oral hypoglycemic agents, amphotericin B, demeclocycline, etc. Systemic inflammation such as amyloidosis may arise, as well as polycystic kidneys and electrolyte imbalances such as hypocalcemia and hypokalemia.

Hypernatremia has a variable clinical expression and depends on how quick its onset is and on the degree of nervous system involvement. In adults it usually remain asymptomatic until reaching levels as high as 160 mEq/l. Thirst can be a guiding symptom, especially in the beginning of the disease, and if the subject urinates significant quantities. The evolution of symptoms to coma and seizures depends on how quick the onset of hypernatremia is; high levels of sodium are tolerated with minimal symptoms, because of the balance maintained with the gradual exit of fluid from the extracellular space. This is impossible to achieve if there is a sudden (within <48 hours) increase in plasma osmolarity at the expense of sodium. Consequently, the intracellular fluid space rapidly de-

creases, contributing to neuronal dehydration, and leading to a series of symptoms proportional to the intensity of dehydration.

14.4 Clinical Management and Treatment

The best approach is to try to eliminate the cause, but sometimes, given the urgency of symptoms, rapid correction of hypernatremia is essential. The correct measurement of volume and urine osmolarity are critical to guide the diagnosis: if there are large volumes of not concentrated urine, the diagnosis will be DI, and the elective diagnostic test will be the desmopressin test to identify whether it is central or neurogenic. In the case of small volumes of urine and a higher concentration of sodium, the kidneys try to conserve water from the extracellular space and excreted sodium, as in hypernatremia of extrarenal origin and iatrogenic diseases, Cushing's syndrome or Cohn's disease. Normal renal osmolarity in children and adults is between 400 and 800 mOsm/kg. Under conditions of fluid restriction for more than 12 hours, levels of osmolarity of 400 mOsm/kg or less could be an index of severe kidney damage. Hypernatremia should be managed taking into account the volume of extracellular space to find out if it is euvolemic or hypovolemic hypernatremia. The amount of water needed by the body can be calculated using the following formula:

Free water deficit = Body weight (kg) x Total body water (%) x ([Serum Na/140] – 1)

Where the percentage of body water (TBW) accounts for approximately 60% by weight, hence, the constant 0.6 times the weight of the patient.
If hypernatremia is hypovolemic, infusion of normal saline (0.9%) is the treatment of choice, until the signs of dehydration decrease. Hypotonic solutions ("D5" - 5% dextrose; hypotonic saline fluids such as 0.45% sodium chloride solution) should then be administered to restore the volume and reverse the hypernatremia.
In cases of euvolemic hypernatremia, as occurs in elderly patients with poor thirst mechanism, oral rehydration therapy is indicated and effective.
In central DI, in addition to water restriction and low sodium diet, desmopressin administration (intranasally or subcutaneously) can help to alleviate the deficit of vasopressin.
In nephrogenic DI it is important to delete the trigger, usually a drug (phenytoin, lithium salts, acyclovir, demeclocycline, amphotericin B); this is sometimes enough to normalize serum sodium. Otherwise, a low-protein and low-sodium diet, supplemented with low doses of hydrochlorothiazide, is critical for relieving the kidney from solute overload.
Serum sodium should never decrease to <0.5 mEq/l/h because a rapid decline in serum sodium can cause cerebral edema. Do not administer more than 50% of the estimated deficit in the first 24 hours. The onset rhabdomyolysis and myelinolysis after aggressive correction of hypernatremia. Rhabdomyolysis and myelinolysis after aggressive correction of hypernatremia have been reported.

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15 Hemodynamic Monitoring

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All science is measurement.
von Helmholtz

15.1 Introduction

The first step in evaluating a patient's hemodynamics is, without doubt, the clinical assessment. Bedside observation of the patient's general appearance, skin temperature, capillary refill, sensory status, diuresis, filling of the external jugular vein and so on, will give the physician an approximate idea of the hemodynamics. However, clinical data are often nonspecific and subjective and can be altered by the patient's concomitant conditions.
Invasive hemodynamic monitoring yields accurate, objective and reliable data about intracardiac and intravascular pressure, blood flow volume and distribution, oxygen supply to tissues and the use thereof by cells. Assessment of hemodynamic status should include measurement of tissue oxygenation (Figure 15.1). In the presence of oxygen, aerobic cellular metabolism produces a significant amount of energy (ATP) and non-toxic and easily removed waste product metabolites (CO_2). In the absence of oxygen, anaerobic cell metabolism produces little energy and toxic metabolites (lactic acid).

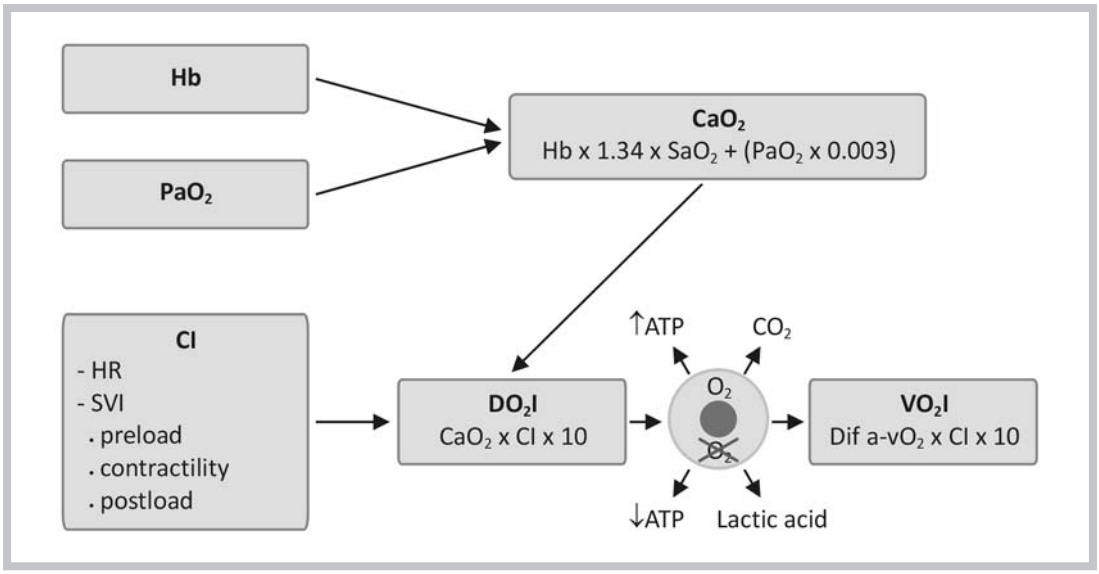

Figure 15.1. **Alveolar partial pressure of oxygen (PaO_2) and hemoglobin (Hb) are determinants of arterial oxygen content (CaO_2). Cardiac index (CI) is derived from the stroke volume index (SVI) and heart rate (HR), oxygen delivery index (DO_2I) and oxygen consumption index (VO_2I).**

15.2 Indications and Complexity of Hemodynamic Monitoring

Hemodynamic data are useful or even essential in proper patient management. As a general rule, the more severe the condition, the greater the complexity and depth of monitoring. A corollary to this is an appropriate risk/benefit ratio, since invasive monitoring is not devoid of complications, along with the cost/benefit ratio in the rational use of health resources, avoiding excessive spending wherever possible.

The information obtained should allow diagnosis, prognosis and effective treatment that will ensure the best outcome for the patient in terms of morbidity and mortality, minimizing risks through a more effective use of medical resources.

Noninvasive monitoring of heart rate, respiratory rate, and blood pressure, electrocardiography (ECG), pulse oximetry and exhaled CO_2 provide comprehensive information of the circulatory status.

Invasive monitoring involves the percutaneous introduction of catheters into the intravascular space to directly measure certain variables from which others can be calculated for more accurate and specific control of a particular hemodynamic situation.

Before a diagnosis can be established, hemodynamic monitoring data are necessary to obtain a quantitative basis which, together with the operator's clinical criteria, can aid in proper decision-making.

15.3 Definitions and Hemodynamic Parameters

15.3.1 Definitions

Preload. The load or volume that distends the left ventricular end-diastolic volume (Figure 15.2). It is determined by the volume of blood at the end of ventricular filling (left ventricular end-diastolic volume, LVEDV) [1]. The LVEDV correlates with left ventricular end-diastolic pressure (LVEDP) in ventricles with normal compliance. In restrictive ventricles (ischemic or hypertrophic) a higher filling pressure is needed to have an adequate volume at the end of diastole. Pulmonary capillary wedge pressure (PCWP) indicates left ventricular preload. The central venous pressure (CVP) is the practical expression of right ventricular preload.

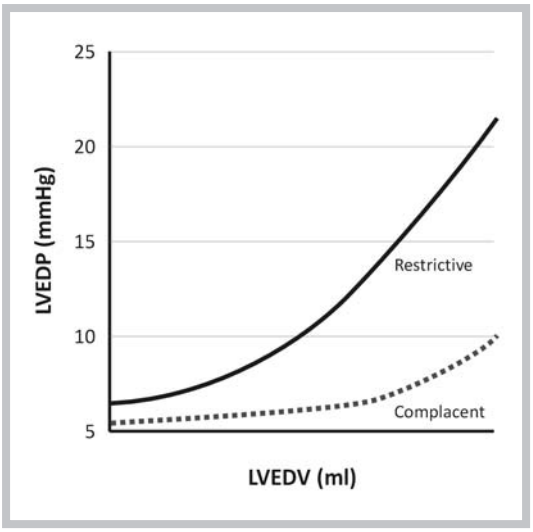

Figure 15.2. Preload: pressure/volume in complacent and restrictive ventricles.
LVEDV = left ventricular end-diastolic volume
LVEDP = left ventricular end-diastolic pressure

Contractility. The ability of cardiac muscle fibre to shorten after elongation. Prior knowledge of ventricular function through ventricular ejection fraction and fractional shortening provide useful baseline information in hemodynamic management. During monitoring the contractile capacity can be roughly related to the contractility index (CI) or the stroke volume index (SVI), although these parameters are also influenced by preload and afterload.

Measured variables	• Central venous pressure (CPV) • Systolic, diastolic, and mean pulmonary artery pressure (SPAP, DPAP, MPAP) • Pulmonary capillary wedge pressure (PW) • Mean arterial pressure (MAP) • Cardiac output (CO) (l/min) • Body surface area (BSA) in m^2
Calculated variables	• Cardiac index (CI) blood flow per minute per m^2 of BSA; normal value: 2.5 to 4.2 l/min/m^2 • Stroke volume (SV): CO/HR • Systolic volume index (SVI): CI/HR • Left ventricular systolic work (LVSW) = SV x MAP x 0.0144 • Left ventricular systolic work index (LVSWI) = SVI x MAP x 0.0144; normal value: 56±6 g/m^2/beat • Right ventricular systolic work (RVSW) = SV x MPAP x 0.0144 • Right ventricular systolic work index (RVSWI) = SVI x 0.0144 x MPAP; normal value: 8.8±0.9 g/m^2/beat • Systemic vascular resistance (SVR) = (MAP - CVP)/CO x 80 (dynes/s/cm^{-5}); normal value: 900-1400 dynes/sec/cm^{-5} • SVR index (SVRI) = (MAP – CVP)/CI x 80 (dynes/s/cm^{-5}) • Pulmonary vascular resistance (PVR) = (MPAP – PW)/CO x 80 (dynes/s/cm^{-5}); normal value: 150-250 dynes/sec/cm^{-5} • PVR index (PVRI) = (MPAP – PW)/CI x 80 (dynes/s/cm^{-5})
Metabolic variables	In addition to pressure and flow rate, tissue oxygenation parameters are also monitored: • Arterial oxygen content (CaO_2) = Hb × 1.34 × SaO_2 + (PaO_2 x 0.003): the amount of oxygen contained in 100 ml of blood • Oxygen delivery index (DO_2I) = CI x CaO_2 x 10: the amount of oxygen supplied to the tissues per m^2 of body surface per minute • Oxygen consumption index (VO_2I) = (C(a-v)O_2) x CO x 10: the amount of oxygen (ml) consumed globally per m^2 of body surface per minute
Hemodynamic parameters	• Heart rate (HR) • Mean arterial pressure (MAP) • Central venous pressure (CVP) • Mean pulmonary artery pressure (MPAP) • Wedge pressure or pulmonary artery wedge pressure (PW) • Cardiac output (CO) • Height and weight to calculate body surface area (BSA)
Calculated hemodynamic parameters	• Cardiac index (CI): CO/BSA (l/min/m^2); normal values: 2.5 to 4.2 l/min/m^2 • Stroke volume (SV): CO/HR • Systolic volume index: CI/HR • Left ventricular systolic work (LVSW) = SV x MAP x 0.0144 • Left ventricular stroke work index (LVSWI) = SVI x MAP x 0.0144; normal value: 56±6 g/m^2/beat • Right ventricular systolic work (RVSW) = SV x MPAP x 0.0144 • Right ventricular stroke work index (RVSW) = SVI x 0.0144 x MPAP • Normal value: 8.8±0.9 g/m^2/beat • Systemic vascular resistance (SVR) = (MAP - CVP)/CO x 80 (dynes/s/cm^{-5}); normal values: 900-1400 dynes/s/cm^{-5} • SVR index (SVRI) = (MAP – CVP)/CI x 80 (dynes/s/cm^{-5}) • Pulmonary vascular resistance (PVR) = (MPAP – PW)/CO x 80 (dynes/s/cm^{-5}); normal values: 150-250 dynes/s/cm^{-5} • PVR index (PVRI) = (MPAP – PW)/CI x 80 (dynes/s/cm^{-5})

Table 15.1 **Parameters in hemodynamic monitoring.**

A somewhat more specific parameter of contractility is the ventricular stroke work index.
Afterload. Determined by the resistance to ventricular ejection, which is opposed to ventricular emptying during systole [2,3]. Left ventricular afterload is expressed as systemic vascular resistance (SVR), which is directly proportional to the pressure difference between the two ends of systemic circulation (mean arterial pressure-central venous pressure, MAP-CPV) and inversely proportional to blood flow (cardiac output, CO). Right ventricular afterload is expressed as pulmonary vascular resistance (PVR), which is directly proportional to the pressure difference between the ends of pulmonary circulation (mean pulmonary artery pressure-pressure wedge, MPAP-PW) and inversely proportional to cardiac output.

15.3.2 Hemodynamic Parameters

Parameters in a hemodynamic profile include pressure and flow data, some measured directly and others calculated therefrom (Table 15.1).

15.4 Pressure Monitoring

Arterial blood pressure and central venous pressure are the most common parameters measured in the ICU patient.

15.4.1 Arterial Blood Pressure

Mean arterial pressure (MAP), the best parameter for assessing global perfusion pressure of all organs, should ideally be between 70 and 100 mmHg. The radial artery is most commonly used for intra-arterial catheter placement, but the brachial, femoral or pedal artery can also be used. In intra-aortic balloon counterpulsation, arterial blood pressure is measured with the same lumen of the balloon catheter.
Perfusion pressure requirements differ depending on the clinical situation and the organ in question. In the postoperative period after cardiac surgery, MAP must be >70 mmHg to ensure good perfusion of the bypass and good coronary blood flow (CBF), but it should be <100 mmHg to minimize postoperative bleeding. In a brain-injured patient with elevated intracranial pressure (ICP), however, MAP must be high enough to ensure adequate cerebral perfusion pressure (CPP). A patient in postoperative renal transplant requires good perfusion pressure to maintain adequate glomerular filtration rate of the graft.

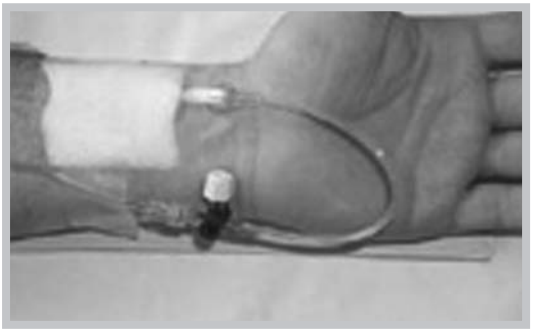

Figure 15.3. Radial artery catheter.

In addition to MAP, systolic blood pressure (SBP), diastolic blood pressure (DBP) and differential pressure (DP) allow us to infer a particular hemodynamic situation. A low diastolic pressure with a high differential may generate (besides aortic insufficiency) a pattern of vasodilatation and high cardiac output (sepsis). By contrast, a small differential pressure, with impingement of the SBP and DBP, can generate a pattern of low cardiac output (hypovolemia, cardiogenic shock).

Figure 15.4. Curve of arterial blood pressure (MAP).

The morphology of the curve offers additional information. Uneven and irregular arterial pressure waves can be seen in certain arrhythmias such as atrial fibrillation; unlike the ECG tracing, the monitor shows a higher pulse rate, i.e., the effective heartbeat is greater. And it also shows the variation in the amplitude of the pulse wave in relation to breathing [4], which is very evident in a patient with hypovolemia or cardiac tamponade (pulsus paradoxus: systolic pressure variation >12 mmHg between inspiration and expiration). This is magnified even more in patients on mechanical ventilation [5]. Pronounced respiratory variation of the pulse wave is also observed in patients with airflow obstruction. Therefore, bedside analysis of the arterial pressure wave is important in hemodynamic evaluation (Figures 15.3 and 15.4).

15.4.2 Central Venous Pressure

The introduction of central venous pressure monitoring in 1962 was the first step in bedside hemodynamic monitoring. The most common vascular access in ICU patients is via subclavian or internal jugular vein puncture. The distal end should be located in the distal part of the vena cava, without entering the right atrium or touching the tricuspid valve, as this can cause arrhythmias. The catheter serves for the infusion of solutions and drugs and to measure central venous pressure (CVP). This is an indicator of the balance between systemic venous return and right ventricular (RV) function. Its normal value is between 8 and 12 mmHg or, more widely, between 5 and 15 mmHg, although this "normal" value may differ depending on the patient's clinical situation. CVP is not correlated with right ventricular end-diastolic volume in critically ill patients, and it does not correlate with left ventricular preload in patients with right ventricular failure or pul-

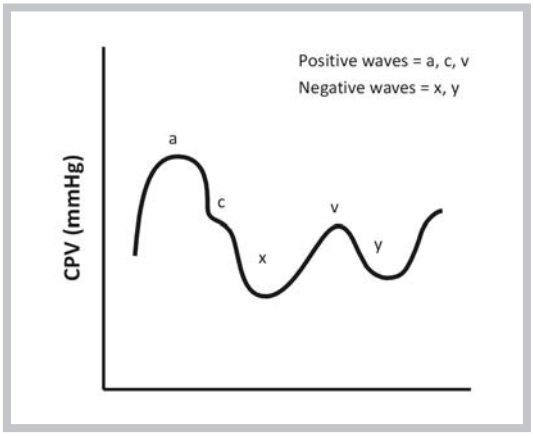

Figure 15.5. Morphology of the central venous pressure (CPV) curve.

monary vascular disease; however, in many cases when these values are extremely low or high, CVP can reflect a reduction or an increase in relative or absolute intravascular volume. The respiratory variation of CVP is due to a drop in CVP during inspiration, which is more marked in a setting of hypovolemia [6]. The greater the drop in CVP, the greater the need for volume replacement. Despite these limitations, CVP in the hands of an experienced operator is a useful parameter in the hemodynamic management of patients in intensive care. Figure 15.5 shows the standard morphology of the CPV curve.

15.5 Pulmonary Artery Pressure and the Swan-Ganz Catheter

The development and clinical application of a pulmonary artery catheter introduced by Swan and Ganz in 1970 provided a relatively simple, safe, fast and accurate way to measure pulmonary artery pressure and to estimate left ventricular end-diastolic pressure through the measurement of wedge pressure or pulmonary capillary wedge pressure.
Use of the Swan-Ganz catheter allows the calculation of cardiac output by the thermodilution method, as well as sampling of mixed venous blood from the pulmonary artery to assess systemic oxygenation.
The primary data are the measured variables; by applying mathematic formulas, other variables called secondary or calculated variables are obtained which complete the spectrum of hemodynamic information (Table 15.1) [7,8].
Later refinements to the original catheter have increased its usefulness, so that we can now continuously monitor cardiac output, determine the right ventricular ejection fraction, continuously measure right atrial pressure and oxygen saturation of mixed venous blood. There are also models that incorporate electrodes that can stimulate the right atrium or the right ventricle like a pacemaker.

15.5.1 Indications for Pulmonary Artery Catheterization

While there are no absolute rules that define the need for a Swan-Ganz catheter, there are clear recommendations for its use in certain contexts, such as acute myocardial infarction (AMI) with hemodynamic compromise. Its usefulness in other situations, such as routine use in cardiovascular surgery patients remains controversial. It can be useful in patients presenting with patterns of shock or severe hemodynamic instability or situations where the physician's experience suggests its use is warranted.

- Diagnosis or guide in the treatment of acute myocardial infarction:
  - Progressive heart failure, acute pulmonary edema.
  - Cardiogenic shock or progressive hypotension [9].
  - Mechanical complications (acute mitral insufficiency).
  - Doubt about the hemodynamic pattern: peripheral hypoperfusion or hypotension unresponsive to fluid administration without pulmonary congestion.
  - Patients with suspected AMI with hemodynamic compromise of the right ventricle.
- Determining the cause of dyspnea and hypoxemia:
  - Patients with coexisting cardiac and pulmonary disease (diagnostic difficulties and therapeutic dilemmas).
  - Patients with AMI and shock of unknown cause.
- Refractory heart failure:
  - Patients with dilated cardiomyopathy, hospitalized for decompensated heart failure, difficult to manage, requiring high doses of inotropes.

- Suspected pulmonary embolism with hemodynamic compromise.
- Septic shock [8,10,11], traumatic shock [12], vasoplegia.

Relative indications are:

- Assessment and management of patients with cardiac tamponade.
- Recurrent pulmonary embolism or pulmonary hypertension of unknown etiology [13].
- Perioperative monitoring in cardiovascular surgery patients.
- Acute Respiratory Distress Syndrome (ARDS).
- Assessment of pulmonary hypertension.
- Cardiac, pulmonary and cardiopulmonary pretransplant evaluation.

Most contraindications are relative and refer to an increased likelihood of complications during catheter placement. The technique is contraindicated in:

- Patients with severe coagulopathy or under thrombolytic therapy: high risk of bleeding.
- Patients with prosthetic tricuspid valve: the catheter can damage or cause valve dysfunction.
- Patients with implantable pacemakers: the catheter can become inadvertently displaced or knotted.
- Patients with pulmonary hypertension: high incidence of pulmonary artery rupture.
- Patients with right-sided endocarditis or vena cava system thrombosis.

15.5.2 Characteristics of Pulmonary Artery Catheters

Catheters can be used in children or adults. Catheters come in lengths between 60 and 110 cm and sizes from 4.0 to 8.0 F, balloon inflation volume 0.5 to 1.5 ml, and balloon diameter 8 to 13 mm. Made of polyvinyl chloride, they are flexible at room temperature and even at body temperature.

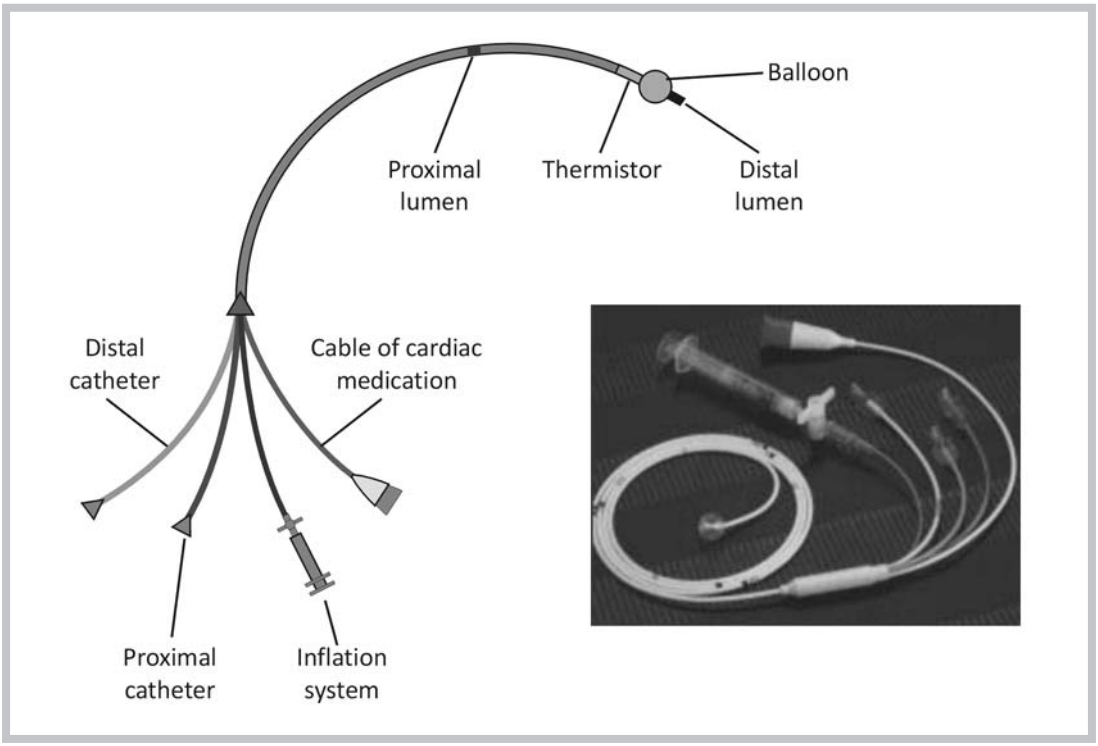

Figure 15.6. **Conventional Swan-Ganz catheter and optic fibre catheter.**

The catheter has markings every 10 cm consisting of black narrow bands from 1 to 4, at 10 to 40 cm, respectively. At the 50-cm mark the band is thicker than the others; the fine bands mark 60, 70, 80 and 90 cm. This helps to determine the location of the catheter tip during placement.
The most widely used conventional catheter is 4 lumens: distal (PA), proximal (RA), thermistor (thermodilution) and via inflation (balloon wedge) (Figure 15.6).
Other catheters incorporate various different features:

- 5 lumens (additional proximal lumen for fluid administration).
- Fibre optic catheter for continuously measuring mixed venous saturation in the pulmonary artery.
- Electrodes for use as a pacemaker.
- An additional lumen for the introduction of a temporary pacemaker catheter.
- A thermocouple to calculate right ventricular ejection fraction by measuring the end-systolic and end-diastolic volumes [14-16].
- A rapid-response thermocouple for continuous measurement of cardiac output by thermodilution.

15.5.3 Vascular Access for Swan-Ganz Catheter Placement

Operator experience dictates the vascular access site selected. In some patients, the depletion of vascular access or the presence of coagulation disorders, burns, or other conditions requires the use of alternative approaches.
Subclavian vein access has the advantage that it is easily accessible, allowing free movement of the arm and neck, with little risk of catheter displacement and reduced risk of thrombosis. The disadvantages are the increased risk of air embolism, puncture or laceration of the subclavian artery with hemorrhage because compression is difficult to apply. It may also cause pneumothorax, emphysema, especially in patients with mechanical ventilation with positive end-expiratory pressure (PEEP) and phrenic nerve or brachial plexus injury.
Internal jugular vein access has the advantage of direct access to the superior vena cava and right atrium, minor risk of catheter movement, low potential for thrombotic complications, lower incidence of arterial puncture and pneumothorax. The disadvantages are the increased risk of air embolism, puncture or laceration of the carotid artery and puncture of the trachea or the endotracheal tube cuff.
Femoral venous access is readily available but increases the chance of infection owing to its proximity to the inguinal area. It is contraindicated in patients with abdominal sepsis; it can impede optimum healing. The involved limb needs to be immobilized, increasing the risk of deep vein thrombosis and pulmonary embolism.
Peripheral venous access via the external jugular vein or basilic vein carries less risk of pneumothorax and can directly control hemostasis. However, it is associated with a higher incidence of infections, involves disabling a vein, and placement is more difficult because central venous access is not direct and there is greater risk of catheter malposition.

15.5.4 Placing the Swan-Ganz Catheter

First of all, explain the procedure to the family and the patient. Before arming the circuit, with 3-way keys and applying enough pressure, the transducer is attached to the patient's arm at the midaxillary line. It is important to proceed in a systematic fashion:
Before catheter placement:

- Verify that the ball is intact.
- Corroborate lumen patency.
- Check thermistor integrity.
- Prepare 2 bottles of saline solution (500 cc) plus 2500 U of heparin:
  - Bottle 1: high-pressure circuit (150-300 mmHg), with Intraflow Flush and Macrodrip. Venous extension connected to the distal lumen of the catheter (PA).
  - Bottle 2: venous extension connected to the proximal lumen of the catheter (RA).
- The transducer is placed at the level of the right atrium
- Calibrate the transducer with atmospheric pressure (zero).

Insert the catheter 40 cm into the brachial vein or 15 cm if using a subclavian or internal jugular puncture. Advance the catheter as guided under fluoroscopy to the pulmonary artery; alternatively, catheter introduction is guided by blood flow.

- Subclavian puncture: at 15 cm, should be the RA curve.
- Central venous pressure: check the RA curve and pressure.
- Inflate balloon with 0.5-1 ml of air.
- Withdraw 2-3 ml of blood with heparinized syringe.
- Scroll down until RV curve is obtained.
- Check the RV pressure curve.
- Normal RV pressure: 25/6 (15) mmHg.
- Blood samples for oximetry.
- Wash the catheter with the high-pressure circuit.
- Advance the catheter to the PA: there should be a sudden increase in pulmonary diastolic pressure.
- Check PA pressure curve.
- Normal pulmonary pressure: 25/10 (18) mmHg.
- Obtain samples for oximetry.
- Continue advancing the catheter balloon inflating it slowly.
- The flow is transported to a segmental branch of the pulmonary artery.
- Locking occurs and balloon pulmonary capillary wedge pressure (PW) is recorded.
- The balloon is deflated and PA pressure curve must be seen again.
- Verify proper catheter position with a chest X-ray.

15.5.5 Characteristic Curves

Figure 15.7 illustrates the typical evolution of the curve morphology.

Right atrium (RA). The curve shows waves (a, c and v) and troughs (y and x). In the absence of tricuspid valve disease, the average pressure of the RA is equal to right ventricular end-diastolic pressure, since both are connected at the time of valve opening.

During ventilation, positive pressure increases the pressure in the RA, whereas in spontaneous breathing, negative intrathoracic pressure decreases the pressure. Therefore, the pressure should be read to the end of expiration.

Right ventricle (RV). When the tip of the catheter enters into the right ventricle, there is a significant change in the structure of the pressure wave, becoming 3 to 4 times greater than that of the RA. Normal values are between 0 and 8 mmHg diastolic pressure, and 20 to 30 mmHg systolic pressure. At this time, there is the highest occurrence of arrhythmias.

Pulmonary artery (PA). When the catheter enters the PA, the curve changes again with a rise in diastolic pressure. The presence of a dicrotic notch on the descent of the curve indicates closure of the pulmonary valve. PA diastolic pressure is higher than RV pressure, which is isolated during valve closing. Normal diastolic pressure is approximately 10 mmHg and systolic pressure between 20 and 30 mmHg.

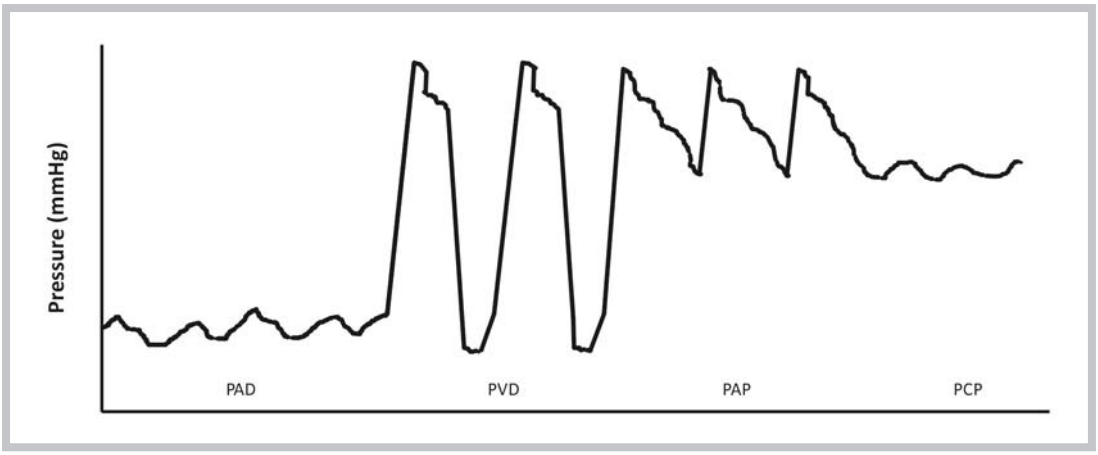

Figure 15.7. Typical pressure curves during Swan-Ganz catheter placement.

Pulmonary artery wedge pressure, pulmonary capillary wedge pressure (PW). With locking of the catheter, the curve flattens when it ceases to be pulsatile pressure. The blood flow is interrupted in a small portion of the pulmonary circulation and is thus connected to the lumen distally, reflecting the left atrial (LA) pressure, which is usually between 5 and 12 mmHg. The mitral valve opens during diastole. The catheter lumen is located in communication with a column of blood that reaches the left ventricle, thus indirectly measuring the left ventricular end-diastolic pressure (LVEDP). Therefore, there is a direct correlation between the PW, LA pressure and the LVEDP [17,18].

Causes damping of the curve. Any of the following may cause damping or defects in the curves:

- Bubbles in the system.
- Clots at the tip of the catheter.
- Transducer failure.
- Bad circuit connection.
- Catheter located distally.
- Lumen contact with vessel wall.

Guidelines for good results. The following items should be considered in pressure measuring:

- Remove air bubbles and blood clots.
- Discard bent or elongated catheters.
- Perform internal and external calibration with a mercury manometer.
- Check the calibration 3-4 times per day.
- Reset to zero before each measurement.
- Measure pressure at the end of expiration.

15.5.6 Measurement of Cardiac Output

The method currently used for cardiac output measurement is thermodilution [19,20]. For this, the computer records the patient's blood temperature from the thermistor incorporated in the catheter, and the temperature of the solution to be injected is recorded by an external thermistor near the solution, which is injected at room temperature (usually 25 °C). The difference between two temperatures should be >10 °C. The amount of solution (usually 10 cc) is entered into the computer, which subsequently determines a constant calculated from the preconditions and the catheter type entered into the program.

The solution is injected rapidly (3 to 5 seconds). The transient drop in blood temperature is recorded and transmitted by the thermistor, generating a thermodilution curve (time-temperature). The normal cardiac output curve has a rising portion, with a rapid increase reaching a peak followed by a gentle descent to return to baseline. The peak represents the lowest recorded temperature and also determines the temperature gradient between the venous blood and the injected solution. The downward slope of the curve represents the time of return to basal blood temperature. Thus, from the volume and temperature of the solution injected, the blood temperature and thermodilution curve, the software calculates the blood flow expressed as cardiac output (CO).
To obtain good results, the following guidelines should be followed:

- Adjust the constant of the computer according to the features used.
- Secure the position of the distal thermistor and the right atrium.
- Use 10 ml of water at room temperature, provided the temperature difference between the environment and the patient's core temperature is >10 °C.
- The solution should be injected rapidly and smoothly.
- The thermodilution curve should be harmonious.
- Rapid infusion of solution should not be performed during measurement.

15.5.7 Complications Associated With the Swan-Ganz Catheter

Atrial and ventricular arrhythmias due to mechanical stimulation of the endocardium may occur during placement, retention or removal of the catheter. The incidence of arrhythmias is higher in patients with myocardial ischemia, heart failure, shock, hypoxemia, hypocalcemia, hypocalcemia, hypomagnesemia and difficult placement of the catheter.
Right bundle branch block may occur due to mechanical irritation of the conduction tissue during catheter insertion. In general, this is not important, unless the patient has a history of left bundle branch block.
Balloon rupture. The absence of resistance to soft balloon inflation, the difficulty of enclaves and the aspiration of blood, all indicate balloon rupture. The average life of the ball decreases with excessive manipulation, averaging between 70 and 80 inflations.
The risks to the patient are air or balloon fragment embolism.
Catheter knotting occurs more frequently when there is enlargement of RA or RV, or the presence of another catheter. In some cases, the catheter can be cut and left in place or removed with a hemodynamic catheterization procedure or surgery.
Infections. Factors that increase the risk of infection include the location of an intracardiac catheter, excessive handling, the need for catheter repositioning, longer use, adherence of microorganisms to it, and severely critical patients. Since the risk of infection increase after 48 hours, the catheter must not remain for longer than necessary.
Thromboembolism. Thrombi can form in any part of the catheter, including the tip. The thrombi can directly occlude the PA branch, resulting in pulmonary ischemia or pulmonary embolism. Subclavian, internal jugular or vena cava thrombosis can also occur, with serious consequences.
Pneumothorax associated with venous access. The postinsertion chest X-ray should be carefully evaluated not only for correct catheter position but also to rule out pneumothorax.
Ischemia and pulmonary infarction result from catheter locking due to malposition or thrombus formation.
Pulmonary artery rupture may result in a small vascular injury or massive hemorrhage. It can be caused by catheter migration, tampering or balloon overinflation. It is more com-

Clinical situation	Hemodynamic pattern	Comments
Hypovolemic shock	↓PW, ↓CO, ↓MAP, ↑SVR	Peripheral vasoconstriction
Cardiogenic shock	↑PW, ↓CO, ↓MAP, ↑SVR	Severe heart disease
Septic shock	↓MAP, ↑MPAP, ↑PVR, ↑CO, ↓SVR	Warm skin, fast capillary refill
Cardiac tamponade	↑CVP, ↑PW, ↓CO, ↓MAP	Pulsus paradoxus, ↓y wave ↓x wave
RV dysfunction	↑CPV > 10, ↓CO, ↓PAP, CPV/PW >0.8	Deep y wave
Massive pulmonary thromboembolism	↓CO, ↓MAP, ↑PMAP, ↑PVR, normal PW	Normal PW, ↑SPAP, ↑DPAP
Chronic pulmonary hypertension	↑CVP, ↑RVSP,↑PMAP, ↑PVR, normal PW	Normal left-side pressures Elevated MPAP and RVSP
Constrictive pericarditis	↑CPV, ↑PW, dip-plateau in RV	Pulsus paradoxus, Kussmaul sign
Restrictive cardiomyopathy	PW > CVP	Echo Doppler for better diagnosis
Tricuspid regurgitation	↑CPV, ↑RVEDP	Prominent v wave
Septal defect	Increased PaO_2 of RA and RV to PA	RV CO >LV CO
Acute mitral regurgitation	PW, ↑v wave	Prominent v wave
Non cardiogenic pulmonary edema	Normal PW	Normal cardiac size

Table 15.2. Hemodinamic patterns.

mon in patients with pulmonary hypertension. It can manifest as intrapulmonary hematoma, mild hemoptysis, massive bleeding, and even shock and death.
The application of positive end-expiratory pressure (PEEP) can decrease bleeding. In extreme cases, emergency thoracotomy with resection of the affected lung lobe may be necessary.

15.5.8 Hemodynamic Patterns

From an analysis of hemodynamic monitoring variables and the clinical situation, we can distinguish different profiles or hemodynamic patterns. In this way, a particular diagnostic and prognostic category can be defined and treatment oriented accordingly. In some cases, such patterns can differentiate between hemodynamic variants of major syndromes, including shock, further subdivided into hypovolemic, septic, cardiogenic and mechanic shock.
In other cases, the patterns may allow us to identify different hemodynamic situations within the same disease, thus aiding in establishing prognosis and initiating a specific therapeutic approach.
Table 15.2 shows various different hemodynamic patterns.

15.5.9 Hypovolemic Shock

Hypovolemia refers to a reduction in intravascular volume due to hemorrhage or fluid and electrolyte loss from various causes. It implies a fall in CVP and PW, i.e., preload, with a consequent reduction in stroke volume. The compensatory response of sympathetic discharge (tachycardia, vasoconstriction) may initially maintain MAP and CO. Arterial hypotension (MAP <60 mmHg or drop >40 mmHg from baseline MAP), with impaired peripheral perfusion (pallor, slow capillary refill) and organ perfusion pressure

(oliguria, altered consciousness) form a hypovolemic shock pattern. Tissue hypoperfusion can cause lactic acidosis, indicating anaerobic tissue metabolism. The oxygen debt that is generated depends on shock duration and depth, and thus, the possibility of recovery, the degree of organ dysfunction or multiple organ failure and survival or death. The therapeutic response is high-flow infusing volume with an appropriate solution for the particular deficit (crystalloids, colloids, blood products), as well as life-sustaining treatment in shock.

15.5.10 Septic Shock

Septic shock is caused by a fall in SVR due to vasodilatation, with a loss in vasomotor tone and impaired microvascular blood flow (hypoperfusion, ischemia). The causes underlying vasodilatation are related to the action of inducible nitric oxide synthase and activation of cellular elements (leucocytes, platelets) which are part of the inflammatory response. It also produces an increase in cardiac output and an increase in mixed venous oxygen saturation in the pulmonary artery. PW may initially be low due to fluid loss which these patients manifest for various reasons, and it can be normalized in initial resuscitation. There is also impaired left ventricular contractility which is masked by the decrease in afterload. This phase, also called hyperdynamic shock, is followed in some cases by a hypodynamic phase, with a decrease in cardiac output and increased SVR, which is known as the cold-shock phase.

15.5.11 Cardiogenic Shock

In 1977 Forrester proposed a classification based on hemodynamic monitoring of patients after acute myocardial infarction (AMI) [21-23], which is still valid today. Different hemodynamic patterns (from I to IV) are generated according to Swan-Ganz catheter measurements. This classification scheme takes account the following parameters cardiac index (CI) (higher or lower than 2.2 l/min/m^2) and pulmonary capillary wedge pressure (PW) (more or less than 18 mmHg). The four hemodynamic patterns carry a different prognosis (mortality <5% in uncomplicated AMI and mortality >70% in cardiogenic shock) (Figure 15.8):

- Hemodynamic Pattern I. CI >2.2 l/min/m^2 and PW <18 mmHg. Normal hemodynamics. Mortality 2-5%. General treatment for AMI.
- Hemodynamic Pattern II. CI >2.2 l/min/m^2 and PW >18 mmHg. Heart Failure. Mortality 12%. Treatment with vasodilators and diuretics.
- Hemodynamic Pattern III. CI <2.2 l/min/m^2 and PW <18 mmHg. Hypovolemia, low cardiac output. Mortality 33%. Treatment with volume expansion, eventually with inotropics.
- Hemodynamic Pattern IV. CI <2.2 l/min/m^2 and PW >18 mmHg. Cardiogenic shock. Mortality 70%. Treatment with vasodilators if possible, diuret-

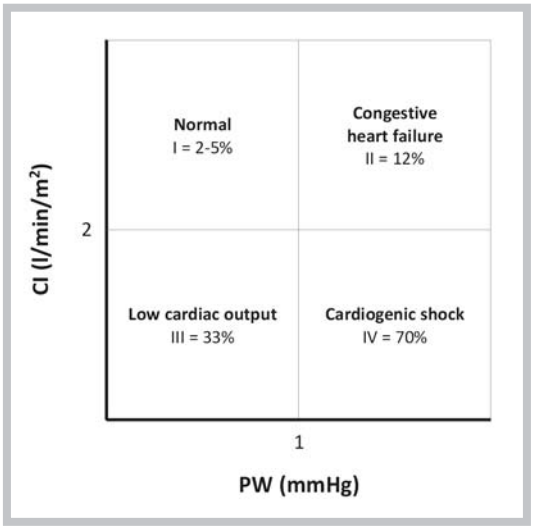

Figure 15.8. Hemodynamic Patterns in AMI (Forrester).

ics, eventually with inotropes, intra-aortic balloon counterpulsation as therapy or as support in revascularization (angioplasty or surgery).

Right ventricular infarction has a particular hemodynamic pattern [24].

15.5.12 Hemodynamic Monitoring in Heart Failure

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial [25,26] compared therapeutic management guided by clinical variables versus management guided by hemodynamic monitoring. There were no significant differences in the endpoints of death or hospitalization at 6 months follow-up. However, the results obtained in the monitored group may have been influenced by the heterogeneity of management.

There is a patient population with a clear indication of hemodynamic monitoring (advanced heart failure, unstable or refractory to treatment). Hemodynamic monitoring-adjusted therapy in these patients can achieve hemodynamic values associated with increased survival.

Building on Forrester's hemodynamic patterns, Stevenson devised a grid of patterns for clinical evaluation in patients with heart failure [27,28]:

Patients with normal perfusion (warm), types A and B, (Forrester I and II) and hypoperfused patients (cold) L and C (Forrester III and IV), above or below the cardiac index limit (2.2 l/min/m^2).

Also considered were patients without pulmonary congestion (dry), types A and L, and those with pulmonary congestion (wet), types B and C, according to PW below or above 18 mmHg.

Most patients hospitalized with decompensated heart failure were admitted with a humid/hot clinical profile (type B pattern) which correlates with a type II hemodynamic profile, i.e., a cardiac index >2.2 l/min/m^2 and pulmonary capillary pressure (PCP) >18 mmHg.

Patients with decompensated chronic heart failure can benefit from hemodynamic monitoring [29,30] since it does not increase mortality and significantly improves symptoms. The objective of improving quality of life is important in patients with advanced heart failure.

Figure 15.9 illustrates the correlation between hemodynamics and clinical characteristics in heart failure.

15.5.13 Hemodynamic Patterns in Critically Ill Patients

Based on the patterns developed from hemodynamic cardiology, we can define a set of hemodynamic profiles involving the global universe of critically ill patients. From a practical point of view, hemodynamic situations in intensive care can be divided using as benchmarks the cardiac index (CI) and pulmonary capillary wedge pressure (PW).

Cardiac index values between 2.0 and 3.5 l/min/m^2 are considered normal; pulmo-

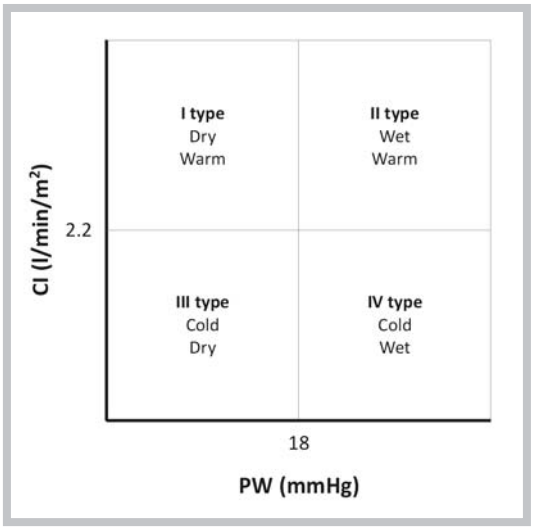

Figure 15.9. Correlation between hemodynamics and clinical characteristics in heart failure.

nary capillary pressure between 8 and 18 mmHg is considered normal.

The lower cut-off value of the cardiac index <2.0 l/min/m^2, as an indicator of circulatory hemodynamic patterns, is arbitrary in pathophysiological terms, and should be demonstrated by tissue hypoxia below this limit. The correlation of tissue perfusion factors such as gastric intramucosal pH or elevated lactic acid levels does not always hold in this situation [31]. The point is that we know many details of the oxygen supply to the tissues, but little about their metabolic oxygen need.

Another important indicator of global tissue oxygenation is the mixed venous oxygen saturation in the pulmonary artery measured continuously. However, it is difficult to measure this on a routine basis. In the postoperative period after cardiac surgery there is a correlation between the decrease in cardiac output and mortality, with a cardiac index <2 l/min/m^2, a point below which mortality significantly increases [32,33]. A cardiac index >3.5 l/min/m^2 is considered high, leading to hyperdynamic circulatory patterns.

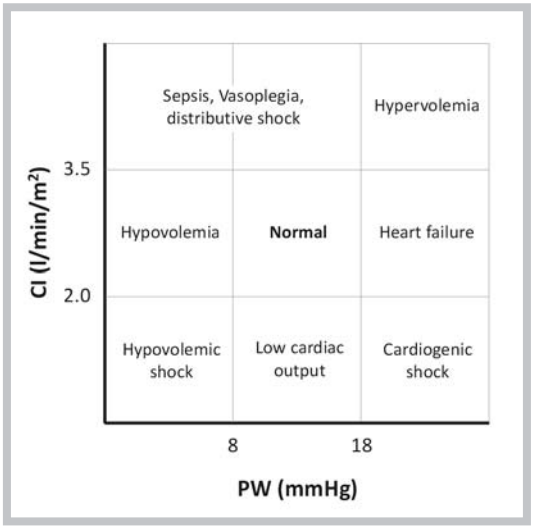

Figure 15.10. Hemodynamic patterns in ICU patients.

We consider pulmonary capillary wedge pressure (PW) values between 8 and 18 mmHg as normal. Patients with PW <8 mmHg and hemodynamic instability (hypotension) improve rapidly with intravascular volume expansion. Otherwise, patients with PW >18 mmHg are generally in volume overload.

Nine hemodynamic patterns are distinguished (Figure 15.10).

These nine patterns are defined by a parameter of preload (PW) and another that results from stroke volume and heart rate, but it can also be roughly considered as a parameter of contractility. Systemic vascular resistance is increased in the lower quadrants, usually increased in the middle lateral quadrants, and reduced in the upper quadrants.

The central quadrant is considered **normal**, with normal values of both CI and PW.

Patients with normal CI and low PW can be considered **hypovolemic**, but do not necessarily require volume expansion if the global perfusion parameters (peripheral perfusion and diuresis) are adequate. In some cases it is necessary to maintain a preload within the limits and to expansion with solutions, as in the maintenance of brain-dead potential organ donors who have polyuria and diabetes insipidus or in patients with postrenal transplant polyuria.

Patients with normal CI and high PW fall within the category of *congestive* **heart failure or pulmonary congestion** due to volume overload with impaired contractility. The proper treatment in these patients is with diuretics, vasodilators and eventually inotropics.

The upper quadrants include patterns of **hyperdynamic circulation** with increased CI. Patients with normal or low PW are generally vasodilated, with low SVR and increased CI, as in septic, distributive or traumatic shock. Vasoplegia also occurs in some patients in the postoperative period after cardiac surgery. In patients with low PW we must correct the hypovolemic component with volume expansion and then assess the response. The use of vasopressors such as norepinephrine, with its alpha dominant effect, is the treatment of choice to increase SVR in these patients, and thus avoid severe hypotension.

Patients with high CI and PW fall into the quadrant of **hypervolemia**, reflecting lung congestion. Usually, these patients are hypertensive and there is a decrease in SVR to compensate the increase in CI. As a typical example, here we can categorize patients with acute renal failure. Vasodilators may be used if the patient is hypertensive or presents with severe pulmonary congestion and dyspnoea. Diuretics and hemofiltration or eventually hemodialysis are necessary to remove the fluid overload.

The lower quadrants include low cardiac output states.

Patients with low CI and low PW can be categorized as having **hypovolemic shock** (shock involves clinical criteria for arterial hypotension and hypoperfusion). Volume expansion is the obvious therapeutic resource, in addition to treating the cause of volume loss.

Patients with low CI and high PW fall into the cardiogenic shock quadrant.

An interesting group comprises patients with low CI and normal PW. This pattern is called simply low cardiac output.

Low cardiac output (LCO) syndrome is well described in postoperative cardiac surgery [32,33] although it may be observed in other contexts as well. The reported prevalence (10-15%) varies widely according to the diagnostic criteria [32,34,35].

The development of LCO may be due to many causes that affect preload, contractility, afterload and heart rate. But the most likely mechanism is systolic and diastolic dysfunction associated with left ventricular ischemia and reperfusion phenomena which produce varying degrees of myocardial injury and stunning. The underlying conditions can be determined by the degree of previous ischemia, defects in intra-operative myocardial protection, incomplete revascularization, and prolonged cross-clamping time, which are closely related to peri-operative ischemic injury. However, other risk factors not strictly related to this may also be relevant to the development of LCO.

The low cardiac output syndrome is usually associated with hypotension and hypoperfusion signs (oliguria, cold extremities, acrocyanosis and metabolic acidosis).

The reported mortality is 10-40%, with a high rate of morbidity (renal failure, prolonged mechanical ventilation, prolonged hospitalization), and a consequent increase in costs.

While the strategies for myocardial protection and surgical technique, including off-pump surgery, have improved in recent years, the risk of patients undergoing heart surgery has also increased, so it is likely that the morbidity associated with this type of surgery has not changed or perhaps even increased.

Strategies to reduce the incidence and impact of low cardiac output include improved methods of myocardial protection in high-risk patients. Moreover, the early detection and aggressive management of patients who develop LCO are critical to minimize the disruption of tissue perfusion that generates the morbidity associated with this complication.

Management includes optimizing the preload by bringing the PW to a value high enough to achieve good pressure/volume for good filling of these ventricles, usually with restrictive diastolic dysfunction. It is also necessary to use inotropic drugs and inodilators (dobutamine, amrinone, milrinone) [36]. In general, vasodilators cannot be given to reduce afterload due to hypotension and vasopressors may even be required.

Usefulness and limitations of using the scheme of nine hemodynamics patterns

Patients with mechanical shock (cardiac tamponade, tension pneumothorax) and right ventricular failure are excluded from this scheme; these situations and should be taken into account when assessing a patient in shock.

While the limits for determining these hemodynamic patterns are somewhat arbitrary, they allow us to categorize patient populations with different degrees of risk and mortality.

These hemodynamic situations can evolve over time [37]. The therapeutic goal is to take the patient to a normal central quadrant, although this is not always possible or not convenient for the patient.

Remember, finally, we treat patients, not numbers. The purpose of hemodynamic monitoring is to provide a quantitative basis which, together with clinical criteria, upon which we can make the best decisions for patient's benefit.

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16 Cardiac Arrhythmias in Nervous System Disorders

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16.1 Introduction

First described in detail by neurosurgeon Harvey Cushing in 1901, the discovery of the Cushing phenomenon led to the recognition of interactions between neurological events and their impact on the cardiovascular system. Central nervous system (CNS) insults can induce abnormalities in heart morphology and rhythm.

Neurological diseases can be detected directly at the heart, as a consequence of genetic and electrolytic changes, or indirectly through changes in the autonomous nervous system or the neurohormonal system. In addition, arrhythmias can cause neurological disease through the increase of thrombogenesis or the reduction of blood flow (cardiac arrest, bradycardia, etc.).

16.2 Stroke

Traumatic brain injury, acute ischemic stroke and hemorrhagic stroke have been associated with arrhythmias. They may be related to autonomous nervous system disorders affecting the cortical structures, particularly the insula (resulting in cardiovascular malfunction). This region may be involved in the control of heart rhythm and rate. Proarrhythmic changes in the cardiac sympathetic-vagal balance have been described after an event involving insula lesions. Cardiac function is modulated by the CNS in two ways: indirectly via humoral mediators such as adrenaline and noradrenaline and directly via the afferent effects of the sympathetic and parasympathetic system.

Hypothalamic lesions frequently result in an increase in catecholamine release and autonomic tone. These changes cause arterial hypertension, an increase in oxygen consumption and vessel spasm, leading to characteristic electrocardiographic (ECG), echocardiographic, enzymatic and histological changes, with subendocardial ischemia, microhemorrhage and focal necrotic lesions.

Hypokalemia is associated with prolongation of the QT interval. Subarachnoid hemorrhage is most often related to ECG changes (25-80%). Closed cranial trauma can produce ECG changes similar to subarachnoid hemorrhage. The ECG alterations most frequently associated with subarachnoid hemorrhage are: ST-T depression, T-wave inversion, U-wave prominence, and prolongation of the QT interval. A wide variety of arrhythmias have been described, such as sinus tachycardia, sinus bradycardia, auricular fibrillation, paroxysmal auricular tachycardia, ventricular extrasystolia, ventricular tachycardia, ventricular fibrillation and first, second and third-degree atrioventricular (AV) block.

Such changes have also been described for ischemic accidents, although in this group of patients the relationship is difficult to establish because of the major prevalence of coronary disease and arteriosclerosis. Typical changes are QT interval prolongation, ST disorders, and T- and U-wave abnormalities.

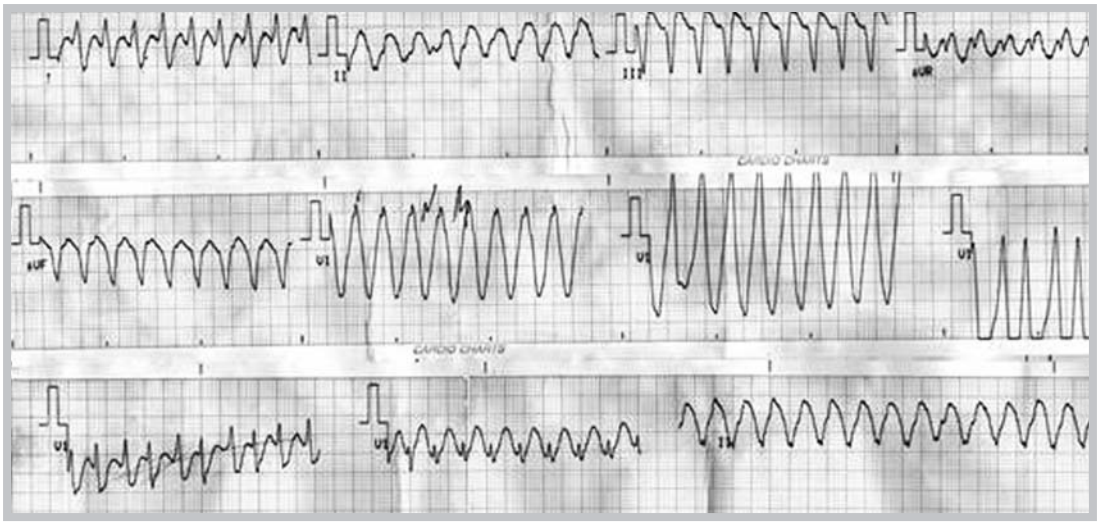

Figure 16.1. An episode of sustained monomorphic ventricular tachycardia.

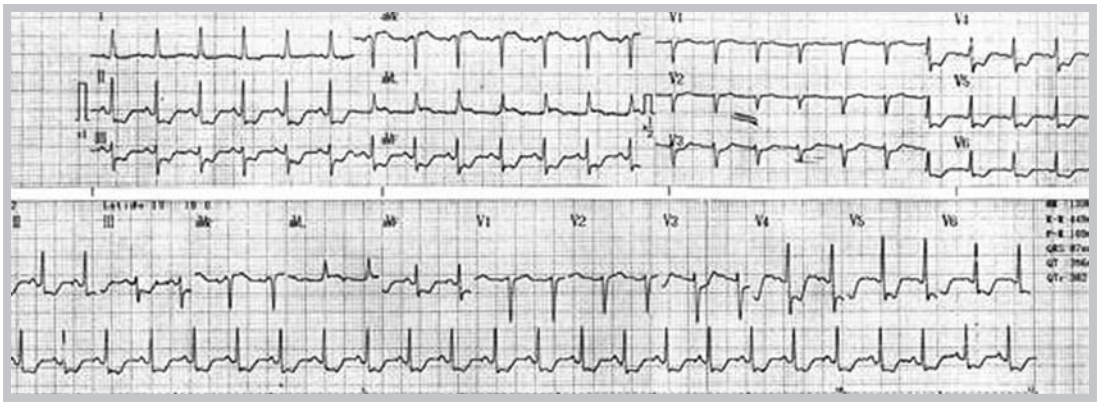

Figure 16.2. 36-year-old patient with traumatic brain injury and inferolateral ST-T depression without angiographically significant coronary lesions.

An increase in intracranial pressure can manifested with ECG changes and Cushing response: bradycardia, AHT and pulse pressure increase.

Treatment is mainly focused on monitoring heart rhythm and controlling electrolytic levels, particularly potassium. Therapy with beta blockers has proved effective in ventricular and supraventricular arrhythmias and in the reduction of myocardial damage related to subarachnoid hemorrhage and head trauma.

16.3 Paroxysmal Essential Hyper- and Hypopothassemia (Periodic Paralysis)

These kinds of paralysis are characterized by weakness episodes associated with increased potassium, though presenting normal K levels. Frequently, the attacks are induced by exercise and exposure to cold weather. Ventricular extrasystoles, ventricular tachycardia and ventricular bidirectional tachycardia are often observed.

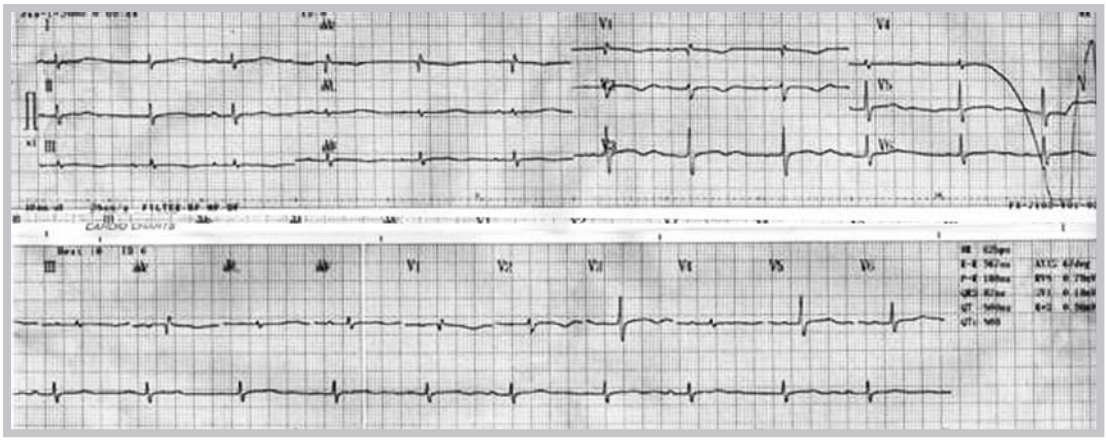

Figure 16.3. **Sinus rhythm with prolonged QT interval.**

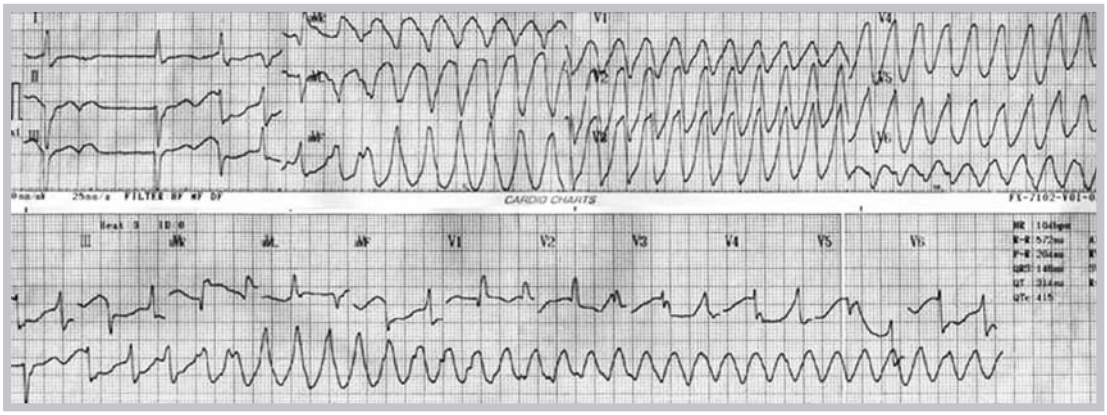

Figure 16.4. **Torsades de pointes. Patient with severe hypokalemia, 1.6 mEq/l paralysis. Strong ventricular arrhythmias, QT prolongation and ventricular extrasystoles are frequent.**

Weakness episodes and arrhythmias usually respond to measures initiated to normalize plasma potassium and mexiletine levels.

Paroxysmal essential hypopothassemia manifests as periodic paralysis attacks, with low potassium levels. Andersen's syndrome refers to periodic paralysis sensitive to potassium, associated with low implantation of the ears, clinodactyly, prolonged QT interval and ventricular arrhythmias. Weakness episodes are intense and prolonged, with attacks induced by exposure to cold weather and post-exercise rest. Carbohydrates can also cause episodes.

Correction of potassium levels usually improves the weakness, although arrhythmias tend to persist. Beta blocker therapy produces an improvement in non-sustained ventricular tachycardia. Anti-arrhythmia 1A-type medications should not be given because they exacerbate weakness and associated arrhythmias with prolongation of QT interval.

16.4 Dystrophy

Duchenne muscular dystrophy can present:

- Conduction disorders with an increase in conduction speed and short P-R (<120 msec.) or prolonged infranodular conduction in some patients.

- Rhythm disorders with sinus tachycardia secondary to alterations in the autonomic system, or due to fibrosis and fat infiltration of the sinus node, which develops a field for intranodal re-entrance; fibrillation and auricular flutter; ventricular extrasystole; ventricular tachycardia with late potential development. Heart death in 25% of patients, equally distributed between sudden death and progression to cardiac insufficiency.

Arrhythmia **treatment** with anti-arrhythmia drugs produces major respiratory insufficiency, besides a major risk of respiratory insufficiency associated with implantation of a heart defibrillator, without improvement in prognosis.

16.5 Myotonic Muscular Dystrophy

Cardiac alterations are mainly arrhythmias, with frequent ECG anomalies including AV blocks, branch blocks, and unspecified delays in intraventricular conduction. It manifests as pathological changes, with unknown mechanisms leading to conduction system degeneration (fibrosis and fat infiltration) of the sinus node, the AV node, the His and Purkinje fibres, and the auricular and ventricular fibres. It may progress to symptomatic myocardiopathy. Reduced conduction with positive late potentials is observed.

Conduction system disorders can progress to complete AV block, requiring a definitive pacemaker. Prophylactic implantation of a pacemaker must be evaluated. 2008 ACC/AHA/HRS guidelines suggest considering, in conduction disorders of myotonic muscular dystrophy patients, implantation of definitive pacemaker in patients with second or third degree symptomatic or asymptomatic AV block.

Auricular tachycardia, auricular flutter and auricular fibrillation are frequent arrhythmias (4%), often well-tolerated by controlled ventricular frequency due to concomitant conduction disorder.

Sudden death occurs in one third of patients and is believed to be caused by secondary asystole, although sudden deaths have been seen in pacemaker-bearing patients. Ventricular arrhythmias have been associated with branch-branch tachycardia.

16.6 Steinert Myotonic Dystrophy

This autosomal dominant disease is caused by a gene on the long arm of chromosome 19. It is clinically characterized by muscular weakness and myotony. Two forms are distinguished: a moderate, slowly progressive form with stationary periods, in which muscular weakness is limited to the forearms and dorsal foot flexors, scarce myotony without CNS disorders, while cataracts and cardiac conduction disorders are frequent; and the classical form characterized by more rapid progression and concomitant florid myotony. Muscular weakness has a characteristic distribution (facial, mandibular, cervical and peripheral flexor); there is usually palpebral ptosis and weakness in the masseter and orbicular muscles. Unlike scapular-humeral dystrophy, the scapular waist is affected late in the course of the disease; and unlike other myopathies, distal muscular weakness in the extremities is worse. Myotony tends to appear between the age of 5 and 25 years and it is characterized by involuntarily maintained muscle contraction when hit by a reflex hammer, for example, to the thenar musculature or when inviting the patient to contract a muscle. These patients tend to have low IQ, apathy, aggressiveness, hypersom-

nia, possibly due to an increase in gliosis, and decreased blood flow as detected by proton spectroscopy studies.
Cardiac alterations are caused by progressive fibrosis in the conduction ways, shown as arrhythmias (first degree AV-block, sinus bradycardia and branch blocks); there is a major risk of sudden death in the early phase of the illness.
Arrhythmias often prompt patients to seek medical attention. It is important to perform periodical evaluation with cardiac echo-Doppler and ECG.

16.7 Emery-Dreyfuss Muscular Dystrophy

This familiar disorder presents with mild weakness in skeletal musculature and frequent and lethal arrhythmogenic disorders. A recessive hereditary disease (less frequently dominant) related to chromosome X, it generates an alteration in the membrane protein emerin. This protein is located in the cardiac desmosomes and is associated with conduction disorders.
The dystrophy presents a triad of precocious contractures of the posterior cervical muscles, elbow muscles and the Achilles tendon, with weakness and slowly progressive muscular atrophy and cardiac alterations.
It is associated with dilated myocardiopathy and a high prevalence of conduction disorders. Conduction disorders, with AV blocks, auricular flutter, auricular fibrillation, sinus arrest, and union-rhythm bradycardia, start to appear in the third and fourth decades of life. Cardiac stimulation becomes necessary by the age of 40-50 years.
Sudden death has been described in association with ventricular tachycardia and auricular fibrillation.
Follow-up and surveillance of ECG disorders by means of Holter monitoring, ECG and echocardiography should be done. With progression of the disease, stimulation with a permanent pacemaker and/or an implantable automatic cardiac defibrillator is recommended.

16.8 Muscular Dystrophy of the Extremities and the Waist

This group of hereditary recessive (type 1) and dominant (type 2) disorders, including subgroups 1B, 2C, is associated with cardiac alterations such as dilated myocardiopathy. Other disorders manifest with the evolution towards progressive AV block, requiring pacemaker implantation. Episodes of sudden death have been described, even with the use of a permanent pacemaker, which suggests ventricular arrhythmias.
Follow-up with ECG, Holter monitoring and echocardiography is recommended, with special attention to at-risk subgroups, and eventual pacemaker implantation.

16.9 Friederich's Ataxia

This cerebrospinal degenerative recessive autonomic hereditary disease is characterized by ataxia of the extremities and torso, dysarthria, loss of deep tendon reflexes, sensorial anomalies, skeletal deformities and cardiac alterations. The genetic disorder is associated with chromosome 9, responsible for production of the protein frataxin.

The severity of the neurological symptoms and cardiac hypertrophy are related to alterations in this protein, which is a mitochondrial protein key to iron homeostasis and cell respiration.
Concentric ventricular hypertrophy is most frequently associated with Friederich's ataxia, although it has been observed with asymmetric septal hypertrophy and/or dilated myocardiopathy in some cases. Concentric ventricular hypertrophy signs are the most frequent ECG findings, with diffuse T-wave inversion. Auricular arrhythmias, as auricular flutter or auricular fibrillation, are generally associated with progression of the disease. Sudden death has been described, although its mechanism is not yet well known. Conduction disorders have not been described.

16.9.1 Treatment

Evolution to a severe dilated myocardiopathy requires treatment of cardiac insufficiency without any specific treatment.

16.10 Kearns-Sayre Syndrome

This encephalopathy results from anomalies in mitochondrial function. Histopathological studies of the skeleton and heart muscles show an abnormal proliferation of mitochondria.
Conduction alterations constitute the most typical cardiac abnormality, dilated myocardiopathy being less frequent. It presents with fibrosis and fat infiltration of the conduction system.

Figure 16.5. Preexcitation syndrome. Sinus rhythm, short PR and delta wave.

Diagnosis is based on the triad ophthalmoplegy, pigment retinopathy and cardiac block, with prolonged HV interval. Preexcitation leading to supraventricular paroxysmal tachycardia has been described. When there is a conduction disorder, prophylaxis with a definitive pacemaker is recommended.

16.11 Leber's Hereditary Optical Neuropathy

Another mitochondrial encephalopathy, characterized by a painless loss of bilateral vision, this pathology is associated with a short PR interval and preexcitation syndromes, with the development of supraventricular arrhythmias.
Preexcitation with paroxysmal tachycardia symptoms indicates treatment of the anomalous conduction.

16.12 Guillain-Barré Syndrome

This is an acute demyelinating inflammatory neuropathy, with malfunction of peripheral nerves, cranial pairs and the autonomous nervous system. Arrhythmias such as bradycardia, asystole, inappropriate sinus tachycardia, auricular fibrillation, tachycardia and ventricular fibrillation are related to the autonomous disorder. It may also be associated with hypertension and diaphoresis. These arrhythmias lead to an increase in mortality.
Intravenous administration of immune globulin or plasmapheresis improves prognosis. Monitoring is important. In patients with rhythm disorders, implantation of a temporary or permanent pacemaker is recommended. Infusion of atropine or isoproterenol before tracheal aspiration manoeuvres is recommended.

16.13 Myasthenia Gravis

This chronic autoimmune neuromuscular disease is caused by the production of antibodies directed against the nicotine receptor of acetylcholine. Producing weakness in voluntarily-controlled muscles, this weakness increases with activity and decreases with rest. The main symptom is fluctuating weakness, which usually starts with the ocular and facial muscles. It is generally associated with thymus gland hyperplasia.
Myocarditis is frequently associated, although arrhythmias such as auricular fibrillation, AV block, asystole, and sudden death have also been observed
Immunosuppressive medication and anti-cholinesterase are part of the typical treatment. These can diminish heart rate and hypotension. Administration of uinidine and propranolol can exacerbate weakness.

16.14 Epilepsy

The estimated annual incidence of epilepsy and sudden death varies between 1/370 and 1/1000 epileptic patients. The incidence is higher in the 20-to-40-year age group and higher still in very symptomatic epileptic patients. Unexpected sudden death is 3.8 to 9.3 times more frequent in epileptic patients than in the general population: 100% of

cases experience generalized tonic-clonic seizures alone or combined with another type of crisis, most complex partial crises having been deduced from what witnesses or doctors said or what the electroencephalogram showed.

Some 60% victims present with a structural cerebral lesion responsible for the attack. This percentage is much lower in non-selected epileptic patients. The types of lesion found were old frontal contusion, old penetrating lesion, chronic subdural hematoma, cortical arteriovenous malformation, tumour or old stroke.

Electrical events during an epileptic attack lead to centres involved in the heart's neurovegetative function, causing cardiac arrest or fatal arrhythmia. It seems that sympathetic, more than parasympathetic, activity reaches the heart, causing a fatal cardiac response associated with the crisis, but it is unclear why this occurs in certain patients. It could be because of a subtle myocardial lesion difficult to demonstrate following habitual autopsy techniques. Some authors have reportedly found small fibrotic areas in the terminal arteries, focal lesions of the myocarditis type and focal endocardiac fibrosis in conduction bundles. These can have their origin, as shown by experimental studies, by intense repeated sympathetic stimulation during the crisis.

According to Lathers et al., electrophysiological evidence of cerebral discharge due to arrhythmogenic potential was induced by generalized crises in anesthetized and mechanically-ventilated cats. Recording two separate branches of the sympathetic cardiac nerve and the vagus nerve, they proved that activity outbreaks occurred in the sympathetic cardiac nerves synchronized with ictal and interictal points of the EEG. With determined doses of the substance used to induce the crises (penthylentetrazol, [PTZ]), the degree of synchronization, variable between both branches of the sympathetic cardiac nerve, could be lost. Therefore, it was suggested that the different branches of the sympathetic cardiac nerve innervate different areas of the ventricular myocardium. The imbalance in the activities of the sympathetic and parasympathetic nervous system branches is thought to provoke a non-homogeneity in heart depolarization and repolarization which allows for the appearance of irritability places, re-entrance circuits and ventricular ectopias. Furthermore, the authors suggested that this mechanism can be activated in a normal crisis in the presence of subtherapeutic levels of anti-epilepsy medication, resulting in malignant arrhythmias and sudden death.

The most important data have been obtained, nevertheless, by stimulation of the hypothalamus, although there are changes in arterial pressure and respiration. However, it seems difficult to believe this to be the highest cerebral level of cardiac representation: there should be cortical mechanisms involved.

As to the type of arrhythmia observed, there were auricular fibrillation, multifocal premature ventricular contraction, ventricular tachycardia, sinus bradycardia, asystole periods and torsades de pointes. Interestingly, we have a patient with a right frontal glioma repeatedly suffering from supraventricular paroxysmal tachycardia which disappeared only after tumour removal. An alternative explanation to this is that the high levels of catecholamines have their role in the production of a neurogenic pulmonary edema observed after the appearance of different brain lesions. Hypoxia conditions could generate acidosis and, consequently, arrhythmias.

Systematic studies of cardiac rhythm alterations during a crisis indicate the appearance of:

- Sinus tachycardia in more than 90% of cases.
- Frequent auricular and ventricular ectopias in more than half of patients.
- Occasionally, periods of ventricular tachycardia, supraventricular paroxysmal tachycardia, bradycardia and even sinus arrest.

Changes in repolarization show up on the ECG tracing as a depression or elevation of the ST segment, T-wave inversion and altered morphology, variation in the R-R interval, increase or decrease of PR- and QT-intervals.

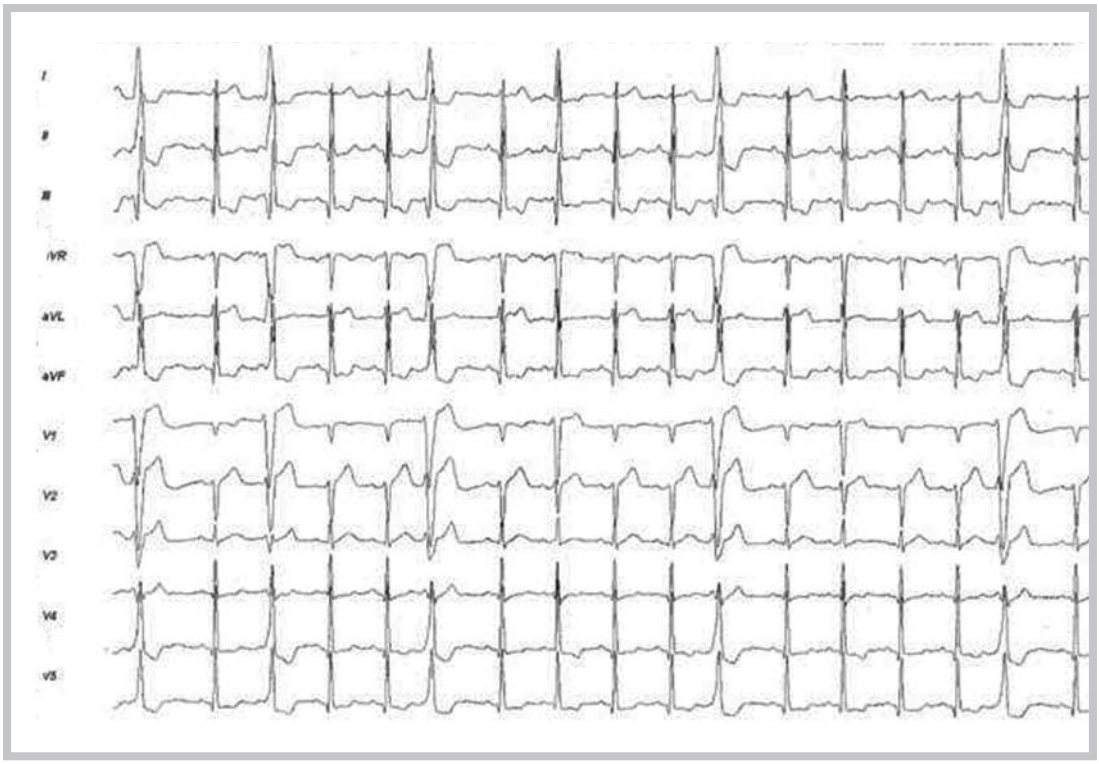

Figure 16.6. Patient with convulsive episodes, with sinus tachycardia and frequent ventricular extrasystole.

Figure 16.7. Sinus tachycardia with vibration of baseline ECG due to muscular tremor.

The induction of arrhythmias by photostimulation in cases of photosensitive epilepsy has also been observed: bradycardia or sinus tachycardia, and sinus arrest coinciding with the start of QRS.

There are patients who, investigated because of cardiac arrhythmias, are incidentally discovered to have epilepsy. Though they do not generally respond to conventional anti-arrhythmia drugs, they actually do respond to epileptic treatment.

Yearly assessment with ECG, 24-hour Holter monitoring and electrophysiological studies, as part of the diagnosis of arrhythmic patients, can help to determine etiology and guide treatment. Successful radiofrequency ablation of ventricular arrhythmias has been described. There is little experience with the use of implanted cardiac defibrillators.

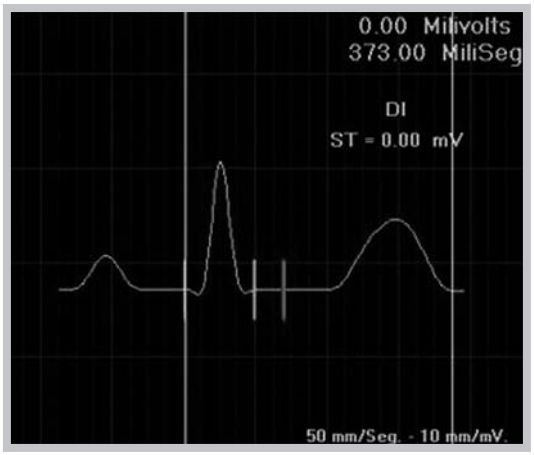

Figure 16.8. **QT interval measured from the beginning of QRS to the end of the T wave.**
QT: 373 msec.
QT corrected following Bazett's formula

$$QTc = QT / \sqrt{RR}$$

Standardization of the interval due to variation in heart rate.

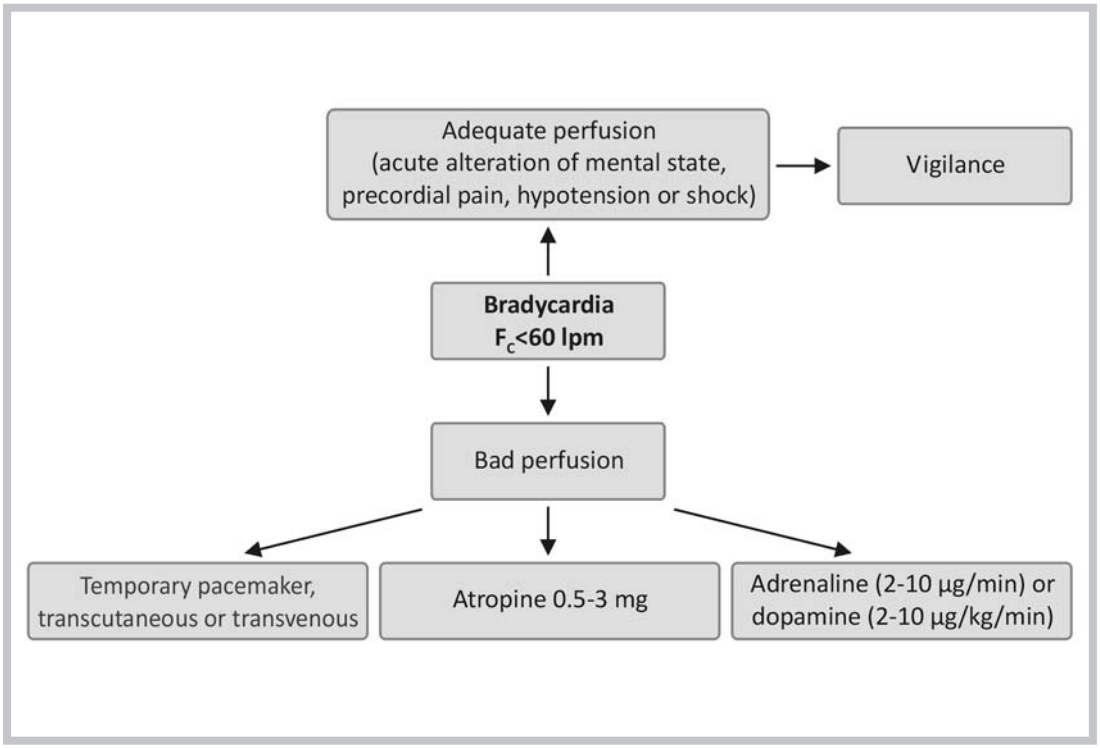

Figure 16.9. **Flow chart for the treatment of bradycardia.**

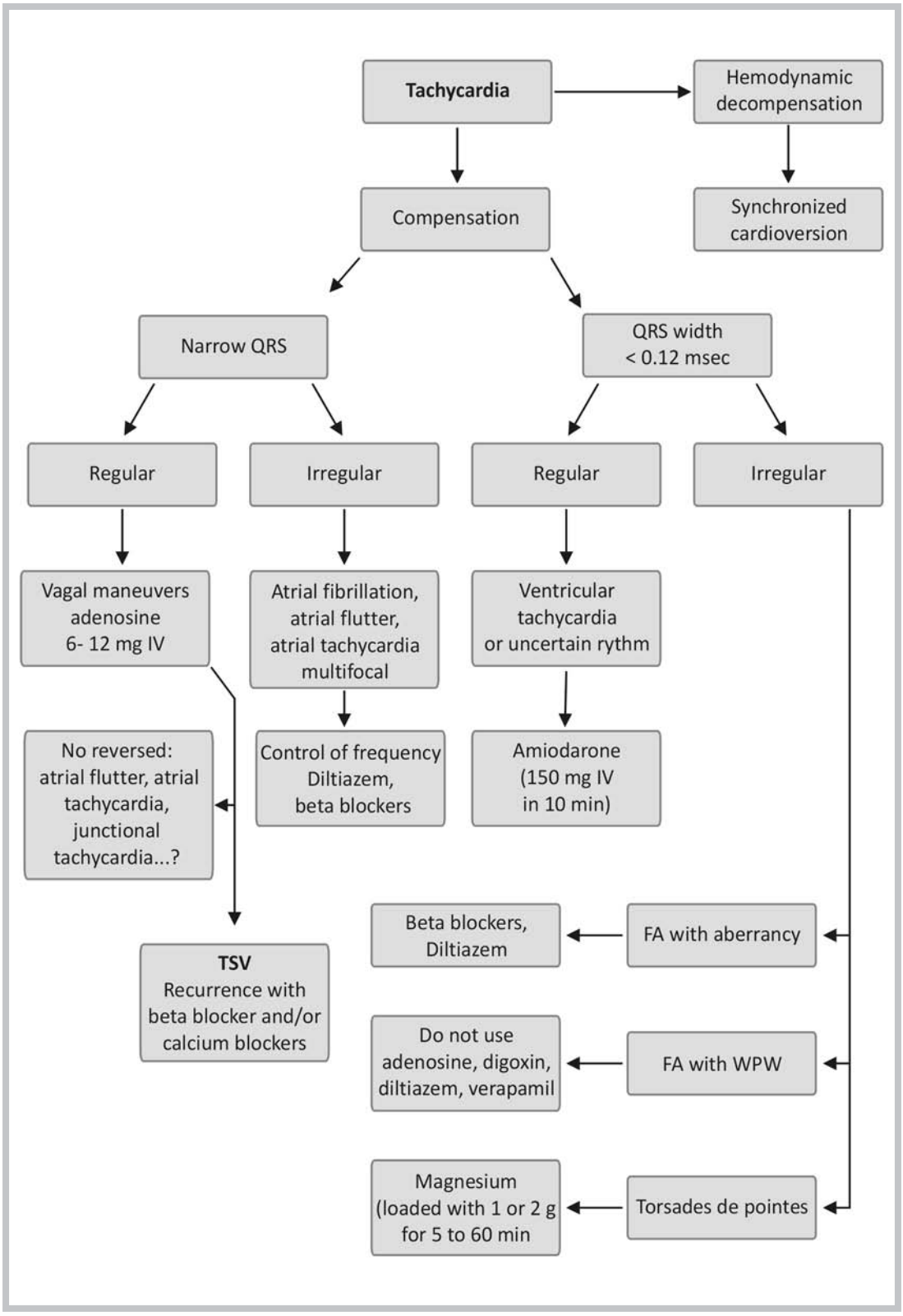

Figure 16.10. Flow chart for the treatment of tachycardia.

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17 Mechanical Ventilation in the Neurologic Critically Ill Patient

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17.1 Introduction

Acute brain injury, mainly head trauma or stroke, are devastating conditions with high morbidity, mortality and long-term sequelae, and huge economical and social costs. Respiratory depression, by itself or as a contributing factor, is one of the main causes of respiratory failure in the neurologic critically ill patient. Respiratory depression induces alveolar hypoventilation, airway obstruction, gastric content aspiration and hypoxemia, among others. The interaction between the respiratory system and the central nervous system (CNS) is so close, that the failure of one will necessarily affect the other, generating vicious circles (Figure 17.1). Therefore, aggressive airway management and ventilatory support are key to managing these patients.

In a large-scale epidemiological study on mechanical ventilation performed in 1998 and involving a cohort of 5,183 ventilated patients, "coma" was cited as the reason for ventilatory support in 17% of the study population, and the mortality rate was 36%. Similar findings were reported by a second study published in 2004, in which 19% of the ventilated patients received respiratory support because of neurologic reasons. The 28-day mortality rate was 48%, 35%, and 28% in patients with hemorrhagic stroke, ischemic stroke, and head trauma, respectively.

During acute head injury, 10 to 30% of patients will develop acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS), jeopardizing vital and functional prognosis. The mortality rate among stroke patients is more than 50%.

There is strong evidence that hypoxia is one of the main causes of secondary neuronal injury after head trauma, nearly doubling mortality. Also, changes in PaO_2, $PaCO_2$, and pH may alter cerebral blood flow (CBF) and intracranial pressure (ICP), further hampering the outcome of neurologic critically ill patients.

This chapter gives an outline of the pathophysiologic interactions between the respiratory system and the CNS, some frequent ventilator-associated complications, and key issues in invasive ventilatory management which could improve outcome in the neurologic critically ill patient.

17.2 Breathing Control and Respiratory Depression

Ventilation relies on sensors and effectors which are closely regulated by the respiratory centre (Figure 17.2). This is composed of several groups of neurons located bilaterally in the medulla oblongata and pons of the brainstem, and is chiefly responsible for ventilatory activity. The respiratory centre is stimulated primarily by the hydrogen ion concentration in the cerebrospinal fluid (CSF) through sensors located in the medulla and carotid bodies. Carotid bodies also respond to changes in PaO_2. Awareness and no-

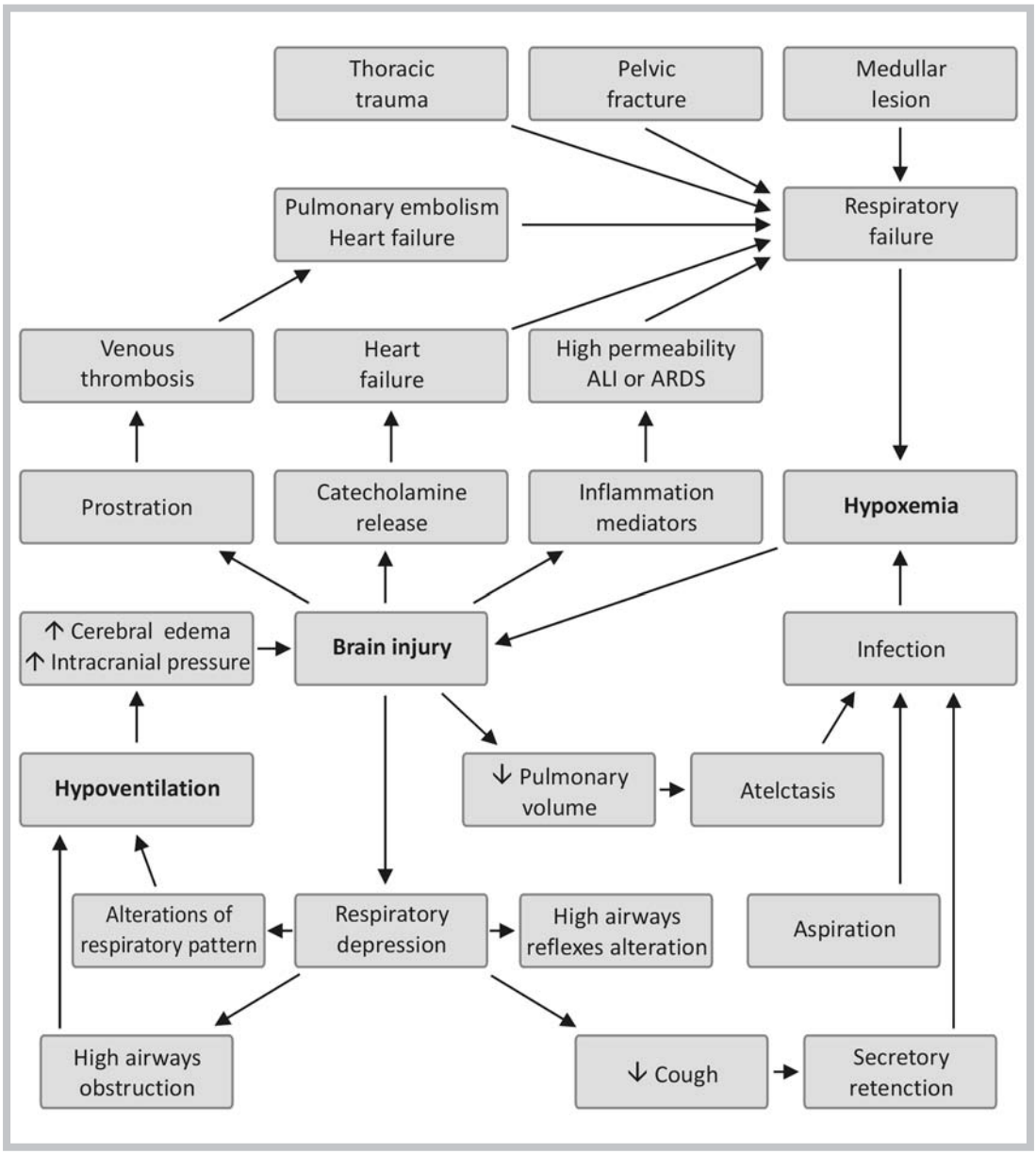


Figure 17.1. **Respiratory problems in brain-injured patients. Respiratory complications may produce secondary brain injury because of hypoxemia and hypoventilation, promoting vicious circles which jeopardize patient outcome.**

ALI = acute lung injury

ARDS = acute respiratory distress syndrome

ciceptive stimulation can also activate the respiratory centre through the reticular formation in the brainstem. Lung mechanoreceptors and cardiovascular baroceptors send information on functional residual capacity.

The respiratory system effectors are responsible for regulating the ventilatory cycle: airway (genioglossus and cricoarytenoideus muscles), and chest wall muscles (diaphragm, intercostal and accessories muscles). Each muscle group maintains a phasic activity for starting and coordinating inspiration, and a tonic activity in charge of maintaining a pat-

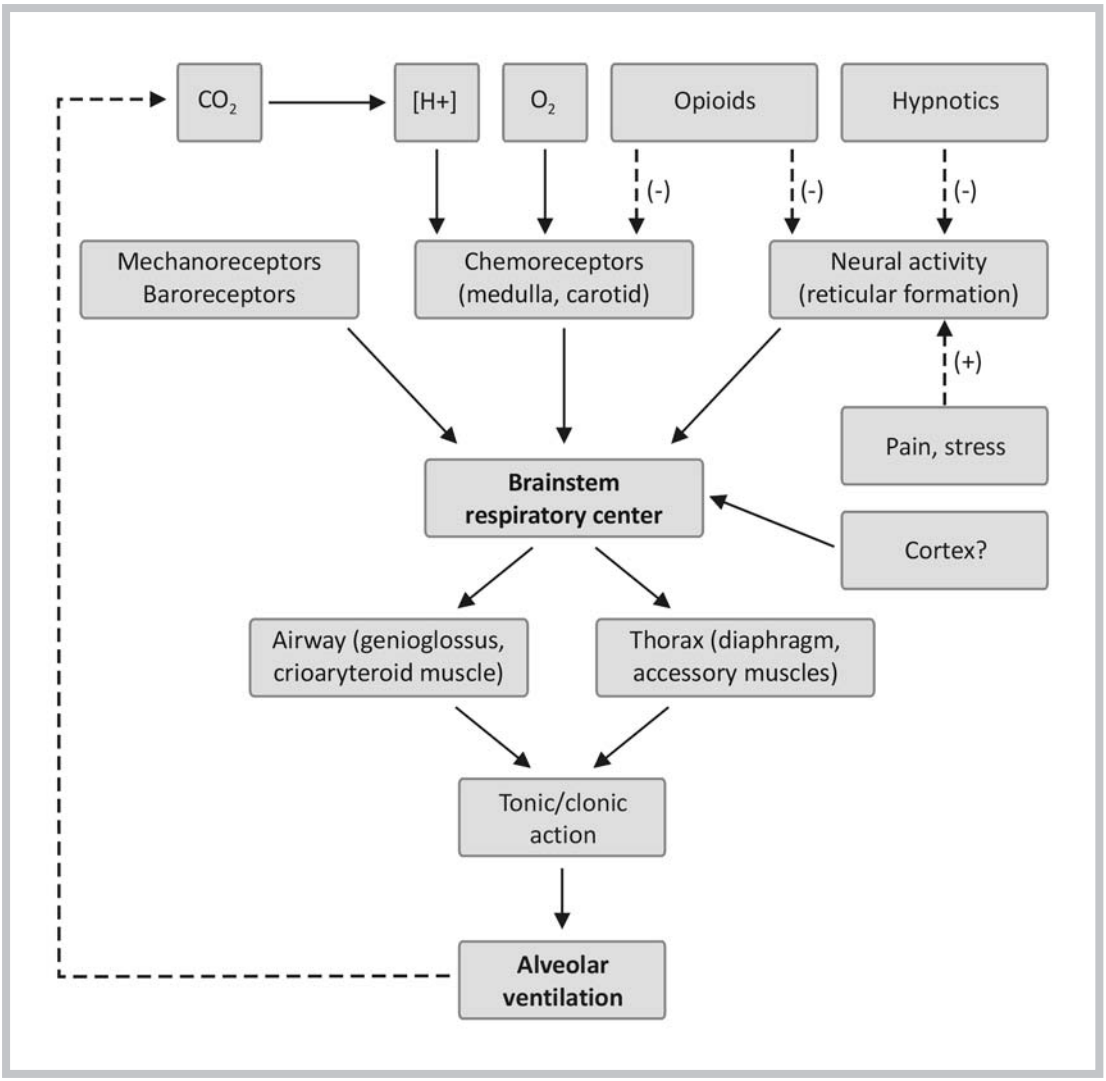


Figure 17.2. **Diagram illustrating respiratory centre function.**

ent airway, muscle tone and residual functional capacity. From these concepts, it is clear why one of the most common complications of brain-injured patients is respiratory depression and airway-related problems (Figure 17.1).

Respiratory depression is a clinical syndrome characterized by a dysfunction of the respiratory centre. Its diagnosis requires a variable but constant altered level of consciousness and breathing abnormalities (Table 17.1). The most common clinical consequences of respiratory depression are apnoea, bradypnoea or periodic breathing abnormalities, and the inability to maintain a patent airway (tongue falling backwards, retention of secretions and hypotonia of pharyngeal muscles), which may result in alveolar hypoventilation. Also, the decreased functional residual capacity may favour the development of atelectasis and hypoxemia (Figure 17.3).

Respiratory depression may be a serious complication in brain-injured patients because hypoxemia and hypercapnia may induce secondary injury (Figure 17.1). Therefore, airway management should be controlled early in patients with progressive drowsiness and coma. And since cyanosis and tachycardia develop late following hypoxemia, per-

manent observation of the patient's level of consciousness and breathing pattern are far more important than preventive measures.

Respiratory depression may also favour the aspiration of gastric contents (Figure 17.1). Patients with trauma and intracranial hypertension may present delayed gastric emptying. It follows that any patient with head trauma or stroke should be treated as a patient with a full stomach at high risk for aspiration. Any sign of vomiting in an unconscious patient is highly suspicious for gastric aspiration. Clinics of aspiration depend on the quality and amount of aspirated liquid, the aspiration of bilious contents or blood being less toxic than acid or food contents. In any case, the chance of secondary infection is high and should prompt antibiotic therapy.

Diagnosis	• Altered level of consciousness
	• Alteration in mechanics and abnormalities of breathing:
	  ▪ Apnea, bradypnea
	• Inability to maintain airway patency:
	  ▪ Hypotonia of pharyngeal muscles
	  ▪ Airway obstruction
	  ▪ Secretion retention

Clinical implications	• Alveolar hypoventilation:
	  ▪ Increased $PaCO_2$ and increased ICP
	• Decreased muscular tone:
	  ▪ Decreased FRC, atelectasis, hypoxemia
	• Aspiration of gastric contents:
	  ▪ Lung infection

Table 17.1. Diagnosis and clinical implications of respiratory depression.
FRC = functional residual capacity
ICP = intracranial pressure

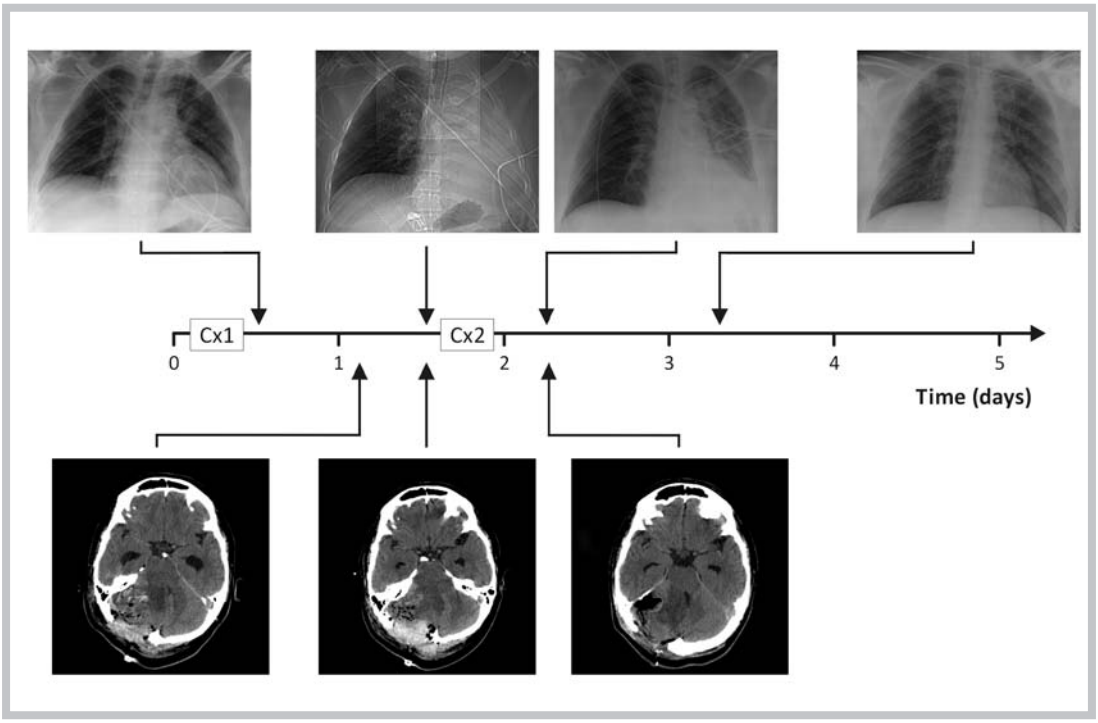
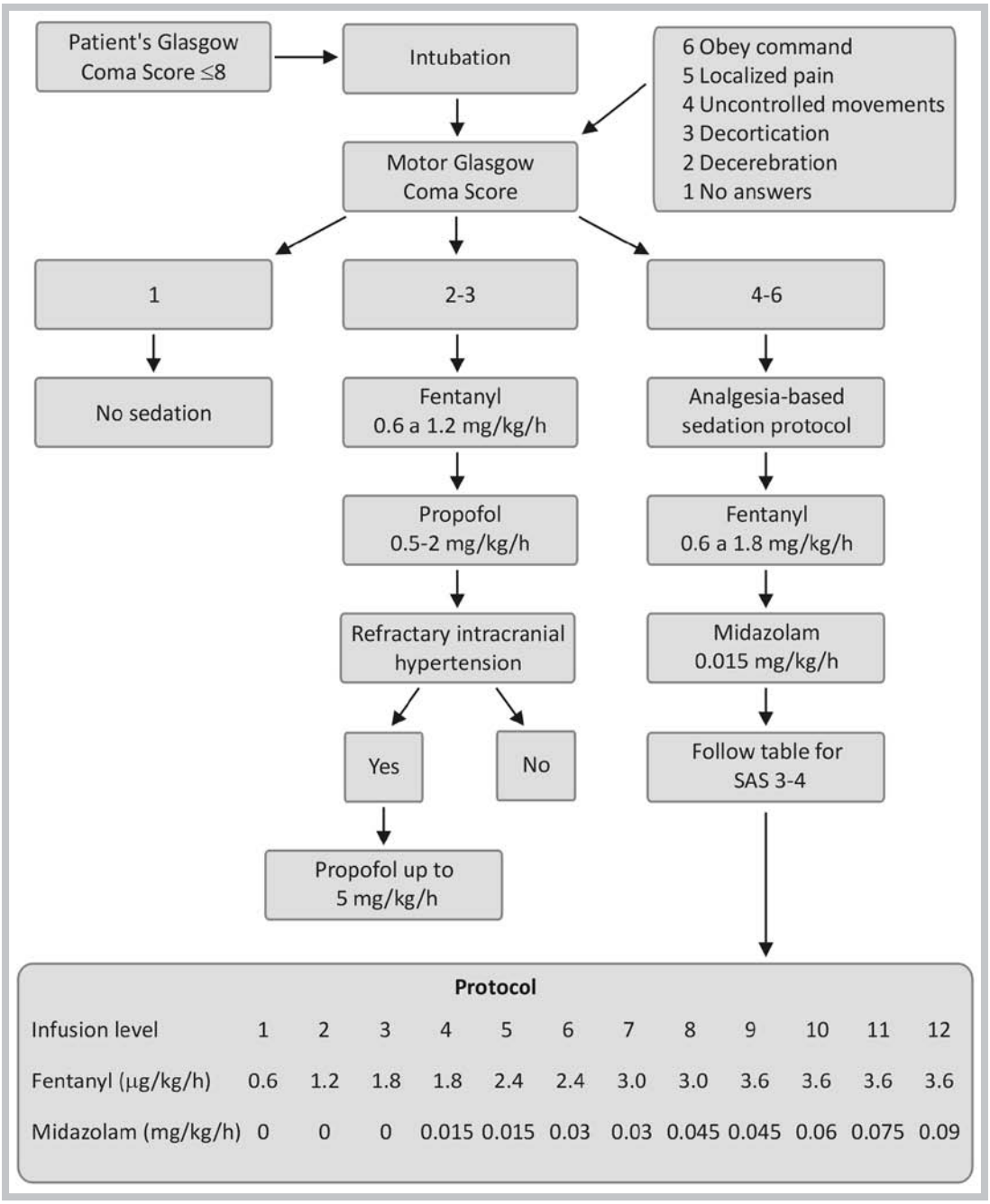


Figure 17.3. A clinical case of respiratory depression.A 29-year-old patient underwent surgery for removal of a tumour of the posterior fossa (Cx1). On the first postoperative day, the patient was drowsy and the CT scan showed edema and partial collapse of the IV ventricle. The patient was carefully observed, but later that day he had to be intubated because of coma. A new CT scan revealed greater collapse of the IV ventricle and postsurgical edema. Total atelectasis of the left lung because of loss of muscular tone, decreased residual lung capacity and decreased cough, was secondary to respiratory depression. The patient was returned to the OR for decompressive surgery (Cx2) and ventilated with positive pressure ventilation and PEEP. A postoperative CT scan showed an expanded IV ventricle. The clinical course was favourable and the patient was extubated two days later.



Protocol

Infusion level	1	2	3	4	5	6	7	8	9	10	11	12
Fentanyl (μg/kg/h)	0.6	1.2	1.8	1.8	2.4	2.4	3.0	3.0	3.6	3.6	3.6	3.6
Midazolam (mg/kg/h)	0	0	0	0.015	0.015	0.03	0.03	0.045	0.045	0.06	0.075	0.09

Figure 17.4. **A sedation scheme for brain-injured patients in use at the Centro de Pacientes Críticos, Universidad Católica de Chile [Riker, 1999].**
SAS = sedation agitation scale

17.3 Sedation

Sedation in brain-injured patients remains controversial because although it favours mechanical ventilation, it also hampers the evaluation of cognitive function, which is the basic and objective monitor of CNS functioning. However, beyond the objective of facil-

itating mechanical ventilation, sedation may decrease oxygen metabolism and intracranial hypertension, and control seizures.

There is no clinical study that evaluates the impact of mechanical ventilation, ventilatory modes or sedation in patients with acute neurologic diseases. Guidelines suggest sedative and analgesic drugs based on their pharmacologic effect on ICP, CBF, or $CMRO_2$, more than on data derived from prospective clinical studies. The choice of drugs and doses when ventilating patients with brain injury is extremely heterogeneous.

Sedation in patients with trauma or stroke should be based on: the necessity of clinical evaluation; oxygen metabolism; intracranial pressure; cerebral blood flow and perfusion pressure among others. The protocol for sedation and analgesia in patients with brain injury (Figure 17.4) at our intensive care unit (ICU) involves:

- Use of opioids as first-line agents.
- Use of an hypnotic agent, usually midazolam or propofol.
- Clinical evaluation of sedation according to the sedation against agitation scale (SAS) and the Glasgow motor scale.
- Intracranial pressure and CPP monitoring (if available).

Goal-oriented monitoring of depth of sedation and periodic adjustment are essential to prevent over- and undersedation, which may affect major outcomes and costs. Oversedation hampers neurologic clinical assessment, increases the risk of hypotension (especially when using propofol and barbiturates), increases mechanical ventilation and ICU and hospital length of stay, and may increase nosocomial infections. Undersedation may increase metabolism, oxygen consumption and intracranial hypertension.

The use of muscle relaxants, widely recommended for preventing fighting in patients with intracranial hypertension, is reserved for patients with severe forms of ARDS, with high sedative requirements or for non-conventional modes of mechanical ventilation.

In non-neurologic patients, sedation protocols have been shown to decrease ICU and hospital length of stay and costs. In neurological critically ill patients, a sedation protocol may also decrease infections and secondary hypoxemia and so improve such major outcomes as long-term cognitive functions.

17.4 Hyperventilation

Modulation of $PaCO_2$ has been used for more than 40 years to control intracranial pressure (ICP). The decrease in $PaCO_2$ levels induces a drop in hydrogen ion concentration (increased pH) in the cerebrospinal fluid (CSF), inducing cerebral vasoconstriction and decreasing cerebral blood volume and ICP.

Despite being highly effective to decrease ICP, hyperventilation is not widely accepted as it may induce a decrease in cerebral blood flow (CBF), a change that lasts longer than the decrease in ICP (Table 17.2). There is also evidence that hyperventilation may exacerbate ischemia in hypoperfused zones of the brain. The only randomized prospective study on hyperventilation

Regional	• Arterial vasoconstriction: decreased CBF • Transient decrease in ICP • Rebound increase in ICP, when normalizing $PaCO_2$
Systemic	• Increase in airway pressure: decreased cardiac output and oxygen delivery • Respiratory alcalosis: decreased oxygen release to tissues • Use of high tidal volume: ventilator-induced lung injury

Table 17.2. Adverse effects (real or potential) of hyperventilation.

CBF = cerebral blood flow
ICP = intracranial pressure
PbO_2 = brain tissue oxygenation
SjO_2 = oxygen jugular saturation

Level I (standard)	• There are insufficient data to support a level I recommendation
Level II (guideline)	• Prophylactic hyperventilation ($PaCO_2$ <25 mmHg) is not recommended
Level III (options)	• Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP • Hyperventilation should be avoided during the first 24 hours after injury when cerebral blood flow (CBF) is often critically reduced • If hyperventilation is used, SjO_2 or PbO_2 measurements are recommended to monitor oxygen delivery

Table 17.3. **Brain Trauma Foundation recommendations on hyperventilation in brain trauma. Modified from [1].**

Mode	• Volume-controlled ventilation
Tidal volume	• Vt 8 (6-9) ml/kg body weight index • Maintain plateau pressure <25 cmH_2O and airway driving pressure <15 cmH_2O
Respiratory rate	• RR 10-12 to maintain $PaCO_2$ 35-40 mmHg • Monitor $ETCO_2$ • Prevent hypoventilation ($PaCO_2$ >45 mmHg)
PEEP	• Low levels of PEEP: 5-10 cmH_2O • If thoracic trauma or lung aspiration: PEEP 8-15 cmH_2O
If refractory hypoxemia	• Consider high recruitment strategies, HFOV and/or prone positioning • Hypoxemia does more harm than hypercapnia
Hyperventilation	• Second tier therapy, transient

Table 17.4. **Initial ventilator programming in brain-injured patients.**
$ETCO_2$ = end-tidal CO_2
HFOV = high frequency oscillatory ventilation

was performed by Muizelaar et al. in 113 patients with head trauma. Patients ventilated with hypocapnia ($PaCO_2$ 25±2 mmHg) had a worse outcome at 3 and 6 months that those treated with eucapnia ($PaCO_2$ 35±2 mmHg). So far, there are no data to show that hyperventilation improves long-term outcome in patients with head trauma or stroke.

We usually try to maintain normo- or light hypocapnia ($PaCO_2$ 35-40 mmHg) in our patients, reserving hyperventilation as a second-line, transient therapy for patients with elevated ICP refractory to hypertonic therapy and with normal CPP (Table 17.4). If hyperventilation needs to be tried, brain tissue oxygen partial pressure (PbO_2) or jugular venous oxygen ($SjvO_2$) measurements are recommended to monitor the effect of ventilation on CBF and cerebral metabolic rate of oxygen ($CMRO_2$). Although CBF is not routinely measured at the bedside, $SjvO_2$ and PbO_2 may help tailor ventilation (Table 17.3). $SjvO_2$ <55% or PbO_2 <15 mmHg suggests increased oxygen extraction, decreased CBF or ischemia. In this setting, hyperventilation may be deleterious and treatment should be oriented to increase oxygen delivery (inotropes or vasopressors), decrease oxygen consumption (sedatives) or decrease brain edema (hypertonic therapy). $SjvO_2$ >65-70% suggests hyperemia, so hyperventilation may be tried as a temporary measure to decrease ICP.

When setting ventilation and $PaCO_2$ goals, they should be adjusted for geographic altitude and temperature, as arterial blood gases are referenced at sea level and at 37 ºC. This last correlation is especially important when applying therapeutic hypothermia.

Arterial $PaCO_2$ levels depend on CO_2 production (V_{CO2}) and are inversely proportional to alveolar ventilation (V_{Alv}), which is the difference between minute ventilation (V_{min}) and dead space (V_{DS}), wherein:

$$PaCO_2 = V_{CO2}/V_{Alv} = V_{CO2}/(V_{min} - V_{DS})$$

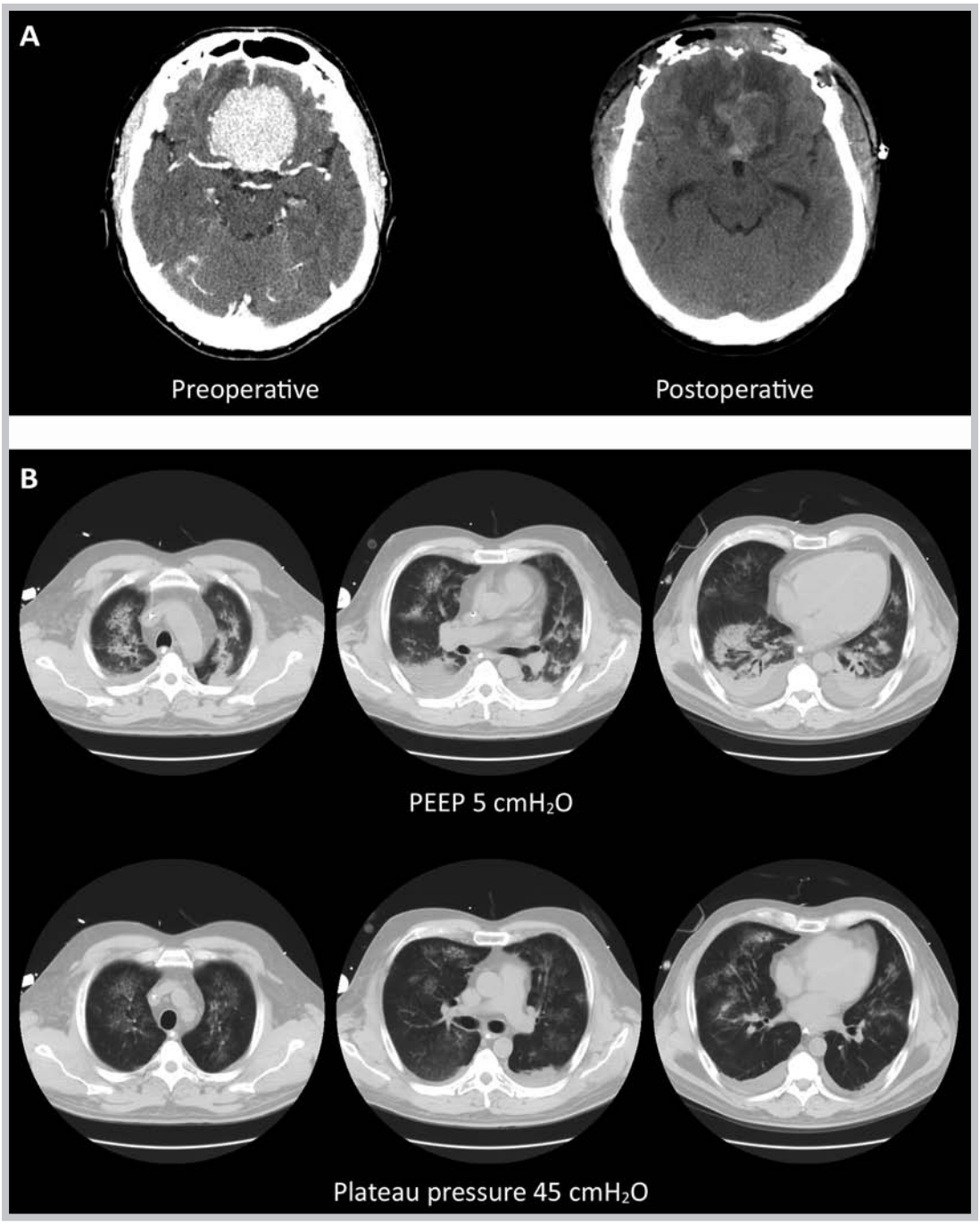


Figure 17.5. High potential for recruitment. A 54-year-old man underwent surgical removal of a large frontal brain tumour. During the postoperative period the patient developed severe agitation which required CNS depressants. At 48 hours, the patient required orotracheal intubation and mechanical ventilation due to respiratory failure secondary to aspiration of gastric contents. The figure shows the preoperative (left) and postoperative (right) head CT scan, and a lung CT scan during a recruitment manoeuvre. In the upper panel, CT slices at the upper, middle and lower zones of the lung during an expiratory pause at 5 cmH_2O PEEP. In the lower panel, the same slices at total lung capacity (TLC), taken during an inspiratory pause (plateau pressure) at 45 cmH_2O. Bilateral infiltrates decreased dramatically at TLC because of a high potential for recruitment. The patient was ventilated with high PEEP levels (12-15 cmH_2O). The clinical and neurologic course were good.

Hence, to decrease $PaCO_2$ levels we can increase minute ventilation (tidal volume or respiratory rate) or decrease dead space. Older textbooks and guidelines did suggest the use of high tidal volume (Vt >10 ml/kg) and low levels of positive end-expiratory pressure (PEEP). This latter concept was based on the idea that PEEP could decrease cephalic venous return and increase ICP.

If we use tidal volume >10 ml/kg, as frequently done in the last decades, there is an increased risk of ventilator-induced lung injury (VILI). Protective ventilation should be applied to all patients with brain injury, limiting Vt to 8 or 10 ml/kg, and further if ALI or ARDS develops. Also, PEEP levels should be tailored to decrease dead space and minimize shunt (Table 17.4).

Unfortunately, most clinical studies on hyperventilation do not describe how they set the ventilator, so it is difficult to make definitive conclusions on the role of ventilation or hyperventilation in patients with acute brain injury and intracranial hypertension.

17.5 Lung Recruitability and Use of PEEP

The use of PEEP (positive end-expiratory pressure) has been debated for more than 30 years. PEEP increases intrathoracic pressure and can decrease venous return, increasing cerebral blood volume and ICP. Although high PEEP levels may be detrimental, there are several reasons that support the routine use of low or moderate PEEP levels, even in patients with ALI.

First, most patients with acute brain injury may present hypoventilation, an increase in lung vascular permeability, a decrease in functional residual capacity, a tendency towards alveolar collapse and development of atelectasis (Figure 17.1). PEEP recruits previously collapsed alveoli, improves lung compliance, decreases shunt, and prevents and improves gas exchange.

Second, overdistention secondary to the use of high tidal volumes is the main cause of ventilator-induced lung injury (VILI). PEEP decreases dead space, allowing the use of lower tidal volumes for ventilatory and CO_2 management. Moreover, PEEP may also stabilize the alveoli, thus preventing the opening and closing of unstable alveoli, which may contribute to the development of VILI. This phenomenon may be specially relevant in patients with severe ARDS and high recruitability (Figure 17.5).

Recruitability, or the potential for recruitment, refers to the capacity of the lung parenchyma to incorporate previously closed alveolar units to gas exchange. Recruitability is highly heterogeneous in patients with acute brain injury, as it is related to impaired lung function (Figures 17.5 and 17.6). High PEEP levels (10-15 cmH_2O) in patients with high recruitability may improve gas exchange and prevent inflammatory response secondary to the opening and closing of a significant mass of unstable lung tissue. However, high PEEP levels in neurocritical patients with low recruitability may induce lung overdistention and increase ICP. Lung mechanics and dead space monitoring are key variables to set the most physiologic PEEP level (Figures 17.5 and 17.6).

The impact of PEEP on ICP depends mostly on its effect on mean airway pressure, as this is the one that best correlates with intrathoracic pressure, hemodynamic disturbances and oxygenation. However, ICP fluctuates more than PEEP after changes in $PaCO_2$, airway pressure or ventilatory mode. In a large-scale clinical study, Cooper et al. found a 1.3 mmHg increase in ICP after increasing the PEEP level by 10 cmH_2O in 33 patients with severe head trauma. Furthermore, the modest change in ICP was related to the effect of PEEP on hemodynamics and respiratory variables without major clinical consequences.

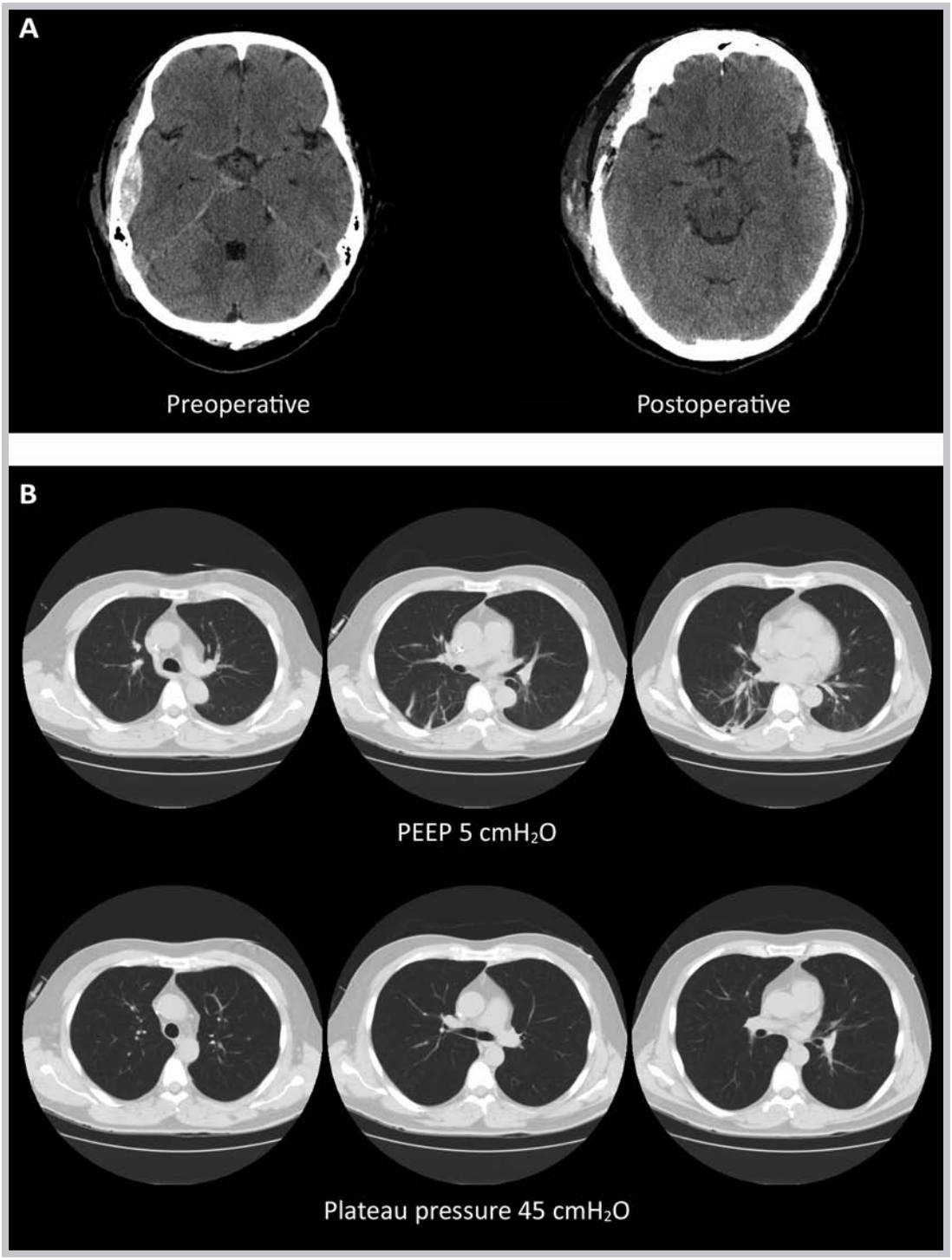


Figure 17.6. Low potential for recruitment. A 53-year-old man was admitted because of a right-sided traumatic epidural hematoma. The figure shows head CT scans before (left) and after (right) surgery (A), and a lung CT scan during a recruitment manoeuvre (B), as shown in the previous figure. At PEEP 5 cmH_2O, only lineal atelectasis are noted. Although these fully disappear at TLC, the benefit is scarce. Note compression and caudal displacement of the mediastinal structures. This patient did not benefit from high PEEP levels. He was extubated soon after surgery and the clinical course was good.

We ordinarily use low PEEP levels (5-8 cmH_2O) in most of our brain-injured patients, trying to decrease FiO_2 to below 0.6 (Table 17.4). This approach is also used by groups who focus on cerebral perfusion pressure (CPP) and ventilation management according to the patient's hemodynamic and respiratory status. Nevertheless, we are cautious in the use of high PEEP levels in patients with low recruitability, as this may overdistend the lung and increase mean airway pressure and ICP (Figure 17.6). In patients with severe brain injury and intracranial hypertension, close monitoring of CPP and ICP, as well as respiratory variables, is essential to titrate and optimize ventilatory management.
In neurocritically ill patients with severe respiratory failure, high PEEP levels or unconventional ventilatory modes may be necessary to prevent hypoxemia. In such patients with low respiratory compliance, changes in ICP after PEEP adjustments are subtle. Recruitment manoeuvres involving high airway pressure over short periods of time may open otherwise collapsed alveoli and have a diagnostic role in assessing recruitability in patients with severe hypoxemia. Their therapeutic role is limited, as several clinical studies in patients with ALI/ARDS have shown a transient increase in oxygenation along with hemodynamic derangement, but without an impact on major outcomes such as hospital mortality or length of stay. In brain-injured patients, especially those with low recruitability, recruitment manoeuvres may be harmful and increase ICP.

17.6 ALI/ARDS and Ventilator-induced Lung Injury

Previously, we mentioned that brain injury and unconsciousness produce hypoventilation, atelectasis, gastric content aspiration and/or an increase in permeability, all conditions which may produce or favour the development of ALI and ARDS. ALI/ARDS is observed in nearly 10 to 30% of patients with acute brain injury and jeopardizes outcome. Simmons et al. found in Vietnam war soldiers who had died of isolated head trauma that 85% of them presented evidence of significant lung injury, including hemorrhage, alveolar edema and congestion, which could not be explained by lung trauma. Bratton and Davis found a 20% incidence of ALI/ARDS in 100 coma patients, with a 2- or 3-fold increased probability of death or vegetative state. Similar data were reported by Holland et al. in 131 patients with head trauma, with a 31% incidence of ALI/ARDS associated with increased mortality (38 vs. 15%; p=0.004).
One of the most important changes in ALI/ARDS management comes from the recognition that mechanical ventilation may harm the lung through a series of mechanisms, collectively termed ventilator-induced lung injury (VILI). Initially, there is a mechanical injury to the lung parenchyma, followed by an inflammatory response which may further amplify damage in and beyond the lungs. Overdistention and the repetitive opening and closing of unstable alveoli generate mechanical stress and strain on the lung cytoskeleton, which may rupture the alveolocapillary membrane, activate endothelial and epithelial cells, and amplify the inflammatory response.
The main factor responsible for VILI is tidal volume (Vt). In a large multicenter, prospective study by the *ARDS network* involving over 800 patients with ALI/ARDS, a tidal volume of 12 ml/kg increased mortality from 31 to 39% when compared with low tidal volume. In patients without ALI/ARDS, a high tidal volume (Vt >10-12 ml/kg) may also induce lung injury. In an observational study involving 86 patients with severe head injury, Mascia et al. showed that 22% of patients developed ALI/ARDS within 72 hours after intubation, high Vt being an independent predictor of this complication. In a prospective, randomized study Determann et al. compared tidal volume of 6 or 10 ml/kg in 150 patients without ALI at the onset of mechanical ventilation (Pa/FiO_2 ≥300). Nearly 62%

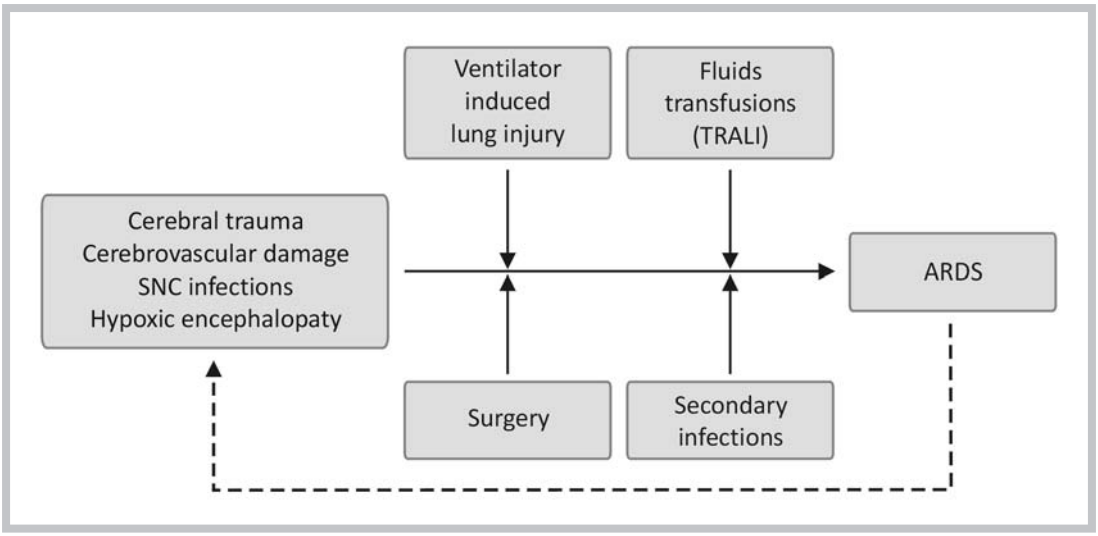


Figure 17.7. **Two-hit hypothesis.**
TRALI = transfusion-related acute lung injury

of the population were neurocritically ill patients (hospitalized for cardiac arrest or neurologic injury). The trial was stopped prematurely for safety reasons because the development of lung injury was higher in the Vt-10 ml/kg group (13.5 versus 2.6%; P=0.01). However, the was no difference in major outcomes as the patients developing ALI were promptly switched to ventilation with 6 ml/kg tidal volume.

More recently, in a prospective, randomized multicenter study involving 118 patients with brain death, the application of a protective strategy (Vt 6-8 ml/kg, PEEP 8-10 cmH_2O) vs. a conventional one (Vt 10-12 ml/kg, PEEP 3-5 cmH_2O) increased the number of patients who met lung donor eligibility criteria (54 to 95%; P=0.001). Lung donor eligibility criteria include a PaO_2: FiO_2 ratio >300 mmHg on FiO_2 1.0, a normal chest X-ray, and peak airway pressure <30 cmH_2O. Finally, the protective strategy doubled the number of patients from whom the lungs could be harvested (54 vs. 27%; P=0.004). This study underscores the importance of protective ventilation even in brain-injured patients with a poor prognosis.

All clinical evidence points to the fact that the lungs are always at risk of VILI, especially when high tidal volume is applied. This is especially relevant in the neurologic population, since high tidal volumes were frequently recommended in the past to induce hypocapnia. Similarly, ALI/ARDS is a complex entity which could be induced or triggered by multiple injuries in a "two-hit" hypothesis (Figure 17.7). Brain injury induces systemic inflammation which can affect distant organs, including the lungs. These lungs, "primed" by circulating cytokines, are exposed to successive inflammatory hits secondary to inadequate ventilation, transfusion (transfusion-related acute lung injury [TRALI]), hydric overload, nosocomial infections, among others, all of which may amplify the inflammatory response and favour the development of ALI/ARDS. In other words, high Vt will induce lung injury in previously injured or inflamed lungs but not in the healthy lung.

17.7 Weaning

Neurocritically ill patients are clearly distinct from the general ICU population: they cannot maintain a patent airway because of unconsciousness. This requirement is different

Main reason for mechanical ventilation in frank recovery	Normal ICP and brain compliance
Hemodynamics	Heart rate and arterial pressure stable
Oxygenation	PaO_2 >60 or $SatO_2$ >90% PaO_2/FiO_2 >250
Level of consciousness	Able to protect and maintain a patent airway

Spontaneous breathing trial	• Muscular strength
	  ▪ VC >20 ml/kg
	  ▪ MIP >-25 cmH_2O
	• Ventilatory drive (workload)
	  ▪ Minute ventilation <10-12 litres
	  ▪ Respiratory rate >10 and <35/min
	  ▪ Tidal volume 5-8 ml/kg
	  ▪ Ventilatory mechanics (cervical and abdominal muscles)
	  ▪ Adrenergic state (tachycardia, hypertension, sweat)

Table 17.5. **Clinical conditions for considering weaning from mechanical ventilation.**

ICP = intracranial pressure VC = vital capacity
MIP = maximal inspiratory pressure

from mechanical ventilation. With regard to weaning, we need to distinguish airway management from ventilatory support, evaluating both the capacity to protect and maintain a patent airway and to ventilate spontaneously (Table 17.5).

Before making the decision to discontinue ventilatory support, it is important to be clear that the reason that initially motivated support is improving and normal brain compliance has recovered. The switch from positive pressure ventilation to spontaneous ventilation may induce an hyperadrenergic state or cardiac failure, leading to hypoxemia and/or hypercarbia, which may increase CBF and ICP, thus jeopardizing neurologic recovery.

Spontaneous breathing trials, through a T-piece or at low levels of PEEP and pressure support, will allow us to evaluate respiratory drive and mechanics. If the patient shows good muscular strength and there is no sign of fatigue (Table 17.5) after 30 minutes to 2 hours, the trial is successful and the endotracheal tube can be withdrawn.

The level of consciousness is fundamental when evaluating the patient's capacity to maintain a patent airway. Salam et al. evaluated three simple clinical elements to discriminate whether the patient will tolerate extubation after having passed a trial of spontaneous breathing: level of consciousness, quantity of endotracheal secretions, and cough peak flows. The level of consciousness is evaluated on four simple tasks: open the eyes; follow with eyes; grasp the hand; and stick out the tongue. In that study, inability to complete the tasks, a cough peak flow <60 l/min or secretions >2.5 ml/h predicted extubation failure.

Delay in weaning in neurocritically ill patients is a risk factor for the development of pneumonia and other ventilator-related complications. However, failed extubation and tracheal reintubation may also favour complications. Early signs of extubation failure should prompt reintubation to avoid hypoxemia, hypoventilation, acidosis and lung aspiration, which could increase morbidity and mortality.

If a patient successfully passes a trial of spontaneous breathing but does not fulfil the criteria for extubation, or, if extubated, presents extubation failure, tracheostomy should be considered.

17.8 Tracheostomy

As mentioned, airway management is crucial in unconscious brain-injured patients. As a general rule, patients with head trauma and a GCS score <8 require invasive airway management (Figure 17.4). There is wide acceptance that laryngoscopy and endotracheal intubation have low morbidity and that a delay in intubation in the unconscious patient may increase morbidity; therefore, endotracheal intubation should be aggressively performed in such patients.

There is no definitive evidence that early tracheostomy (during the first week) improves major outcomes. However, there is a wide heterogeneity in definitions and outcomes in clinical studies and each centre had its own protocols for deciding when to perform tracheostomy. In general, patients with severe head injury, in which a prolonged ICU length of stay may be anticipated, an early tracheostomy may facilitate weaning from the ventilator. For periods shorter than 2 or 3 weeks, endotracheal intubation may be a good alternative. In patients with severe facial trauma, tracheostomy can be a good choice on admission to the emergency department.

In the last 20 years, percutaneous tracheostomy has greatly facilitated the decision-making process. It can be safely performed at the bedside, and it is now widely accepted as a first-choice technique. Tracheostomy in the ICU is an elective procedure, and should be deferred in patients with intracranial hypertension, hemodynamic instability, or infections.

17.9 Conclusions

Brain-injured patients present respiratory problems which, in turn, may affect the brain, inducing secondary neuronal injury and hampering recovery. Ventilatory support maintains ventilation and prevents hypoxemia and hypercapnia (Table 17.6). A judicious application of airway management, sedation, tidal volume and PEEP, based on the pathophysiology of the patient's condition is fundamental to hasten recovery and obtain a good long-term outcome.

Maintain ventilation	• Normocapnia or light hypocapnia ($PaCO_2$ 35-40) • Hyperventilation is second tier therapy
Optimize alveolar recruitment	• Routine use of PEEP (5-10 cmH_2O) • Higher PEEP levels (10-15 cmH_2O) if Pa: FiO_2 <200
Avoid lung injury	• Limit tidal volume (Vt ≤-9 ml/kg body weight index)

Table 17.6. Objectives of mechanical ventilation in brain-injured patients.
PEEP = positive end-expiratory pressure

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18 Surgical Airway Management in the Neurocritically Ill Patient: Timing, Technique, and Complications

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18.1 Introduction

Neurocritically ill patients often require airway management in the emergency department and the intensive care unit (ICU). In most cases, the patient will be successfully intubated in a timely fashion. However, in a minority of patients, intubation may not be possible and a definitive surgical airway will be needed to maintain the patient and avoid additional morbidity. This chapter will describe the indications for establishing a surgical airway, both emergently and electively, the various different types of operation, and the potential risks and benefits of a surgical airway.

18.2 Surgical Airway Management

When head-injured or neurologically compromised patients arrive in the emergency room they should be evaluated in an expedited fashion. The patient's level of consciousness can be assessed according to the Glasgow Coma Scale (GCS), and the airway should be simultaneously inspected. Not infrequently, head-injured patients also have concomitant facial and cervical spine injuries which must alert the physician to potential difficulties in establishing an airway. A definitive airway should be secured in any patient deemed not to be able to protect their own airway. This includes all trauma patients with a GCS of 8 or below, or when other clinical factors are present, such as concomitant neck trauma. According to advanced trauma life support (ATLS) practice guidelines, establishment of the airway is of utmost importance. Loss of airway leading to hypoxia will quickly result in a lethal event or secondary injury in patients with a traumatic brain injury.

18.2.1 Endotracheal Intubation

Oral endotracheal intubation, generally performed with a rapid sequence induction, is the first-line intervention for establishing a secure airway. Care should be taken to maintain cervical spine precautions during intubation, as the majority of these patients have not had clearance of their cervical spine. An assistant can achieve this with in-line immobilization of the head and neck. The assistant can also facilitate intubation by performing a simultaneous jaw thrust. Pre-procedural preparation is of paramount importance for the successful intubation of trauma patients. Availability of multiple laryngoscopes, endotracheal tubes in different sizes, suction, and adequate is required prior to attempting oral endotracheal intubation.

When oral-tracheal intubation has failed, either because of anatomical factors or because of traumatic factors, multiple adjuncts are available to the physician, including laryngeal mask airway, use of gum elastic bougies, needle cricothyroidotomy, and retrograde intubation. The physician in charge of the airway should be adept and knowledgeable with these alternatives; however, they should be employed cautiously as not to prolong episodes of hypoxia or replace a necessary surgical airway. Most institutions have developed "airway carts" in both the emergency department and critical care units that store all the necessary equipment for airway management.

18.2.2 Cricothyroidotomy

A cricothyroidotomy is the only surgical airway that should be performed in an emergent basis on adult patients. This has been traditionally described as an open technique performed with little more than a scalpel and a small endotracheal tube (size, 5.0-7.0 mm). The non-dominant hand is used to immobilize the trachea and larynx. A generous vertical incision is made overlying the previously palpated cricothyroid membrane (Figure 18.1). The scalpel is used to divide the pretracheal tissue and fascia to the level of the membrane. Next, a shallow horizontal stab incision is made through the cricothyroid membrane and the blade is turned 90 degrees. This opening can be gently dilated if necessary with a hemostat, if available, or using one's digit. Finally, an appropriately selected endotracheal tube is placed through the opening and passed in a caudal direction. The tube should be advanced approximately to 5 cm, and the balloon inflated. It should be noted that significant hemorrhage might be encountered by inadvertent division of the branches of the anterior jugular vein, rendering the entire procedure essentially blind. It is because of this that the stabilizing hand becomes of utmost importance in maintaining an appropriate position and should not be moved until the airway has been secured. Bleeding can be controlled secondarily using either suture ligation or ties. Care should be taken to avoid electrocautery as this will likely be an oxygen-enriched field and a potential fire hazard.

Commercial cricothyroidotomy kits are readily available and generally involve a small vertical incision followed by placing a needle through the cricothyroid membrane, passing a guidewire through the needle into the trachea, employing the Seldinger technique to push a dilator and an airway simultaneously into the trachea. Either technique is suitable for an emergent surgical airway and should be performed based on the comfort level of the operator. It is generally advisable that any patient with a cricothyroidotomy be converted to a formal tracheostomy within 24 hours to avoid permanent damage to the larynx. This, however, can be delayed somewhat if the patient's clinical status is too unstable.

18.2.3 Tracheostomy

Tracheostomy should generally be regarded only as an elective procedure. Emergent awake tracheostomy performed under local anesthesia are beyond the scope of this chapter and unlikely to be employed in the neurocritically ill. The benefits of a tracheostomy compared to oral-tracheal intubation include enhanced patient comfort, improved access to the airway for suctioning and pulmonary toilet, improved patient communication, less need for sedation, and decreased vocal cord injuries. Tracheostomy should be reserved for neurocritically ill patients who fail ventilator weaning either due to respiratory function or because of decreased GCS and airway protection issues.

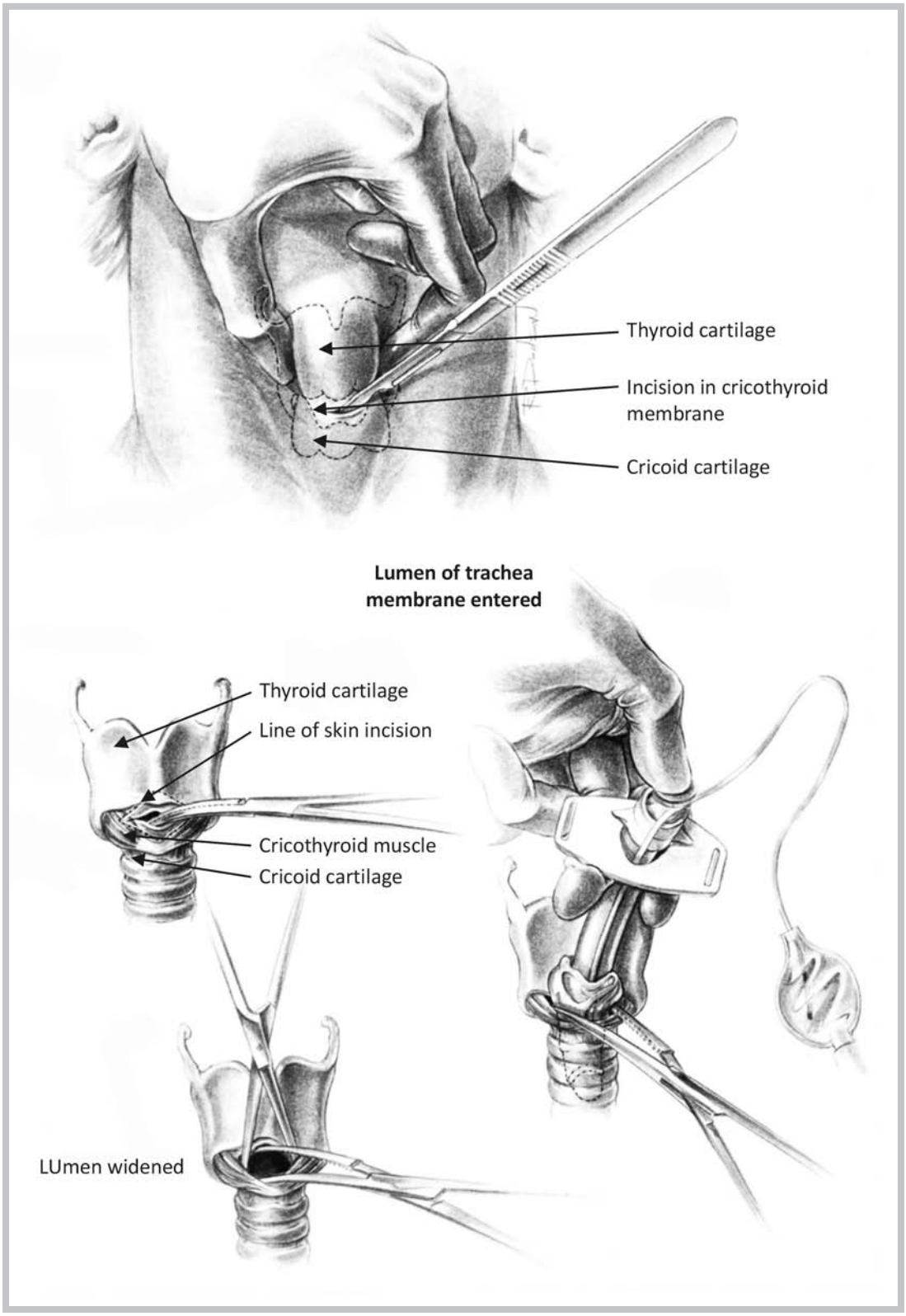

Figure 18.1. **Schematic representation of cricothyroidotomy [8].**

Timing of tracheostomy has changed over the past quarter century. Previously, patients were traditionally maintained intubated with endotracheal tubes for prolonged periods of time. Several studies have evaluated the effect of early tracheostomy. A recent prospective randomized trial in medically critically ill patients deemed to require long term ventilatory support found that those who underwent an early tracheostomy, i.e., within 48 hours, versus those receiving a tracheostomy at 14-16 days, had significantly reduced complications including ventilator-associated pneumonia, accidental extubation, and less damage to the oral cavity. Early tracheostomy was also associated with fewer days in the ICU, days on mechanical ventilation, and a significantly lower 30-day mortality. These findings have also been observed in retrospective studies and a recent meta-analysis [3]. It is the authors' opinion that any patient who is deemed to need prolonged mechanical ventilation be offered an early tracheostomy [2,4], within 72 hours, for all these reasons.

Tracheostomy can be performed safely either in the surgical suite or at the bedside in the intensive care unit (ICU). Our published experience with bedside tracheostomy revealed a 2.9% incidence of major complications and a 3.4% incidence of minor complications. These are comparable to rates reported in the literature for a surgical suite tracheostomy. A comparison of hospital charges shows that tracheostomy is less expensive when performed in the ICU rather than the surgical suite because it incurs no facility or anesthesia fees. Another advantage of bedside tracheostomy is that critically ill patients do not require being transported. While it is these authors' practice to perform virtually all tracheotomies in the surgical ICU [6], we recognize that patient safety takes precedent over financial considerations and suggest that the reader's practice be tailored as such.

Tracheostomy can be performed either open or with a percutaneous dilational technique. An open tracheostomy begins with appropriate patient positioning. This generally entails hyperextension of the neck over a blanket roll if possible, the neck is then prepped and a sterile field created; local anesthetic with epinephrine is given to anesthetize the skin and subcutaneous tissues. A transverse incision is made two fingerbreadths above the sternal notch. The platysma is divided with electrocautery. The midline fascia is incised and the strap muscles are separated. At this point, the thyroid can be gently retracted superiorly, exposing the second and third tracheal rings. This space is incised and widened with Metzenbaum scissors and an inferior tracheal flap is created by incising the lower tracheal ring bilaterally. The endotracheal tube is gradually withdrawn until it is out of the field, and the tracheostomy can then be gently inserted into the trachea and balloon inflated. Placement is confirmed with end-tidal carbon dioxide monitoring and return of appropriate tidal volumes on the ventilator. The tracheostomy is then secured with a tight cloth tied around the neck rather than sutures to the neck. Once the trachea is opened, cautery, because it is a potential fire hazard in an oxygen enriched environment, must never be used. It is our practice to postpone tracheostomy until the patient's oxygen requirement is <50% FiO_2 and there is no coagulopathy.

The percutaneous technique, as originally described by Ciaglia [1], employs a bronchoscope through the endotracheal tube to view the airway; the tube is gently withdrawn to the level of the cricothyroid cartilage. A small vertical incision is then made approximately 2 fingerbreadths above the sternal notch. Hemostats are used to dissect the tissues to the level of the trachea. Next, a large bore needle is introduced into the trachea under direct bronchoscopic visualization. A guidewire is then passed and serial enlarging dilations of the trachea are performed via the Seldinger technique. The tracheostomy can then be placed under direct visualization of the bronchoscope. As opposed to the open technique, these patients should be placed 100% FiO_2 prior and for the duration of the procedure as the bronchoscope limits both oxygenation and ventilation during the procedure.

The advantages of the open technique include no need for muscle relaxants, which are commonly used for percutaneous tracheotomies, and no need for bronchoscopy. Again, a review of hospital charges shows that the percutaneous technique is more expensive because it requires bronchoscopy during the procedure [5]. The advantages of the percutaneous technique are that the patient's neck is not hyperextended for exposure, which is useful in patients with concomitant cervical spine injuries or non-clearance, the minimal dissection causes less bleeding, which is an important consideration in patients who recently received anticoagulants or antiplatelet agents. Also, the percutaneous technique may be easier to perform in patients with a history of neck radiation. Again, we recommend that the practitioner be adept with both techniques and employ each on a selective basis.

Complications of tracheotomies can be divided into operative, postoperative, and late. The most common operative complication is hemorrhage, which occurs in 1-3% of cases, and is usually due to aberrant anatomy, i.e., a thyroidea ima artery. Less common operative complications include pneumothorax (0-4%) and recurrent laryngeal nerve injury. Such complications are generally due to technical error. Postoperative hemorrhage is rare and generally results from a missed bleeding vessel during dissection. Minor bleeding more than 48 hours after placement is generally associated with coagulopathy. Wound infections are rare and are generally averted by not closing the skin incision over an open tracheostomy. Most infections will be treated with a short course of antibiotics only.

Late complications are well described and include tracheal stenosis, tracheomalacia, and tracheoinnominate artery fistula. Fortunately, these complications are quite rare. We advocate the use of minimal leak techniques with high-volume low-pressure cuffs to to avoid the initial mucosal ischemic event precipitating these other complications. Tracheesophageal fistula is an extremely rare event following tracheostomy (1%). Tracheoinnominate artery fistula generally occurs approximately 1-3 weeks postoperatively due to the cuff pressing anteriorly on the innominate artery. Patients present with either a herald bleed event or massive hemoptysis. Control, prior to operative repair, can be obtained by either hyperinflation of the cuff or removing the tracheostomy and occluding it with a finger against the sternum through the stoma. In over 35 years of our ICU experience, a tracheotomy created high between the second and third tracheal rings has never led to the development of a tracheoinnominate fistula.

18.3 Conclusions

The patient with an acute traumatic brain injury will often need to be intubated for either respiratory distress or decreased mental status, raising concerns about their ability to protect their airway. When oral-tracheal intubation is not possible, it becomes imperative to establish an airway in an expedited fashion to avert secondary injury due to prolonged hypoxia. This can be performed in an emergent fashion with a cricothyroidotomy.

Once a patient is intubated and deemed to need prolonged mechanical ventilation or airway protection, an early tracheostomy should be strongly considered. The advantages include decreased sedative requirements, less infectious complications, fewer days on the ventilator, and shortened ICU length of stay. The type of tracheostomy technique and the location of the operation are both secondary considerations. While it is more cost effective to perform bedside open tracheotomies in the ICU, it is more important to perform the procedure safely with the most competent staff available.

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19 Gastrointestinal Disorders in the Neurocritical Patient

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19.1 Gastrointestinal Motility Disorders in the Neurocritical Patient

Gastrointestinal motility disorder (GIMD) is a frequent complication in the critically ill patient. It is estimated that 80% of patients with increased intracranial pressure after cranial trauma and 50% of ventilated patients have abnormalities in gastric emptying. GIMD manifests most frequently as an inhibition of gastrointestinal propulsion and less often as a hyperkinetic movement accompanied by diarrhea or vomiting. The inhibition of motility can affect the entire gastrointestinal (GI) tract or only a part of it. Added to discomfort is the increased risk of complications such as ventilator-associated pneumonia, bacterial translocation, the systemic inflammatory response syndrome (SIRS), sepsis and intolerance to enteral nutrition. Gastrointestinal motility is regulated by complex mechanisms involving the nervous and humoral pathways. The nerve path includes the nerve centres, the intrinsic nervous (intramural plexus) and the autonomic nervous system. Neurohumoral regulation is effected by neurotransmitters and GI peptides.
The causes of GIMD are multifactorial and include:

- Encephalic or spinal injury.
- Abdominal surgery.
- SIRS.
- Sepsis.
- Systemic or regional hypoperfusion and hypoxemia.
- Fluid and electrolyte imbalance.
- Acid-basic imbalance.
- Hyperglycemia.
- Neuroendocrine factors (catecholamines, nitric oxide, 5-hydroxytryptamine, liberating factor of corticotropin-releasing hormone, etc.).
- Drugs: anesthetics, opioids, sedatives, antihypertensives, antihistamines, anticholinergics, sympathomimetics.

Such disorders may be more frequent, more severe or persistent when they coexist with other diseases, including diabetes mellitus, neuropathies, Parkinson's disease, myopathies, amyloidosis, thyroid disease or connective tissue diseases, which themselves affect GI motility.

19.1.1 Gastroparesis

Gastroparesis results in intolerance to enteral feeding and limits delivering nourishment to the critically ill patient. This is particularly problematic when malnutrition is chronic or develops during hospitalisation. Furthermore, a lack of food in the intestinal lumen eliminates the major source of stimulus to maintain splanchnic flow and the integrity of the intestinal mucosae.

Enteral nutrients exert a cytoprotector effect on the GI tract and need to be taken into account in the critically ill patient. When the stomach fails to empty, the absorption of nutrients and medicines is slowed and bacterial colonization occurs. Other serious consequences are the risk of regurgitation and pulmonary aspiration.

Gastric retention is determined by measuring gastric waste, but the definition of excessive residue is vague as is the correlation between increased waste and its adverse consequences. By general consensus, a waste of ≥200 ml is considered excessive. A gastric reflux volume of 500 ml over 24 h indicates impaired gastric emptying.

Pharmacological treatment of impaired GI motility in critically ill patients is clinically challenging because the mechanisms underlying dysmotility are usually complex. The patient's pre-existing characteristics in terms of GI function are diverse and the availability of pharmacological tools is limited.

The beneficial effect of prokinetic drugs derives from their property to stimulate, directly or indirectly, contraction of the intestinal smooth muscle. In the only systematic review conducted to date (18 studies published in the last 20 years) on the effect of metoclopramide, erythromycin and cisapride on GIMD and tolerance showed contradictory results. The main problems with these studies are the small samples and heterogeneity of the populations studied, which makes it difficult to reach definitive conclusions.

Cisapride, a prokinetic drug, 5-HT_4 receptor agonist and 5-HT_3 receptor antagonist, is effective in stimulating motility throughout the GI tract. In 2000 cisapride was withdrawn from the U.S. market and most European countries because of its potential to induce serious and occasionally fatal cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes. These arrhythmias result from prolongation of the QT interval through interaction with the pore-forming subunits of the HERG K^+ channel.

Cinitapride, another prokinetic drug, with a chemical structure and mechanism of action similar to that of cisapride, stimulates 5-HT_4 receptors; unlike cisapride, it is a dopamine D_2 antagonist, although less than metoclopramide. The recommended adult dosage is 1 mg every 8 h. It has not been evaluated in children and its use is not recommended.

The incidence of side effects of cinitapride, when given at therapeutic doses, is very low and does not differ much from that of placebo according to comparative studies. However the technical specifications of the drug warn that it can produce drowsiness or sedation and extrapyramidal reactions (dystonia, late dyskinesia), particularly in elderly patients. Cases of gynecomastia and hypersensitivity reactions have also been described.

The lack of serious cardiotoxic effects described with cisapride is apparently because the HERG channels of potassium concentration required/plasma-free drug concentration is 23,000 for cinitapride (much higher than the usual therapeutic doses) and 73 for cisapride. Although it appears to be safer than the cisapride, because the available information on cinitapride is scarce and studies to date present methodological limitations, its role in the treatment of gastroparesis and GI disorders is not clearly defined.

The prokinetic properties of **metoclopramide** are limited to the upper digestive tract. In critically ill patients it has been shown to produce beneficial effects on the GI tract and tolerance to feeding when administered by the intravenous route, but ineffective when

given via a nasogastric tube. Postoperative ileus is unaffected by metoclopramide. The main limitation of the drug is that it induces extrapyramidal reaction.

Erythromycin, a macrolide antibiotic that stimulates gastric and intestinal motility through direct action on motilin receptors on enteric neurons and smooth muscle cells, increases the pressure of the lower esophageal sphincter by stimulating the cholinergic nerves. Erythromycin administered intravenously is more potent in the relief of gastroparesis than following oral administration. The ability of erythromycin to facilitate gastric emptying and improve tolerance to enteral feeding has been confirmed in two double-blind, placebo-controlled studies in critically ill and mechanically ventilated patients. The impact of erythromycin on colonic transit remains controversial. A systematic meta-analysis of prokinetic drugs for treating gastroparesis reported that the effect of erythromycin on gastric emptying is greater than that of other prokinetic drugs.

The association of erythromycin with torsade de pointes and ventricular dysrhythmias and increased incidence of microbial resistance has motivated some authors to consider its use as a motility agent in critically ill patients to be problematic.

Domperidone acts primarily as an antagonist on peripheral dopamine D2 receptors. It increases esophageal peristalsis and facilitates gastric emptying by augmenting gastric peristalsis and improving antroduodenal coordination. Although domperidone is similar in efficacy to metoclopramide, it causes fewer extrapyramidal side effects because it does not cross the blood-brain barrier.

Neostigmine is a reversible acetylcholine esterase inhibitor that transiently increases the concentration of acetylcholine at its receptors and in this way facilitates parasympathetic and enteric stimulation of GI contractility. The effect of neostigmine injected intravenously to stimulate GI motility is controversial, although postoperative patients usually show a good response to the drug.

The combination of a drug that stimulates the release of acetylcholine from enteric neurons, like metoclopramide, with a drug that inhibits acetylcholine breakdown, like neostigmine, may be successful. Pharmacological options in the treatment of GIMD, the main drugs with prokinetic effects, their mechanism of action and recommended doses are summarized in Tables 19.1 and 19.2.

Therapeutic strategy	Therapeutic options	Individual drugs
Early use of supportive therapeutic options	Stimulant laxatives	Bisacodyl, sodium picosulphate
	Osmotic laxatives	Magnesium salts
	Polyethylene glycol plus electrolytes	Macrogol 3350
	Opioid receptor antagonists	Naloxone
	Reduce use of drugs with an inhibitory effect on GI motility	Anesthetics, sedatives, opioids and adrenergic agonists
Goal-directed specific therapies	Prokinetics for gastroparesis	Erythromycin Metoclopramide Domperidone
	Prokinetics for gastroparesis and intestinal motor inhibition	Erythromycin Metoclopramide plus neostigmine
	Prokinetics for intestinal motor inhibition without gastroparesis	Ceruletide Metoclopramide plus neostigmine

Table 19.1. **Pharmacological options in the treatment and prevention of gastrointestinal motility disorders.**

Drug	Mechanism of action	Site of action			Dose
		Stomach	Small intestine	Colon	
Metoclopramide	Dopamine D_2 receptor antagonist Partial 5-HT_4 receptor agonist Weak antagonist of vagal and central 5-HT_3 receptors	++	+	0	10-30 mg IV/day
Erythromycin	Stimulates gastric and intestinal motility through a direct action on motilin receptors on enteric neurons and smooth muscle cells Increases the pressure of the lower esophageal sphincter by stimulating cholinergic nerves	++	+	0	3x100 mg/day IV maximun use for 3 days
Neostigmine	Acetylcholine esterase inhibitor	0	(+)	+	0.5-1.5 mg once a day, IV, in 250 ml saline, over 1-2 h
Ceruletide	Contraction of the gallbladder and bile ducts by stimulating coordinated propulsive motility from the duodenum to the ileum and inducing segmenting activity of the colon	0/(--)	++	+	40 µg once a day IV, in 100 ml saline, over 30-60 min
Domperidone	Blocks peripheral dopamine receptors	+	(+)	0	30-40 mg, orally

Table 19.2. **Prokinetic drugs: dose, mechanism and site of action.**

0 = No effect
(-) = Effect negative possible
(+) = Effect positive possible
+ = Good positive effect
++ = Very good positive effect

19.1.2 Constipation

Motor dysfunction of the large intestine is common in seriously ill patients; motor function doesn't usually recover within 7-10 days of admission. There is no uniformly accepted definition for constipation in critical patients. As a result, its actual incidence is unknown. An applicable definition in clinical practice is to consider constipation when the patient has not passed stools for 3 consecutive days.

Constipation has not been well studied in critical patients, and its causes have not been clarified in controlled studies. It has been suggested that constipation may be due to alterations in bowel motility secondary to disease process, changes induced by routinely administered drugs (sedatives, opiates, etc.) and by a diet devoid of fibre.

In the evaluation of patients with constipation, we should follow the usual recommendations (clinical assessment of the abdomen, rectal examination and radiological investigations). In the prevention of constipation, the role of dietary fibre is fundamental in patients receiving prolonged enteral nutrition. Dietary fibre in the prevention or treatment of constipation associated with enteral nutrition has not been investigated by controlled studies in neurocritical patients.

The use of enemas for cleaning or laxatives is common. In drug treatment, however, agents of intermediate latency seem preferable to accelerator medications to stimulate intestinal transit as they increase the fecal bolus and act preferentially in the colon.

The lack of adequate bowel movement can lead to bacterial overgrowth and promote intestinal translocation and infectious complications in critical patients. This may be especially important when using digestive decontamination, given that the lack of deposition may counteract the purported effect (elimination of pathogenic intraluminal flora) and it can contribute to the development of secondary infectious complications.
In short, GIMD are common in the neurocritical patient and can lead to an increase in the incidence of complications and prolong stay in the intensive care unit (ICU). Therapeutic options for GIMD in the neurocritical patient include correction of water and electrolytic imbalance, early enteral nutrition, proper use of catecholamines and medications for sedation and analgesia, as well as prokinetic drugs. While the choice of the ideal prokinetic in the critically ill patient is not well established, metoclopramide may be the most reasonable drug. Bearing in mind that the treatment options are still limited for this type of disorder, it is important to identify the diagnostic and therapeutic approach in each case.

19.2 Common Gastroenterological Disorders in Severe Acute Neurological Illness

The severely ill neurosurgical patient tends to develop serious gastrointestinal complications which can be overcome with early diagnosis and appropriate treatment. The most important common gastrointestinal complications are: gastrointestinal bleeding, gastroparesis and diarrhea, which are encountered daily in the intensive care unit (ICU), but can be easily managed with prompt action by the interdisciplinary team.
The incidence of gastrointestinal bleeding is now fairly low due to the increasing use of gastric mucosal protective drugs, but this doesn't necessarily decrease its importance. Several causes have been associated with the presence of varices arising in the distal esophagus and proximal gastric regions and other acid-related causes, such as peptic ulcer and mucosal damage due to stress. Less common causes include the Mallory-Weiss syndrome and vascular lesions. Several risk factors for bleeding have been identified: mechanical ventilation for more than 48 hours, and ongoing coagulopathy.
Other causes, whose importance is variable, are: shock; liver and renal failure; sepsis; multiple trauma; burns over 35% of the body surface area; organ transplantation; spinal cord or head trauma; and a history of previous ulcer disease.
Many different causes of gastroparesis have been indentified, among which diabetes is one of the most common. Other causes include: infections; endocrine disorders; connective tissue disorders like scleroderma; neuromuscular diseases; idiopathic (unknown) causes; cancer; radiation treatment to the chest or abdomen; some forms of chemotherapy; and surgery of the upper intestinal tract.
The presence of gastrointestinal complications has a negative effect on the amount of diet that can be provided to the patient. This nutritional deficit can also adversely affect patient outcome, with an increase in infectious complications, hospital stay and mortality. The use of protocols for the identification and proper management of gastrointestinal complications in critically ill patients may be a beneficial factor in their evolution.
Nutrition in neurocritical patients plays an essential role, since their recovery depends also on it. Critically ill patients require early nutritional support to attenuate the physiological response to the illness, so the administration of adequate and early food decreases the progression of the multiple organ dysfunction syndrome (MODS). This will also result in reducing metabolic complications and infections.

19.2.1 Gastrointestinal bleeding

Introduction

Gastrointestinal (GI) bleeding is defined as the extravasation of blood in the GI tract from a bleeding site between the upper esophageal sphincter and the angle of Treitz or duodenojejunal flexure. Upper gastrointestinal bleeding (UGIB) is currently an uncommon complication (1-2%), although it is a cause of increased mortality. The two most common causes are gastrointestinal bleeding (GIB) due to peptic ulcer and secondary to portal hypertension.

Lower gastrointestinal bleeding (LGIB) is less common than UGIB, and tends to be self-limiting. Bleeding due to "stress ulcer" or acute gastric mucosal disease is the most common cause of bleeding in less severe cases and is closely related to the underlying disease and the degree of multiorgan dysfunction. Several factors, most notably mechanical ventilation in the strict sense and prolonged ICU length of stay, have been implicated in bleeding due to "stress ulcer". Improvement in hemodynamics and oxygenation, the use of enteral nutrition and the administration of gastric mucosal protective drugs are appropriate tools for the prevention and treatment of bleeding due to acute gastric mucosal injury in critically ill patients.

GI bleeding can have a significant effect on the nutritional management of patients. Often, GI bleeding, irrespective of its size or type, leads to the withdrawal of enteral nutrition or delays its start. However, this decision cannot be justified in all cases: the reason for withdrawing enteral diet in patients with bleeding due to "stress ulcer", peptic ulcer without risk of bleeding according to the endoscopic image, the Mallory-Weiss syndrome, angiodysplasia or LGIB should not be the risk that the diet increases bleeding, as there is no pathophysiological explanation for this. On the contrary, as indicated, there is evidence that enteral nutrition can protect the gastric mucosa and have a beneficial effect on both the prevention and treatment of mucosal injury.

Incidence

UGIB is one of the most common causes of emergency care, with an incidence of 100-150 cases per 100,000 inhabitants per year.

It is the main gastroenterological emergency and the leading cause of cancer death (10-14%), associated with co-morbidities and age.

UGIB is much more common in men than in women and increases with age; 75-100% of critically ill patients have mucosal damage within 24 hours after ICU admission.

Etiology

The most common causes of GI bleeding are primarily (each: 75% incidence in critically ill patients): hemorrhagic gastritis, gastric ulcer, duodenal ulcer (acid peptic disease).

As a secondary cause (each account for 5-15% of HVD causas): esophageal varices, duodenitis, esophagitis, mallory-Weiss syndrome.

The Mallory-Weiss syndrome refers to tears in the gastro-esophageal mucosa which are responsible for 5-10% of UGIB. The classic features are nausea, vomiting or gagging cough (arcadas de tos), and a previous history of hematemesis.

Three different types of bleeding due to stress-induced mucosal disease may occur in ICU patients: the first is occult bleeding, defined as a gastric aspirate or positive stool guaiac test, and is the most prevalent one. The second is obvious or overt bleeding: in most cases it is not clinically relevant and refers to the presence of hematemesis, melanemesis, hematochezia or melena. The incidence of obvious bleeding is only 5%. The third is clinically significant or relevant bleeding (1-4%) and is clinically evident with

hemodynamic instability and a hemoglobin decrease of 2 g/dl. ICU patients commonly develop problems in the proximal GI tract as a result of severe psychological stress.

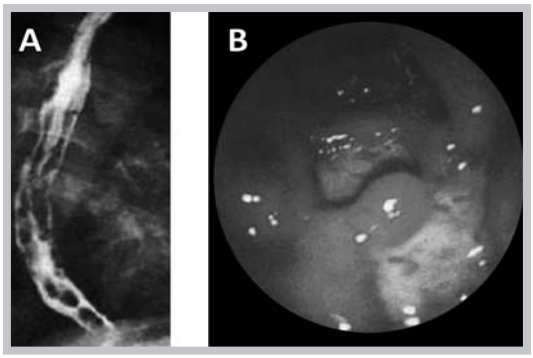

Figure 19.1. **Causes of gastrointestinal bleeding. A). Esophageal varices. B). Crohn's Disease.**

Prophylaxis

One of the leading causes of morbidity in patients hospitalized for any other cause is GI bleeding, although not all patients have the same risk of developing it as an intercurrent event. True prophylaxis is reserved for patients without underlying gastroduodenal pathology but with risk factors. Drugs should be administered before injury occurs.

Prophylaxis of this kind of bleeding must be established rationally and based on the risk factors of each case. Until recently, prophylactic treatment was indefinitely based on the use of antisecretory drugs because many bleeding ulcers progressed to hemorrhagic exacerbation within 2-3 years.

Different types of medications are used: traditional antacids (magnesium and/or aluminium hydroxide); sucralfate; histamine receptor antagonists (H_2 antagonists); proton pump inhibitors (PPIs); misoprostol and pirenzepine via oral and intravenous administration because they are dosed by bolus or infusion. The goal is to raise the pH over 4.0 and keep it there as long as possible to avoid renewed long-term bleeding.

19.2.2 Gastroparesis

Introduction

Literally, gastroparesis means "stomach paralysis". Gastroparesis is a syndrome defined by delayed gastric emptying essentially of solids, without evidence of mechanical obstruction. When the stomach works normally, gastric contraction helps to grind the ingested food and then propels the pulverized food into the small intestine, where digestion and absorption of nutrients continue.

The clinic of gastroparesis may range from mild forms, in which the patient reports dyspeptic symptoms such as early satiety, postprandial fullness or nausea, to severe forms with gastric retention that manifests as repeated vomiting, even with significant nutritional impairment.

Etiology

Although there are several causes leading to gastroparesis, one of the most common is diabetes, but there are also infections, endocrine disorders, connective tissue disorders like scleroderma, neuromuscular diseases, idiopathic causes (unknown) cancer, radiation treatment to the chest or abdomen, some forms of chemotherapy, and surgery of the upper intestinal tract.

Any surgery performed in the esophagus, stomach and duodenum may result in vagus nerve injury, which transmits sensory and motor responses (muscle) to the intestine: normally, the vagus nerve sends impulses through neurotransmitters to the stomach smooth muscle to produce contractions and propel gastric contents. If the vagus nerve is injured during surgery, gastric emptying may not occur. Symptoms of postoper-

- Narcotics for pain control
- Tricyclic antidepressants
- Calcium channel blockers
- Clonidine
- Dopamine agonists
- Lithium
- Nicotine
- Drugs containing progesterone

Table 19.3. **Drugs preventing gastric emptying.**

ative gastroparesis may develop immediately or years after surgery.

On the other hand, the use of some medications, especially narcotics for pain control with calcium channel blockers and some antidepressants, may delay gastric emptying and gastroparesis-like symptoms (Table 19.3). People suffering from eating disorders like anorexia and bulimia may also develop gastroparesis. Fortunately, gastric emptying can be restored and symptoms improve, while normalizing food intake and improving eating habits and feeding schedules.

19.2.3 Gastrokinetic-prokinetic Agents

In many patients with gastroparesis, prokinetic agents accelerate gastric emptying and improve nausea, vomiting and postprandial fullness sensation.

Metoclopramide

Metoclopramide was the first drug developed as a prokinetic and antiemetic agent. It has a D_2 antidopaminergic action and is also a serotonin 5-HT_4 receptor agonist. It acts on dopamine receptors in the stomach and intestine, as well as in the brain. By stimulating stomach contractions, it promotes better emptying. It can act on the part of the brain responsible for controlling the gag reflex, and therefore may reduce the sensation of nausea and the urge to vomit.

For some people, the use of this medication is limited owing to the side effects of agitation and facial spasms or tardive dyskinesia. Metoclopramide can also cause painful swelling of the breast and nipple discharge in both men and women. It is not recommended for long-term use. The recommended dose is 10 to 20 mg every 8 h orally, about 20 minutes before meals.

Domperidone

Domperidone also has an antidopaminergic action, but with the advantage that very little crosses the blood-brain barrier, so it has far less side effects at the central level. Chronic administration of domperidone can improve gastric dysrhythmia, which correlates with clinical improvement, but is not accompanied by significant changes in gastric emptying, thus suggesting the existence of an electromechanical dissociation. The recommended dose is 10 to 20 mg every 8 h orally, about 20 minutes before meals.

Erythromycin

Erythromycin, an antibiotic of the macrolide family, acts as a potent gastrokinetic agent and a motilin receptor agonist on intestinal smooth muscle. Intravenous erythromycin is followed by a normalization of gastric emptying of both solids and liquids; a beneficial effect persists with oral erythromycin but is much less than after parenteral administration.

The effectiveness of erythromycin in the long-term treatment of gastroparesis is controversial, since it seems to be accompanied by a progressive loss of efficiency, probably due to a tachyphylactic effect. Moreover, erythromycin has side effects such as ototoxicity in patients with renal failure or pseudomembranous colitis, which sometimes lead to discontinuation of its administration. Another fact to consider is that the use of this an-

tibiotic as a prokinetic agent carries the risk of inducing bacterial resistance. The recommended intravenous dose in acute cases is 3 mg/kg every 8 h. The oral dose is 250-500 mg every 8 hours, about 20 minutes before each meal.

Cisapride

Cisapride, a serotonin 5-HT_4 receptor agonist, and to a lesser extent, a serotonin 5-HT_3 receptor agonist, is another drug frequently used in the treatment of gastroparesis. Its administration, both oral and intravenous, enhances gastric emptying of digestible and indigestible solids.

It binds to serotonin receptors in the stomach wall, leading to contraction of the smooth muscle of the stomach and improvement in gastric emptying. At the end of 1990s, cisapride was withdrawn from the market due to reported complications of cardiac arrhythmias in patients with a history of arrhythmia or coronary artery disease who used this drug. Now, it is once again available, though its use is restricted. People who have underlying kidney or heart disease should not take cisapride.

19.2.4 Diarrhea

Diarrhea is a symptom typical to many pathological conditions, especially in diseases of the GI tract. It is a consequence of an alteration in GI mechanisms involved in the absorption and secretion of fluids, electrolytes and nutrients.

Etiology

Diarrhea is common in ICU patients, and its incidence is estimated between 20 and 60%. All medical staff associate diarrhea in the ICU with tube feeding, but not always does the cause reside in the process of feeding or schedule. The main factors associated with diarrhea in the ICU are drugs (antibiotics, antacids, with magnesium and others), intesti-

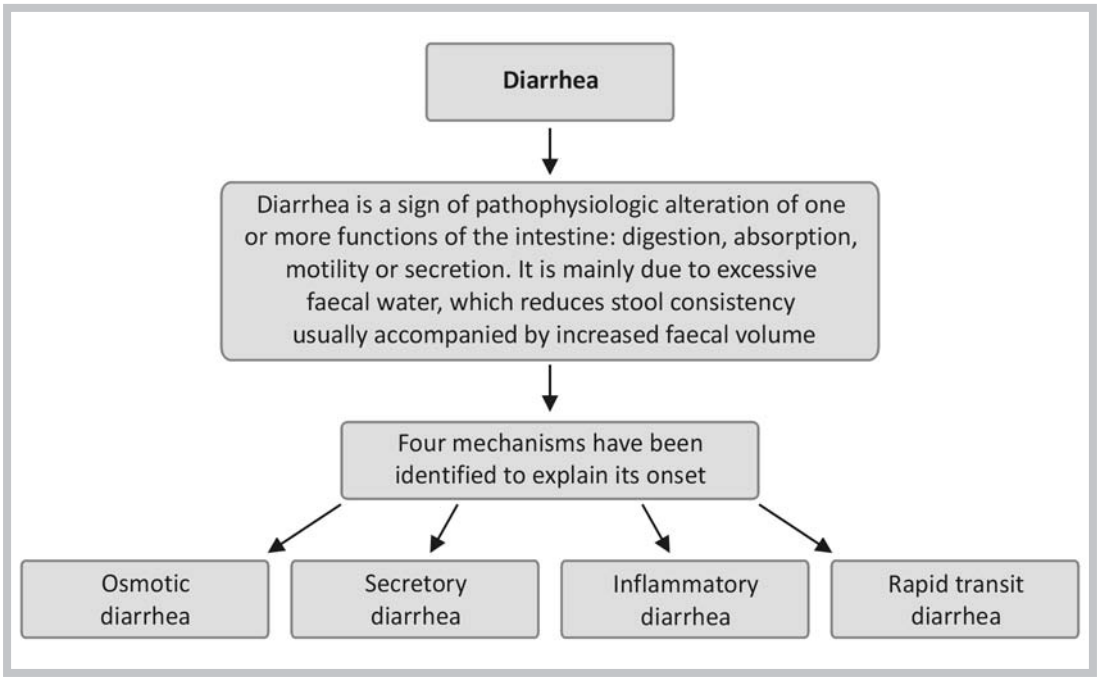

Figure 19.2. Types of diarrhea.

nal mucosal injury, bacterial or viral infection, and the administration of large volumes of hyperosmolar liquid preparations directly into the small intestine.

The causes of acute diarrhea are variable and can be classified in different ways, one of which is infectious (viral, bacterial, parasitic and fungal) and non-infectious.

The majority of enteric pathogens that cause acute diarrhea penetrate the body through the oral route and colonize the intestine before the onset of symptoms of diarrheal disease. A key step in the colonization process, in almost all cases, is bacterial adherence to the intestinal epithelium. Often, the mechanisms of adhesion of bacteria and protozoa are very specific and are mediated by interactions of receptor-ligand type. This process often uses lecithins or similar molecules (adhesins) which interact with hydrocarbon fractions of the membrane of the microvilli. The mechanisms by which enteropathogens cause diarrhea are various, but two broad categories are distinguished: those increasing intestinal secretion; and those reducing intestinal absorption.

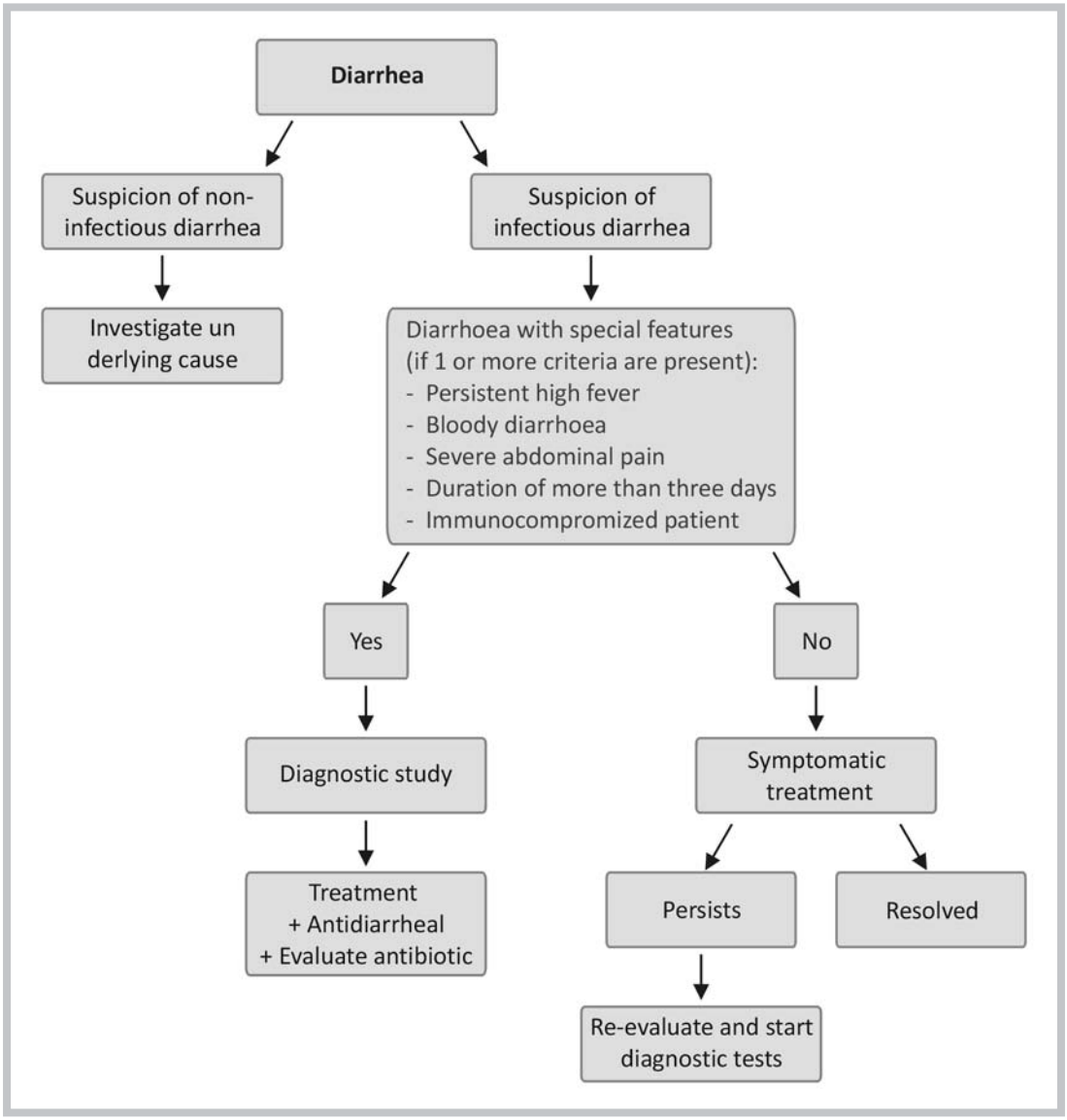

Figure 19.3. Flow chart of the management of acute diarrhea.

Diagnosis

For **acute diarrhea**, the most common diagnosis is established on the basis of the clinical history and features without recourse to other examinations. The latter may be indicated in severe processes or when the patient may be at increased risk (elderly, immunocompromised, etc.). In such cases, the most important diagnostic test in acute diarrhea is microbiological analysis of stool, usually culture for enteropathogenic bacteria and direct examination of the stool sample under optical microscopy to rule out the presence of parasites. It may be necessary to repeat this study to rule out with certainty the presence of pathogenic microorganisms (disease-producing pathogens). Figure 19.3 summarizes the management of acute diarrhea.

The study of a patient with **chronic diarrhea** can be daunting. Based on the multiple triggering causes, several laboratory tests could be described. However, the basis for establishing the diagnosis is a complete and thorough medical history, along with physical examination. At the beginning, even simple analytic studies such as blood testing can be ordered. With this information we can establish the mechanisms involved, direct causes, and nutritional and hydration status of the patient, the latter being key to treatment. At first, and depending on the suspected diagnosis, other investigations may be indicated, such as a fasting test (to demonstrate lactose intolerance), an examination of the large intestine by endoscopy (proctosigmoidoscopy in cases of suspected irritable bowel syndrome), colonoscopy, stool microbiology.

Other suitable tests include determining the fat (maldigestion or fat malabsorption), blood, leukocytes or laxative content of the stool. The presence of blood and leukocytes (inflammatory cells) suggests an inflammatory process, underlining the importance of microbiological examinations. Imaging studies such as upper GI endoscopy or radiological examination of the small intestine can also be useful.

19.2.5 Nutrition in Neurocritical Patients With Gastrointestinal Problems

The quality of nutrition plays an active role in everyday activities, emotional reactions, affectivity, as well as genesis of the cognitive substrate. Every year, thousands of people suffer serious head injuries with devastating effects on neurological function and the consequent deterioration in their quality of life. For four decades, advances in nutritional support in critically ill patients were not applied to severe neurosurgical patients, and, despite the predictability of the impact that these injuries have on body homeostasis and the profound metabolic effects on the hematopoietic, immune and muscular systems, treatment consisted of waiting, sometimes delaying for weeks the initiation of nutritional support.

Today, many studies on early nutritional support in severe neurosurgical patient suggest that early nutrition can lower the risk of infection and death of the neurologic patient.

Early or Late?

The critically ill patient requires early nutritional support which attenuates the physiological response to illness, so as to decrease the progression of multiple organ failure (MOF) with the adequate and early administration of food and to reduce metabolic complications and infections. Previous studies had shown that early nutrition lowers the risk of morbidity due to superinfection. However, while starting early enteral or parenteral support is not sufficient, it does provide an adequate supply of energy intake to cover the energy needs of these patients.

Enteral or Parenteral?

In any patient in critical condition, treatment will aim to reducing the risk of intestinal atrophy and bacterial translocation, for which enteral nutrition has become the main strategy to stimulate mucosal trophism. This principle is important and in most protocols enteral nutrition is included as an essential part of treatment. Sometimes, it is difficult to achieve caloric needs enterally early due to serious disorders in intestinal transit as a result of ECT and intracranial hypertension; therefore, the benefits of early nutrition are lost. This is especially true for gastric feeding, because gastroparesis is much longer than jejunal ileus.

Some studies, such as that by Young et al. suggest a better prognosis for patients fed with parenteral nutrition. The development of naso-esophageal probes, the early use of endoscopic gastrostomy, the use of new and improved prokinetic agents [Altmayer et al., 1996] and the basic formulas that favour absorption [Taylor et al., 1999] have improved the use of the enteral route, increasingly diminishing dependency on the parenteral route to supply the calories needed. Initially, it is recommended to start nutrition as soon as the patient has been revived and is hemodynamically stable.

Unless there are formal contraindications or an overt intolerance is documented, enteral nutrition is the technique of artificial nutrition of choice. This concept is applicable to any patient, even to gastroenterological patients. If a portion of the GI tract is functional, it must be used: enteral nutrition is more physiological, and brings more benefits to the patient's recovery, while aiming to quickly reach the resting energy expenditure. Parenteral support can be gradually decreased as enteral nutrition is increased.

Uncontrollable diarrhea with dehydration and/or electrolyte imbalance, or acute GI bleeding may preclude enteral nutrition. As a second step, parenteral nutrition can be initiated as soon as possible to prevent depletion.

In enteral nutrition, the route and the quantity of calories needed for the patient's energy expenditure should be determined. As the symptoms of diarrhea or bleeding decrease, the possibility of initiating enteral nutrition or mixed nutrition should be considered in order to gradually discontinue enteral nutrition.

In general, the frequency of potentially serious complications is greater with parenteral nutrition than with enteral nutrition. Until recently, the fundamental difference between them was the risk of catheter sepsis in parenteral nutrition. Although the risk is ultimately minimized, there are still differences in morbidity favouring enteral nutrition, especially with regard to metabolic disorders or liver problems related to artificial nutrition, which are more frequent and severe with parenteral nutrition.

Schedules

A naso-esophageal probe should be placed and an oligomeric formula started where the size of the macronutrient polymer is lower. Its use is indicated in cases of lower digestion or absorption capacity. Protein intake is provided as dipeptides and tripeptides and a very small portion of tetrapeptides and pentapeptides, keeping very limited the incorporation of amino acids, in addition to high osmolarity that they give to the formula, for the proper absorption of dipeptides and tripeptides.

These formulas contain a significant proportion of medium-chain triglycerides. Carbohydrates are supplied, as in the polymers, in the form of maltodextrin. In addition, the formula must be enriched with arginine, ribonucleotides and omega 3 fatty acids. Enteral nutrition should be started at low infusion volumes and then gradually increased, as tolerated, until all calorie supplements can be supplyied by this route.

Nutritional Monitoring

Once the nutritional regimen has been initiated, the physician will need to know the extent to which repletion of body behaviours considered strategic occurs to ensure the

success of pending medical-surgical action. Nutritional monitoring should serve as a feedback mechanism for changes in the scheme of nutritional support if the patient fails to respond as expected.

19.2.6 Conclusions

One of the most common problems in critically ill patients is GI complications during the stay in the ICU. The most clinically relevant complications include GI bleeding and complications associated with enteral feeding. Currently, GI bleeding is uncommon thanks to the use of mucosal protective agents and the increasingly widespread use of enteral nutrition. A common complication of enteral nutrition is diarrhea, which may result from improper use of formula or patient intolerance to the type of formula given. Furthermore, some medications such as sorbitol can cause diarrhea. GI complications have a negative effect on the amount of diet that can be provided to the patient. This nutritional deficiency can also adversely affect patient outcome, with an increase in infectious complications, hospital stay and mortality. The use of protocols for the identification and proper management of GI complications in critically ill patients may be a beneficial factor in their evolution.

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20 Nutritional Support in Critically Ill Patients

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20.1 Introduction

The critically ill patient presents with a metabolic picture in which a large amount of energy is needed in order to maintain hemostasis. The higher metabolic rate leads to a greater demand for calories, proteins, vitamins and electrolytes. If this situation is not taken into account, malnutrition will inevitably ensue. Malnutrition can develop quickly, with direct physiologic consequences for respiratory, cardiac, renal and gastrointestinal function, as well as a higher risk of infection, all of which increase complications and prolong intensive care stay. The incidence of death in trauma patients is higher when weight loss reaches 30%. This is why assessment and nutritional support are vitally important.

20.2 Metabolism During Injury

Glucose requirements are much higher following injury than during starvation. The stress response begins in the central nervous system (CNS) and includes the sympaticoadrenal axis, hormones, cytokines and acute phase proteins, all reactions which maintain high levels of circulating substrates.

In reaction to injury, nerve impulses are rapidly transmitted to the hypothalamus that responds by augmenting the release of corticotrophin-releasing factor, stimulating the pituitary gland to secrete ACTH, which augments the secretion of cortisol by the adrenal cortex. Corticotropin-releasing factor (CRF) stimulates the sympathetic system to release epinephrine by the adrenal medulla and norepinephrine in the sympathetic nerve endings.

Catecholamines, together with hypothalamic stimulation, increase the release of somatotrophic hormone (STH), which may be part of a feedback control system. These catecholamines produce hyperglycemia and increase glucagon secretion by stimulating pancreatic alpha cells. Insulin is also elevated in small amounts and the insulin: glucagon ratio is reduced, which stimulates glycogenolysis, gluconeogenesis and lipolysis (Figure 20.1).

Injury also stimulates the release of cytokines such as interleukin 1 (IL-1) and tumour necrosis factor alpha (TNF-α) which increase the synthesis of acute phase proteins, causing hyperinsulinemia and the release of counterregulatory hormones (cortisol, catecholamines and glucagon). Interleukin 6 (IL-6) induces hepatic synthesis of acute phase proteins. In patients under stress, especially in sepsis, hyperglycemia results from peripheral insulin resistance, increased levels of catecholamine hormones such as glucocorticoids and glucagon, increased hepatic and renal gluconeogenesis, as well as reduced intracellular glucose oxidation. Lipolysis is increased, with the release of fatty acids and glycerol, which is why fatty acids may constitute the main source of energy in the cells. Ketone production may be inhibited during injury as a result of various not well known mecha-

nisms. Muscle proteolysis during stress augments the release and production of alanine by branched-chain amino acids and their rapid uptake by the liver, with increased hepatic gluconeogenesis. Amino acids derived from muscle proteolysis are converted into

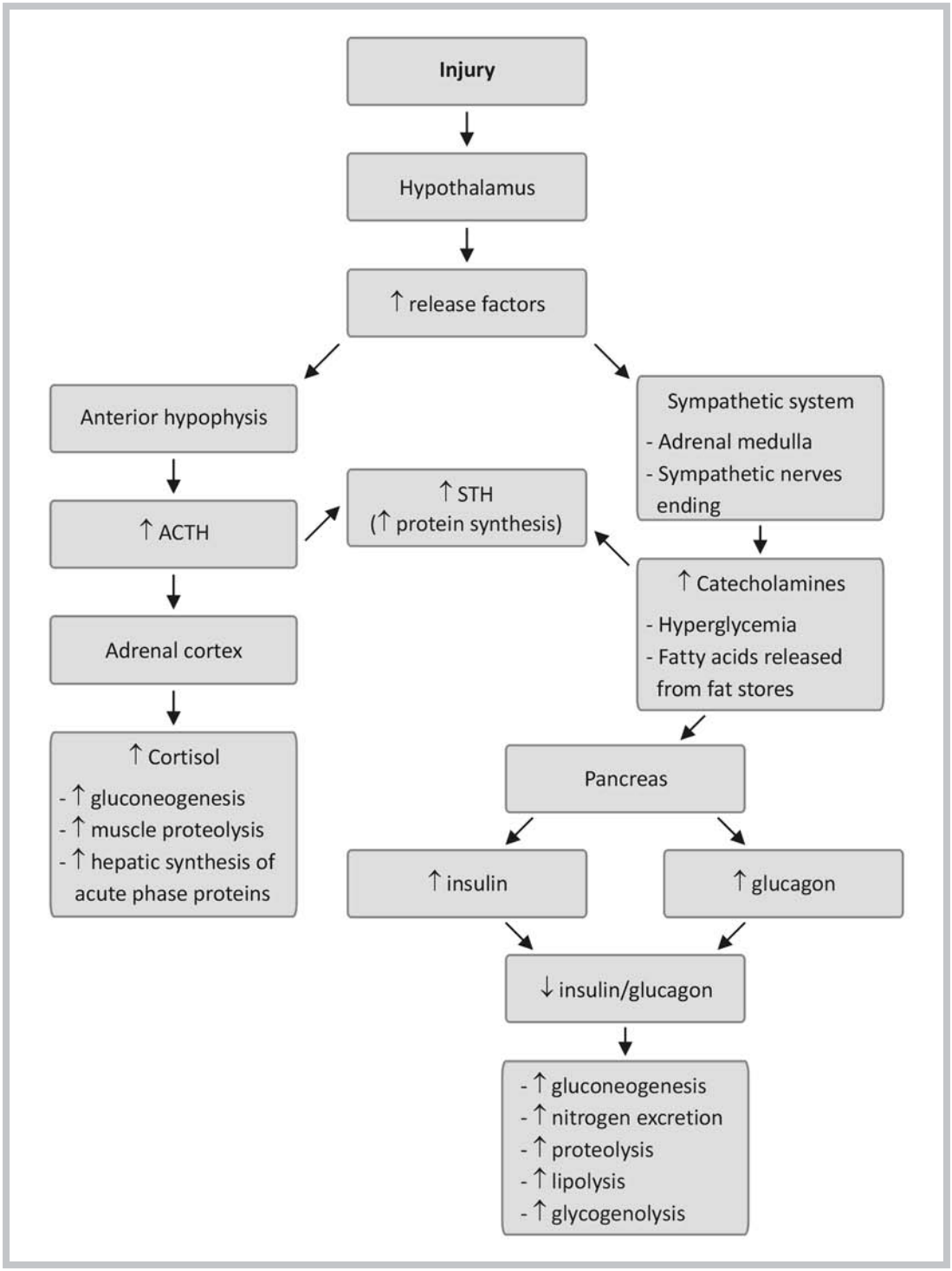

Figure 20.1. Schematic representation of the reactions to injury.

glucose and the rest goes into the synthesis of new liver protein, as evidenced by increased acute phase reactants.
When injury is not properly managed, the effective use of glucose is impaired, which will later affect fatty acid and ketone utilization and eventually the ability to use amino acids as an energy source. When muscle loss due to proteolysis is about 10% of body cell mass, the patient begins to deteriorate, and a loss of 30 to 50% of the body cell mass will end in death.
It should be noted that in patients with acute brain injury the metabolic control centre is damaged by the primary injury, so systemic response is more intense and prolonged than in other types of insults.

20.3 Assessment of Nutritional Status

The use of artificial nutrition has generated the need for an effective method to assess nutritional status in hospitalized patients. Because there is no simple method to define nutritional status, it is very important to have a comprehensive approach that includes careful medical history taking and anthropometric measurement, coupled with laboratory biochemical studies that can provide data about functional proteins and the patient's immune status as well.
The first step in assessing nutritional status is the clinical examination, as it will usually reveal elements that may indicate or suggest the presence of malnutrition. There are well-defined manifestations of a specific nutritional deficit; however, combined or partial clinical syndromes are most often observed. The classic malnutrition symptoms or signs are shown in Table 20.1. Other types of malnutrition are related to the lack of specific nutrients (electrolytes, minerals, oligoelements and vitamins). This lack can be isolated or combined and is often associated with the aforementioned disorders, which is why it may be masked by clinical manifestations.
A complete clinical examination includes evaluation of quantitative data obtained from objective and comparable studies which can be grouped as anthropometric and biochemical (biological indicators) measurement, immune status, and the nutritional prognostic index.

20.4 Anthropometric Measurement

Body weight is a simple guide to the patient's nutrition status, although it expresses the nature of tissue loss and may have errors of interpretation when there is dehydration

Malnutrition type	Marasmus (protein-energy malnutrition)	Kwashiorkor (protein malnutrition)	Mixed
Muscular mass	Very decreased	A little changes	Decreased
Visceral protein	A little changes	Very decreased	Decreased
Edema	Absent	Present	Present
Lymphocytes count	Decreased	Decreased	Decreased
Skin tests	Non-reactive	Non-reactive	Non-reactive

Table 20.1. Malnutrition. Classic types.

or edema. Because this parameter alone has relatively little value, other ways to assess body weight have been described.
Current weight as the **ideal weight percentage** can be calculated as follows:

% ideal body weight = actual weight x 100/ideal weight

Values are:
- Normal >90%.
- Mild malnutrition 80-89%.
- Moderate malnutrition 70-79%.
- Severe malnutrition <70%.

Current weight as **usual weight percentage** is equal to:

% usual weight = current weight x 100/usual weight

Values are:
- Normal >95%.
- Mild malnutrition 85-94%.
- Moderate malnutrition 75-84%.
- Severe malnutrition <75%.

Modified body weight or **recent weight change** is equal to:

% modified body weight = (usual weight – current weight) x 100/normal weight

Weight loss >10% indicates malnutrition, but even minor losses are reason for concern.

Triceps skinfold provides an estimate of subcutaneous fat which accounts for almost half of the body fat. It should be taken in the not-dominant arm (usually left) with the patient in the standing position or sitting with the arm hanging next to the body. If the patient is lying down, the arm should be placed with the forearm flexed over the chest. Measurement is taken at the midpoint between the acromion and the olecranon on the back of the arm. The fold thickness is measured with a Lange caliper or another type of instrument. A pressure of about 10 g/mm^3 should be applied, taking three measurements and then calculating the average value.
Standard values are 12.5 mm in men, and 16.5 mm in women. The obtained measurement is compared with the standard value using the formula:

% standard value = current measurement x 100/standard measurement

Values >80% indicate that adipose tissue is preserved; values <80% indicate loss of body fat. It is a useful index for assessing the degree of malnutrition, since changes in subcutaneous fat happen slowly.
Upper arm circumference is an indicator of muscle mass. Measurement should be taken in the half of the extended arm, at the midpoint between the spinous process of the acromion and the olecranon. The values can be compared using percentile tables or compared with the standard values using the formula:

% standard value = current measurement x 100/standard measurement

The reference values are 29.3 cm in men and 28.5 cm in women.
Values <85% indicate malnutrition.

Arm muscle mass is used to estimate body muscle mass, indicating protein reserves. The formula is:

Arm muscle mass = upper arm circumference (cm) – 0.31416 x triceps skinfold (mm)

The current measurement is compared with standard values (25.3 cm in men and 23.2 cm in women):

% standard value = current measurement x 100/ standard measurement

Values >80% indicate adequate muscle mass; values <80% indicate protein mass deficit.
Body height is obtained by dividing the height (cm) and the wrist circumference (cm) at the level of the styloid process.

Body height = height (cm)/wrist circumference (cm)

Values in men are:
- Normal <9.6.
- Light malnutrition 9.6-10.4.
- Moderate malnutrition >10.4.

Values in women are:
- Normal <9.9.
- Light malnutrition 9.9-10.9.
- Moderate malnutrition >10.9.

Creatinine-height index is an estimate of muscle mass because creatinine is formed from creatine only in the muscle. In patients with normal renal function this value is relatively constant for a given weight and height. This index is defined as the relationship between urinary creatinine excretion over 24 hours and the expected urinary excretion in a normal adult of the same size.

Men		Women	
Height (cm)	Creatinine (mg/dl)	Height (cm)	Creatinine (mg/dl)
157.5	1288	147.3	830
160.0	1325	149.9	851
162.6	1359	152.4	875
165.1	1386	154.9	900
167.6	1426	157.5	925
170.2	1467	160.0	949
172.7	1513	162.6	977
175.3	1555	165.1	1006
177.8	1596	167.6	1044
180.3	1642	170.2	1076
182.9	1691	172.7	1109
185.9	1739	175.3	1141
188.0	1785	177.8	1174
190.5	1831	180.3	1206
193.0	1891	182.9	1240

Table 20.2. **Urinary creatinine values according to sex and height.**

Creatinine-height index: = current urinary creatinine x 100/ideal urinary creatinine

The ideal urinary creatinine is obtained from tables (Table 20.2).
Creatinine-height index values <60% indicate a severe depletion of somatic proteins; values between 60 and 80% indicate a moderate depletion.
Errors in anthropometric measurement are due to methodological inaccuracies. Some authors argue that there is an insufficient correlation between these measurements and body nitrogen.

20.5 Biochemical Measures (Biological Indicators)

20.5.1 Estimated Somatic Protein Mass

Excretion of urinary 3-methylhistidine (3-me-his): 3-methylhistidine is formed from histidine methylation and is found only in the myofibre protein in the muscle. During muscle breakdown, actin and myosin proteins are released, but as they cannot be reused for protein synthesis, they are excreted with the urine, which provides an index of muscle catabolism. Each gram of muscle protein releases 4.2 micromoles of 3-methylhistidine.
Values depend on the pathological situation:

- Simple fasting <100 µmol/24 hours.
- Elective surgery 130±20 µmol/24 hours.
- Trauma 200±20 µmol/24 hours.
- Sepsis 450±50 µmol/24 hours.

20.5.2 Creatinine Urinary Excretion

Creatinine is produced by creatine metabolism. In patients with normal renal function, urinary excretion correlates with the total organic creatinine value.
Normal values: 23 mg/kg/day in men and 18 mg/kg/day in women.
These values vary according to renal function and nutritional intake of the patient.

20.5.3 Estimated Visceral Protein Mass

It refers to the measured plasma proteins synthesized by the liver.
Albumin, the main protein produced by the liver, maintains plasma oncotic pressure and is involved in the transport of various substances. It is not a good indicator of malnutrition, since it has a long half-life (16-21 days) and its concentrations are reduced and recovered very slowly during changes in nutritional status.
Values are:

- Normal 35 g/l.
- Mild depletion 30-34 g/l.
- Moderate depletion 25-29 g/l.
- Severe depletion <25 g/l.

Albumin levels <28 g/l lead to the development of edema because of the decrease in plasma oncotic pressure.
Prealbumin, a protein involved in the transport of thyroxine, has a half-life of 2 days and is present in a small pool in the body which decreases quickly with any sudden demand

for protein synthesis, as in trauma or acute infection. It is useful as a short-term nutritional index.
Values are:
- Normal 15-30 mg/dl.
- Mild depletion 10-14 mg/dl.
- Moderate depletion 5-9 mg/dl.
- Severe depletion <5 mg/dl.

Transferrin (TFN), a betaglobulin synthesized in the liver, conjugates the iron in plasma. Its half-life (t ½) is 8 to 10 days. It belongs to the group of acute phase reactive proteins and shows more precisely the changes in acute visceral proteins (depletion and repletion) due to its short half-life and small pool. It can be measured by radial immunodiffusion or calculated from total iron binding capacity (TIBC) with the following formula:

$$TFN = (0.8 \times TIBC) - 43$$

Values are:
- Normal 250-400 mg/dl.
- Mild depletion 150-250 mg/dl.
- Moderate depletion 100-150 mg/dl.
- Severe depletion <100 mg/dl.

Retinol binding protein, a specific protein that transports vitamin A alcohol is bound to prealbumin. Since it is filtered by the glomerulus and excreted by the kidney, it rises in renal disease. It is a sensitive index of subclinical malnutrition and a good responder to nutritional recovery because it breaks down within about 10 to 12 hours.
Normal range is 2.6-7 mg/dl.

Fibronectin is a protein with a half-life of less than 2 days. It has a very important relevance, more than other proteins, and is also used in monitoring the patient.
Values are:
- Normal range 320-360 mg/dl.
- Mild depletion 230-319 mg dl.
- Moderate depletion 200-229 mg/dl.
- Severe depletion <200 mg/dl.

Values <200 mg/dl are associated with increased mortality.
Techniques for measuring visceral proteins do not provide an accurate assessment of nutritional status, as they are influenced by factors other than malnutrition. There is a direct correlation between albumin, transferrin and fibronectin depletion with higher morbidity and mortality, delayed healing and decreased resistance to infection.

20.5.4 Measurement of Immune Response

Immune function is reduced in malnutrition, which is associated with higher morbidity and mortality from infectious diseases.
Decreased total lymphocyte count (TLC) is related to depressed cellular immunity, according to the following formula:

$$TLC = \% \text{ lymphocytes} \times \text{total white blood cells}/100$$

Values are:
- Normal >2000/mm^3.
- Mild immune deficiency 2000-1200/mm^3.

- Moderate immune deficiency 1200-800/mm^3.
- Severe immune deficiency <800/mm^3.

Skin tests indicate the cell-mediated immune state; to perform it are used antigens as the purified protein derivative antigens (PPD), Candida, mumps, histoplasma, and streptokinase-streptodornase and trichophytum. Intradermal hives appear on the anterior forearm when 0.1 ml of each of the antigens is given. Reading should be performed at 24 to 48 hours.

Values are:

- Positive or reactive: wheal >5 mm.
- Negative or non-reactive: wheal <5 mm.

A patient is considered immunocompetent when he has a good response (>5 mm) to two or more antigens. Anergy is defined as negative reaction to all antigens. These tests are less useful in patients with cancer, cirrhosis or in those under immunosuppressive therapy, because they may be incompetent due to the immunological condition itself, even when nutritional status is adequate.

20.5.5 Nutritional Prognostic Indexes (NPI)

These indices are very important to establish a relationship between nutritional status, as evaluated by objective parameters (anthropometric, biochemical or immune status) and morbidity and mortality. The index described by Buzby is derived by the formula:

$$NPI = 158 \text{ to } 16.6\ (Alb) – 0.78\ (TS) – 0.20\ (ST) – 5.8\ (DHR)$$

where: Alb = serum albumin (g/l); TS = triceps skinfold (mm); ST = serum transferrin (mg/dl); DHR = delayed hypersensitivity response.

Results are:

- No reaction = 0.
- Induration <5 mm = 1.
- Induration >5 mm = 2.

The result indicates the probability of occurrence of complications due to malnutrition, the most important of which is sepsis. Based on this index, several authors have applied multiple linear regression analysis using two or three variables which showed good correlation with severe complications and mortality, thereby generating various indexes, the most useful of which in our practice is:

$$NPI\ (Alb\text{-}DHR) = 55 \text{ to } 10.2\ (Alb) – 9\ (DHR)$$

DHR is used as the skin response to five antigens, scored as 1 when it is normal and 0 if there is anergy.

The values associated with a greater probability of complications are:

- NPI (Buzby) >40.
- NPI (Alb-DHR) >18.

20.5.6 Energy Expenditure

Living organisms need energy for all sorts of biological activities such as the synthesis of cellular material, transport of substances against a concentration gradient, muscle contraction, and production of heat to maintain body temperature constant. Nutrients (carbohydrates, fats and proteins) are transformed to provide the energy needed

for body functions. When energy intake exceeds consumption, the energy is stored, resulting in weight gain. Conversely, when energy expenditure exceeds intake, the deficit is made up for by the body's reserves, resulting in weight loss.

Basal energy expenditure (BEE), also known as basal metabolic rate (BMR) or basal metabolic index (BMI), refers to the production of energy per unit of time in basal conditions, defined as physical and mental rest, soon after awakening in the post-absorptive stage (about 12 hours after the last meal) and normal body temperature (18-26°C). This is the minimum energy consumption during physiological conditions. The liver, brain, heart and kidney consume 60% to 70% of BEE, although they account for only 5% to 6% of body weight, which reflects their high metabolic activity. In contrast, the muscles constitute 40% of body weight and use only 18% of BEE, depending on the activity of respiratory muscles and those required to maintain posture. BEE depends on cellular processes such as ion pump, synthesis and degradation of cellular constituents in which the protons cross the mitochondrial membrane, and also respiratory muscle and myocardial contraction. BEE is generally between 1500 and 1800 kcal/day and can be predicted by several methods (Table 20.3).

Body weight (kg)	BEE (kg Kcal/day)
50	1316
55	1411
60	1509
65	1602
70	1697
75	1784
80	1872

Table 20.3 Normograms.

Harris-Benedict formula:

$$\text{BEE (men)} = 66.5 + 13.75\ (W) + 5\ (H) - 6.75\ (A)$$

$$\text{BEE (women)} = 65.5 + 9.56\ (P) + 1.84\ (H) - 4.7\ (A)$$

where: W = weight (kg), H = height (cm), A = age (in years).

BEE is expressed in kcal/kg. This formula has the advantage that it can be rapidly calculated and is easy to apply, although errors of up to 30% of total calories have been reported.

Resting energy expenditure (REE) refers to the energy expenditure at basal conditions. The difference between BEE and REE derives from food-specific dynamic actions and thermogenic response, which is the increased energy expenditure caused by nutrition itself. REE is equal to BEE increased by 10%. It is reported that the REE of patients with traumatic brain injury is 140% on average. Barbiturates, propranolol and muscle relaxants can decrease hypermetabolism, although this has not proved to influence the prognosis.

Total energy expenditure (TEE) refers to the caloric intake to be administered to maintain body weight. It is usually obtained from BEE, and it takes into account the degree of catabolism associated with the disease or injury.

Different forms of production have been described:

$$\text{TEE (Rutten)} = \text{BEE} \times 1.75$$

This formula is unreliable because it does not adequately reflect the involvement of patient's physical activity or increased activity in situations of stress.

$$\text{TEE (Long)} = \text{BEE} \times \text{activity factor} \times \text{stress factor}$$

Clinical conditions	Correction factors
Prolonged fasten	0.85-1.00
Non complicated postoperatory period	1.00-1.05
Fever*	1.10-1.13
Peritonitis	1.05- 1.25
ARDS	1.20
Long bone fracture	1.15-1.30
Infection:	
Mild	1.20
Moderate	1.30
Severe	1.50-1.60
Head trauma	1.60
Burns	
10 to 30 % body mass	1.50
30 to 50 % body mass	1.75
More than 50 % body mass	2.00

Table 20.4. **Correction factors in different clinical conditions.**
* For each temperature grade above 37ºC or fever lasting more than 24 hours, increase occurs.

The activity factor (AF) corresponds to the degree of patient mobilization. In critically ill bedridden patients it is 1.20 (20% increase in BEE) and 1.30 in awake patients. Some authors use an average of 1.25 in all situations. This factor does not take into account paralyzed patients or ventilated patients under muscle relaxation. In mobile patients, one must use expenditure energy (EE) tables which link it with the type of activity. The stress or aggression factor (AF) corrects the EE for different conditions and is obtained from tables that have been created for this purpose. Table 20.4 describes the one used in our unit.

Another way to calculate TEE is by indirect calorimetry, which determines the amount of energy lost as body heat. This method measures the amount of energy expenditure of all metabolically active cells in the body, which is equal to TEE.

To calculate TEE by this method, one must know the concentration of inspired (FiO_2) and expired oxygen (FeO_2), inspired and expired CO_2 fractions ($FiCO_2$ and $FeCO_2$, respectively), inspired and expired minute volume (IMV and EMV), CO_2 production (VCO_2) and the respiratory quotient (RQ). This is done using the following formulas:

$$VO_2 \text{ (l/day)} = FiO_2 \times IMV - FeO_2 \times EMV$$

and

$$VCO_2 \text{ (l/day)} = FeCO_2 \times EMV - FiCO_2 \times IMV$$

Using these parameters, the Weir formula allows the calculation of TEE with three levels of accuracy.

Using only VO_2 in the formula $TEE = 4.83 \times VO_2$, the energy expenditure can be estimated with a minimum of accuracy. The combined use of VO_2 and VCO_2 increases the level of accuracy and allows the calculation of respiratory quotient (RQ):

$$RQ \text{ (TEE)} = 3.9 \times VO_2 + 1.1 \times VCO_2$$

Finally, the incorporation of protein metabolic factor into the evaluation of blood gas production and consumption allows for greater accuracy and to determine the oxidation of each nutrient separately.

$$TEE = 3.94 \times VO_2 + 1.1 \times VCO_2 - 2.17 \times No$$

Where No denotes urinary nitrogen.

Nutrient		Kcal/g	VCO_2 (l/g)	VO_2 (l/g)	RQ	Caloric value per liter of O_2
Carbohydrates	Monosaccharides	3.75	0.75	0.75	1	5
	Polysaccharides	4.30	0.83	0.83	1	5
Proteins		4.20	0.75	0.94	0.80	4.5
Fats		9.30	1.39	1.96	0.71	4.7
Ethanol		7.10	0.98	1.46	0.67	4.9
Ordinary diet		-	-	-	0.82	4.8

Table 20.5. **Energetic value for different nutrients.**
VO_2 = oxygen consumption
VCO_2= carbon dioxide production
RQ = respiratory quotient

It has been found that the exclusion of No generates an error of less than 25% in calculating TEE. Determining the respiratory quotient (RQ) is valuable for estimating the nutrients that are mainly oxidized. The nonproteic physiological RQ ranges from 0.71 to 1.2, which indicates the oxidation of fats and carbohydrates; when it is about 0.7, it depends only on the oxidation of fat; if around 1, it indicates that only carbohydrates are oxidized; and when greater than 1, this suggests that the carbohydrate supply is excessive and lipogenesis is occurring.
The difficulties with this method are that VO_2 and VCO_2 vary constantly; therefore, computers are used to process and analyze the data every minute to obtain a 24-hour average.
The combustion characteristics of each nutrient are related to its chemical structure. Table 20.5 presents the energy characteristics of different nutrients.

20.6 Nutritional Requirements

The energy requirements of different essential elements, as well as vitamins, minerals and water, vary in the hypercatabolic and critically ill patient in relation to the normal patient.
Energy requirements. The patient's energy needs are equivalent to TEE and determine the caloric intake to be provided to maintain body weight. If the objective is to achieve anabolism and weight gain, 1000 kcal should be added to the calculated value, which will increase a weight gain of approximately 1 kg or 2 pounds per week. Normometabolic patients must receive at least 25% of TEE as carbohydrates to save proteins. Since stressed patients have a higher need of carbohydrates to save proteins and maintain high-energy deposits in the tissues, at least 50% of TEE should be supplied as carbohydrates. When carbohydrates are used as the sole source of energy, the needs are around 500 up to 650 g/day. Total carbohydrates should be calculated at a rate of 2 g/kg/day in normal patients and 4-6 g/kg/day in hypercatabolic conditions.
The use of a high caloric intake based exclusively on carbohydrates can lead to essential fatty acid deficiency, liver dysfunction with elevated enzymes, inhibiting the synthesis of very low density lipoprotein (VLDL), increased hepatic triglyceride synthesis, decreased lung surfactant production and increased CO_2 production.
To avoid problems caused by the use of carbohydrates as the sole source of energy, it is recommended to associate them with fats, which have multiple functions, as well as

providing metabolic energy reserve in the adipocytes. Also, phospholipids are formed in the cell membrane and act as intracellular modulators (prostaglandins). Lipids can be used two times per week, with the aim of providing essential fatty acids (linoleic acid), or administered as an energy source, thus supplying some of the calories calculated. The daily fat requirement is 1 to 2 g/kg/day under basal metabolic conditions, which is higher in catabolic situations (3-5 g/kg/day).

The proportion of carbohydrates and fats to be administered varies according to different sets of criteria and the patient's illness. Some authors recommend using no more than 60% of nonprotein calories as fat, stating it should not exceed 100 g/day, although some set the limit as high as 75% of TEE.

Fat emulsions are not well tolerated in certain clinical situations, such as Gram-negative sepsis, neonatal hyperbilirubinemia and carbohydrate and lipid metabolic disorders.

Studies published in the 1960s reported on the need to differentiate long-chain triglycerides (LCT) from medium-chain triglycerides (MCT), highlighting the benefit of the latter because of their high caloric value, similar clearance and metabolism to glucose.

LCT emulsions of fatty acids containing 12 to 24 carbons undergo hydrolysis to fatty acids and glycerol in the intestinal lumen, which are esterified after being re-absorbed to form triglycerides that bind to proteins and phospholipids, forming chylomicrons. They then enter the lymphatic system and finally the blood, where they are distributed to the tissues.

MCT emulsions of fatty acids containing 6 to 12 carbons, mainly octanoic acid, esterified cholesterol are hydrolysed in the intestine five times faster than LCT (although some authors note that they do not need to be absorbed hydrolyzed) and their free fatty acids are absorbed twice faster. They then go directly to the portal vein and are transported to the liver and other tissues as free fatty acids or bound to albumin. They have the advantage of not being stored as fat in the body and are oxidized quickly and completely.

The use of LCT as the sole source of fat produces lipid deposition in the heart, kidneys and lungs, because less than 10% are oxidized and the rest is stored as neutral fat.

The use of MCT alone delivers more calories more rapidly than LCT. MCT are also associated with decreased fatty infiltration but do not prevent essential fatty acid deficiency. At present, the combined use of LCT and MCT is considered most advantageous; therefore, LCT solutions with 25 to 50% MCT are recommended.

In enteral nutrition, MCT should be introduced in small amounts, increasing them gradually to a daily intake of 50 to 100 g.

MCTs are ketogenic, so they are contraindicated in diabetic patients or in those with ketosis and acidosis, in which the capacity of extrahepatic tissues to use ketone bodies is saturated. They should not be used in patients with liver cirrhosis, as the medium-chain fatty acids are metabolized in the liver and liver function is reduced. Octanoic acid accumulates in these patients, so symptoms may appear similar to hepatic encephalopathy.

Protein requirements. In the body there is usually a loss of protein due to the synthesis and degradation of body proteins. The main protein losses occur through the urine and feces, the latter due to intestinal secretions and cell desquamation. In addition, there is minimal loss through the skin and during menstruation in women.

In healthy patients there is a positive nitrogen balance when nonprotein calories are provided for each gram of nitrogen (300-350/1) (7% of TEE). In hypercatabolic and critically ill patients, because urinary nitrogen elimination is increased, the patient needs more protein in relation to the total calories, as protein should comprise about 10 to 20% of TEE. In this particular situation, a ratio of nonprotein calories per gram of nitrogen (100 to 150/1) must be maintained. In septic patients this ratio should be 80 kcal of nonprotein nitrogen per gram of nitrogen.

In patients with acute brain injury, the estimated daily intake of nitrogen should be between 0.3 and 0.5 grams of nitrogen per kilogram of body weight per day.
Protein requirements can be calculated in the ways described below.
From 10 to 20% of TEE as proteins: it must be remembered that each gram of protein provides 4 kcal and that with each 6.25 g of protein 1 g of nitrogen is released (1g of protein is equivalent to 0.16 g of nitrogen).
Using tables that show the daily losses of nitrogen in different clinical situations (replacement must equal losses).
Measured urea in 24-hour urine: nitrogen excretion in urine is the final product of protein metabolism to obtain energy; therefore, the protein requirements can be determined by calculating the daily losses of nitrogen from the elimination of urea in 24-hour urine. For the proper calculation of nitrogen excretion, a steady diet should maintained for 24 to 48 hours beforehand.

Urea in 24 – hour urine (g/24 hours) = urine volume (l/24 hours) x urea in urine (g/l)

The urea molecule is not entirely composed of nitrogen. To obtain the real amount of nitrogen that it contains, it must be divided by 2.14.

UUN (g/24 hours) = urea in 24 – hour urine (g/24 hours) / 2.14

Where urinary ureic nitrogen (UUN) represents 80% of total urinary nitrogen losses (total urinary nitrogen or TUN). The latter can be calculated when 20% of UUN is added to itself.

TUN = UUN + 20% UUN

Added to the obtained value must be 2 to 4 g due to losses by the skin and feces, although these values may be higher in patients with diarrhea, burns, and extensive wounds or diffuse exfoliative dermatitis.
Calculation from TEE, using the desired ratio: nonprotein calories per gram of nitrogen.
When using amino acids as a nitrogen source, some measures should be taken into account:

1. Replacement of the total nitrogen lost.
2. Provide at least 20% of essential amino acids.
3. Provide a ratio of essential amino acids/total amino acid of 1/1 to 1/3.
4. Provide a ratio of essential amino acids per gram of nitrogen of 3.28.
5. The nutrient solution should include all the essential amino acids and traces of the nonessential ones.

Water requirements. Water requirements vary according to clinical status. In basal conditions the daily amount of water required is 25 to 35 ml/kg/day, and these needs increase in hypercatabolic states up to 50 to 70 ml/kg/day. Multiple factors modify water losses, such as high-protein diets, fever, polyuria, vomiting and kidney failure. It is advisable to deliver 1 ml water per kcal provided. It should be taken into account that before admonistering high volumes of fluids, cardiac and renal function and the patient's water balance should be evaluated.

Recommended doses	Nitrogen (g/kg/day)
Minimal daily doses	0.072
Recommended basal doses	0.128
Dosis for minimal stress	0.200
Dosis for moderate stress	0.240
Dosis for severe stress	0.280-0.320

Table 20.6. Nitrogen daily requirements.

Vitamin requirements. Vitamins are essential for nutrition; they are involved in protein metabolism, in extracting energy from carbohydrates and fats, as well as in tissue synthesis. Their needs are not well established, although various investigations have determined their baseline values, which can increase three- to fivefold in hypercatabolic states.

Vitamin requirements may be affected by changes in diet, use of some medications, diseases such as malnutrition, sepsis and trauma, and artificial nutrition, primarily parenteral nutrition. Inadequate or marginal intake in these situations can cause vitamin deficiency.

Vitamins are broadly classified into fat-soluble and water-soluble. The deficit of the water-soluble vitamins occurs more easily because the fat-soluble vitamins are stored in the body and have a slower turnover (Table 20.7).

Water-soluble vitamins should be supplied daily. Vitamin B12 should be taken 2 or 3 times a week and at very wide intervals thereafter.

Fat-soluble vitamins should be administered once a week and vitamin K twice a week.

Requirements of electrolytes, minerals and trace elements. These substances are involved in multiple cellular functions and various enzyme systems. Their needs in basal conditions are considered, and they are increased in hypercatabolic states (Table 20.8). When there are no solutions with trace elements, these can be provided by plasma transfusions given weekly or twice a week.

Vitamins	Daily requirements
Fat soluble	
A (retinol)	4000 UI
D (calciferol)	400 UI
E (tocopherol)	15 mg
K	200 µg
Water soluble	
B1 (thiamine)	3 mg
B2 (riboflavin)	3.6 mg
B3 (niacin)	15 mg
B6 (pyridoxine)	4 mg
Pantotenic acid	40 mg
Folate	0.4 mg
B12 (cyanocobalamin)	5 µg
Biotin	100-200 µg
C (ascorbic acid)	100 mg

Table 20.7. Vitamins daily requirements.

	Daily requirements
Electrolite	
Sodium (Na^+)	1-2 mEq/kg
Chlorus (Cl^-)	1-2 mEq/kg
Kalium (K^+)	0.9-1.2 mEq/kg
Calcium (Ca^{++})	5 mEq/kg
Phosphorus (P^-)	2 mmol/kg
Magnesium (Mg^{++})	0.3 mEq/kg
Nutritional trace	
Iron (Fe^{++})	10-100 mg
Zinc (Zn)	20 µg
Cobalt (Co)	70 µg
Iodine (I)	25 µg
Copper (Cu)	11 µg
Manganese (Mn)	20 µg
Fluorine (F)	1.5-4 mg
Chromium (Cr)	50-200 µg
Selenium (Se)	20-200 µg
Molybdenum (Mo)	150-500 µg

Table 20.8. Electrolytes and nutritional elements daily requirements.

20.7 Artificial Nutrition

Artificial nutrition refers to that condition in which nutrients are not supplied by common dietary foods. It can be administered via different routes. A primary form of treatment, artificial nutrition plays an important role in the comprehensive care of critically ill patients since a nutritional deficit can interact with the disease and prolong the healing process or have devastating consequences.

The goals of artificial nutrition are to:
- Decrease catabolism and promote anabolism.
- Strengthen defence mechanisms.
- Hasten the healing process.
- Maintain or restore muscle mass and function.
- Maintain normal oncotic pressure to prevent edema formation.
- Promote recovery.
- Reduce recovery time, morbidity and mortality.

The routes of administration are enteral nutrition and parenteral nutrition, discussed below.

20.8 Enteral Nutrition

Enteral nutrition refers to the therapeutic delivery of nutrients to the gastrointestinal tract where they are absorbed and assimilated. It is an optimal way to provide nutrients as it is more physiological, maintains the integrity of the intestinal mucosa, and has fewer complications. During the course of critical illness, the gut almost always remains inactive because of ileus or other frequent problems that prevent feeding and require nasogastric aspiration.

Besides its role in the digestion and absorption of nutrients, the intestine also acts as an enteral flora barrier which prevents host invasion by microorganisms or their toxins. In patients who receive no food or nutrients into the digestive tract, the intestinal mucosa become more permeable to the passage of germs and their products into the bloodstream, leading to chronic hypermetabolism and multiple organ failure.

Enteral nutrition has the following advantages:
- Lower cost.
- Safe and effective for long periods.
- Lower incidence of complications (no central venous catheter complications).
- Positive physiological effects.
- Preserved integrity of the intestinal mucosa by intraluminal delivery of nutrients
- Maintenance of the sequence of intestinal and hepatic metabolism before the passage of nutrients into ystemic circulation (digestion, absorption, hormone-substrate interaction).
- Stimulation of the production of secretory IgA.
- Reduction of the metabolic response to stress.

20.8.1 Nutrient Management Methods

In **bolus administration** nutrients are deposited in the stomach which regulates the flow of the formula into the small intestine. The gastric emptying rate depends on the volume and osmolality of the formula. This method requires a small staff and special equipment. From the metabolic point of view, it is generally effective. Volumes of 200 to 400 ml 4 to 6 times a day can cause nausea, vomiting, diarrhea, cramps and bloating, with a high risk of aspiration.

Intermittent administration is given in small amounts of 80 to 160 ml from 20 to 30 minutes every hour; however, tolerance is poor in some patients and the technique is impractical since it occupies a lot of nursing staff time. An alternative way for use in patients requiring prolonged enteral nutrition involves continuous administration of enteral solutions at a rate of 160 ml/hour for 12 hours.

Continuous administration is better tolerated in patients with severe disease and is more useful for duodenal or jejunal nutrition, thus avoiding the arrival of large volumes of fluids to the jejunum. Isotonic solutions should be started at an infusion rate of 50 ml/hour, and then gradually increased, as tolerated, up to 80 ml/hour. The concentration and volume of nutrients should not be modified simultaneously, but the required volume and concentration should be obtained within 24 to 48 hours.
If intolerance develops, the volume or concentration of the diet should be reduced to the previous level of tolerance, and then increased after sufficient time for adaptation has elapsed. Wherever possible, regulators should be equipped with a flow or infusion pump to reduce the possibility of inadequate volumes, resulting in less bloating and diarrhea, lower residual volume and less risk of aspiration.

20.8.2 Routes of Administration

Intragastric nutrition is indicated when there is a good level of consciousness, normal cough reflex and adequate gastric emptying. This allows normal enzymatic activity on the nutrients. Due to the stomach's reservoir capacity and the dilution by gastric secretions, the osmotic load of the diet is not a problem; therefore, highly concentrated solutions can be initiated early.
The volume should be increased every 24 to 48 hours until it covers the total nutritional requirement with an intermittent bolus of 300 to 400 ml each, every 3 to 4 hours. If the nasogastric tube (NGT) has a suitable gauge, feeds can be administered by gravity for 20 or 30 minutes. Pumps are indicated if the patient is receiving viscous solutions.
The gastric residual should be controlled before each administration and administration discontinued if it is >150 ml. The patient should be rechecked after 2 hours and feeding can be restarted if the gastric residual is less than the stated value. If the NGT is in the duodenum, gastric residual can be up to 300 ml of fluid before deciding on temporary suspension. This route of administration of nutrients may not be used in neurocritical patients because of the risk of aspiration. In unconscious patients or in patients with deteriorated gag reflex, the NGT should be placed away from the pylorus to reduce the risk of aspiration.
Intestinal nutrition (duodenal or jejunal). The tube should be placed distal to the Treitz ligament to decrease the risk of aspiration. The technique for tube placement may be blind (high failure rate) or by endoscopy, fluoroscopy or ultrasound-guided. The use of prokinetic agents facilitates, at least in theory, the passage of the pylorus, regardless of the technique. Also, these tubes can be positioned by invasive methods such as endoscopic percutaneous jejunostomy, radiological percutaneous jejunostomy and traditional surgery or by laparoscopy.
Use of enteral nutrition, mainly jejunal nutrition, is suitable for early postoperative feeding, is safe and effective, as intestinal paralysis is predominant in the stomach and colon, and also it causes poor pancreatic stimulation.
Bolus administration of hyperosmolar solutions in the small intestine can cause bloating, diarrhea and electrolyte disturbances. To avoid these adverse effects, volumetric pumps can be used and solutions with half of the desired concentration should be started at infusion rate of 50 ml/hour.
If undesirable effects do not occur, then the gastrointestinal volume can be increased from 25 to 50 ml/hour every 24 hours until the daily volume is reached. The concentration of the solutions must be increased till the total osmolality of the nutritional formula is obtained.
The most important limiting factor in intolerance to the diet is the osmolar load (intake per unit time) received by the digestive tract, so a gradual increase in the infusion rate,

but not the concentration of the formula, is recommended, while maintaining a caloric density of 1 kcal/ml.
Accordingly, protocols has been devised under which the quantity should be 20 ml/hour for the first 6 hours and then incremented by 10 ml/hour every 6 hours until the desired volume is reached, or to start with 20 ml/hour for 8 hours with increments of 20 ml/hour every 8 hours until the infusion rate matches the requirements. If the patient develops diarrhea, and antidiarrhetic may be given, but if it persists or other adverse effects arise, feeding should be suspended for 48 hours.
In other nutrient administration methods, the location of the NGT should be verified before use, patients should be placed in the semisitting position, not less than 30 degrees elevation of the head. The presence of abdominal distention, diarrhea or other side effects have to be checked periodically. After feeding, the NGT should be washed and irrigated with 20 ml of water.

20.8.3 Classification of Enteral Diets

Nutritionally complete diets can provide adequate nutrition without the need for another source, are indicated in patients with normal proteolytic and lipolytic activity; they require normal motor ability, digestive and nearly normal absorption by the small intestine. These diets are composed of intact proteins, complex carbohydrates, varying amounts of fat, waste, vitamins and minerals and can be used as the patient's total nutritional support. There are several different types, described below.
Homogenized diets are prepared with natural foods under technical homogenization; they differ from normal food only in consistency and method of administration through a catheter. Other features are a high-fibre content, very viscous (requiring large calibre NGTs) and many contain lactose, which may be unsuitable for patients with lactase deficiency. The nutrient quantity is variable and there is a higher risk of aspiration. These diets are prepared from milk, yogurt and ice cream, and other nutrients are added. They are indicated in patients with normal intestinal function but requiring nutrition by NGT.
Milk-based diets use milk as the main protein source and other sources of protein like eggs are added; calories are provided as lactose, dextrins, milk fat and soybean or corn oil. They are poorly tolerated in patients with disaccharidase deficiency and can cause diarrhea.
Lactose-free diets use eggs and soybeans as the protein source. Nonproteic calories are provided as oligosaccharides from glucose, dextrin and fat derived from soybean or corn oil. These diets are useful in patients with lactase deficiency, have low viscosity, and can be administered via small-calibre tubes. In addition, they are sterile, because their preparation is commercial. Nutritionally complete diets can be normal in protein, with a protein intake <20% of total calories, or high in protein, which contain 20% or more protein in relation to the supply of calories. These diets also can be enriched with fibres, contain MCT, or high in caloric concentration.
Basic diets or formula-defined (monomeric or oligomeric) diets (also called chemically defined diets or peptides diets) are composed of nutrients that require minimal digestion, so they are easily absorbed by the duodenum and proximal jejunum. They consist of carbohydrates as oligosaccharides, sucrose and glucose, short-chain peptides (oligopeptides) or L-amino acids and medium-chain fatty acids, and small amounts of essential fatty acids and vegetable oils. These factors cause little gastric residue and small intestinal contents, which reduce the frequency of bowel movements and decrease colonic bacterial flora. Osmolality is high due to the low-molecular-weight nutrients; they are lactose-free and can be low in fat. They have a calorie density of 1 kcal/ml, reduce gastric acid secretion, but are expensive. They may be useful in patients with reduced inte-

stinal absorption surface and in those with impaired digestion or absorption ability. Prolonged use can cause essential fatty acid deficiencies.

Modular or nutritionally incomplete diets. Each module consists of one or more nutrients (proteins, fats and carbohydrates). The modules are combined to produce a complete diet. They have high molecular density and may be useful in patients who require fluid restriction.

Diets for special situations have been created to cover the nutritional needs in specific diseases. There are low-calorie diets for patients with respiratory failure, with the aim to reduce CO_2 output; there are formulas with essential amino acids for renal failure patients, and fortified formulas with branched-chain amino acids for patients with liver failure and high metabolic stress. In addition, there are immuno-enriched diets with arginine or omega 3 fatty acids and diets enriched with glutamine which is involved in intestinal barrier integrity.

Because of the vast variety of formulas for enteral nutrition, the diet composition and the proportion of different nutrients in the formulas should be reviewed before use.

20.8.4 Complications

Enteral nutrition is a simple and reliable technique, but complications can appear, which are described below.

Mechanical Complications

Mechanical complications are related to tube placement and maintenance, tube type and its anatomical position:

They can be related to **nasoenteral tubes**; for example:

- Misplacement of the tube in the pharynx, esophagus, airways and lungs increases the risk of aspiration. Intracranial insertion of the tube has been described in patients with skull fracture of the anterior fossa.
- Upper respiratory airway impairment during prolonged catheterization and use of rubber or plastics tubes can lead to: pharynx irritation, difficulty in salivation, increased airway secretions, dry mucous membranes, erosions or necrosis of the nasal mucosa and the posterior wall of the larynx, causing bleeding, infections (pharyngitis, sinusitis and otitis media).

These complications can be reduced with the use of flexible, small diameter tubes, changing the tube position and with the use of lubricants and topical decongestants.

Also **intestinal tract injuries** can uoccur, such as: gastresophageal reflux, esophagitis, esophageal stricture, tracheesophageal fistula, rupture of esophageal varices, and mumps.

Gastrostomy and jejunostomy include: technique-related complications, separation of the stomach or jejunum of the abdominal wall, surgical wound infections, cellulitis at the site of tube entry at the skin, abdominal wall abscess, necrotizing fasciitis, suture dehiscence and hernia, bleeding, gastric prolapse through the gastrostomy.

Complications related to stroma care may cause skin irritation if there is extravasation of digestive juices.

Catheter-related complications are:

- Movement or tube misplacement.
- Tube placement may occlude the pyloric antrum.
- Inadvertent output or external migration of the tube.
- Leakage of intestinal contents.
- Excessive granulation tissue around the exit of the tube.

- Gastrocutaneous, gastrocolic or enteroenteric fistula.
- Volvulus.
- Peritonitis.
- Intestinal obstruction.
- Gastric atony or delayed gastric emptying in the gastrostomy.

Other mechanical complications are: accidental tube displacement or migration, tube obstruction by foods or drugs (can be prevented by irrigating the catheter with 20 ml of water after use), and gastresophageal reflux due to lower esophageal sphincter insufficiency.

Metabolic Complications

Hypertonic dehydration is caused by hyperosmolar formulas that cause extracellular fluid leakage into the intestinal lumen resulting in intracellular dehydration. This can be averted by adding water to the body, orally or parenterally.

Hyperhydration is due to the administration of large amount of liquids with the nutritional solutions, especially in patients with heart, renal or liver diseases. Restriction of volume and fluid balance is necessary.

Hyperosmolality is a severe form of dehydration which occurs in elderly patients and situations of stress. Patients present as pseudodiabetics with sufficient reserves of insulin to prevent ketosis but inadequate to control hyperglycemia, resulting in polyuria, glycosuria, osmotic diuresis and nonketotic hyperosmolar coma. Tube feeding should be reduced or discontinued, and simple insulin and hypotonic fluids should be given.

Essential fatty acid deficiency is when fat intake is inadequate or poorly tolerated.

Hypoglycemia can occur in diabetic patientswho receive insulin or because of their disease (pancreatitis, stress, etc.) when normal diet is suppressed.

Electrolyte imbalances can occur, with sodium, potassium, magnesium or other electrolyte impairment.

Other possible complications are: hypoprothrombinemia, renal failure, and vitamin deficiency.

Gastrointestinal Complications

Increased gastric residue is caused by nutrition through a NGT or gastrostomy. Various factors are involved, such as inappropriate body position, gastric distension, formula consistency, osmolar load concentration, fat and amino acid concentration in the diet, as well as neuroendocrine imbalance or use of drugs that reduce gastric motility (anticholinergics, antacids, analgesics, sympathetic-mimetics, antihistamines, etc.). Gastric residue is increased when NGT aspiration is 200 ml or more, and 100 ml when there is a gastrostomy. When this complication appears, the diet should be temporarily suspended for 1 to 6 hours and prokinetic agents as metoclopramide or cisapride should be given. It is always necessary to find and control the cause.

Vomiting or regurgitation is caused by gastric intolerance and problems related to diet such as osmolality, fat and bacterial contamination. They are more common in intermittent nutrition regimes (bolus) and agitated patients. When it occurs, the diet should be temporarily suspended, the causes determined and corrected, and prokinetic drugs initiated.

Abdominal distension is caused by microbial contamination of the diet and an imbalance between nutrient supply and functional capacity of the intestinal tract, as well as intestinal diseases. To correct this situation, the diet must be suspended and the cause determined.

Constipation is caused by increased intestinal water absorption in patients with inadequate blood volume or on a low-residue diet. Prevention with the use of dietary fibre is discussed.

Diarrhea associated with enteral nutrition (DAEN) refers to an increase in the number of loose stools (stool volume >200 ml). Criteria to raise the diagnosis depend on stool frequency, consistency and volume (3 or more loose stools per day or >2000 ml/day).
The mechanisms of diarrhea associated with enteral nutrition are multiple and include:

- Use of hyperosmolar formulas during duodenal and jejunal nutrition.
- Lactose in the diet causes osmotic diarrhea in patients with disaccharidase deficiency (lactase), which can be congenital or acquired during severe malnutrition in critically ill patients.
- Diets rich in fats and vitamin A may cause diarrhea in patients with pancreatic insufficiency or other causes of malabsorption.
- Diets with a low quantity of sodium (<90 mEq/l) lead to an increased secretion of water and sodium in the jejunum.
- Volume infusion rate exceeding the absorptive capacity of the small intestine.
- Diet or NGT contamination can be a reservoir of germs and a cause of infectious diarrhea.
- Intestinal bacterial overgrowth and infection by *Clostridium difficile* causes infectious diarrhea.
- Several drugscause diarrhea, such as some antibiotics, antacids, laxatives, prokinetic agents, antiarrhythmics (quinidine), digoxin, sympathomimetic agents, antihypertensives, NSAIDs, bronchodilators and H_2 antagonists.
- Hypoalbuminemia due to decreased intestinal absorption.

Infectious Complications

Aspiration pneumonia is more common in patients with an altered level of consciousness, gastric retention, vomiting or regurgitation. The gastric content goes into the lungs and causes injuries aggravated by the hyperosmolality and acidity of the aspirated content. This can be prevented by keeping the patient in an appropriate position (head elevated 30° or more during feeding) and using volumetric pumps and small internal diameter NGTs. It is necessary to determine if gastric retention occurs and if so, then nutrition must be suspended.
Tracheal colonization is caused by gastric or nasopharyngeal flora that infect the lungs and cause nosocomial bronchopneumonia. It is controlled by using acidified enteral diet and intermittent nutrition.
Enteral NGT contamination occurs because the tube acts as a reservoir for germs that cause infectious diarrhea. This can be avoided by washing the tube after use; equipment and connections must also be changed daily, and the nutritional formula should not be retained for more than 4 to 6 hours at room temperature.
Contraindications are: vomiting and /or intractable diarrhea, gastrointestinal bleeding, high output intestinal fistulas, paralytic ileus, intestinal obstruction, diffuse peritonitis, and shock.

20.9 Parenteral Nutrition

In this intravenous technique all the necessary elements are brought together to meet the body's nutritional demands. It is Indicated in many clinical situations including: altered integrity of the intestinal tract, inability of oral intake for 5 days or more, negative caloric and nitrogen balance in patients whose digestive function is unable to improve the balance over a period of 7 days.

20.9.1 Routes of Administration

Parenteral nutrition can be given via a peripheral vein or a deep vein. It is classified in:

- **Central parenteral nutrition**. Nutrient intake via a central vein with a high calibre and high blood flow which facilitates rapid dilution of the hyperosmolar solutions and peripheral distribution in isotonic concentrations. The full nutritional requirements are provided to the patient in 12 to 24 hours and can be administered until the patient is able to tolerate enteral or oral nutrition.
- **Peripheral parenteral nutrition**. Nutrient intake is via the superficial venous system, using a formula with lower osmolality of about 800 mOsm/l. Its use is also limited to short periods. The venipuncture should be rotated daily, so the patient must have multiple veins available.

Before starting parenteral nutrition, the patient should meet the following requirements: stable hemodynamics, appropriate oxygenation, adequate blood volume, normal electrolyte concentrations, and pH close to normal.

20.9.2 Nutrient Characteristics

Central parenteral nutrition can be classified according to the proportion of nutrients:

- **Total parenteral nutrition** is based on the administration of amino acids and dextrose. Fat emulsions are used only to prevent deficiency of essential fatty acids.
- **Complete parenteral nutritio**n uses carbohydrates and fats as the main energy source, but amino acids also are used. Because of its composition, it is close to the normal diet. Different sources of nutrients have specific characteristics.

Sources of amino acids. Crystalline amino acid solutions containing mixtures of essential and nonessential amino acid L-shaped isomers are easily assimilated by the body. There are many products available. The one we most commonly use is Aminoplasmal, which is a mixture of amino acids with a pattern close to that of normal plasma, containing 8 essential amino acids, of which are 2 semi- and 10 non-essential, all in L form. Electrolytes can be added or not. Available in two concentrations:

Aminoplasmal L-5 provides 8 g of nitrogen with 50 g of protein and 200 kcal/l of solution. The osmolality is 595 mOsm/l, allowing its use via peripheral veins. The maximum recommended infusion rate is 120-180 ml/hour.

Aminoplasmal L-10 is an amino acid solution that provides 16 g of nitrogen, 100 g of protein, and 400 kcal/l. The osmolality is high (1040 mOsm/l), so it is given only through the central veins. The maximum infusion rate is 120 ml/hour.

There are other crystalline amino acid solutions similar to those described. Since the protein concentration, electrolyte content and carbohydrate combination depend on the manufacturer, it is advisable to check the characteristics of different products before use.

Human albumin has scant value as a source of amino acids because the proteins need to be broken down to allow the amino acids to be used. It is useful to maintain plasma oncotic pressure and prevent edema due to hypoalbuminemia.

Sources of carbohydrates. Hypertonic dextrose is a solution that provides a large number of calories with low volume and high hypertonicity. It is a source of physiological energy available in different concentrations (Table 20.9). When glucose concentrations >10% are used, they must be supplied by a central vein due to their high osmolality and low pH which cause phlebitis in peripheral veins. Use is optimal when administered at 4 to 5 mg/kg/min. The administration of >7mg/kg/min, even with the addition of insulin, increases the rate of glucose clearance, but not its oxidation, so glucosuria

Concentration (%)	Glucose (g)	Provide (kcal)
5	50	200
10	100	400
20	200	800
30	300	1200
50	500	2000

Table 20.9. Dextrose administration every 1000 ml.

and osmotic diuresis can occur. More than 300 to 400 g per day should not be provided. Carbohydrate tolerance decreases with stress.

Fructose is a caloric source independent of insulin and does not need insulin to be phosphorylated. It provides the same amount of calories as dextrose and has different strengths. It causes less hyperosmolality than glucose, is metabolized more rapidly and transformed into liver glycogen. It has the disadvantage that it can cause lactic acidosis and requires the administration of large volumes of liquid. It is useful in diabetic patients with insulin resistance, but it has shown no advantages over glucose.

Sorbitol provides the same amount of calories as dextrose and the use of insulin is not needed. It is oxidized in the liver and converted to fructose. It may cause melituria and osmotic diuresis because it is not absorbed by the renal tubule. It is available in 10% and 30% concentrations. It is useful in diabetics and in patients with liver damage because of its anticetogenic and protective liver function properties.

Xylitol is a five-carbon polyol derived from xylose; its metabolism and utilization depends little on insulin. It offers the same amount of calories as dextrose and is available in concentrations of 5% and 10%. Mixtures are used with 30% of calories as xylitol and 70% as glucose. Reported side effects include jaundice, hyperuricemia, severe acidosis, elevated liver enzymes, and deposits of calcium oxalate crystals in kidneys and other organs.

Ethanol provides 7 kcal/g but induces hepatic metabolism disorders.

Fat sources. Cottonseed oil derivatives were once used, but they cause overload syndrome. Currently, solutions derived from soybean oil are manufactured (<1 micron particles), similar to chylomicrons, so they are engulfed by the Kuppfer cells in the liver and degraded by the lipase enzyme. Fat emulsions provide a high number of calories (kcal/g) with a small volume of liquid. Since these solutions are very susceptible to bacterial contamination and proliferation, other substances should be added.

Long-chain triglycerides are polyunsaturated and are composed of soybean oil, egg yolk phospholipids, and glycerol; they have a high calorific value (kcal/g), with the contribu-

Product	Lipofundin			Lipovenous		
Composition (every 1000 ml)	S-10	S-20	MCT/ICT10 %	MCT/ICT20 %	10 %	20 %
Soy oil (g)	100	200	50	100	100	200
Phosphatide soy (g)	7.5	15	-	-	12	12
Xilitol (g)	50	50	-	-	-	-
MCT (g)	-	-	50	100	-	-
Egg yolk's phosfolipids (g)	-	-	12	12	12	12
Glycerol (g)	-	-	25	25	25	25
Phosfate (mmol)	-	-	14.5	14.5	-	-
Caloric contribution (kcal)	1058	1908	-	-	1100	2000
Osmolality (mosm/l)	345	380	-	-	310	360

Table 20.10. Composition and energetic value of lipids solutions.

tion of essential fatty acids and low osmolality (isotonic), so they can be given via peripheral veins. They are not eliminated with the urine or feces. Their administration in large amounts can lead to impaired function of neutrophils and the reticuloendothelial system (RES), with poor bacterial clearance.

Medium-chain triglycerides are esters of saturated fatty acids with chains of 6 to 12 carbon atoms; the source is coconut oil. They provide 8.1 kcal/g. Their use is advantageous because they do not require carnitine for metabolism (beta-oxidation), so that they oxidize quickly, do not block function of the RES and are never stored. They do not contain significant amounts of essential fatty acids.

Currently, there are recommended products that combine LCT and MCT to reap the benefits of both. The main products available are shown in Table 20.10.

In many centres, mixtures of nutrients are prepared in the pharmacy under sterile conditions in a laminar flow chamber. Emulsions of lipids are combined at 10% or 20%, amino acid solutions at 5% or 10% and 70% dextrose. Lipids should be mixed with amino acids before mixing with dextrose acid solutions, electrolytes, vitamins and trace elements may be added in sufficient quantity. Ethylene vinyl acetate bags must be used instead of polyvinyl chloride to prevent lipid-bag interaction.

Technical measures and care. The solutions used in parenteral nutrition are hypertonic, and they must enter into the bloodstream through a catheter positioned inside a large-calibre vessel with high blood flow. The superior vena cava is preferred since it can be canalized by any method and technique.

Besides the complications of deep vein catheterization, the main problems associated with this therapy are sepsis and metabolic complications. Preventive measures must be taken into account:

- Deep venous catheterization. Maintain good catheter insertion technique with very good skin preparation.
- Infusion systems. Avoid the use of central venous pressure (CVP) measuring equipment in the same line used for parenteral infusion. In addition, blood, plasma or other medicines should not be given through the line, nor should blood for lab studies be drawn from the infusion line. A 0.45 micron filter should be inserted in the infusion line, and the whole system, except for the catheter, should be changed every 12 to 24 hours.
- Solution care. Contamination of solutions should be avoided because nutrients facilitate growth and multiplication of microorganisms. Other products should not be added to these solutions, except insulin which is added to hypertonic dextrose.
- Administration of carbohydrates. Hypertonic dextrose should be administered slowly and progressively; the initial infusion rate should not exceed 50 ml/hour and can be incremented daily by 25 ml/hour up to 125-150 ml/hour, as needed. Metabolic status should be monitored by blood glucose and glucosuria every 12 hours every 4 to 6 hours. Serum glucose should be 200-250 mg/dl (11-14 mmol/l) and glycosuria should not exceed 2 g/dl (Benedict's solution turns orange). Hypertonic dextrose infusions should not be stopped abruptly, as rebound hypoglycemia may occur due to the large amount of circulating insulin as a result of pancreas stimulation. Insulin supplement must be supplied at the beginning of parenteral nutrition in patients with insufficient endogenous insulin production, while keeping in mind that on successive days these needs may decrease due to pancreas stimulation.
- Administration of amino acids. Amino acids must be supplied simultaneously with nonprotein calories for the synthesis of proteins and not as an energy source. The amino acid solutions do not maintain the plasma oncotic pressure, so colloids such as albumin should be added. We must remember that blood, plasma and albumin are ineffective as a nitrogen source, since hemoglobin has no isoleucine, globulins

take 10 days to break down into their amino acids, and albumin takes between 16 to 21 days.

- Management of lipids. When fats are not used, a deficiency in essential fatty acids appears with adverse symptoms and signs. The composition of the phospholipidic cell membrane is also altered. Abnormal serum lipid levels lead to the development of fatty liver disease. Fats should be administered progressively in a drip, starting from 0.5 to 1 ml/min, then gradually increasing them up to 2 ml/min or less. The total dose should not exceed 1000 -1500 g over a period of 10 to 14 days. Lipid infusions should be suspended 12 hours before any dialysis procedure so as to prevent lipid losses. Blood lipid levels are controlled by their appearance in refrigerated serum: a cloudy appearance indicates the presence of chylomicrons and the lipid infusion must be stopped. In this situation, some authors recommend the addition of heparin to clear the plasma, which is controversial, because although heparin increases the activity of lipoprotein lipase with increased clearance of triglycerides, it also raises the level of fatty acids and free glycerol, which can be harmful.
- Other measures. It is very important to maintain proper nitrogen, caloric and electrolyte balance. When parenteral nutrition lasts for several days, vitamins should be provided in higher doses than the usual requirements. After the first week of treatment, calcium, magnesium, phosphate and trace elements also must be provided.

Peripheral parenteral nutrition. Peripheral parenteral nutrition refers to the intake of essential nutrients (amino acids, carbohydrates, lipids, electrolytes, vitamins, trace elements and water) through a peripheral vein. The fragility of the peripheral veins limits the osmolality of the solutions that can be used and restricts the calories that can be given in the form of dextrose. The cornerstones of peripheral parenteral nutrition are fat emulsions with low osmolality, high caloric density, and protective effects on vascular endothelium (not accepted by some authors).

Among the advantages of peripheral parenteral nutrition is mainly that central venous catheter-related morbidity can be prevented, metabolic changes are fewer, and it does not require trained personnel to be inserted. This technique is recommended in patients with not very high energy requirements; good peripheral veins are required, and the site of venipuncture should be changed every 24 to 48 hours. It is mainly used in:

- Short-term nutritional support (up to 15 days).
- Patients with repeated septic episodes during central parenteral nutrition.
- Patients with subclavian vein thrombosis.
- Difficult or dangerous central venous catheterization technique.
- Surgical patients with marginal nutritional status.

20.9.3 Three Nutrient Management Systems Using the Peripheral Route

System One. Provides amino acids, electrolytes and water and preserves functional proteins. Energy needs are covered by lipolysis owing to low levels of insulin which occur when glucose has not been administered. It is used for 3 to 5 days in patients with moderate stress, well-nourished or obese patients.

System Two. The patient receives amino acids, carbohydrates, electrolytes and water. It conserves body protein and energy needs with exogenous glucose. It is used in the immediate postoperative period and may last from 5 to 10 days.

System Three. Provides amino acids, carbohydrates, fats, electrolytes, vitamins and water. It is used in situations of mild to moderate catabolism because it preserves body protein. Energy needs are covered with carbohydrates and fats which provide 30 to 60% of

caloric intake, since fats in the presence of amino acids save nitrogen as well as glucose. It can be used for 15 days.
The main complication of this technique is the damage to vessel intima caused by hypertonic solutions. To avoid this, the use of small doses of cortisol and heparin has been encouraged, which reduces the incidence of phlebitis. It is necessary to change the venipuncture site every 24 to 48 hours to avoid thrombophlebitis. The disadvantages of the method depend on the volume of liquid needed to provide the calories, and the instability of flow volume in the peripheral veins, so infusion pumps should be used.

20.9.4 Complications

Complications may arise frequently during parenteral nutrition. Complications related to central venous catheterization and infusion systems, metabolic complications related to the use of carbohydrates, lipids, amino acid or electrolyte imbalance (Table 20.11), and septic complications have all been described. Because of malnutrition, sepsis is common in patients receiving parenteral nutrition, as is the risk of concomitant infections in abdominal wounds, the urinary tract and respiratory system. The problem is compounded by the use of broad spectrum antibiotics, drugs or clinical situations that reduce immunity and the improper handling of venous catheters and infusion systems. In patients where prolonged parenteral nutrition is particularly long, there is a high prevalence of infection with Candida species that grow easily in nutrient solutions. Hyperglycemia also occurs frequently and is observed in 25% of patients receiving parenteral nutrition. The causes are several, including glucose overdose, high infusion rate of carbohydrates, inadequate secretion of endogenous insulin, insulin resistance, stress that increases the production of hyperglycemic hormones such as cortisol, catecholamines and glucagon to stimulate gluconeogenesis, hyperglycemic effects of drugs (e.g., corticosteroids, diuretics, phenytoin).
Monitoring and controlling blood glucose is very important in neurocritical patients as it has been suggested that hyperglycemia worsens hypoxic ischemic brain injury and worsens the prognosis. Glucose levels >150 mg/dl should be corrected quickly with insulin. Rebound hypoglycemia can be avoided with the gradual withdrawal of parenteral nutrition and achieving adequate energy intake with oral or enteral nutrition before discontinuing parenteral nutrition.

Dependent on carbohydrates	Dependent on amino acids	Dependent on lipids	Related to electrolites, minerals and vitamins
• Hyperglycemia • Hypoglycemia • Increased CO_2 production • Phosphates depletion syndrome • Liver dysfunction	• Metabolic acidosis • Increased urea serum level • Serum amino acids imbalance • Hyperamoniemia • Hyperuricemia	• Deficit of essentials fatty acids • Hyperlipidemia • Colloidal reaction • Overload syndrome • Ketoacidosis • Encephalopaty	• Overhydration • Dehydration • Hypernatremia • Hyponatremia • Hyperchloremia • Hypochloremia • Hypokaliemia • Hypocalcemia • Hypophosfatemia • Hypomagnesemia • Deficit of nutritional trace • Hypovitaminosis

Table 20.11. **Parenteral nutrition. Metabolic complications.**

Liver dysfunction and excess carbon dioxide production (harmful especially in patients with respiratory failure) can be avoided by providing 20 to 40% of total calories as fats. Complications related to the administration of amino acids are rare. The essential fatty acid deficiency is due to an inadequate management of lipids, with little contribution of essential fatty acids such as linoleic, linolenic and arachidonic acid. Of these, only linoleic acid is very important in the diet, as others can be synthesized from it. The clinical features of essential fatty acid deficiency include diarrhea and malabsorption due to epithelial changes in the intestinal mucosa. Dryness and peeling of the skin, hair loss and increased susceptibility to infections can also be found, as well as thrombocytopenia and decreased platelet aggregation, with a tendency to bleeding, increased fragility of red cells with hemolytic anemia and increased capillary permeability. Further noted are increased intracranial pressure, liver function abnormalities, osteoporosis and delayed wound healing. To avoid these complications, linoleic acid should be provided at minimum dose of 25 mg/kg/day, with 10% fat emulsion two or three times a week. Hyperlipidemia can appear during fat infusions or after their suspension; their magnitude and duration depends on the dose and disappears within 2 to 4 days after lipids have been suspended. It is diagnosed by the appearance of turbid, lipemic serum refrigerated in a sample taken 12 hours after cessation of the infusion. Adverse reactions to lipid emulsions (dyspnoea, allergic skin reactions, headache, sweating) are rare. A reduction in infusion rate or its discontinuation prevents or lessens these side effects. When patients require high daily energy intake, large amounts of volume are needed, which can lead to volume overload. Electrolyte disorders may be diverse and should be taken into account. Vitamin and mineral deficiencies are rare if nutrient preparations are properly managed. It has been suggested that with careful monitoring the rate of complications may be less than 5%.

20.9.5 Contraindications to Parenteral Nutrition

Contraindication are related to the nutrients used.

Contraindications to the use of carbohydrates. Glucose is not contraindicated. In diabetic patients, enough insulin should be supplied to prevent or control hyperglycemia. Fructose and sorbitol are contraindicated in patients with 1.6 diphosphatase lactase deficiency and in those with methyl alcohol poisoning.

Contraindications to the use of lipids are the following:

- Hypoperfusion syndrome: low cardiac output syndrome, heart failure, and shock.
- Vascular lesions: myocardial infarction, stroke, arteriosclerosis, thrombophlebitis.
- Other: pregnancy, active duodenal ulcer, metabolism of fats, severe anemia, severe liver failure, use of MCT – ketogenic conditions, and severe liver disease.

Contraindications to the use of amino acids are shock and liver failure.

20.10 Assessment and Monitoring of Artificial Nutrition

After the initiation of artificial nutrition it is necessary to make observations that allow us to know whether it is achieving its objectives and, on that basis, make necessary changes. Among the items we should consider:

- Body weight is actually a very general measure to be considered in the success of nutritional support, since it depends on the patient's water balance. It is most useful after long periods of nutrition to assess the progress of the patient.

- Nitrogen balance (BN) is the most practical way to evaluate the effectiveness of nutrition and it is also essential for calculating the daily needs of amino acids and other nutrients. It is obtained by calculating the difference between nitrogen input and output. Nitrogen balance should be between -5 and + 5 g/day and the optimal value is +1 to +5 g/day.
- Caloric balance (CB) controls input and caloric loss. Energy intake (EI) is calculated from the sum of the calories of all the nutrients provided. Caloric expenditure (CE) is similar to total energy expenditure (TEE); the result of caloric balance can be -5 to +5% of TEE, stated as an optimal value when it is between -100 and + 100 kcal.
- Other methods to assess the goals of artificial nutrition include: 1) Normalization of serum albumin, transferrin and fibronectin; 2) Reduction of urinary 3 methylhistidine; 3) Positive intradermal tests.

In artificial nutrition monitoring, acid-base and electrolyte balance should be evaluated, as well as metabolic status and the emergence of complications. The frequency of carrying out such determinations should not be guided by a fixed schedule, but rather as needed case by case. The following items are to be taken into account:

- Body weight: daily.
- Caloric, nitrogen and hydromineral balance: daily.
- Benedict and Imbert: initially, every 3-4 hours. If severe glucosuria appears, it may be necessary to perform these more often to obtain control (every 6 hours).
- Serum glucose: initially, every 12 hours to control the solution rate, then daily or every 2 days.
- CBC: daily at the beginning of nutrition, then every 3 or 4 days, especially if intravenous lipids are used, due to the possibility of hemolysis.
- Daily determination of urea in 24-hour urine.
- Urea and serum creatinine: daily during the first 3 days or if there is kidney damage; every 3 or 4 days in other clinical conditions.
- Serum electrolytes: every 12 hours the first 2 or 3 days, then daily when values have stabilized.
- Electrolytes in urine: daily for the first 2 or 3 days or if there is increased loss of electrolytes after 3 or 4 days.
- Urine and plasma osmolality: daily.
- Turbid, lipemic serum (Friderickson test): every day when using lipids as an energy source. Keep in mind that blood should be drawn 12 hours after the infusion of fat is finished.
- Other tests to be performed at the beginning of artificial nutrition and weekly thereafter include: calcium and phosphorus, lipids, serum iron, total and fractionated proteins, transaminases, bilirubin and alkaline phosphatase, Coombs test when using intravenous lipids, uric acid, transferrin, and fibronectin.

Blood gasses should also be evaluated when necessary and coagulation when initiating therapy, and then depending on the suspicion of abnormal clotting.

20.11 Is There a Specific Nutritional Formulation for Patients with Brain Injury?

At present writing, there is no published study comparing different formulations, whether enteral or parenteral, in patients with traumatic brain injury. It was recommended that protein intake should be about 15% of total energy expenditure, taking into account

the significant daily loss of nitrogen that appears in this kind of patient. Other formulations are based on reports from publications on nutrition in intensive care in general. Overall nutritional support is recommended to provide 1.5 to 2 g/kg protein, a ratio of 80 non-protein calories per gram of nitrogen added, and the total kcal for in a 24-hour period is about 25 kcal/kg.

There is some evidence that the use of branched-chain amino acids may improve the prognosis in septic patients, however, it has not been studied in this type of patient. The use of glutamine supplements and immunomodulatory diets containing glutamine, arginine, omega-3 fatty acids and nucleotides has not been investigated in patients with acute brain injury. A class II study showed increased scores on the Glasgow Coma Scale when zinc supplement was given.

20.11.1 When to Start Nutrition in Neurocritical Patients

Nutritional support should begin without delay because catabolism begins quickly. Usually, it should not be delayed more than 72 hours, with total replacement on the seventh day because 2 or 3 days of gradual increase in nutrients are needed for the total replacement of caloric and protein needs, whether via the stomach or jejunum. It should be similar in cases where parenteral nutrition needs to be started: during the first 72 hours after injury and with a caloric intake below the calculated total energy, which must be achieved by the seventh day. A review of randomized controlled studies investigating the time or route of administration of nutritional support in patients with head trauma found that early nutrition may be associated with a tendency to better prognosis in terms of survival and disabilities.

20.11.2 Enteral Nutrition vs. Parenteral Nutrition

Some authors prefer to start feeding through the stomach, but it has been estimated that 80% of patients with increased intracranial pressure after head trauma and 50% of ventilated patients (a common situation in patients with severe brain injury) have abnormal gastric emptying with the risk of aspiration and pneumonia. Better tolerance of nutrient can be obtained by starting at 25 ml per hour and then increasing the volume every 12 hours to achieve the desired objective. Continuous feeding is better tolerated than bolus feedings. The jejunal or postpyloric route of nutrition through a tube, placed by endoscopy or fluoroscopy, is preferred by most authors because of better tolerance, lower risk of aspiration, and greater nitrogen retention than with gastric feeding. In our service, either for technical reasons and/or resources, postpyloric tube placement is not a common procedure, or there is more experience in the last years with early gastrostomy or gastrojejunostomy in patients who rarely recover consciousness during the first week. This method of nutrient management via a NGT is better tolerated. There is also a low incidence of pneumonia and fewer indications for intravenous feeding. Parenteral nutrition, as stated above, is not recommended in patients with severe brain injury. Although studies on laboratory animals have shown that parenteral nutrition can worsen cerebral edema, the available evidence in humans suggests that this is not a clinical problem.

The 2007 Brain Trauma Foundation guidelines state that has no method has been clearly demonstrated superior to another with regard to complications or discharge status.

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21 Acute Renal Injury in the Neurocritical Patient

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21.1 Introduction

Acute kidney injury (AKI), also known as acute renal failure, refers to a sudden decline in renal function, with disorders in fluid balance, electrolytes and acid base status due to loss of small solute clearance and decrease in the glomerular filtration rate (GFR). The term AKI reflects more accurately the spectrum of diseases from subclinical injury to complete organ failure.

21.2 Epidemiology of Acute Kidney Injury

The incidence of AKI has risen. Depending on how defined, between 35 and 66% of critically ill patients develop AKI, with a substantial increase in morbidity and mortality. On average, between 5 and 6% of critically ill patients with AKI in the critical care unit (CCU) require renal replacement therapy (RRT). The reported mortality due to AKI varies considerably, depending on the definition of AKI and the patient population evaluated (e.g., sepsis, trauma, cardiovascular surgery or contrast-induced nephropathy). Most studies found that mortality increases proportionally with increasing severity of AKI. In patients with severe AKI requiring RRT, mortality is about 50 to 70%. AKI requiring RRT is an independent factor of hospital mortality: even small changes in plasma creatinine (PCr) are associated with increased mortality.
The morbidity associated with AKI in the CCU is a less appreciated consequence, but it is associated with prolonged hospital stay, higher risk of chronic kidney disease (CKD) and end-stage renal disease (ESRD).

21.3 Definition of AKI in Critically Ill Patients

There are more than 35 definitions of AKI in the literature. In 2002, a group of experts formed the Acute Dialysis Quality Initiative (ADQI) and proposed the RIFLE classification scheme (R: risk, I: injury, F: failure, L: Loss, E: end-stage) specifically for AKI in critically ill or terminal patients (Table 21.1). Using the parameters of PCr and/or GFR and urine output, they defined three levels of severity and two prognostic classes.
Changes in serum creatinine as measured with the RIFLE method are applied in relation to a baseline serum creatinine value (BSCV). But since this is unknown in most patients, the modification of diet in renal disease (MDRD) formula (Table 21.2) was devised to estimate the BSCV, according to gender, race and age group, assuming a normal GFR (75 to 100 ml/min/1.73 m^2).

Risk	One or more of the following: • 1.5 fold increase in serum creatinine • decrease (>25%) in GFR • urine output <0.5 ml/kg/h for 6 hours
Injury	One or more of the following: • 2-fold increase in serum creatinine • decrease (>50%) in GFR • urine output <0.5 ml/kg/h for 12 hours
Failure	One or more of the following: • 3-fold increase in serum creatinine • decrease (>75%) in GFR • serum creatinine ≥4 mg/dl when acute increase ≥0.5 mg/dl • urine output <0.3 ml/kg/h for 24 hours • anuria for 12 hours
Loss	Persistent AKI or complete loss of renal function: presence of AKI >4 weeks
End	End-stage renal disease: requirement of renal replacement therapy >3 months

Table 21.1. **RIFLE criteria for AKI diagnosis and staging (2004).**

$$GFR = 186 \times SC^{-1.154} \times Y^{-0.203} \times 0.742^{\circ} \times 1.21^{*}$$

$$186 \times SC^{-1.154} = (Y^{-0.203} \times 0.742^{\circ} \times 1.21^{*})/\text{normal GFR}$$

$$SC^{-1.154} = (Y^{-0.203} \times 0.742^{\circ} \times 1.21^{*} \times 186)/\text{normal GFR}$$

where:
SC = serum creatinine; Y = years of age; ° in females; * in blacks

The RIFLE method's validity and predictive ability for mortality have been evaluated in critically ill patients in several trials. In their review of studies which used this system between 2004 and 2007, Ricci et al. examined 24 studies involving a total of 71,000 patients. They noted that the studies had several weaknesses: small cohorts; selected subpopulations of critically ill patients; lack of "urine output" criterion; and single-centre design. What the studies did show, however, was the first mortality rates of AKI (31.2%) diagnosed according to a uniform definition. A striking finding was that the relative risk of death was higher when renal dysfunction was more severe (18.9%, 36.1% and 46.5% for mortality as risk, injury and failure, respectively).
In 2008, Bagshaw et al. published a multicentre evaluation of AKI diagnosed according to the RIFLE classification within the first 24 hours after admission (120,123 patients in

Age (years)	Black male (mg/dl)	White male (mg/dl)	Black female (mg/dl)	White female (mg/dl)
20-24	1.5	1.3	1.2	1.0
25-29	1.5	1.2	1.1	1.0
30-39	1.4	1.2	1.1	0.9
40-54	1.3	1.1	1.0	0.9
55-65	1.3	1.1	1.0	0.8
≥65	1.2	1.0	0.9	0.8

Table 21.2. **Estimated baseline creatinine value.**

57 Australian CCUs from 2000 to 2005). They reported an AKI incidence of 36.1% (Risk = 16.2%, Injury = 13.6%, Failure = 6.3%), being more common in patients over 65 years of age, female gender, with comorbidities and admitted for medical causes, mainly cardiac, septic or liver diseases. Worsening in RIFLE category was correlated with an increased length of stay in hospital and the CCU and, as Ricci et al. had found, with higher mortality.
Recently, the ADQI group and representatives of the American Society of Nephrology (ASN), the International Society of Nephrology (ISN), the National Kidney Foundation (NKF) and the European Society of Intensive Care Medicine Acute Kidney Injury Network (AKIN) proposed a new diagnosis and classification system (Table 21.3) modified from the RIFLE scheme:

- The Risk, Injury and Failure categories were replaced with three numerical stages of severity (1, 2 and 3), while retaining similar cut-off points for PCr and urine output.
- The method's sensitivity was enhanced by including in Stage 1 increases in PCr ≥0.3 mg/dl, based on studies showing that this small change was associated with higher risk of mortality.
- Implementation of RRT was eliminated as a severity criterion because patients classified in the Failure category who received RRT could be included in Stage 3, given that the starting time of RRT varies across different populations and countries due to variability of resources and criteria.
- An "acute" change in serum creatinine was specified as occuring within 48 hours, based on evidence that the worst prognosis observed with these small increases occurs during this period. Unlike RIFLE, the AKIN system considers increases in PCr in relation to the value recorded at admission rather than in relation to a theoretical baseline creatinine.
- It was noted that these criteria should be applied only after having achieved an optimal state of hydration because the blood volume status can modify PCr values.

In 2008, Bagshaw et al. carried out a retrospective comparison between the RIFLE and AKIN schemes on the same 120,123 patients evaluated the same year, and reported similar sensitivity, robustness and predictive ability of both methods. The study revealed several weaknesses, however: assessment of AKI was performed only within 24 hours of the patient's admission to the CCU; detailed urine output and weight of patients were unknown; and there was no record of the proportion of cases undergoing RRT.
Except for the use of diuretics or the presence of urinary obstruction, diuresis is still considered a more sensitive parameter of intrarenal hemodynamic changes than biochemical markers or solute clearance. It is also more likely to be used in CCUs and general care wards owing to its easy identification.

AKIN stage 1	One or more of the following: • Acute increase* in serum creatinine ≥0.3 mg/dl (≥26.4 µmol/l) or 1.5 to 2-fold • Urine output <0.5 ml/kg/h for more than 6 hours
AKIN stage 2	One or more of the following: • Acute increase* in serum creatinine (>2 to 3-fold) • Urine output <0.5 ml/kg/h for more than 12 hours
AKIN stage 3**	One or more of the following: • Acute increase in serum creatinine >3-fold • Serum creatinine ≥4 mg/dl when acute increase* ≥0.5 mg/dl • Urine output <0.3 ml/kg/h for 24 hours • Anuria for 12 hours

Table 21.3. **AKIN criteria for AKI diagnosis and staging (2007).**
* "Acute" changes in serum creatinine refer to those which occur within 48 hours of the last recorded value
** Includes patients receiving RRT

The RIFLE system assumes that the use of this parameter enhances the method's sensitivity. The AKIN scheme also recognizes that this marker of renal dysfunction becomes impaired before PCr values increase, thus offering a sensitive and easy tool to identify patients with AKI. Recently, Bagshaw et al. demonstrated that the use of urine output in the RIFLE scheme has prognostic and predictive value for length of CCU and hospital stay and for mortality.

Both the RIFLE and AKIN schemes set an arbitrary urine output value derived from the initial definitions of Kellum, which state that a patient with a urine output <800 ml in 24 hours can be defined as an AKI patient, or the equivalent of 30 ml/h, i.e., 0.5 ml/kg/h for a 70-kg patient. Although these figures are theoretical, neither the RIFLE nor the AKIN scheme specifies how often measurement should be taken, and it is unknown whether they are applicable to catheterized patients in whom measurements are taken every 2, 4 or even 6 hours, or in those with spontaneous urination.

21.4 Diagnosis of AKI in Critically Ill Patients

Procedures and parameters for diagnosing AKI (PCr) and determining its etiology (clinical history, physical examination, renal ultrasound, fractional excretion of sodium [FENa], fractional excretion of urea [FEU], plasma urea and urine sediment) are available in the CCU. However, no single marker may be accurate enough to estimate GFR and to indicate injury. A simple analogy of this problem is the use of cardiac enzymes (troponin specific to cardiac muscle) as a "surrogate marker" of cardiac muscle injury in acute myocardial infarction. This marker of cardiac injury does not provide information on changes in global cardiac function and myocardial performance. To evaluate cardiac performance, more examinations are needed. Extending this analogy to critical care nephrology, the surrogate markers for GFR (e.g., urea and creatinine), however, are not sufficiently specific for detecting acute kidney injury. What we urgently need are markers that incorporate function and injury in critical care nephrology.

The diagnosis and etiological classification of ARI depend largely on the detection of changes in endogenous conventional markers of renal function: serum levels of plasma creatinine and urea, and, less frequently, other urine tests. Although conventionally used, these markers have their limitations as none reflect dynamic changes in GFR nor do they reflect kidney injury. Moreover, these endogenous markers require time to accumulate before they can be detected as abnormal levels in serum, thus potentially delaying the diagnosis of AKI.

Serum creatinine is an amino acid compound derived from the non-enzymatic conversion of creatine in skeletal muscle and subsequent hepatic metabolism of creatine through the methylation of amino acetic acid to form creatinine. Creatinine clearance is the most common tool to estimate GFR, and serum creatinine levels typically show an inverse relationship to GFR (in stable situations). Like urea, there is no evidence of toxicity caused by creatinine accumulation in the blood. However, there are limitations in the use of serum creatinine as a marker of renal function:

- The production and release of creatinine in serum may be highly variable. Differences in age, gender, food intake (e.g., vegetarian or creatine supplements) and muscle mass (e.g., neuromuscular disease, malnutrition) can cause baseline serum creatinine values to vary significantly. Similarly, certain diseases can predispose to a variable release of muscle creatinine. For example, serum creatinine may rise more rapidly during rhabdomyolysis due to the release of preformed creatinine from damaged muscle or peripheral metabolism of creatine phosphate to creatinine in ex-

tracellular tissue. Critically ill patients may present abnormal liver function and a dramatic reduction in muscle mass, both of which can significantly alter creatinine metabolism. Other factors contributing to increased creatinine production include muscle catabolism in trauma patients, fever, and immobilization. Its production can be reduced in liver disease, in patients with reduced muscle mass and in the elderly. The volume of creatinine distribution (total body water) influences plasma creatinine and can increase dramatically in critically ill patients. However, like creatinine clearance, plasma creatinine does not accurately reflect GFR in non-equilibrium conditions such as AKI. Creatinine clearance overestimates GFR in patients with AKI because, as GFR decreases, tubular secretion of creatinine increases; therefore, urinary excretion is much greater than the filtered load, resulting in a potentially gross overestimation of GFR. During the evolution of AKI, plasma creatinine levels may underestimate the degree of dysfunction, while the opposite is true as far as kidney function will recover.

- About 10 to 40% of serum creatinine is cleared by tubular secretion into the urine. This effect has the potential to "hide" a substantial initial decline in GFR.
- Many drugs (e.g., trimethoprim, cimetidine) may alter creatinine secretion, leading to transient and reversible increases in serum creatinine levels.
- Although less frequent, the accuracy of serum creatinine assays may be reduced, leading to artificial increases in serum creatinine levels in diabetic ketoacidosis; increased serum concentration of acetoacetate may interfere with selected tests (e.g., with the alkaline picrate method) and cause false elevations in serum creatinine regarding Jaffe's reaction. Similarly, some drugs may have similar effects (e.g., cefoxitin).
- Various equations to evaluate kidney function can be applied to predict creatinine clearance or GFR. They are based on demographics and biochemical indices (e.g., gender, age, race, weight, blood creatinine and albumin) but they have not been validated in patients with AKI. All equations use serum creatinine and, therefore, have the same limitations as serum creatinine for the assessment of GFR in patients with AKI. There are few data on the use of equations to estimate GFR in patients with AKI.

Changes in serum creatinine are aspecific, do not discriminate between the nature and the type of renal insult (ischemic, nephrotoxic) or the site and extent of tubular or glomerular injury, and serum creatinine levels are relatively insensitive to small changes in GFR. Moreover, changes in serum creatinine "may fall behind" the changes in GFR, both its increase and its decline, for several days. Finally, because serum creatinine is influenced by potential interventions in AKI (creatinine removed by RRT), its specificity to assess renal recovery is even more problematic.

Plasma urea, a by-product derived from the metabolism of water soluble low-molecular-weight proteins is used as serum marker of retention and removal of nitrogenous solutes. The accumulation of urea per se is thought to predispose to metabolic biochemical and physiological side effects such as increased oxidative stress and impaired function of Na-K-Cl co-transporters, which are critical in regulating intracellular water and potassium, and alterations in immune function. In addition, retention of uremic toxins may contribute to such secondary organ dysfunctions as acute lung injury.

Similarly to serum creatinine, urea levels exhibit a non-linear and inverse relationship to GFR. However, measuring urea levels to estimate GFR is a problem due to extra-renal factors which influence its endogenous production and renal clearance, regardless of the GFR.

The urea production rate is not constant. Urea values can be modified by high protein intake, critical illness (sepsis, burns, trauma), gastrointestinal bleeding, or drugs such as steroids or tetracycline. The use of steroids in the CCU is a fairly common practice and may increase protein catabolism. Critically ill patients with chronic liver disease may

have almost normal urea levels due to reduced protein production and restriction and, at the same time, normal serum creatinine levels due to either decreased hepatic production of creatinine or loss of muscle mass, despite significant reductions in GFR and impaired renal function.

The rate of renal clearance of urea is not constant. Approximately 40-50% of filtered urea is passively reabsorbed by the proximal and distal tubule cells. In states of volume depletion with low cardiac output, there is an increased reabsorption of sodium and water in the proximal tubule cells, with a corresponding increase in urea reabsorption. The urea concentration can increase far beyond the rate of change in serum creatinine and doesn't represent a reduction in GFR.

Overall, urea concentration is a poor marker of GFR. It doesn't represent real-time changes in GFR and requires time to accumulate. In addition, urea doesn't really reflect "acute" kidney injury. Relying on serum levels of urea leads to delays in the diagnosis of AKI.

Urine output can be used as a "crude" dynamic measurement of renal function. It may be a more sensitive marker of changes in renal hemodynamics than biochemical markers for the clearance of solutes. The importance of dynamic changes in urine output has been recognized because such changes are integrated into the RIFLE and AKIN classifications. Generally, however, urine output lacks sensitivity and specificity as a marker of renal function or AKI in critically ill patients in whom the excretion of free water and solutes is altered. At times, critically ill patients with severe AKI, characterized by elevated serum creatinine or retention of nitrogenous solutes, can maintain normal or even high urine output.

The term AKI spans the whole spectrum from prerenal azotemia to acute tubular necrosis (ATN), and from functional impairment to structural injury. Numerous tests have been described as a "replacement" for tubule cell function and have been and still are used for the detection and classification of AKI, particularly in the diagnosis of prerenal azotemia and ATN. Although easy to perform, they lack sensitivity and specificity for the early characterization of AKI, particularly in critically ill patients. In addition, the causes of prerenal azotemia and structural injury commonly coexist in critically ill patients. Until we have other diagnostic tools, different from the current ones, and in the absence of validated new biomarkers, prerenal azotemia is often a retrospective diagnosis made only after fluids challenge.

Fractional excretion of sodium (FENa) is based on the fact that filtered sodium is avidly reabsorbed in the renal tubules of the glomerular filtrate in prerenal azotemia, in which tubular function remains intact, resulting in FENa <1%, while FENa is >1% in tubular injury, as in ATN. Although physiologically sensitive, in clinical practice the diagnostic accuracy of FENa is poor and its value has been questioned.

FENa is often >1% in patients receiving diuretics and has been found to be <1% in various settings, including sepsis, rhabdomyolysis, and exposure to contrast media. Carvounis et al. suggested that the fractional excretion of urea (FEU) is more sensitive and specific for discriminating between prerenal azotemia and ATN, especially if diuretics have been administrated. However, this study had important methodological errors.

Not all tests have been tested and questions remain whether they are useful for the diagnosis and classification of AKI in critically ill patients. Also, they don't quantitatively measure kidney injury nor do they provide any information about prognosis. We must remember that the classification of AKI in prerenal azotemia and ATN is arbitrary and that both probably exist as a continuum of injury and that their separation in terms of diagnosis also has its clinical and prognostic limitations.

Proteinuria is frequently detected in critically ill patients. Microalbuminuria is defined as <300 mg/g of creatinine or proteinuria >300 mg/g of creatinine. Proteinuria is more

commonly encountered in the elderly, patients with diabetes, chronic kidney disease, or shock. A high albumin/creatinine ratio (>100 mg/g) is associated with increased mortality.

The detection of microalbuminuria is suggestive of increased capillary permeability to proteins, with a predictive and prognostic value of disease severity and mortality. However, no studies have assessed the value of microalbuminuria in predicting the course of AKI in patients admitted to the CCU. The detection of low-molecular-weight proteins of tubular origin has been described in critically ill patients with AKI and sepsis. No study has evaluated *a priori* urinary protein excretion as a marker of AKI or as a predictor of decline in renal function or recovery in critically ill patients.

The classic urinary profile of ATN is represented by tubular epithelial cells with large casts, brown casts or casts with mixed cells, whereas fine granular casts can sometimes be detected in prerenal azotemia.

Few studies have assessed urinary sediment in AKI in critically ill patients. Moreover, the value of urine sediment to classify AKI pathogenesis and severity is imperfect and often fails to correlate with traditional urinary biochemical markers or derived indices. There are no clinical studies to date that have evaluated *a priori* the value of urine sediment and microscopy as a marker of renal function or AKI. Urine microscopy should be performed when systemic vasculitis, rapidly progressive glomerulonephritis or a pulmonary-renal syndrome is suspected.

In conclusion, these conventional markers are familiar to the CCU team though they are not ideal, have limitations, and none reflect real-time changes in GFR or genuine injurious processes in the kidney. Moreover, they may lead to delayed recognition of AKI and delay proper support and therapeutic interventions.

Fortunately, the application of innovative technologies such as functional genomics and proteomics in humans and animal models of AKI has discovered new genes and gene products that have emerged as biomarkers. Biomarkers are required to:

- Identify the primary site of injury (proximal tubule, distal tubule, interstitium, or vasculature).
- Indicate the duration of renal failure (AKI, chronic renal disease or re-exacerbation of chronic renal failure).
- Identify the pathogenesis of AKI (ischemia, toxins, sepsis, or a combination thereof).
- Stage risk and prognosis (AKI duration and severity, need for renal replacement, hospital stay, mortality).
- Define the course of AKI.
- Monitor the response of AKI to various interventions.

New and promising markers of AKI have been proposed and are currently under evaluation. These include a plasma panel (neutrophil gelatinase-associated lipocalin [NGAL] and cystatin C) and a urine panel (NGAL, IL-18 and KIM-1). Because they are sequential biomarkers, it is likely that panels for the diagnosis of AKI may be useful at the time of initial insult and to assess the duration of AKI (analogous to the diagnostic panel in chest pain) and to predict global prognosis regarding RRT and mortality. What is likely is that diagnostic panels will allow us to distinguish between different types and pathogenesis of AKI.

21.5 Common Causes of AKI in Critically Ill Patients

The causes of AKI in critically ill patients are multifactorial and often result from a combination of hypovolemia, sepsis, pharmacological therapy, and hemodynamic alterations.

Often, a single cause cannot be isolated, further complicating the search for effective therapeutic interventions in this complex disease.
Sepsis is the most common cause of AKI in critically ill patients, accounting for up to 50% of cases. AKI is common after cardiac surgery, occurring in up to 40% of patients without pre-existing renal disease and associated with increased morbidity and mortality with an elevated PCr of only 0.3 mg%. AKI in trauma patients is multifactorial (e.g., hemorrhagic shock, abdominal compartment syndrome, rhabdomyolysis) and occurs in up to 31% of adult trauma patients.
The kidneys are very sensitive to intra-abdominal hypertension and intra-abdominal pressure over 12 mmHg associated with AKI. A sustained intra-abdominal pressure of 20 mmHg in association with a new organ dysfunction may be associated with AKI in more than 30% of cases. Rhabdomyolysis occurs in 28% of trauma patients with AKI requiring RRT.
Pharmacological therapy is a common cause of AKI, accounting for about 20% of all causes of AKI in critically ill patients. The mechanisms inducing AKI are multiple, including acute interstitial nephritis (AIN), direct tubular toxicity (e.g., aminoglycosides) and hemodynamic abnormalities (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors). AIN is an underrecognized cause of AKI in the CCU and is associated with pharmacological therapy. Because of the relative paucity of clinical findings, however, a high index of suspicionis needed for diagnosis.

21.6 Prevention and Management of AKI in Critically Ill Patients

The primary prevention of AKI in the CCU is limited to those conditions in which the time of injury is foreseeable, such as exposure to contrast media, cardiac surgery, and chemotherapy. Unlike most cases of community-acquired AKI, almost all cases of AKI in critically ill patients originate from more than one insult (Tables 21.4 and 21.5). In critically ill patients the first insult is often unpredictable. Therefore, prevention of AKI in the CCU relies on the prevention of secondary injury in a patient at high risk of AKI, as the patient is critical. In a retrospective study of over 5000 critically ill patients (6), AKI developed in 67% and occurred after CCU admission in 45%.
The general principles of secondary prevention of AKI include:

- Recognition of underlying risk factors which predispose patients to AKI (e.g., diabetes, arterial hypertension, chronic renal disease, age, cardiac and hepatic dysfunction);
- Maintenance of renal perfusion, prevention of hyperglycemia and nephrotoxin exposure to these high-risk patients.
- Primary prevention of contrast-induced nephropathy (CIN) includes hydration, N-acetylcysteine (NAC) and the use of low hypo-osmolar or iso-osmolar nonionic contrast volumes. No strategy has been completely effective in preventing CIN. Risk factors for its development include diabetes, chronic kidney disease, arterial hypotension, absolute or relative depletion of intravascular volume.

- Sepsis
- Major surgery
- Low cardiac output
- Hypovolemia
- Nephrotoxic medications
- Trauma
- Abdominal Compartment Syndrome
- Rhabdomyolysis
- Obstruction of urinary flow

Table 21.4. **Common causes of AKI in critically ill patients.**

Intuitively, critically ill patients constitute a population at high risk for CIN owing to frequent hemodynamic abnormalities, multiorgan dysfunction, routine use of nephrotoxic medications, and concomitant co-morbidities. Of the many randomized controlled trials (RCTs) on the prevention of CIN, only one was specifically carried out in critically ill patients.

Exogenous	• NSAIDs • Aminoglycosides • Amphotericin B • Penicillins • Acyclovir • Chemotherapy • Contrast media
Endogenous	• Rhabdomyolysis • Hemolysis • Tumour lysis syndrome

Table 21.5. **Nephrotoxins causing AKI in critically ill patients.**

Adequate fluid resuscitation is a well-established measure to reduce the risk of CIN, while the choice of fluid remains controversial. Five meta-analyses of sodium bicarbonate suggested a beneficial effect of saline solution. However, there is considerable heterogeneity across studies. The latest RCT did not demonstrate superiority between the two fluids in relation to the primary objective of a reduction >25% in GFR within 4 days of exposure to contrast material.

NAC (N-acetyl cysteine) is an antioxidant which reduces the risk of CIN as compared with placebo. Since 2003 more than 10 meta-analyses have been published on the role of NAC in the prevention of CIN. The conflicting results may be attributable to the heterogeneity of the study populations. There are conflicting data on the possibility that NAC itself can reduce PCr without affecting GFR. The use of nonionic hypo-osmolar or iso-osmolar contrast media is clearly associated with a reduction in CIN when compared with high osmolarity agents.

Due to the absence of sufficient data on critically ill patients, we are forced to extrapolate the best available evidence obtained in other patient populations. Therefore, the generally accepted recommendations in relation to the prevention of CIN are:

- Avoid the use of endovascular contrast media if other imaging techniques are available.
- Use either saline or sodium bicarbonate as volume expanders.
- Although its use is questionable, NAC is a safe, inexpensive agent and can reduce the risk of AKI.
- Whenever possible, avoid the use of other nephrotoxic drugs in the patient.
- Use low volumes of hypo- or iso- osmolar contrast media. More studies are needed to determine the true role of these preventive measures in critically ill patients.

The management of critically ill patients with AKI revolves around optimizing hemodynamics and renal perfusion, correcting metabolic abnormalities, and providing adequate nutrition in the attempt to mitigate the progression of injury. Volume resuscitation, vasopressor and/or inotropes are required to optimize renal perfusion.

Extrapolating from experimental data, it appears that the human kidney is less able to self-regulate (maintain blood flow and GFR within a wide range of perfusion pressure) in AKI. Therefore, a priority in the prevention and management of AKI is to maintain normal hemodynamics and avoid volume depletion. A mean arterial pressure >65 mmHg is a generally accepted goal, however, available data are limited.

The paradigm of renal blood flow (RBF) in AKI with sepsis is based on experimental observations and in humans with hypovolemic shock; it states that renal hypoperfusion occurs during AKI. This reasoning implies that restoration of adequate RBF should be our initial objective to protect the kidney in critically ill patients (septic or not). However, we don't know the RBF in septic patients because it cannot be measured continuously in humans beings, and its intermittent assessment can be done only with highly invasive means.

In experimental trials of AKI in the context of sepsis it was observed that RBF is reduced globally after the induction of sepsis or endotoxemia. This not only reduce glomerular filtration but also, if hypoperfusion is severe and prolonged, metabolic deterioration as well, with a reduction of high-energy phosphates, possibly resulting in cell death, acute tubular necrosis and severe AKI.

Other studies have shown that the renal circulation is involved in the systemic vasodilation seen during severe sepsis and septic shock; therefore, RBF is not reduced and the development of AKI in the context of sepsis occurs in the absence of hypoperfusion and in the presence of adequate and even increased renal perfusion.

Brenner et al. developed a percutaneously placed catheter for the measurement of RBF by thermodilution in eight critically ill patients with AKI. They demonstrated that sepsis-induced AKI occurred despite normal RBF values. During sepsis, patients in the CCU typically show features of hyperdynamic circulation.

The reason for the discrepancy between experimental and clinical studies in terms of RBF may be entirely related to the experimental model (including the animal used and the kind of insult practiced), different measurement methods, frequency of measurement and, most importantly, the state of systemic circulation (hypodynamic or hyperdynamic). Indeed, it is consistantly observed that, once a hyperdynamic state exists, hypoperfusion/global renal ischemia may not necesssarily be present.

In a recent review of the literature on experimental models of sepsis and AKI, Langenberg et al. reviewed 160 experimental studies on induced sepsis and aspects of renal function or dysfunction and measurement of RBF by one or more available techniques. In almost one third of the studies, RBF remained preserved or increased in experimental sepsis. At multivariate logistic regression analysis, cardiac output was the only predictor of RBF, i.e., sepsis with elevated cardiac output was associated with preserved or increased RBF, and sepsis with low cardiac output was associated with reduced RBF. As mentioned, most patients seen in the CCU with sepsis have an elevated cardiac output.

Using a sepsis model in sheep, Langenberg et al. continuously measured cardiac output and RBF while inducing a septic circulatory state of high cardiac output with the infusion of *Escherichia coli*. According to this model, the researchers were able to show that in hyperdynamic sepsis in an aware mammal of considerable size, RBF is markedly increased and renal vascular resistance decreased.

In this context, GFR is markedly reduced, with a three-fold increase in serum creatinine and an equivalent reduction in creatinine clearance. Consistent with these findings, renal recovery from AKI in sepsis is associated with reduced cardiac output, increased renal vascular resistance, and reduced RBF. These observations suggest that changes in renal vascular activity (vasodilation) may be important in the loss of glomerular filtration pressure during the first 24-48 hours of sepsis. The findings also provide “proof of concept” that glomerular filtration pressure can be lost in AKI in the context of sepsis, with a marked increase in RBF. On the other hand, it could be argued that AKI in the context of sepsis may represent a “hyperemic form of AKI.”

Glomerular filtration pressure, in turn, is determined by the relationship between the afferent and efferent arterioles. When the afferent arteriole contracts, the filtration pressure falls and GFR and urine output decrease. Conversely, when the afferent arteriole expands and the efferent arteriole expands further, RBF increases markedly, however, the pressure in the glomerular capillary falls. In this sense, GFR also decreases. This could be the scenario in human sepsis. Unfortunately, little is known about RBF during severe sepsis and septic shock.

In conclusion, renal hypoperfusion may be important in AKI in the context of sepsis associated with hypodynamic states (a rare finding in patients in the CCU) but it may not

play a role in the development of AKI during hyperdynamic sepsis (observed in most patients in the CCU with sepsis and severe AKI).

The degree to which RBF is dependent on systemic arterial pressure varies significantly according to age, underlying disease and acute illness or underlying conditions. We could say that the threshold of mean arterial pressure where RBF is dependent is not static varies according to each patient and each patient varies according to the changing conditions of their clinical status.

In septic shock,the most common cause of AKI in critically ill patients, vasopressor therapy is instituted to raise arterial pressure during resuscitation. The standard is to infuse the volume to improve hemodynamic parameters rather then to achieve adequate values. It is very difficult to define “adequate hemodynamic parameters”; and if vasopressors are administered in conjunction with fluid resuscitation, over-resuscitation with fluids and its well-documented side effects could be avoided. As there are no RCTs to date comparing vasopressors, there is no evidence that a vasopressor improves the prognosis of AKI.

While the infusion of dopamine may temporarily improve urinary flow, the renal dose of dopamine does not reduce the incidence of AKI, the need for RRT nor improve the prognosis of AKI. Besides, low-dose dopamine may worsen renal perfusion in critically ill patients with AKI and is associated with increased oxygen demand by the myocardium, with increased incidence of atrial fibrillation. In addition, we must take into account the extra-renal effects of dopamine, including negative immunomodulator effects. There is wide consensus on the potential dangers of dopamine, with no evidence of its beneficial effects for the prevention and treatment of AKI.

Fenoldopam is a dopamine D-1 receptor agonist administered for treating hypertensive crisis (5). Paradoxically, low-dose fenoldopam increases RBF without systemic effects. Studies validating the observations reported in a meta-analysis on fenoldopam could provide evidence that the drug might supplant the need for RRT.

Our primary goal in volume resuscitation is to restore circulating volume to prevent or alleviate organ injury. The kidneys receive 25% of cardiac output and are highly sensitive to hypoperfusion due to a true or relative hypovolemia. That is why the choice of fluid in AKI is a major question. While crystalloid solutions are still preferred in routine care, the debate over the use of colloidal solutions continues.

The SAFE study involved nearly 7000 patients who received either crystalloids or colloids as resuscitation solutions. The study showed no difference in survival between the two treatment groups. In a post hoc analysis performed on a patient subset, resuscitation with albumin was associated with increased mortality in critically ill patients after head injury. In contrast, there was a trend toward improved survival in patients with septic shock who had received albumin. There is no evidence supporting the use of albumin over crystalloids for improved survival in a heterogeneous population of critically ill patients.

Synthetic colloids, hydroxyethyl starch (HES) and dextrans are widely used, despite multiple reports that warned of undesirable effects on renal function. Small studies have shown an increased risk of AKI while using HES; and more recently a systematic review of 12 randomized trials showed an increased risk of AKI with the use of HES in patients with sepsis. In contrast, the largest retrospective analysis to date (SOAP study) exploring the effects of HES on renal function did not find HES to be an independent risk factor of AKI or need for RRT. Dose and preparation vary across the studies. Adverse effects have been related to molecular weight, the lower-molecular-weight compounds being the less involved in AKI.

The question of fluid management isn’t limited to the type of fluid administered; the amount of fluid administered is also very important as well. Critical illness is a dynamic

process requiring frequent evaluation and integrated monitoring to assess the status of blood volume and fluid requirement.

In a RCT of patients with the acute respiratory distress syndrome (ARDS), conservative strategy with fluids reduced the days on mechanical ventilation and did not increase the need for RRT. Furthermore, in an observational study involving over 3000 patients, an association between a positive fluid balance and increased mortality in patients with AKI was demonstrated. However, the question remains whether positive fluid balance is a marker of disease severity or is really a true cause of poor prognosis: these observations deserve further investigation.

Although the beneficial effects of intensive insulin therapy on mortality in critically ill patients remains controversial, two large RCTs showed that with strict glycemic control there was a reduction in the incidence of AKI and in the need for RRT. However, a more detailed secondary analysis strongly suggested that strict glycemic control may have a "renoprotective" effect in critically ill patients.

In contrast, in a recent prospective RCT assessing the effects of strict or intensive vs. conventional control of blood glucose in more than 6000 critically ill patients, no difference was found in the number of patients requiring RRT. However, the overall incidence of AKI was not reported in this study. Therefore, it is unclear whether strict glycemic control has a renoprotective effect and whether this is attributable to the toxic effect of blood glucose or a beneficial effect of insulin. These findings require further evaluation, particularly because strict glycemic control may be associated with a high frequency of episodes of hypoglycemia.

The nephrotoxic medication is a contributing factor in up to 25% of cases of AKI in critically ill patients. Identifying high-risk patients is key. Aminoglycosides are associated with significant nephrotoxicity. Although the daily dose of aminoglycosides has been shown by some studies to reduce the incidence of AKI, later meta-analyses found comparable efficacy but did not show a significant reduction in nephrotoxicity. Standard amphotericin B has been associated with AKI in 25 to 30% of patients. The lipid formulations of amphotericin B are preferred due to the reduction of nephrotoxicity.

The use of diuretics in the prevention and treatment of AKI is not based on any prospective clinical study. Diuretics can increase urine flow but do not have a decisive impact on mortality. Mehta et al. demonstrated that the lack of response to diuretics was associated with an increased risk of death and lack of recovery of renal function. In hindsight, in a large prospective, multicentre, international study Uchino et al. Found no increase in mortality, leaving the question unanswered about the use of diuretics in the prevention and treatment of AKI. Although oliguric AKI has been associated with a worse prognosis than non-oliguric AKI, there is no evidence to support measures to "convert" an oliguric in a non-oliguric AKI by using diuretics. The use of diuretics has not been demonstrated to shorten the duration of the AKI, reduce the need for RRT or improve the patient's global prognosis. In a recent RCT the use of furosemide was compared vs. placebo in the recovery phase of AKI requiring continuous renal replacement therapies (CRRT). Furosemide increased urine output and the fractional excretion of sodium (FENa) but did not improve renal recovery. In a study of epidemiological surveillance worldwide, nephrologists and intensivists reported their uncertainty regarding the use of furosemide in the prevention and treatment of AKI, supporting any initiative to undertake a definitive RCT. Probably, furosemide is indicated in cases of volume overload, but we must not delay the indication of RRT in patients with AKI and fluid overload.

Malnutrition in hospitalized patients is associated with increased mortality. The assessment of nutritional status in critically ill patients is limited by the lack of reliability of conventional markers. For example, prealbumin is excreted mainly by the kidneys and therefore may be "falsely elevated" in patients with AKI. AKI patients are hypercatabolic

patients with a negative nitrogen balance due to increased catabolism and altered protein synthesis.
Unfortunately, the recommended amount of protein is still controversial and current recommendations are based on expert opinions owing to lack of evidence from RCTs. The consensus recommends 20 to 30 kcal/kg/day and 1.5 grams of protein/kg/day. However, several studies have demonstrated a reduction in the negative nitrogen balance with up to 2.5 grams of protein/kg/day.

21.7 Indications and Initiation of Renal Replacement Therapy in AKI

The conventional indications for initiating RRT in AKI include volume overload, hyperkalemia, metabolic acidosis and manifestations of the uremic syndrome such as encephalopathy and pericarditis. RRT is also indicated in cases of poisoning where the toxin or drug can be dialyzed. These indications are well accepted, but subject to interpretation. How do we assess the degree of volume overload, hyperkalemia or metabolic acidosis? If diuretic therapy was initiated before RRT, which dose causes resistance to diuretics?
In many patients, however, RRT is initiated in the absence of specific indications in response to a persistent oliguria unresponsive to fluid therapy or progressive azotemia without uremic manifestations. There are different patterns of implementing RRT and no uniform standard of care: wide variations prevail in daily practice.
In the past, the paradigm of management of severe AKI was that patients died of uremic complications rather than renal injury. The corollary of this view was that the management of RRT was merely circumscribed to ensure that patients do not succumb to hyperkalemia, metabolic acidosis or volume overload, preventing overt complications of uremia such as encephalopathy and/or pericarditis. During the last decade, this paradigm has been challenged by data from different studies showing that AKI is an independent risk factor for mortality. It has been recognized that the specific management of RRT can impact on the prognosis of AKI and that optimizing renal support can reduce the high mortality.
The experience of the wars in Korea and Vietnam led to the concept of “prophylactic hemodialysis”, a term coined by Teschan and colleagues almost 50 years ago. Teschan and colleagues described their experience using “prophylactic hemodialysis” in 15 patients with oliguric AKI treated at the Renal Branch of the U.S. Army. The aim was to prevent uremic symptoms and their complications, for which dialysis should be started early with urea levels <200 mg/dl, with the aim of maintaining urea <150 mg%, with even daily frequency.
Although there was no control group, the authors argued that the results contrasted dramatically with the past experience of the same group when they began dialysis in the conventional manner. A posteriori multiple retrospective and observational studies carried out in the 1960s and 1970s compared early initiation of hemodialysis vs. late initiation of therapy, using blood urea nitrogen (BUN) values as the parameter. All studies demonstrated improved survival with early initiation of hemodialysis.
The first prospective trial of prophylactic dialysis in AKI was reported by Conger et al.: 18 patients with post-traumatic AKI were assigned to an intensive hemodialysis regimen that maintained the predialysis BUN <70 mg% and creatinine <5 mg/dl or to a non-intensive regimen in which hemodialysis was not initiated until BUN and serum creatinine reached 150 mg/dl and 10 mg/dl, respectively, or there were other indications

for initiating therapy (hyperkalemia, volume overload or uremic encephalopathy). Survival was 64% (five out of eight patients) in the intensive group as compared with 20% (two out of ten patients) in the non-intensive group (p=0.14). Gastrointestinal bleeding and Gram-negative sepsis were less frequent in the arm of the intensive hemodialysis group.

Ten years later, Conger et al. reexamined the intensity of hemodialysis in 34 patients. Matched patients were randomly assigned to the intensive regimen designed to maintain predialysis BUN <60 mg/dl and serum creatinine ≤5 mg/dl when plasma creatinine reached 8 mg% or to an intensive regimen in which BUN and plasma creatinine were allowed to reach 100 mg/dl and 9 mg%, respectively. While the therapeutic strategies were not designed to strictly assess the time of initiation of therapy, the average time from the start of AKI to the initiation of hemodialysis was 5±2 days in the intensive regimen group compared with 7±3 days in the non-intensive regimen. Mortality was higher in the intensive treatment group; however, because of the small sample, the difference was not statistically significant (p=0.73).

On the basis of these data, it has been suggested that in the absence of specific symptoms, hemodialysis is to be started when BUN reaches approximately 100 mg%, but there is no additional benefit associated with earlier or more intensive initiation of therapy.

Several studies published in the late 1990s re-examined the topic, focusing only on the time of initiation of continuous renal replacement therapy (CRRT). In their retrospective analysis, Gettings et al. related time of initiation of CRRT and prognosis of 100 consecutive patients with post-traumatic AKI. Patients were classified according to early or late initiation of therapy and according to baseline BUN, using a cut-off value of 60 mg% to separate the two groups. In the early initiation group, CRRT was begun on day 10±15 after admission (average BUN, 43±13 mg/dl) as compared with the start of therapy after 19±27 days (average BUN, 94±28 mg/dl) in the late group. Survival was 39% in the early initiation group compared to 20% in the late group (p=0.041). The patient demographics, disease severity, and disease severity scores in the two groups were comparable, but a higher percentage of patients in the late initiation group had multiple organ failure or sepsis. Although the timing of initiation of therapy may reflect the variable randomization in medical behavior, it is more likely that the patients' individual characteristics contributed to decisions not to randomize regardless of time of initiation of therapy. For example, 56% of patients in the early initiation group were oliguric on the first day of CRRT compared to 39% in the late initiation group. Therefore, the observed differences in prognosis may have been due to unreported differences underlying the decision to initiate early versus late therapy. Similar results have been reported in two retrospective analyses of time onset of CRRT in patients after cardiac surgery.

Piccinni et al. described the use of early isovolemic hemofiltration in oliguric patients with sepsis. They compared the prognosis in 40 patients with sepsis and oliguria in which high-volume hemofiltration was started (45 ml/kg/h) without net removal of fluid within 12 hours after CCU admission compared with 40 historical controls in which replacement therapy was initiated according to conventional indications. In patients treated with isovolemic hemofiltration, survival at 28 days was 55% compared with 27.5% in the historical control group. Although the authors described isovolemic hemofiltration in terms of early therapy, the comparison of the interval between the onset of renal dysfunction and initiation of therapy was not provided by biochemical indices of renal function and the initiation of renal support was similar, with a trend toward higher concentration in BUN and serum creatinine in the isovolemic hemofiltration group (110±38 mg/dl vs. 120±30 mg/dl and 1.7±2 vs. 1.8±2, respectively), suggesting that the time of initiation was not significantly different between the two groups.

Liu et al. analyzed data from the beginning of RRT (continuous and intermittent) of the Program to Improve Care in Acute Kidney Injury, a multicentre observational study of AKI. They evaluated 243 patients who received RRT in the early group and a late initiation group based on BUN (76 mg/dl) at initiation of RRT. Although the patients in the late group (BUN >76 mg/dl) had a reduced burden of organ failure, the survival rate at 14 and 28 days in this group was 75% and 59%, respectively, being somewhat lower than in the early initiation group (BUN >76 mg/dl) in which the survival rate was 8% and 65%, respectively.
After adjusting for age and clinical factors and staging for the site and initial modality of RRT in multivariate analysis, the relative risk of death associated with the initiation of dialysis with more severe azotemia (using the early initiation group as a comparator) was 1.85 (95% confidence interval [CI], 1.16-2.96). We also found an increase in relative risk of death in the high BUN group (2.07; 95% CI 1.30-3.29).
We should consider several limitations when analyzing the results of these retrospective studies. First, the use of BUN as a "replacement" for the measurement of the duration of AKI is problematic. Urea production is not constant, with a wide range among patients and even in the same patient, as is the degree of stress.
Similarly, the volume of distribution of urea in critically ill patients is highly variable and inconstant. Therefore, the rate of increase in BUN may vary among patients and may even vary in an individual patient over time. Second, there is a bias due to indications. Renal support was initiated because of oliguria in the early groups and due to azotemia and hyperkalemia in the late groups in both studies of AKI in post-operative cardiac patients. Although the reasons for early and late initiation in the studies by Gettings and Liu were not specified, it is likely that early initiation was due to volume overload and electrolyte disturbances, whilst the late initiation was indicated most likely because of progressive azotemia. We do not know if there is a relationship between the indication of therapy and prognosis.
In all four studies there were limited analyses in patients who received RRT, ignoring the subgroup of patients with AKI who recovered or died without RRT.
A recent study by Bouman et al. randomly grouped 106 critically ill patients with AKI into three groups:

- Early initiation with high-volume CVVHD (n=35).
- Early initiation with low-volume CVVHD (n=35).
- Late initiation with low volume CVVHD (n=36).

where CVVHD: continuous venovenous hemodiafiltration.
Treatment was initiated early within 12 hours to meet the requirements to be included in the study (presence of oliguria >6 h despite hemodynamic optimization or measured creatinine clearance <20 ml/min in urine collection of 3 hours), whereas in the late initiation group, RRT was initiated when BUN was >112 mg/dl, hyperkalemia >6.5 mEq/l or in the presence of pulmonary edema.
There were no significant differences in survival among the three groups. However, mortality at 28 days for these patients was only 27%, substantially lower than the mortality rates reported in other studies of critically ill patients with AKI, suggesting a lesser degree of severity in this patient group.
Current data do not allow us to know what the right time is for initiating RRT in AKI. We do not know if starting early or conservatively improves survival: the question remains unanswered. Although observational studies suggest a better outcome with early initiation, this can only reflect the inclusion of patients with less organic injury, in whom the prognosis is better regardless of the therapeutic strategy.
All observational studies focus on the problem of patients with AKI who require RRT. However, most patients with AKI do not require RRT. To answer this question, research should include all patients in whom the initiation of RRT is considered.

The timing of initiation of RRT in AKI patients remains uncertain. Conventionally, its initiation is accepted in case of volume overload, hyperkalemia, metabolic acidosis, progressive increase in uremia even without specific symptoms. However, there are no precise definitions of these indications in patients with AKI. In addition, observational studies and retrospective analyses have suggested that early initiation may improve survival. Nonetheless, the lack of inclusion of patients with AKI who met the inclusion criteria for early therapy but never received RRT limits the validity of these analyses. In order to carry out well-designed studies, we need more reliable biomarkers of renal injury, which are predictors of the clinical course of AKI.

21.8 Dose of Renal Replacement Therapy in Acute Kidney Injury

Three of the six prospective RCTs on RRT dose in critically ill patients have suggested that high doses of dialysis improve prognosis, especially by reducing mortality. In 2000, Ronco et al. published the first RCT investigating the results of three different ultrafiltration rates (20, 35 and 40 ml/kg/h). While mortality was high in all three groups, it was significantly lower in the two groups that received dialysis at the higher ulrafitration rates, with no difference in complications among the three groups. The single centre trial took years to complete and the percentage of sepsis-related AKI was lower than those usually observed in the CCU.

In 2002, Shifft et al. in a prospective, randomized study found that daily dialysis was superior to dialysis on alternate days. There were significantly fewer episodes of hypotension in the daily dialysis group (5 vs. 25%). Mortality was lower in the daily dialysis group (28 vs. 46%). An important limitation of this study was that the dose of dialysis delivered was significantly lower than that prescribed; therefore, the daily dialysis group received only an “adequate dialysis dose” compared to contemporary standards of treatment. In essence, the study compared “adequate” therapy vs. “inadequate” therapy.

Saudan et al. demonstrated that adding dialysis to continuous venovenous hemofiltration (CVVH) improved survival at 28 and 90 days when compared to CVVH alone in 206 critically ill patients (39 vs. 59% and 34 vs. 59%, respectively), suggesting that clearance of small solutes is important.

In contrast, three prospective RCTs found no difference in mortality. Bouman et al. found no difference in mortality when comparing early hemofiltration at high ultrafiltration rate, early hemofiltration at low ultrafiltration rate vs. late hemofiltration at low ultrafiltration rate, with an average ultrafiltration dose of 48, 20 and 19 ml/kg/h, respectively.

More recently, Tolwani compared two different doses of ultrafiltration (20 vs. 35 ml/kg/h of CVVH) and found no differences in mortality at 30 days between the two groups. Of note is that the dose delivered in the two groups was 17 and 29 ml/kg/h, respectively.

In 2008, the Acute Renal Failure Network published a multicentre study comparing the results of two RRTs, an intensive therapy vs. another conservative therapy. The intensive care group received daily dialysis, CVVHD or sustained low-efficiency dialysis (SLED) at an ultrafiltration rate of 35 ml/kg/h while the conservative therapy group received dialysis on alternate days (three times per week) with CVVHD or SLED at an ultrafiltration rate of 20 ml/kg/h. The patients were allowed to switch between intermittent and continuous regimens according to their hemodynamic stability, but they remained in the therapeutic group initially assigned. AKI was considered multifactorial in 59% of patients. No benefit was found with the use of intensive RRT compared to the conventional, less in-

tensive therapy. There were no significant differences in mortality, rate of renal function recovery, duration of replacement therapy or progression of non-renal organ failure. In our opinion, this study has some limitations: definition of AKI (referred to ATN); time of initiation of RRT (not standardized in the study); unclear transition from unstable to stable over time.

In 2009, the DO.RE.MI. group led by Ronco published a study comparing CVVHD at a rate >35 ml/kg/h or intermittent hemodialysis (IHD) six times per week vs. CVVHD at an ultrafiltration rate >35 ml/kg/h or IHD less than six times per week. In this multicentre, international trial involving 15,200 patients, no benefit in survival was observed between the two treatment modalities. The intensive regimen was associated with a shorter stay in the CCU and duration of mechanical ventilation.

Finally, the RENAL study involving 1508 patients compared two therapeutic modalities of CVVHD (25 vs. 40 ml/kg/h) and reported no differences after 90 days in mortality between the two groups.

Important factors to consider when evaluating the results from the available evidence are the differences between the patient populations studied, the use of convective techniques alone or the combination of convective and diffusive modalities and, in particular, the difference between the indicated dose and that actually delivered to patients.

Findings of negative assays should not be interpreted as “the dose is unimportant.” As the work of the Acute Dialysis Quality Initiative (ADQI) concludes, the clearance given to the patient should be monitored throughout the whole renal supportive therapy. No specific recommendations can be made about dialysis dose for patients with specific diseases at this time. A minimum dose of RRT, however, needs to be delivered in AKI. The best evidence supports the use of an ultrafiltration rate ≥35 ml/kg/h for CVVH and CVVHD. Also recommended is that the prescription should exceed the dose calculated as “adequate” because of the known gap between the prescribed dose and the real one delivered to the patient.

A systematics based on solute removal in relation to the dose appears to be too restrictive, albeit operationally relatively simple, and, by analogy to terminal chronic renal failure, it could be linked to prognosis.

We might initially start from a hypothetical point with “zero dose” or “no therapy”, which would have a negative prognosis of 100%. From there we would enter a “dose-dependent” zone, where any dose increase, however small, would result in improved prognosis. This may be true until a point where further dose increments do not improve the prognosis and the dose-prognosis relationship begins to enter a plateau or plateau phase. This area can be called “dose-independent” or “dependent on the practice or art” or “dependent on the severity.” Beyond this point, survival is not affected by an increase in treatment but rather by the level of severity of the patient’s conditions.

Currently, the cutoff for CRRT is 35 ml/kg/h; in a septic population, however, the cutoff could be raised to 45 ml/kg/h or even more. The current recommendation based on available data is to ensure a dose of Kt/V of 1.2 to 1.4 for the intermittent modality. In our opinion, the use of Kt/V to adjust the dose of intermittent modalities involves extrapolating the results obtained in patients with chronic renal disease on a regular hemodialysis schedule of three times a week, while it doesn’t seem appropriate to do so in critically ill patients with AKI. The plateau level can be defined by other factors beyond the treatment dose. In critically ill patients with AKI, these conditions of adequacy of RRT have not yet been explored, but may be important in the final prognosis. Further studies should focus on other aspects beyond the dosage (e.g., volume control, acid-base status, toxicity, etc.) and evaluate their relationship with the prognosis.

21.9 Methods of Renal Replacement Therapy in Acute Kidney Injury

Treatment options for replacing renal function in critically ill patients are intermittent hemodialysis (IHD) and various continuous techniques of renal replacement: continuous venovenous hemofiltration (CVVH); continuous venovenous hemodialysis (CVVHD); continuous venovenous hemodiafiltration (CVVHD); sustained low-efficiency dialysis (SLED); and extended daily dialysis (EDD). The suitability of one over another, particularly in critically ill patients, has been the subject of heated controversy.

Continuous techniques and SLED are better tolerated by patients with abnormal hemodynamics. From the point of view of efficacy in the extraction of solutes, a better control of homeostasis has been attributed to CRRT, due to its prolonged effect, absence of a "rebound effect" (post-procedure increase in blood solutes, such as urea), and potential clearance of inflammation-related molecules, sepsis and the multiple organ dysfunction syndrome (MODS) in critically ill patients with AKI.

Several studies have compared the results of IHD with CRRT in the evolution of AKI. Since most studies are retrospective and not randomized in design, it is difficult to draw valid conclusions owing to the differences in the severity index. A higher mortality for patients undergoing CRRT has been reported, but when adjusted for the severity index, no differences can be attributable to the type of therapy.

In a large, randomized prospective trial, Mehta et al. sought to compare both techniques. Mortality was higher in the CRRT-treated group than the IHD-treated group in both the CCU (59.5 vs. 41.5%) and the hospital (65.5 vs. 47.6%). But despite randomization, the CRRT patients had a higher APACHE III score and more patients had liver failure. The many uncontrolled factors in this study preclude definitive conclusions. In a meta-analysis, Kellum et al. found no differences in mortality between intermittent hemodialysis and CRRT. However, the quality of the reviewed studies was poor and only three of them were prospective. In a subanalysis, after adjusting for study quality and severity index, a beneficial effect of CRRT on survival was found (RR = 0.72, 95% CI 0.60-0.87; $p < 0.01$). In six studies involving patients with similar severity, mortality was lower with CRRT (RR = 0.48, 95% CI 0.34-0.69; $p < 0.0005$). Despite the secondary analysis, the meta-analysis concluded that there was insufficient evidence to support a specific therapy in AKI. Moreover, Tonelli et al. in another meta-analysis also found no survival benefit with one technique compared to another.

Recently, a program to improve care in AKI carried out a retrospective study comparing the results of different RRT modalities in 368 patients (CRRT, n=206 vs. IHD, n=192). As compared with IHD, CRRT was associated with an increased relative risk of mortality. The authors acknowledged that the patients in the CRRT arm were more severely ill and that the results might have been influenced by that.

In a recent paper, Vinsonneau et al. reported a prospective, randomized trial in 21 CCUs over a period of three and a half years. The primary endpoint was mortality at 60 days after having randomized 360 patients with AKI to receive CVVHD or IHD in centres that were familiar with both technologies. The election criterion was changed after eight months because the inclusion rate was too low. There was no difference in mortality in either group, concluding that patients with AKI as part of MODS can be treated with IHD. The trial was well designed and performed; to date, it is the best example of a randomized controlled study comparing the two techniques. However, the study began more than seven years ago: the practice of different purification techniques has changed considerably since then. One change is related to the dose delivered in renal support vs.

prescribed treatment. But because there was no information about the dose in either arm, no definitive conclusions can be drawn.

The question of which treatment is best is influenced by the nature of a study. CRRT may be better in terms of total water and solute removal in a 24-hour-period and hemodynamic tolerance, but IHD can remove much more water and solute per hour and does not require continuous anticoagulation or complete patient immobilization. The problem, however, is not to achieve high efficiency within a short period of time; instead, our goal is to achieve the best blood purification and restoration of homeostasis with the lowest possible rate of complications. If it is true that all patients with AKI as part of MODS can be treated with IHD, it follows then they can be safely treated with CRRT.

In patients with cerebral edema, intermittent treatment could worsen the patient's clinical condition due to the influx of fluid into the brain tissue after dialysis. After a hemodialysis session, the cerebral density decreases due to deviations of osmotic fluid. These alterations induced by intermittent therapy would not occur with CRRT, which could be used in patients at risk for cerebral edema.

In the last two decades, technological advances in IHD have dramatically reduced the incidence of IHD-induced intradialytic hypotension. These advances include the introduction of machines that control volume, the use of biocompatible synthetic membranes, and the use of dialysate containing bicarbonate, and the delivery of higher doses of dialysis.

Schortgen et al. reported a lower rate of hemodynamic instability during IHD with the implementation of an algorithm designed to improve hemodynamic tolerance of IHD, which consists of priming the circuit with saline, sodium in the dialysis solution >145 mEq/l, discontinuing therapy with vasodilators, and setting the solution temperature to <37°C.

There have also been improvements in CRRT. The use of bicarbonate in replacement fluid is available today.

Ideally, CRRT and IHD coexist according to the needs of each patient, which we call an "à la carte menu." Whether one technique may be superior to another is a fruitless artificial discussion.

As designed in Vinsonneau's protocol, a change from one treatment to another seems reasonable when clinical status changes. Although this routine seems to make sense, it has never been validated.

The random selection of patients for one dialysis method or another, regardless of their clinical, can produce results that will be difficult to generalize in daily practice. A decade ago, debate raged about the best systematic disconnection of the patient from the mechanical ventilator. Perhaps electing one method rather than another is difficult, and the way in which the disconnection technique is performed may have a greater effect on the possibility of disconnection than the method itself. The design of future studies should include other prognostic parameters besides mortality.

Recently Uchino et al. reported the results of an observational, prospective trial involving 54 international centres with 1258 patients treated with RRT for AKI. CRRT was the most common initial treatment modality (80%) followed by intermittent therapies (16.6%). Patients who were initially treated with CRRT required vasopressors and mechanical ventilation more often than those requiring intermittent renal replacement therapy (IRRT). The "unadjusted" raw hospital survival rate was lower (35.8 vs. 51.9%; $p < 0.001$). However, the absence of dialysis dependence at hospital discharge was higher for CRRT (85.5 vs. 66.2%; $p < 0.0001$). The multivariate logistic regression analysis showed that the choice of CRRT was not an independent predictor of hospital survival or hospital days without dialysis. However, the choice of CRRT was a predictor of a lack of dialysis dependence at hospital discharge among survivors. Other studies found similar results.

Hybrid therapies developed in the last decade provide a feasible compromise solution in this eternal dispute. Depending on variations in the selection and removal of solutes (convection or diffusion), they such therapies are known under a variety of names: sustained low-efficiency dialysis (SLED), (Marshall et al.); prolonged daily intermittent therapy (Nakay et al.); extended daily dialysis (Kumar et al.). In theory, the intent is to maximize the benefits of each therapy, continuous and intermittent, including the efficient removal of solutes with a minimum solute disequilibrium, reduction of the ultrafiltration rate with hemodynamic stability, optimizing the delivery of the prescribed dose, low need for anticoagulation, and enhancement of patient mobilization.

Initial studies have shown the feasibility and potentially high clearance associated with such treatments. Recently, Baldwing et al. randomly assigned 16 patients to treatment with CVVH or extended daily dialysis with filtration (EDD) for three consecutive days and compared the control of small solutes, acid-base status and electrolytes. No significant differences were found between the two therapies in relation to urea and creatinine levels during the three days. All electrolyte abnormalities before treatment were corrected as a result of treatment, except in one patient in the CVVH group who developed hypophosphatemia at 72 hours. After three days of treatment, a mild metabolic acidosis remained in the EED group compared with the CVVH group.

It is now possible to generate ultrapure replacement fluid and to administer it in the CCU at a lower cost than CRRT in large quantities and for shorter periods of time. Hemofiltration may be combined with diffusion. It is possible to perform three to four hours of standard IHD or CRRT at 35 ml/kg/h of ultrafiltration. SLED is performed with a dialysate and blood flow rate of 150 ml/min for eight hours during the day or, as an alternative, for 12 hours at night. It is also possible to combine an initial therapy with CRRT in the first two or three days when the patient is in the hyperacute phase, followed by SLED when recovery begins.

If we consider the teaching of ventilatory modalities, the RRT modalities are similar to those of ventilation, and can be changed according to therapeutic objectives, patient's needs and stages of disease.

Restricting the management of critically ill patients with AKI to one therapy or another is a simplistic approach. So far, there is no prospective, randomized trial with sufficient power to provide solid evidence for electing any one type of treatment. Given that this would require 660 patients in each of the two study arms, it is arguable whether a study of this kind can be carried out. The different clinical situations and variables to consider support the view to individualize treatment according to need. Various different techniques can be complementary, even in the same patient.

21.10 Conclusions

AKI-realted morbidity and mortality of in the critically ill patient requiring dialysis are high. Dialytic strategies that can reduce their impact are not universally accepted. The lack of sensitive markers of uremic toxicity and of fully assessed indices of dialysis in AKI hinders the determination of well-defined therapeutic goals. Another problem is the underestimation of the volume of urea distribution by anthropometric methods, which can lead to prescribing an inadequate dialysis dose. The high burden of comorbidity in AKI patients in the CCU is another obstacle when it comes to elucidating the potential benefit of dialysis in its evolution. Adequate dialysis dose in AKI is not consensual. Some practices seem to be more effective, but there is no sufficient scientific evidence. Replacement treatment in AKI patients needs to be flexible, adapting the technique (IHD SLED

or CRRT) to the patient's clinical status, as measured by urine output, hemodynamic status, and the number of affected organs. Treatment should be adjusted to the needs of the individual patient and not the other way round. Furthermore, we should consider an "à la carte" dialysis therapy, according to the suitability of each patient, individualizing the starting time, dose and time of initiation of RRT for each patient when we meet them. As we go forward we will need define new disease groups that may benefit from the effects of purification and determine the appropriate treatment necessary to ensure optimal performance.

Currently, renal replacement is intended as a replacement for purification, but the first steps have already been taken to realize a concept of renal substitution in which not only the elimination functions are controlled but the synthesis mechanisms specific to the native kidney are also applied.

In light of the above, we can say that RRTs are continuous evolving in terms of basic concepts (patient characteristics, definition of new indications), current definitions (a good marker of treatment intensity or proper dose), technical aspects (appropriate material), or consensus on the most suitable type of RRT from among the many available.

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22 The Brain and the Abdomen: Closer Than You Think

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22.1 Introduction

Intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) are a relatively common occurrence in ICU patients, as was demonstrated by Malbrain et al. [1,2]. Interest in this topic has increased dramatically over the last few years leading to a rapidly growing body of evidence regarding all aspects of IAH. The deleterious effect of IAH on organ function has been well documented [3,4]. Especially the organs lying within or adjacent to the abdominal cavity (e.g. the kidney) are at risk due to decreased blood supply and direct pressure on the organ involved [5]. However, also distant organs, such as the heart and the brain, are influenced by IAH in ways that are not yet completely understood [6,7]. Several animal studies and human clinical studies have described the relationship between intra-abdominal pressure (IAP) and intracranial pressure (ICP) [8-13] and some have offered insights into the mechanisms involved [7,14-19]. Some small series describing successful treatment for patients with IAH and intracranial hypertension (ICH) have also been published [10,20].
In this chapter we will summarize all research findings concerning the relationship between the abdomen and the brain, offer an overview of current knowledge on this fascinating topic and make a few clinical recommendations based on the findings described.

22.2 The Relationship Between IAP and ICP

22.2.1 Animal Studies

The first report describing a relationship between IAP and ICP was published in 1994 by Josephs et al. of the Boston University School of Medicine who induced IAH in a porcine model (by installing a pneumoperitoneum) and observed a concomitant increase in ICP but no significant decrease in cerebral perfusion pressure (CPP) [11]. The same effect could be observed when the added insult of brain injury (by inflating a balloon in the epidural space) was induced. The authors explained this phenomenon by formulating a hypothesis based on the modified Monro-Kellie doctrine. The Monro-Kellie doctrine recognizes three main contents in the cranial space: vascular, cerebrospinal fluid (CSF) and parenchyma. The doctrine states that, in adults, changes in one or more of these contents result in reciprocal changes in the remaining compartments. The imbalance of the contents produces an ICP increase when buffer mechanisms are exhausted. In other words, ICP reflects the relationship between the volume of intracranial contents (vascular, CSF, and parenchyma) and the volume of the cranial vault. In their brain injury model, Josephs et al. increased the intracranial volume directly by inflating an epidural balloon [11]. At the same time they indirectly increased the vas-

cular contents by inducing a pneumoperitoneum which decreases thoraco-abdominal compliance and reduces venous outflow from the brain, thus producing an ICP rise. A combined effect of pneumoperitoneum and endotoxemia on cerebral perfusion has been observed in pigs [21].

The confirmation of Josephs' hypothesis came a few years later. Using a porcine model of acutely elevated IAP, Bloomfield et al. clarified the mechanisms by which IAH increases ICP and decreases CPP, evaluated the effect of intravascular volume expansion upon ICP and CPP and studied the relationship between IAP, pleural pressure (PP), CVP and ICP [8,9]. They measured the effects of elevated IAP upon ICP and CPP before and after intravascular volume resuscitation [8]. IAP was increased in 5 anesthetized swine by inflating an intraperitoneal balloon until 25 mmHg above baseline. Intravascular volume was then expanded and, finally, abdominal decompression was performed.

Bloomfield demonstrated that elevated IAP increases CVP, PP, ICP and decreases cardiac index (CI), mean arterial pressure (MAP) and CPP. Moreover, volume expansion, in the presence of elevated IAP, further raised the ICP and CPP (because of a larger increase in MAP). An interesting finding was that an IAP greater than or equal to 25 mmHg produced a statistically significant decrease in CPP, even in animals without head injuries.

The results of this study confirmed that the mechanism of increment of ICP is mechanical. In accordance with the Monro-Kellie doctrine, the authors demonstrated that cerebral venous outflow via the jugular venous system was impeded by a significant rise in the CVP. This phenomenon was amplified by volume expansion, due to the additional rise in CVP. The authors suggested that the functional obstruction of the jugular venous system and the ensuing obligatory increase in the volume of the cerebral vascular space, are the mechanisms responsible for the increased ICP caused by elevated IAP.

One year later, the same group published a new study with a similar setup, only this time the pigs were divided into two groups [9]. The first group was treated as mentioned before, the second group underwent sternotomy and pleuropericardotomy before increasing IAP. Interestingly, in the second group, sternotomy and pleuropericardotomy abolished all effects of increased IAP, except the decrease in CI, which supports the hypothesis formulated in the first study (Figure 22.1).

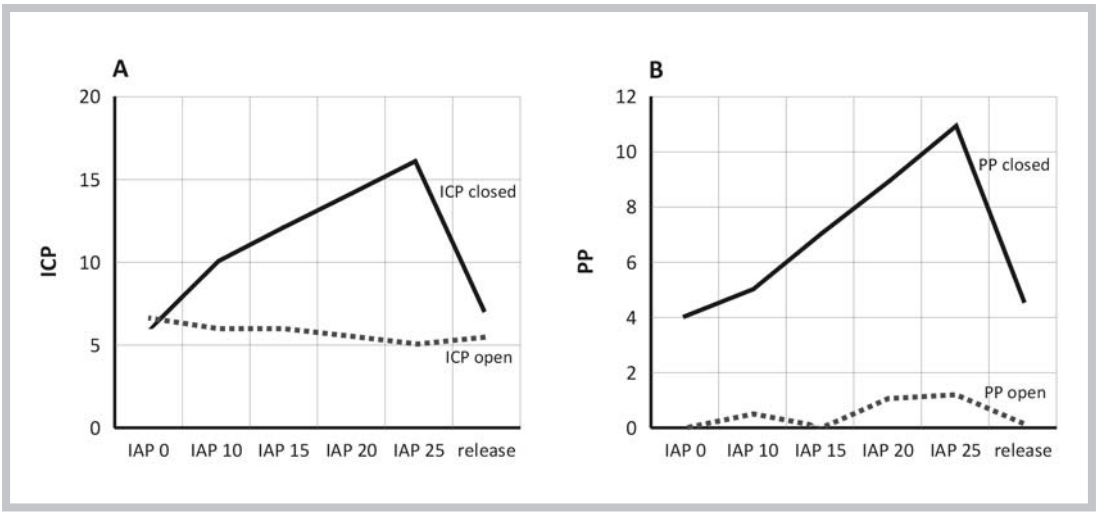

Figure 22.1. **Effect of increasing intra-abdominal pressure (IAP) in closed and open-chest animals on intracranial pressure (ICP) and pleural pressure (PP). A. ICP: solid line closed chest, dotted line animals with thoracotomy. B. PP: solid line animals without sternotomy, dotted line animals with sternotomy. Modified from Bloomfield [9].**

In a similar study in 5 pigs, Rosin et al. found no significant change from baseline in ICP when the IAP was 5 mmHg [22]. However, ICP and CPP were affected by increasing the IAP to 15 and 25 mmHg ($p = 0.035$ and 0.04 for ICP respectively). They concluded that low-pressure laparoscopy may reduce the adverse effects of pneumoperitoneum on ICP and CPP. It may therefore be advisable to use low pressures in laparoscopic surgery, especially when changes in ICP or renal perfusion may have significant clinical implications [22,23].

Hanel et al. measured cerebral hemodynamics in 10 pigs during laparoscopic insufflation to 12 mmHg [24]. Pneumoperitoneum significantly ($p < 0.05$) increased CVP from 6.3 ± 2.1 to 11.1 ± 3.0 mmHg and sagittal sinus pressure from 8.0 ± 2.8 to 11.9 ± 3.0 mmHg. However, bilateral internal carotid artery blood flow (46.0 ± 7.4 vs. 47.7 ± 7.1 ml/100 g per minute), cortical cerebral blood flow, CBF (263 ± 115 vs. 259 ± 158 tissue perfusion units), and subcortical CBF (131 ± 145 vs. 133 ± 149 tissue perfusion units) did not change during CO_2 pneumoperitoneum. The increases in sagittal sinus pressure are likely related to decreases in cerebral venous drainage caused by increases in IAP.

Other studies looked at the effect of combined abdominal and thoracic binding (ATB) on neurologic function during CPR: mean ICP was higher during ATB (46 ± 2 mmHg) than conventional CPR (20 ± 2 mmHg) [25]. However, the net brain perfusion pressure gradient (carotid artery pressure – ICP) was greater with ATB (14 ± 3 mmHg) than with conventional CPR (5 ± 0.4 mmHg). Cerebral blood flow was significantly greater during ATB CPR (32 ± 7% of pre-arrest cerebral flow) than during conventional CPR (3 ± 2%). They conclude that ATB CPR substantially improved brain perfusion by enhancing CPP in this experimental dog model. The same results were found by Ratjen et al. in lambs [26].

Palafox et al. looked at the effect of MAST suit on ICP in dogs [27]. During MAST inflation, they found a rise in ICP that mirrored the rise in CVP and never reached potentially harmful levels in the hemorrhaged animals and animals with a mass intracranial lesion. In the animals with cardiac tamponade and tension pneumothorax, inflation of the abdominal portion of the MAST suit produced a marked rise in CVP and ICP. This was altered by either relieving the lesion or reducing the pressure of the abdominal portion of the MAST suit.

Schob et al. compared the pathophysiological neurologic effects of carbon dioxide, helium and nitrous oxide pneumoperitoneum in 24 pigs [28]. The mean ICP increased significantly in all groups during peritoneal insufflation compared with the control group ($p < 0.005$). The CO_2-insufflated animals also showed a significant increase in $PaCO_2$ ($p < 0.05$) and $ETCO_2$ ($p < 0.05$), as well as a decrease in pH ($p < 0.05$). After inflating the epidural balloon the ICP remained significantly higher in animals inflated with CO_2 as compared with the He and N_2O groups ($p < 0.05$). They concluded that peritoneal insufflation with He and N_2O resulted in a significantly less increase in ICP as compared with CO_2. That difference was most likely due to a metabolically mediated increase in CPP. Further studies need to be conducted to determine the safety and efficacy of using He and N2O as inflation agents prior to attempting diagnostic or therapeutic laparoscopy in patients with potential closed head injuries.

In conclusion, these laboratory studies clearly showed that an IAP rise decreases the thoracic-abdominal compliance and increases intrathoracic pressures. This in turn reduces cerebral venous outflow, causing an ICP elevation.

22.2.2 Clinical Studies

Despite the convincing results of the previously mentioned animal studies, interest in this subject in human clinical research is very recent. In 1995, two early case reports

were published that confirmed the results of the animal studies [29-31], but the first well conducted clinical study evaluating the relationship between IAP and ICP was published by Citerio et al. in 2001 [15]. They conducted a prospective non-randomised observational study to systematically measure the effect of increased IAP in 15 patients with traumatic brain injury. IAP was increased by positioning a soft 15-l bag of water on the patient's abdomen. Naturally, patients could only be included in this study after the acute phase of their injury, when no intracranial hypertension was present. All patients

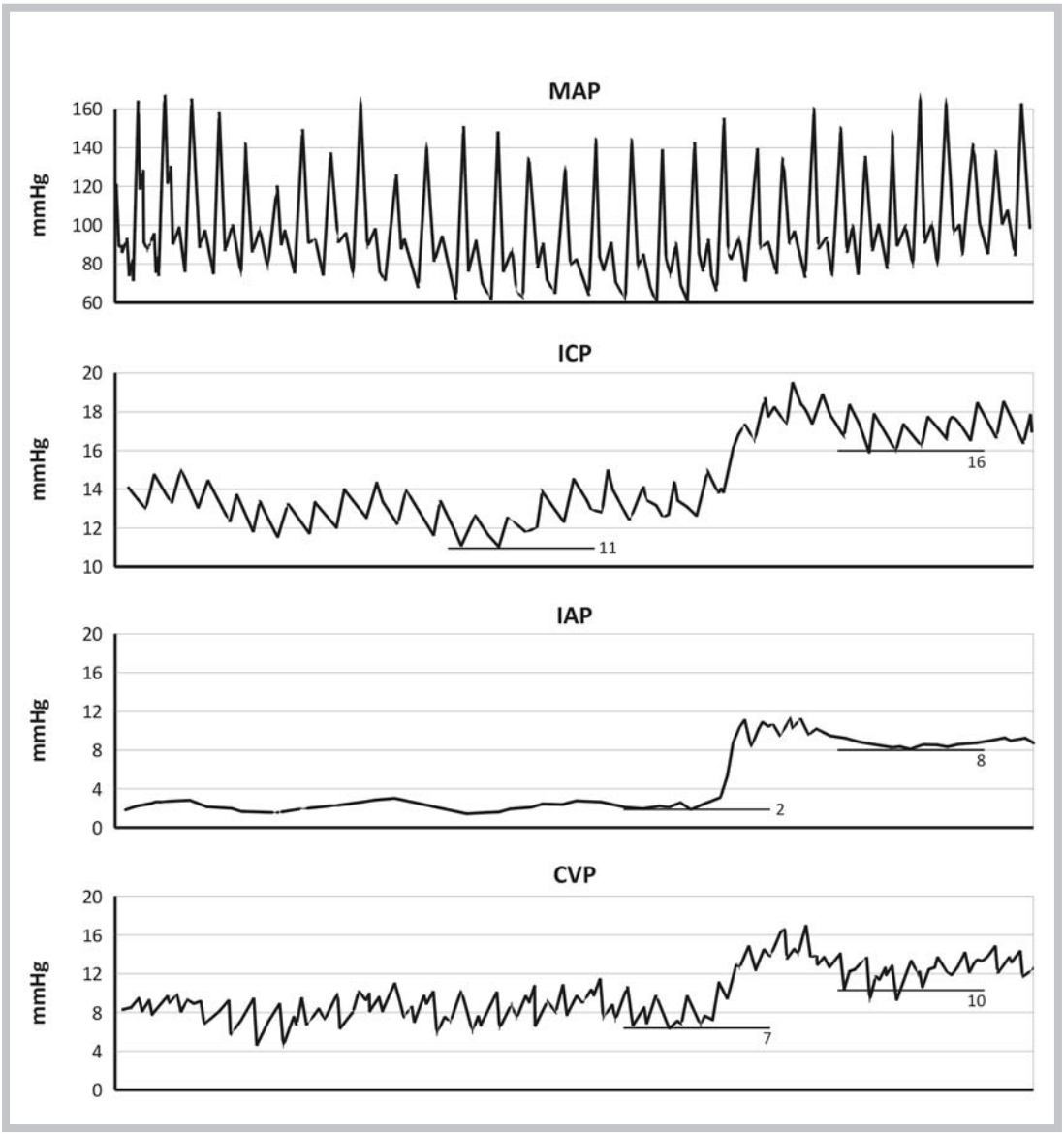

Figure 22.2. **Effect of increased IAP, obtained with a weight application in a single patient. Computerized tracings are from top to bottom: MAP = mean arterial pressure; ICP = intracranial pressure; IAP = intra-abdominal pressure; CVP = central venous pressure. The IAP increased from 2 to 8 mmHg, this resulted in an increase in CVP from 7 to 10 mmHg and an increase in ICP from 11 to 16 mmHg. Hence the transmission from the abdomen to the thorax compartment can be calculated as ΔCVP (= 10 – 7) divided by ΔIAP (= 8 – 2) or thus 50%, and the transmission from the abdomen to the cranial compartment can be calculated as ΔICP (= 16 – 11) divided by ΔIAP (= 8 – 2) or thus 83%. Modified from [7,15].**

were intubated and mechanically ventilated. Many parameters were measured: IAP, MAP, CVP, ICP, CPP, jugular bulb pressure (IJP), jugular bulb oxygen saturation and compliance of the respiratory system, divided into pulmonary and chest wall components. The authors found that placing a weight on the patient's abdomen generated a significant increase in IAP and a concomitant and rapid increase in CVP, IJP and ICP. All these changes required only seconds to reach a plateau and remained stably increased until the IAP returned to baseline after the weight removal (Figure 22.2).

Curiously, in this study a rise in MAP was observed, allowing for maintenance of a constant CPP in spite of increased ICP. This is not in concordance with the animal studies. This may be due to the lower levels of IAP generated in this human study compared to the animal studies and the use of different sedatives in animal and human studies or it may represent a true physiologic mechanism where increased intrathoracic pressure facilitates systolic ejection (although venous return is decreased). A second interesting finding from this study is that respiratory system compliance decreased significantly in all patients and this decrease was exclusively due to decreased compliance of the thoracic wall. Lung compliance did not change at all.

These findings confirm the hypothesis that IAH displaces the diaphragm upward, reducing the chest wall compliance and therefore respiratory system compliance. The pressure in the abdominal compartment (IAP) is directly transmitted to the thoracic compartment, where it increases intrathoracic pressures (CVP, esophageal pressure), and thereafter to the cerebral compartment (causing an increase in IJP and ICP). In other words, the ICP rise appears to be the result of an obstruction to the cerebral venous drainage, causing elevation of pressure in the intracranial compartment.

Deeren et al. found similar results in 11 patients with nontraumatic brain injury [20]. They found tight associations between IAP and ICP, ΔIAP and ΔICP, and ΔIAP and ΔCPP even at only slightly increased levels of IAP (Figure 22.3). In total eleven patients were studied with simultaneous IAP and ICP-monitoring because of ischemic (in four), hem-

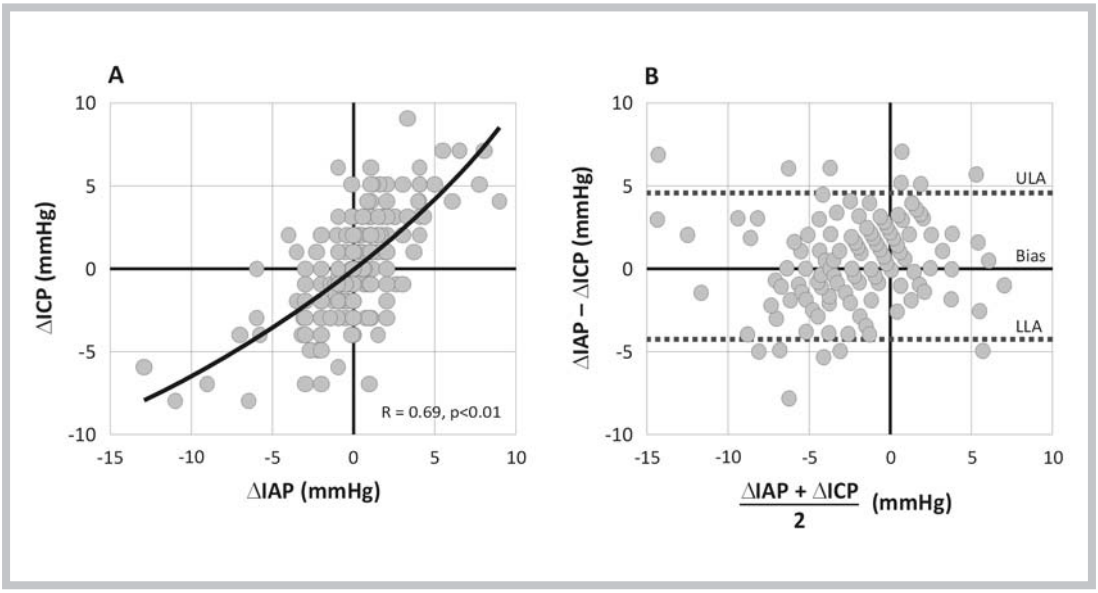

Figure 22.3. **(A). Regression analysis between ΔIAP versus ΔICP (positive correlation). (B). Bland-Altman plot of ΔIAP and ΔICP.**

IAP = intraabdominal pressure
ICP = intracranial pressure
LLA = lower limit of agreement
ULA = upper limit of agreement

orrhagic (in five) and metabolic (in two) encephalopathy. Two hundred fourteen consecutive paired data sets were compared. The mean IAP of each patient ranged from 3.8 to 11.8 mmHg, with a mean ICP from 6.7 to 15 mmHg and mean CPP from 70.8 to 123 mmHg. For ICP, the regression coefficient associated with IAP was 0.64 (standard error = 0.05; 95% confidence interval = 0.56 to 0.73; $p < 0.001$, partial correlation = 0.70). For CPP, the regression coefficient associated with IAP was -1.36 (standard error = 0.3; 95% confidence interval = -1.94 to -0.78; $p < 0.001$; partial correlation = -0.30). Cooke investigated key symptoms and signs of raised ICP in 39 patients after laparoscopic abdominal surgery and compared them with a control group of 33 patients after open operations [32]. They found that the incidence of headache and nausea was significantly higher in the laparoscopic group than in the control subjects and they concluded that these results could be explained by raised intracranial pressure exacerbated by the CO_2 pneumoperitoneum, and that this effect is not mediated by raised expiratory CO_2 levels intraoperatively.

In an ophtamologic journal, Neville et al. have published a study in which 15 patients with normal opening pressures on lumbar puncture who were referred for CSF analysis, were asked to artificially increase their IAP through a Valsalva maneuver [33]. All patients were able to elevate their CSF pressure to values above 25 cmH_2O and one patient achieved a value of 47 cmH_2O! The authors were prompted to perform this study after the observation that patients were referred for fundoscopy due to increased CSF pressure while they had no symptoms of intracranial hypertension.

Recently several reports have been published alluding to neurologic deterioration related to increased IAP in patients with ventriculoperitoneal shunt (VPS) dysfunction [34-36]. These reports provide anecdotal evidence that transient and easily reversible increases in the IAP of adults with VPS can result in dysfunction. Although it may not be practical to delay shunt revision while attempting to correct constipation, meteorism, ileus, or small bowel obstruction, clinicians treating patients with these abdominal conditions should be aware that they could cause transient VPS failure [37]. Martinez-Lage et al. describe constipation as an under-appreciated cause of VPS malfunction in children and advise pediatric neurosurgeons to investigate the abdomen first before considering surgical valve revision of the VPS [38]. In a similar way colonoscopy can increase ICP [39]. Several reports also pointed towards obesity as a cause of increased IAP leading to idiopathic ICH and pseudotumor cerebri [40-43]. Interestingly, negative abdominal pressure, weight loss and bariatric surgery have been demonstrated to reduce the clinical signs of ICH (headache, blurred vision, etc.) and ICP [44-48]. Furthermore recent weight gain may be associated with relapses of idiopathic ICH [49]. Obesity associated sleep apnea may also be associated with idiopathic ICH [50, 51]. Sahuquillo et al. performed a study in 60 patients requiring a VPS for hydrocephalus [52]. They recorded BMI and measured IAP during the shunt surgery and found that there was a linear relationship between IAP and BMI. They conclude that the assumption that IAP is close to 0 mmHg does not apply in obese or overweight patients and neurosurgeons should take IAP into account when selecting both the most adequate differential pressure valve to be implanted and in which distal cavity to place the distal catheter to avoid shunt underdrainage induced by high IAP.

22.3 Clinical Importance of IAH in Patients at Risk for ICH

According to the previously mentioned modified Monro-Kellie doctrine, ICP remains constant over a relatively wide range of intracranial volume. In this plateau phase, an in-

crease in intracranial volume due to e.g. cerebral edema, hematoma or mass lesion, will be compensated by the evacuation of cerebrospinal fluid through the foramen magnum at the base of the skull. However, when these compensation mechanisms are exhausted at higher intracranial volumes, any small increase in volume produces a marked increase in ICP rapidly leading to ICH (Figure 22.4).

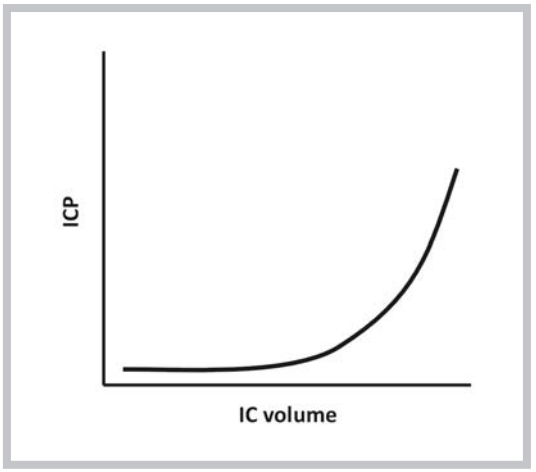

Figure 22.4. **Relationship between intracranial volume (IC volume) and intracranial pressure (ICP) according to the Monro-Kellie doctrine.**

When we combine this concept with the findings of the previously mentioned experimental and clinical studies we can speculate that in the presence of ICH the effect of increased IAP probably induces a more profound and harmful increase in ICP due to a different starting ICP position on the intracranial PV curve and different strain on the compensatory capacity. Therefore, it is crucial to measure IAP in patients with ICH at risk for IAH (or *vice versa*). These findings are of great importance for patient care, for example in trauma patients, since abdominal trauma is commonly associated with head trauma and therefore patients with combined ICH and IAH may be more common in the ICU population than previously thought. Scalea et al. recently published a study describing 102 consecutive patients with severe TBI who underwent decompressive craniectomy (DC) for intractable intracranial hypertension [53]. Twenty-four patients in this series also had decompressive laparotomy (DL) due to what the authors describe as multiple compartment syndrome (MCS). The found that both DC and DL reduce ICP and can be used in sequence and conclude that MCS should be considered in multiply injured patients with increased ICP that does not respond to therapy. Joseph et al. performed a retrospective study and found that in their institution 17 patients in a period of 3 ½ years underwent DL for refractory intracranial hypertension [10]. All had failed maximal therapy including 14 who had had DC. Mean ICP was 30 ± 8.1 mmHg (range 20-40 mmHg) before decompression. No patients had evidence of abdominal compartment syndrome (ACS). Before decompression mean IAP was 27.5 ± 5.2 mmHg (range 21-35 mmHg). After abdominal decompression ICP dropped precipitously by at least 10 mmHg to a mean of 17.5 ± 3.2 mmHg (range 10-25 mmHg). The authors conclude that decompressive laparotomy can be a useful adjunct in the treatment of ICH failing maximal therapy following TBI.

Another obvious risk population are patients with existing VPS [52]. In the event of neurologic deterioration in these patients during critical illness, IAP should be monitored and IAH should be treated promptly. IAP should also be monitored in critically ill, sedated and mechanically ventilated patients with VPS since neurologic examination is unreliable in these circumstances. Table 22.1 summarizes the neurologic effects of increased IAP.

- Intracranial pressure ↑
- Cerebral perfusion pressure ↓
- Cerebral blood flow ↓
- Jugular bulb saturation ↓
- Cerebral venous outflow ↓
- Cerebrovascular resistance ↑
- Idiopathic intracranial hypertension in morbid obesity
- Pseudotumor cerebri in morbid obesity
- Neurologic effects reversed after bariatric surgery or weight loss
- Neurologic deterioration during laparoscopy

Table 22.1. **Neurologic effects related to IAP.**

Case reports and small series applying these concepts in clinical settings are beginning to appear in literature with an increasing frequency. For example, in a review on cough, exertional and sex headaches Cutrer et al. find that these symptoms are triggered by increased IAP and that they may be the manifestation of an underlying, potentially serious cause [54]. They advocate the elimination of intracranial structural or vascular abnormalities in the presence of these headaches. Eberhart et al. have published a review on the prevention of postoperative nausea and vomiting in post-craniotomy patients and discuss the importance of avoiding sudden increases in IAP due to vomiting in this risk population [55].

22.4 Treatment Options

A few studies have addressed the issue of treatment of ICH in the presence of IAH. A group of the Adams Cowley Shock Trauma Center of Maryland published a paper on the use of decompressive laparotomy for the treatment of intractable ICH after traumatic brain injury [10]. This technique was used in 17 patients whose intracranial hypertension was unresponsive to maximal therapy. The decompression resulted in a marked decrease in both ICP and IAP. In 6 patients the decrease in ICP was transient and all patients died. The remaining 11 had sustained decreases in ICP and IAP and survived, made neurologic recovery and were discharged to a rehabilitation facility. The same remarks were posted in a letter by Lyons [56]. Bloomfield also described the successful management of a patient with severe multisystem injury in whom abdominal decompression dramatically reduced high ICP unresponsive to medical measures [31].
Deeren et al. published a clinical study in 2005 describing the relationship between IAP and ICP in patients with nontraumatic brain injury (Figure 22.5). In four of these patients IAP and ICP measurements were obtained before and after administration of a neuromuscular blocker [20]. Both IAP and ICP decreased and CPP and abdominal perfusion pressure (APP) increased significantly after administration of a 10 mg bolus of cisatracu-

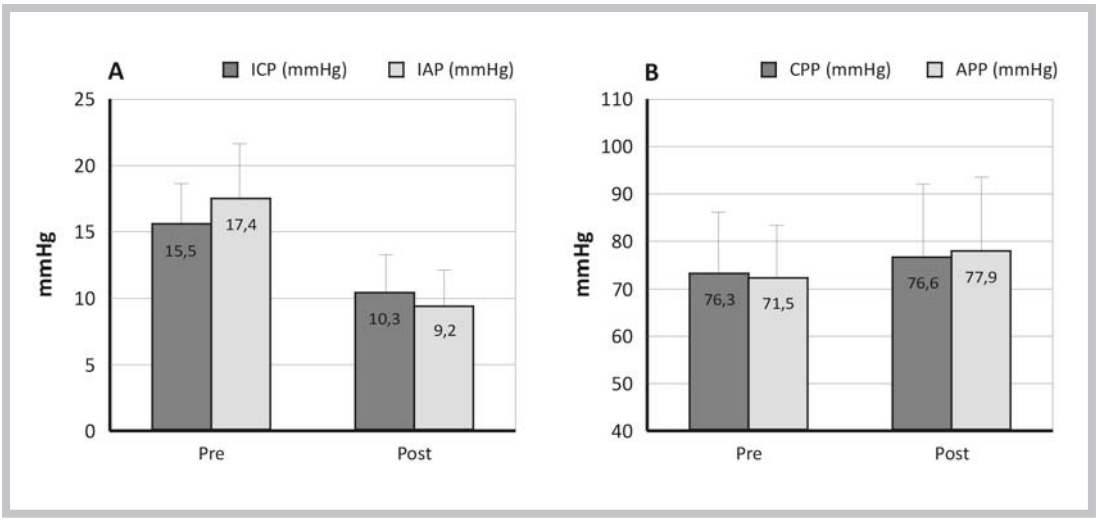

Figure 22.5. **Bar graphs showing IAP and ICP (A) and APP and CPP (B) before (pre) and after (post) neuromuscular blockade (10 mg cisatracurium) bolus administration. Modified from [20].**

APP = abdominal perfusion pressure
CPP = cerebral perfusion pressure
IAP = intraabdominal pressure
ICP = intracranial pressure

rium. Both IAP and ICP also dropped towards levels that are generally accepted to be safe. These results not only suggest that ICH in patients with IAH can be treated by administration of neuromuscular blockers, they also lend more support to the notion that there is a causal, rather than circumstantial, relationship between IAH and ICH. While neuromuscular blockers exert their effect on IAP through improved compliance of the abdominal wall, it is highly unlikely that they have any direct effect on ICP since the skull is a closed box lined by bony structures that are not responsive to neuromuscular blockers. Some other treatment options have been described, such as continuously applied negative abdominal pressure or nonsurgical abdominal decompression [44,57]. Both techniques will not be described here in detail. The findings of Deeren et al. suggest that ICH can be treated in the presence of IAH by reducing IAH [20]. The treatment of IAH as such lies beyond the scope of this text.

Preventive measures to avoid increase in ICP in patients who need to undergo abdominal surgery include the avoidance of induced pneumoperitoneum or if needed changing the type of insufflation gas [28,58].

22.5 Clinical Recommendations

Naturally, all patients with intracranial hypertension need to be treated according to all accepted international standards and guidelines regarding ICH in their specific clinical situation. Although no randomized clinical trials have been conducted on any aspect of treatment of IAH, let alone the specific situation of ICH combined with IAH, we feel it is possible to make a few clinical recommendations based on the results of the previously mentioned animal and human studies.

- IAP monitoring is essential for all traumatic or nontraumatic patients at risk for ICH or IAH (according to the risk factors published by the World Society for the Abdominal Compartment Syndrome) [59].
- The presence of increased IAP can be an additional “extracranial” cause of intracranial hypertension in patients with abdominal trauma without overt craniocerebral lesions.
- In all patients with ICH and in patients with VPS, preventive measures should be undertaken to avoid increase in IAP (the specific techniques involved lie outside the scope of this text).
- In all patients with IAH, a possible association with ICH should be considered and preventive measures should be taken (head of bed elevation, avoid constipation, avoid hypervolemia, hypernatremia and hyperthermia, etc.) [60].
- Neurologic status should be frequently monitored in patients with IAH
- Avoid hypervolemia in patients with IAH to prevent further increase in ICP. This may be difficult to achieve in a clinical setting, however, since volume management of these patients is complicated by the lack of reliable hemodynamic monitoring parameters. The use of routinely measured cardiac filling pressures is not reliable in the presence of IAH. This problem can be mediated by using (estimated) transmural filling pressures or by using volumetric hemodynamic monitoring parameters with PiCCO (Pulsion Medical Systems, Munich, Germany) [6].
- Consider using APP (abdominal perfusion pressure; APP = MAP – IAP) as a resuscitation target in patients where ICP is not available and CPP can not be used as a target.
- Provide adequate treatment for IAH, especially if ICH or a VPS is also present.
- Avoid laparoscopy in patients at risk for ICH. The pneumoperitoneum used for laparoscopy creates a situation analogous to experimental settings of IAH and ICH in

which detrimental effects on ICP have been observed. This is especially important in trauma patients with associated brain and abdominal injuries.

- In patients with refractory ICH, decompressive laparotomy may be considered as a rescue therapy in the presence of IAH [56]. Although promising results have been published, further research is necessary to appropriately define indications for this practice.

22.6 Conclusions

A close relationship between IAP and ICP has been observed in several animal and human studies. The clinical impact of this association is dependent on the baseline ICP and the compensatory reserve of the patient. Some studies have reported good results in treating refractory ICH by abdominal decompression in patients with concomitant IAH. Clinicians should be aware of the different interactions between intra-abdominal, intrathoracic and intracranial pressures and be able to intervene adequately in the complex situation of combined intra-abdominal and intracranial hypertension. Monitoring of IAP and ICP in risk patients is essential.

In this review we summarized the current state of knowledge on this fascinating topic and formulated some clinical recommendations for management. It remains clear, however, that the complex phenomenon of IAH is still not completely understood and recommendations may change in the future as more clinical research is conducted.

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23 Endocrinology of Acute Brain Injury

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° Drs. Sherlock and Cooper are authors of the II part (23.2)

23.1 Basic Anatomy, Physiology and Changes in Acute Brain Injuries

23.1.1 Introduction

Endocrine changes during critical illness have attracted growing attention from clinicians and the importance of an intact hypothalamo-pituitary-adrenal (HPA) axis for metabolic and immunological homeostasis during stress is now well recognized. Pituitary function is an essential regulator of a variety of adaptive responses that allow survival during critical states of any cause. Because the mechanisms regulating pituitary hormone secretion are mainly located in the hypothalamus and brainstem, acute brain injury might be expected to modify the neuroendocrine responses more than any other type of critical illness.

Traumatic brain injury (TBI) is a worldwide health problem, a major cause of disability and death among young adults, and a cause of neuroendocrine dysfunction. The prevalence of hypopituitarism in the chronic phase after TBI is nearly 25%, with growth hormone (GH) and follicle-stimulating hormone/luteinizing hormone (FSH/LH) deficiencies more common than other pituitary hormone deficiencies. Studies on acute TBI are too few to determine the prevalence of pituitary dysfunction; however, despite some controversial results, most show that all hormonal axes may be affected to different extent during the period of critical illness after TBI (Table 23.1).

Currently available published data are heterogeneous due to differences in patient selection, injury severity, study design, ethnicity of the population, methodology and timing of assessment. Moreover, earlier studies were not specifically designed to determine the frequency of acute hypopituitarism after TBI; instead, they tried to correlate neuroendocrine changes with the severity of head trauma. More recently, the type and frequency of pituitary hormone deficiencies have been investigated in more detail in brain-injured patients during the critical period (Table 23.1).

Nontraumatic brain injury includes ischemic stroke, intracerebral hemorrhage and aneurysmal subarachnoid hemorrhage. Although few studies to date have described acute neuroendocrine changes in nontraumatic brain-injured patients, what they do suggest is that there are substantial hormonal changes in nontraumatic brain injury as occur in TBI (Table 23.1).

Although the physiological changes during critical illness and the neuroendocrine sequelae of brain injury are slightly different in pediatric patients, the studies including adult patients (over age 14 years) are widely used as reference. Therefore, the management and treatment recommendations outlined in this chapter cannot be applied to pediatric patients.

Study	Number/Type of brain injury	Time to testing	Axes tested	Main findings
Fleischer, 1978	15/TBI	10-25 days	TH, GT	Central hypothyroidism and hypogonadism
King, 1981	6/TBI	72 h	TH, GT, ST, LT	No trends in hormone levels
Feibel, 1983	14/TBI, 9/ICH	12-36 h	HPA	High cortisol level despite high-dose dexamethasone
Hackl, 1991	21/TBI	Acute phase	TH, HPA, ST, LT	High cortisol and T4 levels; low prolactin level; impaired GH response to arginine stimulation
Della Corte, 1998	22/TBI	1-5 days, days 15 and 16	TH, HPA, ST, LT	Low cortisol (days 2-7); high IGF-I (days 7 and 15); exaggerated GH response to GHRH; low T3; normal TSH; prolactin unchanged
Cernak, 1999	31/TBI	7 days	TH, HPA, GT	High cortisol (days1+2); high TSH (days 1-3); low testosterone
Agha, 2004	50/TBI	Median 12 days	TH, HPA, ST, GT, LT	16% ACTH, 18% GH, 2% TSH and 80% with FSH/LH deficiencies; 52% with high prolactin
Dimopoulou, 2004	34/TBI	Median 21 days	TH, HPA, ST, GT, LT	53% of patients with abnormal result in at least 1 hormonal axis; cortisol hyporesponsiveness and hypogonadism most common abnormalities
Cohan, 2005	80/TBI	1-9 days	HPA	53% of patients with acute secondary adrenal insufficiency
Tanriverdi, 2006	52/TBI	24 h	TH, HPA, ST, GT, LT	10% ACTH, 20% GH, 6% TSH and 42% with FSH/LH deficiencies; 12% with high prolactin
Klose, 2007	46/TBI	0-12 days	TH, HPA, ST, GT, LT	76% of patients with central hypogonadism or hypothyroidism
Tanriverdi-Ulutabanca, 2007	104/TBI	24 h	TH, HPA, ST, GT, LT	9% ACTH, 20% GH, 4% TSH and 40% with FSH/LH deficiencies; 18% with high prolactin
Schwarz, 2003	22/IS	On admission, days 3, 5, 7, 9	TH, HPA, LT	Abnormally low plasma ACTH and cortisol levels; low TRH stimulation of plasma TSH and prolactin
Dimopoulou-Kouyialis, 2005	21/ ICH, 12/IS	72 h postextubation	TH, HPA, ST, GT	33% ACTH, 45% GH, 36% TSH and 39% with FSH/LH deficiencies
Tanriverdi-Dagli, 2007	22/SAH	24 h	TH, HPA, ST, GT, LT	23% ACTH, 23% GH, and 32% with FSH/LH deficiencies; 22% with high prolactin

Table 23.1. **Studies on anterior pituitary function in patients with traumatic brain injury (TBI) and nontraumatic brain injury (BI) during the period of critical illness.**

GT = gonadotropic
HPA = hypothalamo-pituitary-adrenal
ICH = intracerebral hemorrhage
IS = ischemic stroke
LT = lactotropic
SAH = aneurysmal subarachnoid hemorrhage
ST = somatotropic
TH = thyroid

The principal aims of this chapter are: 1) to review the anatomy of the HPA axis and the physiologic hormonal changes after acute stress; 2) to describe and differentiate adaptive and pathological hormonal changes after acute brain injury; 3) as informed by current evidence-based data, to define the diagnosis and management of pituitary hormone deficiencies, and adrenal insufficiency and diabetes insipidus in particular; and 4) to alert clinicians to situations in which interventions and treatment may be unnecessary.

23.1.2 Anatomy of the Hypothalamo-pituitary-adrenal Axis and Endocrinology of Normal Stress Response

Functional Anatomy of the Hypothalamo-pituitary-adrenal Axis

Figure 23.1 illustrates the functional anatomy of the HPA axis and Table 23.2 summarizes the physiologic effects of pituitary hormones.

The hypothalamus is formed by the anterior and inferior parts of the walls of the third ventricle. It is interrelated to the pituitary gland via the stalk, which is derived from the median eminence, a region of the floor of the third ventricle. The median eminence receives endings from the hypothalamic neurons that produce releasing and inhibiting factors which regulate the function of the anterior pituitary hormones. The pituitary gland weighs about 0.5 to 1 grams and is divided into an anterior (adenohypophysis) and a posterior lobe (neurohypophysis). It sits in the sella turcica immediately behind the sphenoid sinus.

Anterior pituitary hormones are regulated by hypothalamic releasing and inhibitory hormones and the negative feedback action of the target glandular hormones at both the pituitary and hypothalamic levels. Among the pituitary hormones, only prolactin secretion is increased in the absence of hypothalamic influence, since it is mainly under tonic suppression through prolactin inhibitory factor (dopamine) (Table 23.2).

All anterior pituitary hormones are secreted in a pulsatile fashion and tend to follow a diurnal pattern. Antidiuretic hormone (ADH; vasopressin) is produced by the supraoptic and paraventricular nuclei of hypothalamus and travels in the axons through the pituitary stalk to the posterior pituitary gland. The chief physiologic stimulus of ADH secretion is an increase in serum osmolality and a decrease in plasma volume, resulting in water reabsorption at the level of the distal and collecting ducts of the kidney. Small increments in serum osmolality >290 mOsm/kg induce prompt secretion of ADH.

The blood supply of the hypothalamus is provided by the small branches of the arteries of the circle of Willis. Arterial supply to the anterior pituitary gland, median eminence, and stalk is derived from the superior hypophyseal arteries. These arteries form the primary vascular plexus and converge into venules to form the long and short hypophyseal portal veins. These veins descend to the pars tuberalis and pars distalis of the anterior lobe, where a secondary plexus of sinusoidal capillaries is formed. The long portal veins pass through the diaphragma sella, thus being vulnerable to mechanical compression from brain or pituitary swelling or direct stalk injury. In contrast, the short portal veins originate below the diaphragma sella.

The anterior pituitary lobe, particularly its lateral aspects, receives its blood supply indirectly after passage through the median eminence and portal vessels. Any interruption of the portal vessels may result in anterior pituitary dysfunction. In contrast, the neurohypophysis receives its direct arterial blood supply from the inferior hypophyseal arteries.

	Hypothalamic regulatory hormone	Target gland/ secreted feedback hormone	Major physiologic effects of pituitary hormones	Clinical findings of pituitary hormone deficiency
Anterior pituitary hormone				
ACTH	CRH, ADH	Adrenal/cortisol	Several vital functions via cortisol such as vascular integrity and blood pressure maintenance, response to stress, immunomodulatory effects	Weight loss, weakness, dizziness, vomiting, circulatory collapse, fever, shock, hypoglycemia, hypotension, hyponatremia
GH	GHRH, somatostatin	Multiorgan/IGF-I from liver	Direct effects or via IGF-I. Promote growth, control protein, lipid and carbohydrate metabolism, control memory function	Adults: visceral obesity, fatigue, impairment of attention and memory, premature atherosclerosis
TSH	TRH	Thyroid/T4,T3	Control energy metabolism and vital functions	Tiredness, cold intolerance, dry skin, cognitive slowing, bradycardia, hypotension
Gonadotropins (FSH/LH)	GnRH	Ovary and testis/ E2, T	Control reproductive function	Infertility, decreased libido, deceased muscle mass, osteoporosis
Prolactin	PIF (Dopamine)	Breast	Milk production, immunomodulatory effects?	Agalactia
Posterior pituitary hormone				
ADH	-	Kidney	Conservation of body water and plasma osmolality	Polyuria, polydipsia, hypernatremia
Oxytocin	-	Breast and uterine	Stimulates milk ejection and uterine contraction	?

Table 23.2. Components of the hypothalamic-pituitary-adrenal axis: hormones secreted by the pituitary gland, hypothalamus and target organs. Major physiologic effects of pituitary hormones and the clinical findings of pituitary hormone deficiencies.

ACTH = adrenocorticotropin hormone
ADH = antidiuretic hormone
CRH = corticotropin-releasing hormone
E2 = estradiol
FSH = follicle-stimulating hormone
GH = growth hormone
GHRH = growth hormone-releasing hormone
GnRH = gonadotropin-releasing hormone
IGF = insulin-like growth factorLH = luteinizing hormone
PIF = prolactin release-inhibitory factor
T = testosterone
T3=triiodothyronine
T4 = thyroxine
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone

23.1.3 Endocrinology of Normal Stress Response

The physiologic response to stress involves the activation of the stress regulatory centres in the central nervous system, which, in turn, activates the HPA axis and the auto-

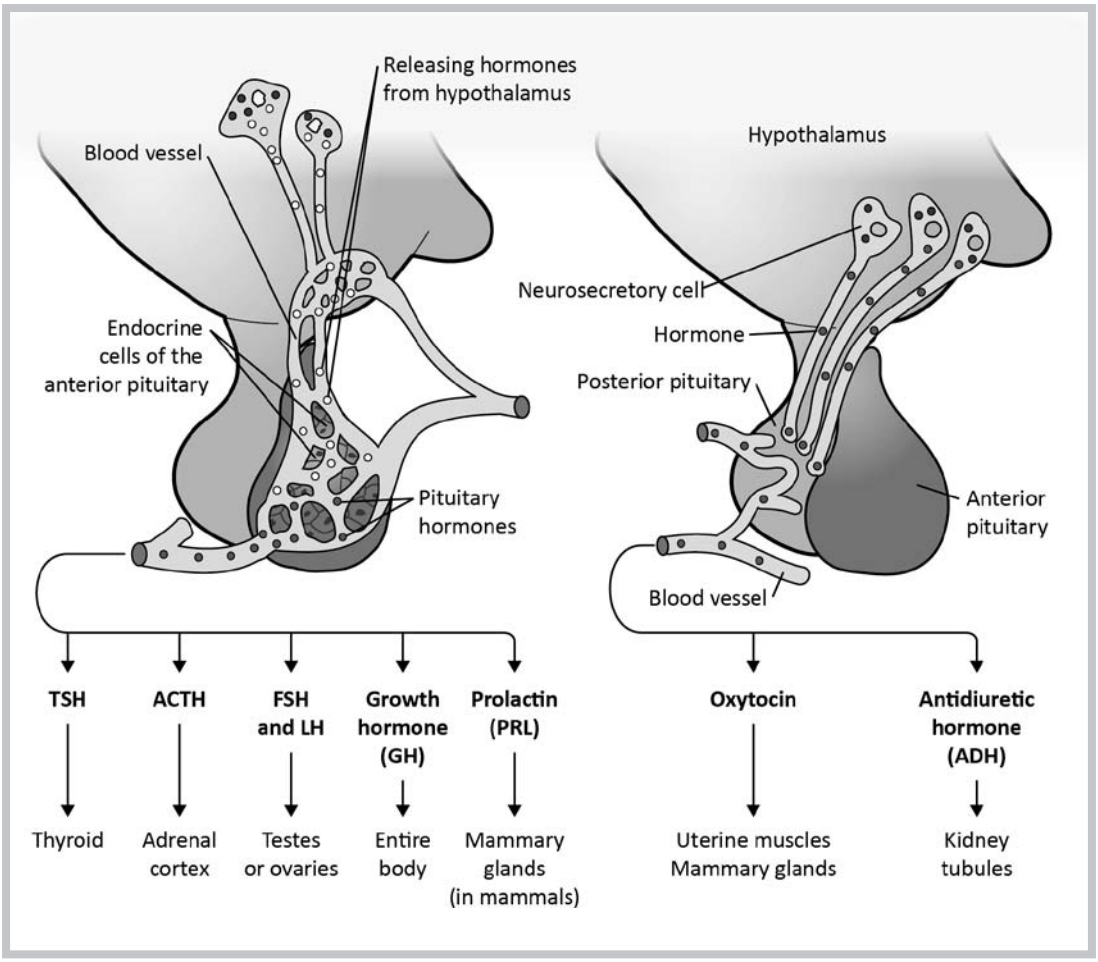

Figure 23.1. **Functional anatomy of the hypothalamic-pituitary-adrenal axis.**
* The target gland hormones also work as feedback hormones (negative feedback) at the hypothalamic and pituitary levels

nomic nervous system. The brain, hippocampus and amygdala in particular, are closely involved in the stress response. The stress response is predominantly regulated by the sympathoadrenal system, which includes the sympathetic nervous system and the adrenal medulla, and by the HPA axis. The stress system also influences other hypothalamo-pituitary axes (those controlling gonadal, thyroidal, and growth functions) and exerts complex effects on immune/inflammatory reactions. The end hormones of the neuroendocrine system, particularly glucocorticoids and catecholamines, act to maintain behavioural, cardiovascular, metabolic, and immune homeostasis during stress.

Severe acute stress, as occurs in critically ill patients, leads to strong activation of the HPA axis. Activation of the HPA axis involves increased secretion of corticotropin-releasing hormone (CRH) and antidiuretic hormone (ADH), also called arginine vasopressin, which enhances CRH activity. CRH stimulates the production of adrenocorticotropin hormone (ACTH), causing the adrenal cortex to produce more cortisol and dehydroepiandrosterone. Additionally, CRH activates the sympathoadrenal system at the same time. Following road accidents or during major surgery or sepsis, the human body can increase its glucocorticoid production by 5- to 10-fold. An adequate increase in glucocorticoid production is therefore crucial for survival and is required to cope with the severe stress during critical illness.

23.1.4 General Principles of Pituitary Hormone Changes During the Acute Phase of Brain Injury

Alterations in pituitary function during the acute phase of brain injury result in a temporary increase or decrease in pituitary hormone concentrations in blood circulation. Recent data revealed differences between alterations in hypothalamic-pituitary function in the acute phase (the first hours to days) and those in the prolonged phase or chronic phase (from 10 to 15 days beyond) of critical illness. During the acute phase, the secretory pattern of pituitary hormones inactivates anabolic target hormones. This response has been suggested to be beneficial and adaptive. In prolonged critical illness when the patient continues under intensive medical care, the pulsatile secretion of the anterior pituitary hormones generally decreases because of decreased hypothalamic stimulation, and this underlies the impaired anabolism in critical care patients.

The normal pituitary gland responds to acute brain injury with two sorts of secretory patterns: increased production of ACTH, prolactin (PRL) and growth hormone (GH), and decreased or unchanged production of gonadotropins (FSH and LH), and thyroid-stimulating hormone (TSH), associated with a decreased activity of their target organ. Changes in circulating hormone levels become apparent during the first hours or days after trauma and may persist for the duration of the acute critical illness. These hormonal alterations reflect the acute adaptive response to the injury and may be influenced by the type of injury and pharmacological therapy given to treat the critical illness (glucocorticoids, narcotic analgesics or dopaminergic agents). The basic philosophy of the neuroendocrine response after acute brain injury may be summarized as follows: these adaptations are initially protective for the human body; however, if they are inadequate, as in pituitary dysfunction or excessive, they may be harmful and cause endocrine, metabolic and immune disturbances. Therefore, the most important target for intensive care should be to differentiate adaptive response from pathological hormonal changes and to avoid unnecessary interventions.

23.1.5 Anterior Pituitary Dysfunction in the Acute Phase of Brain Injury

The Hypothalamo-pituitary-adrenal Axis

The HPA axis status is the most extensively investigated endocrine function in critically ill brain-injured patients (Table 23.1). Patients normally present with increased cortisol levels. These changes may persist up to 10 to 15 days after brain injury and are essential for maintaining vascular tone and endothelial integrity. Initially, cortisol increase is mediated by ACTH. Later, other substances, mainly cytokines and catecholamines, act as mediators. The diurnal variation of cortisol may be preserved or abolished.

TBI studies investigating the association between cortisol dynamics, severity of TBI (assessed by the Glasgow Coma Scale, GCS) and outcome prediction have yielded controversial results. Some investigators concluded that higher cortisol values are associated with more severe head trauma and with a worse clinical outcome, whereas others found lower cortisol values in the most severely injured patients with brainstem dysfunction or in brain-dead victims. Still other studies found no correlations between baseline cortisol and TBI severity. Acute adrenal failure after TBI may occur as a consequence of ischemia or direct trauma to components of the HPA axis, a secondary form of adrenal insufficiency. In addition, primary failure of the adrenal gland due to a systemic inflammatory response after the release of pro-inflammatory mediators may complicate recovery from

TBI. The only difference between primary adrenal failure and secondary adrenal failure is the presence of mineralocorticoid deficiency. However, because the common clinical problem is due to hypocortisolism, it is not practical to differentiate primary from secondary adrenal failure in routine clinical management, commonly called adrenal failure. Throughout the text, HPA axis insufficiency and adrenal failure are used interchangeably. According to clinical studies, the incidence of adrenal failure after acute TBI is 10-50% (Table 23.1). The incidence of HPA axis insufficiency during the acute phase is generally 20-25%, which signals a high risk. Although the data are heterogeneous, critically ill patients with nontraumatic brain injury may also experience adrenal failure. Recent studies suggest that around 25-30% of patients with ischemic stroke or aneurysmal subarachnoid hemorrhage have HPA axis insufficiency during the acute phase (Table 23.1). Current evidence suggests that HPA axis insufficiency immediately after brain injury is associated with poor neurological outcome, greater need for vasoactive drug therapy, hyponatremia, relative or absolute hypocalcemia, hemodynamic instability, and rapidly progressive hypotension, all of which may increase the risk of death. Therefore, such clinical signs/symptoms should prompt their urgent investigation as a possible cause of adrenal insufficiency during acute care.

Algorithm for Diagnostic Testing and Management

The adequacy of cortisol secretion in critical illness, including brain injury, remains a diagnostic challenge because the normal range for baseline or stimulated cortisol levels in critically ill patients is inadequately defined. Recent published guidelines recommend acute anterior pituitary hormone evaluation in all patients with moderate-to-severe TBI, but those with documented baseline skull fracture, increased intracranial pressure or diabetes insipidus require specific attention. There are no defined selection criteria for patients with nontraumatic brain injury; however, in all brain-injured patients the best selection criteria for endocrine evaluation, particularly of the HPA axis, are clinical findings (Table 23.2) and high clinician suspicion.

Serum basal cortisol measurement is the primary test to evaluate the HPA axis. Although a morning cortisol test is recommended by some authors, stress will decrease the normal diurnal variation in cortisol release, making random values acceptable. Cortisol will be low in most cases of both primary and secondary adrenal failure. The actual concentration that defines a low value is somewhat controversial because of the expected increase in cortisol in response to brain-injury-induced stress. The amount of cortisol required cannot be predicted from the severity of injury and it may change as the clinical status changes. Although some authors suggest random basal cortisol levels <25 μg/dl or 36 μg/dl, a cortisol concentration <15 μg/dl (410 nmol/l) are acceptable as a diagnostic value for adrenal insufficiency in critically ill brain-injured patients. In patients lower values and clinical findings consistent with adrenal insufficiency, there is no need for further stimulation testing in routine clinical practice.

ACTH may also be directly measured to differentiate primary from secondary adrenal failure. As mentioned, differentiation between primary and secondary adrenal failure is not warranted in critically ill brain-injured patients in routine clinical practice. Additionally, because ACTH measurement is not routinely available in most hospital laboratories, urgent measurement is not recommended.

In patients with basal cortisol levels between 15 and 25 μg/dl and suspicious clinical findings, then ACTH stimulation testing is warranted. Standard-dose ACTH stimulation test (after blood sampling for baseline cortisol measurement, 250 μg ACTH is administered intravenously and cortisol measured at 30 and/or 60 minutes after stimulation) is routinely used in the diagnosis of primary or secondary adrenal insufficiency. In normal

conditions, peak cortisol response after ACTH stimulation >20 μg/dl is defined as adequate cortisol response. In critically ill brain-injured patients, however, the best cut-off value after standard ACTH stimulation test is yet to be defined. The recommended value of 25 μg/dl (690 nmol/l) seems more realistic as a cut-off higher than that used in an outpatient setting because the peaks achieved during this test are, on average, higher than in patients without stress or severe illness.

In some studies, low-dose (1 μg) ACTH stimulation was used for the diagnosis of adrenal insufficiency during acute brain injury. More sensitive than standard testing, its main advantage in mild HPA axis insufficiency is early diagnosis, because the higher pharmacological amount used in standard-dose ACTH testing may allow a partially dysfunctional gland to release a sufficient amount of hormone to appear falsely normal. However, low-dose ACTH testing is not routinely used or recommended in critically ill brain-injured patients because there is no diagnostic cut off value for intensive care unit settings. Low-

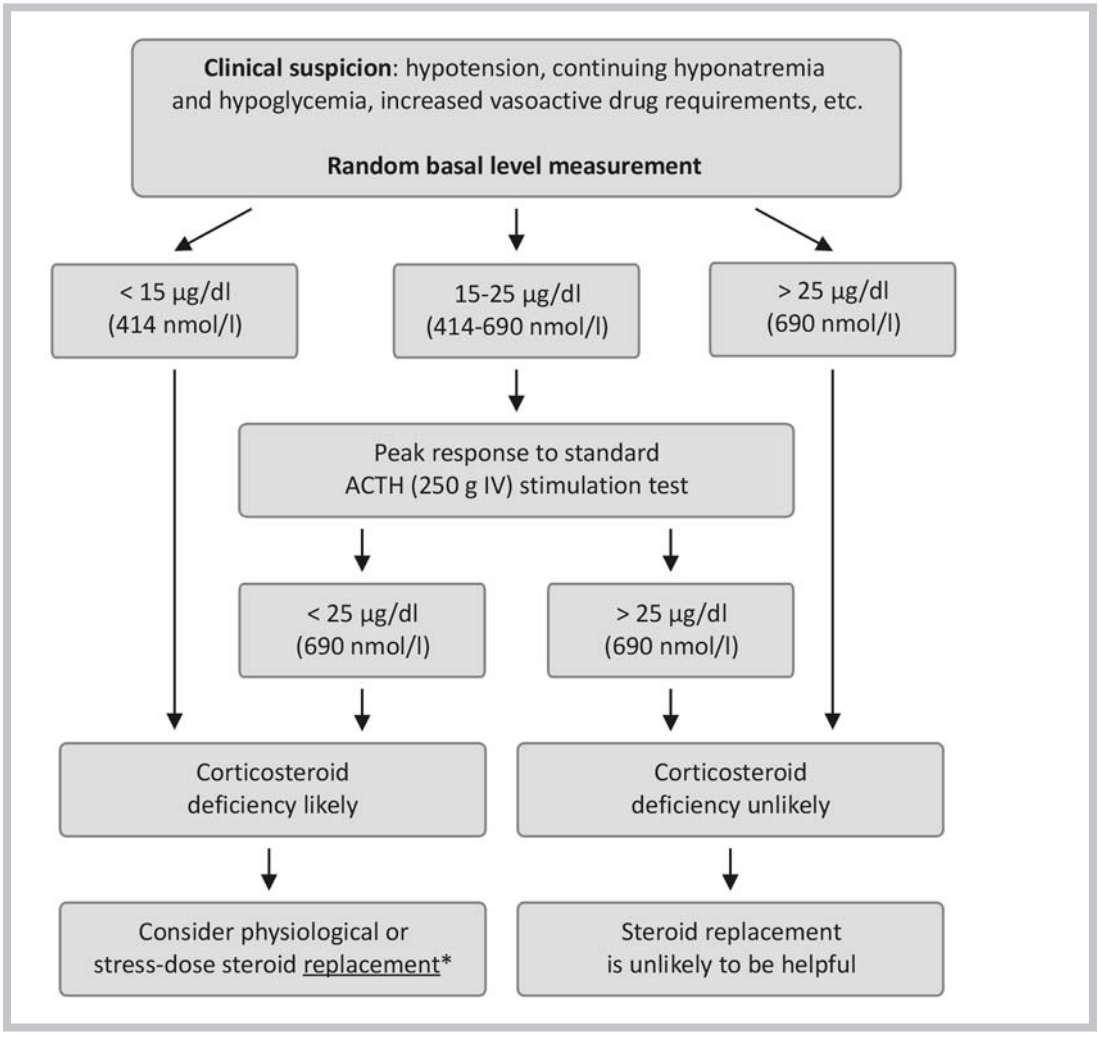

Figure 23.2. **Algorithm for the management of adrenal insufficiency in brain-injured patients in the acute phase.**

*It is proved that a pharmacological dose of corticosteroid replacement is not useful and may be harmful. In stable patients, physiological dose (hydrocortisone 10 mg IV every 8 h), in unstable patients with severe clinical findings, stress dose (hydrocortisone 50-100 mg IV every 8 h or an IV infusion of about 15 mg/h) steroid replacement is recommended

dose ACTH testing may gain a place in the workup of HPA axis evaluation in critically ill patients and may be used routinely in the near future.

Because serum cortisol concentrations may vary, the magnitude of serum cortisol response to ACTH stimulation was also considered critical in the diagnosis of adrenal failure and the identification of a patient's status as a responder (change from baseline cortisol of at least 9 μg/dl) or non-responder to stimulation. But a recent study showed no positive correlation between this criterion and survival. Current guidelines recommend this classification only in septic shock. Therefore, we do not recommend using this criterion in the diagnosis of adrenal insufficiency in patients with acute brain injury.

Finally, cortisol is measured in the blood as both an unbound ("free") form, which is the biologically active hormone, and as cortisol bound with corticosteroid-binding globulin (CBG). CBG is commonly low in critical illness/injury, especially when serum albumin is <2.5 g/dl and it may be one of the causes of an apparent low cortisol serum concentration. Measurement of free cortisol has been suggested as a more accurate assessment of adrenal output. Testing methods for CBG and free cortisol are rarely available, however. Several research groups have recently investigated the use of salivary cortisol concentration as a surrogate marker for serum free cortisol levels. Salivary cortisol measurement is simple to obtain and easy to measure in most laboratories. The data on the utility of salivary cortisol in critically ill brain-injured patients are currently insufficient.

The diagnosis and the management of adrenal insufficiency are briefly summarized in Figure 23.2.

Treatment

Large scale clinical studies such as the Corticosteroid Randomization After Significant Head Injury (CRASH) trial and literature reviews have indicated that routine corticosteroid administration at high doses or pharmacological doses (30 mg/kg methylprednisolone) to all patients with moderate/severe TBI is not indicated or may be harmful.

It is generally agreed, however, that therapy should be provided for patients with confirmed hypoadrenalism in whom clinical circumstances, such as hypotension, hyponatremia and hypoglycemia, warrant intervention. The steroid replacement dose should be titrated based on the critically ill patient's clinical status and requirements. In patients with adrenal insufficiency as determined according to previously discussed criteria (Fig. 23.2) and stable, replacement with hydrocortisone (10 mg IV every 8 h) could be sufficient initially. When severe stress is present and the patient is not stable 50-100 mg of hydrocortisone IV every 8 h or an IV infusion of about 15 mg/h is recommended (Fig. 23.2). Dexamethasone or methylprednisolone at equivalent hydrocortisone doses could be used as alternatives. It is important to note that dexamethasone does not have any mineralocorticoid activity. Addition of a mineralocorticoid is not usually required, but may be considered when hyponatremia is significant and the patient has proven primary adrenal failure.

The optimal duration of corticosteroid supplementation is unknown, but it should be continued until the patient's clinical situation has improved and when there is no need for vasopressor therapy.

The Thyroid Axis

Several changes in circulating thyroid hormone concentrations occur in acute critical illnesses including brain injury. The conversion of T4 (thyroxine) to T3 (triiodothyronine) in peripheral tissues is dramatically reduced and an altered form of T3, reverse T3 (rT3), is generated. Serum measurement will characteristically show a low T3; normal or low T4 and normal TSH have been synonymously referenced as the euthyroid-sick syndrome or low T3 and/or low T4 syndrome. These changes appear immediately after brain injury,

can persist for at least 2 weeks and may normalize after the acute illness has resolved. True "central" hypothyroidism occurs in 4 to 15% of patients following brain injury. The presence of low free T4 and low TSH level is diagnostic for central or secondary hypothyroidism; except for academic purposes, stimulation testing for diagnosis is not warranted in clinical practice. Impaired thyroid axis, however, should be confirmed in the absence of other medications known to reduce TSH production/release (e.g., dopamine, high-dose glucocorticoids). Although the evidence is not strong, some studies demonstrated that central hypothyroidism was associated with prolonged coma following TBI, poor neurological outcome, and higher mortality as compared to patients in whom TSH did respond to TRH stimulation.

Thyroid hormone replacement during the acute treatment of TBI or nontraumatic brain injury has not been reported previously. Prospective studies demonstrated that TSH deficiency (central hypothyroidism) is generally transient and that most of the changes resolve after 3 months. In critically ill burn or medical patients, acute thyroid hormone replacement therapy was not shown to produce short-term improvement.

Therefore, based on current evidence we do not recommend thyroid hormone replacement in the acute phase of brain injury. If TSH deficiency persists for more than 2 weeks and the clinical findings are compatible with hypothyroidism, the patient could be treated after steroid replacement if adrenal insufficiency is present.

The Somatotropic Axis

A reduced GH response to GHRH or other stimulation soon after severe TBI occurs in approximately 18% of patients. Early after TBI, basal plasma GH is within normal limits or high, and insulin-like growth factor (IGF-I) is normal or low. Peripheral resistance to GH action (probably due to decreased GH-receptor expression), manifested by high basal GH concentrations with low IGF-I, has been reported in patients with critical illness including brain injury. This seems to be an adaptive response because GH is an anabolic hormone: in the acute phase of critical illness, catabolism is the initial response to provide fuel for vital organs. Based on basal hormone levels and dynamic tests, current studies (Table 23.1) demonstrate that 20 to 50% of brain-injured patients have GH deficiency. Prospective data confirm that most patients with GH deficiency during acute phase recover within 3 to 12 months after brain injury.

GH and IGF-I levels in the acute phase are not generally correlated with trauma severity. Some studies investigating the correlation between GH response to provocative tests and prognosis or clinical outcome in the early post-TBI period have reported conflicting results.

To date, no studies have investigated the effects of GH replacement therapy in the acute phase of brain injury in patients with GH deficiency. In a recent randomized, prospective, double blind, placebo controlled study by Hatton et al., IGF-I and GH therapy within 72 hours of TBI produced sustained improvement in metabolic and nutritional endpoints. But the GH status of the TBI patients in this study was not defined. A large multicenter study by Takala et al. showed that the administration of high doses of GH in critically ill patients doubled the mortality instead of improving the outcome.

Therefore, GH supplementation is not currently recommended during the acute phase of brain injury. Future confirmatory data are needed to determine the effects of physiological dose GH replacement in GH-deficient patients with prolonged critical illness at the catabolic state.

The Gonadotropic-lactotropic Axis

After brain injury, and after TBI in particular, a substantial decrease in testosterone and low gonadotropin (FSH/LH) levels develop shortly after injury and deteriorate over the

ensuing days. The magnitude of the decline in testosterone was correlated with head trauma severity in some studies but not in others. The pituitary-ovarian axis is comparably depressed.
The incidence of hypogonadism in critically ill TBI patients varies between 20 and 80%. In most patients, hypogonadism improves within 3-6 months after injury. The current data suggest that these changes in the gonadotropic axis in the acute phase of brain injury are adaptive and transient; therefore, gonadotropin replacement is not recommended in the acute phase.
Prolactin (PRL) may increase, remain normal, or decrease in acute brain injury. Baseline PRL is negatively correlated with head trauma severity, as expressed by the Glasgow Coma Scale score. Hyperprolactinemia is reported in 20 to 50% of patients with acute brain injury. Although the mechanism and the effects are not known, this response is thought to be adaptive.

23.1.6 Posterior Pituitary Dysfunction in the Acute Phase of Brain Injury

Inadequate ADH secretion due to posterior pituitary dysfunction results in central diabetes insipidus (DI). DI following TBI is less common than anterior lobe injury, occurring acutely in around 20-25% of patients. Most patients recover from DI, but rarely (6-7%) persistent DI may occur. While DI is a well-recognized complication of TBI, the data one patients with other causes of brain injury are scarce.
The primary symptoms of DI are thirst and polyuria in conscious patients. In critically ill patients, the main clinical findings are increased daily urinary volume (>3 litres) and hypernatremia. If volume is significantly reduced, hypernatremia may cause weakness, altered mental status, seizures and coma. The diagnosis of DI in brain-injured patients with clinical suspicion is confirmed by measuring plasma and urine osmolality. The urine is inappropriately diluted for the degree of serum osmolality, usually urine osmolality < 200 mOsm/kg and specific gravity < 1005 with plasma osmolalite >295 mOsm/kg. The most commonly used agent to treat central DI is the ADH analogue desmopressin, which has a longer half-life and almost no pressor activity. It may be administered intranasally at a dose of 5-20 µg once or twice daily. In critically ill patients, desmopressin is more commonly given IV, IM or subcutaneously (2-4 µg once or twice daily), which is 5-10 times more potent than via intranasal route. The effectiveness of the treatment is established by measuring urinary volume and plasma sodium concentration.
Despite the hypernatremic dehydration induced by ADH deficiency, hyponatremia also develops in many patients during the acute period of brain injury due to an inappropriate release of ADH (syndrome of inappropriate antidiuretic hormone, [SIADH]). The reported prevalence of this abnormality is 2.3-36%. As a rule, TBI-induced SIADH is transient.
Symptoms of SIADH vary depending on the degree of hyponatremia (serum sodium levels < 130 mEq/l and < 125 mEq/l in severe cases) and rapidity at which it develops. SIADH is a diagnosis of exclusion of other hyponatremia causes. Renal, adrenal and thyroid function must be normal to establish the diagnosis. In BI patients with HPA axis dysfunction, SIADH can only be diagnosed after appropriate corticosteroid replacement. A low (280 mOsm/kg) serum osmolality is consistent with SIADH. An inappropriately elevated urine osmolality (>100 mOsm/kg) and urine sodium (>40 mEq/l) concentration are consistent with SIADH. Most cases are self-limiting and the cornerstone treatment is fluid restriction. Early diagnosis and treatment of posterior pituitary dysfunction after brain injury is important for maintaining water homeostasis and electrolyte balance in critically ill patients.

23.1.7 Pathophysiology of Pituitary Dysfunction Following Acute Brain Injury and Predictive Value of Hormonal Changes

There are several mechanisms underlying hypothalamo-pituitary dysfunction due to TBI including hypoxic insult or direct mechanical injury to the hypothalamus, the pituitary stalk, or the pituitary gland; compression from hemorrhage, edema, or increased intracranial pressure; and vascular injury to the hypothalamus or the pituitary gland. Autopsy findings in patients who died of TBI showed evidence of injury to the hypothalamus, the pituitary gland or the pituitary stalk in 26-86% of cases. Rotational acceleration-deceleration can cause shearing injury of axons, as commonly seen in the midline structures of the brain. This may represent a possible mechanism of hypothalamic pituitary dysfunction after TBI. In nontraumatic brain injury, evidence for the possible mechanisms of pituitary dysfunction is lacking; however, vascular injury seems to be the most possible cause in the pathogenesis of nontraumatic brain injury. The exact mechanisms of acute hormonal response and pituitary dysfunction due to brain injury remain to be elucidated and further clinical and experimental studies are warranted.
Recent prospective studies in patients with TBI and SAH revealed that most of the acute phase hormonal changes are transient and do not predict pituitary dysfunction at 6 months and 12 months after brain injury. Current guideline recommendations advise evaluation of pituitary function in all TBI patients with moderate and severe injury at 3 to 6 months and again at 12 months after trauma, regardless of acute hormone deficiencies.

23.1.8 Conclusions and Key Concepts

- Alterations in pituitary function may occur during the acute phase of brain injury and most of these hormonal changes are adaptive responses to acute stress.
- These adaptations are initially protective for the human body; however, if inadequate as in pituitary dysfunction or excessive, they may damage health.
- Differentiating adaptive responses from pathological hormonal changes and avoiding unnecessary interventions are important goals.
- Except for clinically significant adrenal insufficiency and DI, other endocrine alterations do not seem to require any therapeutic intervention in brain-injured patients during the acute phase.
- Serum basal cortisol measurement is the primary test to evaluate the HPA axis. Clinical findings consistent with a cortisol concentration < 15 µg/dl (410 nmol/l) are accepted as a diagnostic value for adrenal insufficiency.
- In stable patients, physiological dose replacement with hydrocortisone (10 mg IV every 8 h) could be sufficient. When severe stress is present and the patient is not stable, 50-100 mg of stress-dose hydrocortisone IV every 8 h or an IV infusion of about 15 mg/h is recommended. Steroid replacement is not recommended unless adrenal dysfunction is confirmed. The pharmacological steroid dose should be avoided in all brain-injured patients.
- The main clinical findings of DI in critically ill patients are increased daily urinary volume (>3 litres) and hypernatremia.
- For the diagnosis of DI, urine is inappropriately diluted for the degree of serum osmolality, usually urine osmolality < 200 mOsm/kg and specific gravity < 1005 with plasma osmolalite >295 mOsm/kg.
- The most commonly used agent to treat central DI is desmopressin; it may be administered intranasally at a dose of 5-20 µg once or twice daily. In critically ill patients,

desmopressin is more commonly given IV, IM or subcutaneously (2-4 μg once or twice daily), which is 5-10 times more potent than via the intranasal route.
- Most acute phase hormonal changes are transient and do not predict pituitary dysfunction at 6 months and 12 months after brain injury.

23.2 Endocrinology of Acute Brain Injury Secondary to Traumatic Brain Injury (TBI) and Subarachnoid Hemorrhage (SAH)

23.2.1 Introduction

The hypothalamus and anterior pituitary gland are critical in the higher co-ordination of a number of hormonal axes including the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-thyroid (HPThyroid), hypothalamic-pituitary-gonadal axis (HPGonadal), the synthesis and secretion of prolactin and growth hormone. The posterior pituitary along with the osmoregulatory centre in the supraoptic and paraventricular nuclei of the anterior hypothalamus controls salt and water balance via the hormone arginine vasopressin (AVP, also known as anti-diuretic hormone) and the thirst response.
HPaxis dysfunction (hypopituitarism) can occur due to a spectrum of pathologies including pituitary and sellar tumours and their treatment, cranial radiotherapy, vascular insults (SAH, pituitary apoplexy and hypotensive pituitary infarct), TBI, inflammatory, infiltrative and autoimmune disorders. These insults can lead to defects in one or more of the HPaxes.
The recognition of HPaxis dysfunction is important as it is associated with increased morbidity and mortality in the acute (particularly due to ACTH deficiency) and chronic phase. Tomlinson et al. have reported a Standardized Mortality Ratio of 1.87 in a cohort of 1,014 patients with longstanding, treated hypopituitarism so one might hypothesize that the mortality may be higher in an undiagnosed cohort.

23.2.2 Hypopituitarism in Acute Cerebral Injury

In recent years two important new causes of hypopituitarism have been recognized and widely studied, TBI and SAH. Over the past seven years ten studies of endocrine function have been performed in the chronic phase after TBI which included a total of 749 patients and revealed a prevalence rate of 35% for some degree of HPaxis dysfunction. Five studies have systematically assessed HPaxis function in the recovery phase following subarachnoid hemorrhage in a total of 122 patients and have reported some degree of HPaxis dysfunction in 48%.
The incidence of TBI is between 80 and 235 cases per 100,000 and the incidence of SAH is 10 cases per 100,000, however South America may have even higher incidences, particularly of TBI. Therefore when combining these figures, conservatively, it would lead to an incidence of 31 cases of HPaxis dysfunction attributable to TBI and SAH per 100,000 population per year. Therefore a large number of patients with HPaxis dysfunction may remain undiagnosed. This failure to diagnose hypopituitarism and the associated increased morbidity also has economic consequences; in the USA it is estimated that five million persons are living with the sequelae of TBI at a lifetime cost of $600,000 to $1.9 million per person.

HPaxis dysfunction may occur very early after acute cerebral injury or may take weeks and months to develop. At the early stage the most important deficiency not to miss is that of the HPA axis where the resulting hypoadrenalism can be fatal, and deficiency of AVP that results in diabetes insipidus and severe hypernatremia. At a later stage deficiency of any and multiple anterior pituitary hormones can occur, a problem that can be difficult to recognize and may only be identified with specific endocrine testing. These axes will be discussed in turn focussing on the prevalence and consequences of dysfunction both early and later in the course of acute cerebral injury.

23.2.3 The Hypothalamic-pituitary-adrenal Axis

During stress there is normally a dramatic activation of the HPA axis leading to increased cortisol levels in the circulation. This increase in cortisol is primarily due to increased production of corticotrophin-releasing hormone (CRH) from the hypothalamus which in turn causes the release of adrenocorticotrophin (ACTH) from the anterior pituitary. ACTH acutely stimulates the adrenal to synthesize and release cortisol but there is also a trophic action on the adrenal cortex. This increases the future capacity of the adrenal to release cortisol in response to ACTH. Outpatient testing for adrenal insufficiency is predominantly by ACTH stimulation tests (short Synacthen/Cosyntropin tests). In conditions that directly damage the adrenal, the response to this test is poor due to direct impairment of cortisol production. In conditions where ACTH production is impaired, the loss of the trophic action of ACTH leads to an atrophied adrenal cortex that responds poorly to an acute ACTH stimulation.

After acute cerebral injury the appropriate response of the HPA axis is to substantially increase cortisol production. Unfortunately there are a number of factors that can impair this response. Direct damage to either the hypothalamus or pituitary can impair ACTH release. Anesthetics can impair these responses even if the pathways are anatomically intact. The use of etomidate as an induction agent during anesthesia has been linked to impaired responsiveness of the adrenal cortex to ACTH. This effect is marked when etomidate use is prolonged and was associated with a dramatic increase in mortality of critically ill patients. Fortunately etomidate use is of less importance when used for short duration in patients without severe sepsis.

The adequacy of the HPA response to acute cerebral injury is also very difficult to test. Most importantly outpatient tests for adrenal insufficiency are dangerously unreliable in this setting. Acute ACTH deficiency is the likely cause of adrenal insufficiency in this setting but the adrenal gland will still maintain responsiveness to exogenous ACTH. Thus an increase or a high peak value on an ACTH stimulation test will be falsely reassuring. Other tests that examine the whole of the axis such as the insulin tolerance test (ITT) or metyrapone test are contraindicated in the setting of acute cerebral injury. The only reliable measure is thus a basal measure of serum cortisol. Even this is a complex measure in critical illness. The rise in cortisol level with trauma is roughly proportional to the underlying severity of injury but there is no easy way of determining in an individual whether a serum cortisol is appropriate. Most of the cortisol in the circulation is heavily bound to corticosteroid-binding globulin (CBG), with only a small percentage available as “free” hormone. During severe illness however the synthesis of CBG decreases and its clearance increases. This leads to an increase in the proportion of “free” cortisol. Currently we cannot reliably measure “free” cortisol in an individual patient. There are also changes in the tissue binding of cortisol during severe illness, especially sepsis that might reduce the effectiveness of cortisol in counteracting inflammatory pathways. This has led to the concept of relative or functional adrenal insufficiency where the level of cortisol,

although normal or high by some measures, is still inappropriately low for the clinical situation. No test has been developed to date that can accurately diagnose these states. As mentioned before, currently the only reliable test of the HPA axis in the first few weeks after acute cerebral injury is a serum cortisol, ideally taken early in the morning (e.g. 0800). A level of less than 400 nmol/l (15 µg/dl) in a sick patient strongly indicates HPA axis dysfunction. A level in excess of 700 nmol/l (25 µg/dl) indicates that HPA axis dysfunction is unlikely. Between these two values there will be uncertainty and the decision whether to treat with replacement glucocorticoids will depend on the severity of injury in association with any potential clinical features of adrenal insufficiency. In patients where deficiency is likely, the standard procedure is to use hydrocortisone at a dose of 50 mg tds until the patient's condition is improving. The hydrocortisone dose can then be gradually reduced down to a replacement of 20 mg am and 10 mg pm until the patient becomes fit for endocrine testing (e.g. ACTH stimulation test), to determine whether this treatment is needed long-term.

HPA axis dysfunction has been reported to occur acutely in ~ 12% of patients with TBI. In about 50% of patients this subsequently improves. Some patients without preexisting dysfunction subsequently develop HPA dysfunction and thus the prevalence of abnormalities at 12 months is again about 12%. Patients with delayed onset adrenal dysfunction can be identified by standard outpatient tests for adrenal insufficiency such as the ACTH stimulation test or ITT.

23.2.4 Hypothalamic-pituitary-gonadal Axis

In the healthy individual, the gonadal axis is controlled by pulsatile release of gonadotrophin releasing hormone (GnRH) from the hypothalamus, which in turn stimulates secretion of the gonadotrophins luteinizing hormone (LH) and follicular stimulating hormone (FSH) from the pituitary, which acts on the testes/ovary to control germ cell synthesis and sex hormone secretion.

During critical illness, in males, testosterone levels decrease significantly in the acute phase (first few days), despite maintenance of circulating gonadotrophin concentrations. It has been postulated that high levels of cytokines seen in critical illness are responsible, and that the acute reduction in testosterone levels reduces unnecessary anabolism, thus possibly conferring a survival advantage.

If the patient survives the acute phase, but does not immediately recover, a period of prolonged critical illness may follow, during which a decrease in gonadotrophin secretion superimposes itself upon the pre-existing testosterone deficiency. This produces a state of central and peripheral impairment of the gonadal axis. Although hyperprolactinemia can occur during critical illness as a stress response and hyperprolactinemia can cause hypogonadotrophic hypogonadism, the high prolactin levels seen in critical illness do not appear to contribute significantly to depressed gonadotrophins in males.

The changes in sex steroids that occur with critical illness in women have not been as extensively studied, and studies are in general confined to post-menopausal populations.

After recovering from critical illness, gonadotrophins and sex steroid levels typically normalize. However if the initial insult was one that may have compromised the hypothalamic-pituitary gonadal axis, such as TBI or SAH, chronic deficiencies may occur (HPGonadal axis dysfunction develops in 12.5% and 5.9% of patients respectively). This can be diagnosed in men as a low testosterone with inappropriately low or normal gonadotrophins and in women it often presents as amenorrhea and low estrogen with inappropriately low or normal gonadotrophins. Thus far, attempts at restoring the gonadal axis with agents such as GnRH have produced a partial and transient response only. Addi-

tionally, it remains to be seen whether successful reactivation of this axis will have beneficial or deleterious effects for the acutely critically ill patient and therefore it is not recommended at present.

23.2.5 Thyroid Axis

Thyroid hormone synthesis is tightly regulated by a negative feedback loop including thyrotrophin releasing hormone (TRH) from the hypothalamus and thyrotrophin (TSH) from the anterior pituitary. TSH stimulates the production and release of T4 and T3 from the thyroid gland.

There are multiple changes which occur within the HPThyroid axis in critical illness, these changes described below give rise to "sick euthyroid syndrome". Within two hours of the initial insult during critical illness, circulating T3 levels decrease, and rT3 levels increase. Two mechanisms underpin the increase in rT3; a marked reduction in deiodinase 1 activity (leading to decreased clearance of rT3) and an increase in deiodinase 3 activity (increasing conversion of T3 to rT3).

Given prolonged states of critical illness, a central impairment superimposes itself upon these peripheral changes, manifesting as a significant and sustained reduction in pulsatile TSH secretion and T4/T3 levels. With recovery of the thyroid axis, transient increases in TSH are often seen. To date no trials have demonstrated significant improvements in mortality following any form of thyroid hormone replacement therapy, and therefore its use is not recommended in this scenario. For this reason thyroid function tests should be avoided in the critical care setting unless specific signs and symptoms of thyrotoxicosis or hypothyroidism are present as they can often be misleading and may lead to inappropriate therapy.

As before, in critical care following TBI or SAH there is a specific neuroendocrine insult and these patients are at increased risk of developing longstanding secondary hypothyroidism. Deficiencies in TSH have been observed in 4.1% of patients in the recovery phase following TBI, and 5.9% following SAH.

23.2.6 Growth Hormone/IGF-I Axis

GH is a polypeptide released from the anterior pituitary whose main physiological control is by growth hormone releasing hormone (stimulatory) and somatostatin (inhibitory) along with inputs from other hormones, peptides and cytokines. Insulin growth factor-I is synthesised in response to GH predominantly in the liver but also in the kidney, muscle and bone/cartilage. Several changes occur in GH and IGF-I concentrations in critical illness. In post operative patients GH concentrations are increased, whereas they can be normal in sepsis patients, and normal to low, with low secretory pulse amplitude in polytrauma patients. As mentioned before, the question whether GH therapy in an ICU setting will improve outcome was addressed by Takala et al. This study investigated the effect of high dose GH (0.07-0.13mg/kg/ body weight) in patients who had been in ICU for 5-7 days and were expected to stay in ICU for 10 days or more. This study reported a negative effect of high dose GH in this patient population with an increased length of ICU stay and in-hospital mortality rate (39-44% in patients who received GH compared to18-20% in the patients who received placebo). The authors concluded that in patients with prolonged critical illness, high doses of GH are associated with increased morbidity and mortality. There have been a number of criticisms since regarding this study particularly related to the high dose of GH which lead to elevated IGF-I levels which could have lead to insulin resistance and aggravated concealed hypoadrenalism and hypothyroidism. GH therapy therefore is not advocated in this setting.

23.2.7 Neurohypohyseal Dysfunction in Traumatic Brain Injury

Disorders of salt and water balance are common in the neuro-intensive care setting. In this setting hyponatremia may be due to a number of pathophysiologies including SIADH, Cerebral Salt Wasting Syndrome (CSWS), glucocorticoid deficiency, hypovolemia and injudicious intravenous fluid use. Disorders of salt and water balance are particularly common following TBI and SAH. Most available information regarding the occurrence of disorders in water balance following TBI has been derived from retrospective case note studies. Agha et al. have reported that in 50 patients prospectively studied following TBI, cranial diabetes insipidus (CDI) occurred in 13 patients (26%) in the acute phase; of these, 9 had recovered by 6 months and a further 1 by a year follow up, therefore 3 (6%) patients developed permanent CDI following TBI. The development of CDI was associated with lower initial GCS ($r = -0.39$, $P = 0.005$) indicating a more severe initial insult and a poorer outcome as measured by the Glasgow outcome score at 1 year ($r = -0.45$, $P = 0.001$). Also in this study 7 patients (14%) had acute hyponatremia which was attributed to SIADH and this had resolved in all patients at 6 months.

It is essential that the correct pathophysiology of hyponatremia be diagnosed as treatment of hyponatremia due to SIADH is fluid restriction and hypovolemic hyponatremia and CSWS is fluid resuscitation with 0.9% saline (Table 23.3). CDI is diagnosed in the presence of polyuria associated with hypotonic urine and hypertonic plasma and if left unchecked will lead to the development of hypernatremia. Many patients with traumatic brain injury will develop CDI which is only transient, however some may develop permanent CDI. The treatment of acute CDI depends greatly on the patients GCS. In the conscious patient treatment should be a combination of SC desmopressin and allowing the patient to drink according to their thirst (as in the vast majority of patients the thirst response to plasma hyperosmolality is intact and will allow the patient to drink until normo-osmolar). However, if there are neurological sequelae of brain injury/hypernatremia these patients may need monitored infusion of hypotonic solutions. In the unconscious patient treatment should be a combination of SC desmopressin and hypotonic solutions to normalize plasma sodium. The use of stat doses of SC desmopressin in response to polyuria (>500 mls of urine in 2 hours) allows one to assess recovery of the neurohypophysis. If there is no recovery of CDI then the patient should be transferred onto oral or nasal DDAVP (Desmopressin Acetate Tablets). Importantly some patients may develop a classic Triple Phase Response in which they get initial CDI, which is followed a couple of days later by SIADH but ultimately end up with permanent CDI.

Importantly, patients with CDI or any abnormality of sodium need regular assessments of plasma sodium (may need multiple assessments per day in the acute phase of treatment to prevent to rapid correction which can lead to significant sequelae such as central pontine myelinolysis, particularly when treating hyponatremia).

	SIADH	CSWS
Plasma Na^+	Low	Low
Blood urea	Normal/low	Elevated
Blood pressure	Normal	Normal/ postural drop
Urine volume	Low	High
Urinary Na^+	High	High
CVP	Normal	Low

Table 23.3. **Syndrome of inappropriate antidiuretic hormone secretion (SIADH) vs. Cerebral Salt Wasting Syndrome (CSWS).**

23.2.8 Natural History of TBI and Implications for Testing

It is well recognized that many posterior and anterior pituitary abnormalities following TBI are transient. Agha et al. assessed the natural history of TBI in 50 consecutive patients with TBI. This study revealed that

many of the deficiencies diagnosed in the acute phase had recovered by 6 months. Hyperprolactinemia and gonadotrophin deficiencies were particularly likely to recover. ACTH deficiency recovered in half and GH recovered in two-thirds. Conversely, some patients who were not deemed to have a deficiency in the acute phase developed deficiencies at retesting 6 months following TBI (no more new deficiencies were encountered when retested at 1 year post TBI). This data, along with the data from other studies, illustrate that there are dynamic changes in hypothalamic pituitary function in the acute phase post TBI but also up until 6 months following insult. These data have implications for the assessment of the GH, gonadal and thyroid axes in patients following TBI. Assessment of the GH, gonadal and thyroid axes is not necessary in the acute phase because there is currently no evidence that acute phase replacement of these hormones in the deficient patient improves outcome. All patients with moderate or severe TBI should have anterior pituitary assessment performed in the post-acute phase, which will vary considerably between patients but is usually between 3 and 6 months after injury. The choice of the stimulation test(s) for GH and ACTH reserves will depend on the preference and experience of the unit and normal responses will need to be defined locally. At that point, if no abnormalities are found, no further assessment will be necessary (Figure 23.3). However, if hypopituitarism is detected, replacement therapy with glucocorticoids, sex steroids and T4 should be given, as appropriate. Although no study has yet examined the impact of GH treatment on rehabilitation in patients with post-traumatic GHD, a trial of GH replacement in such patients during the rehabilitation phase may be considered. In patients with documented anterior hypopituitarism at 3-6 months post-TBI, repeat anterior pituitary assessment at 1 year may be considered if the clinical or biochemical parameters raise the possibility of delayed recovery.

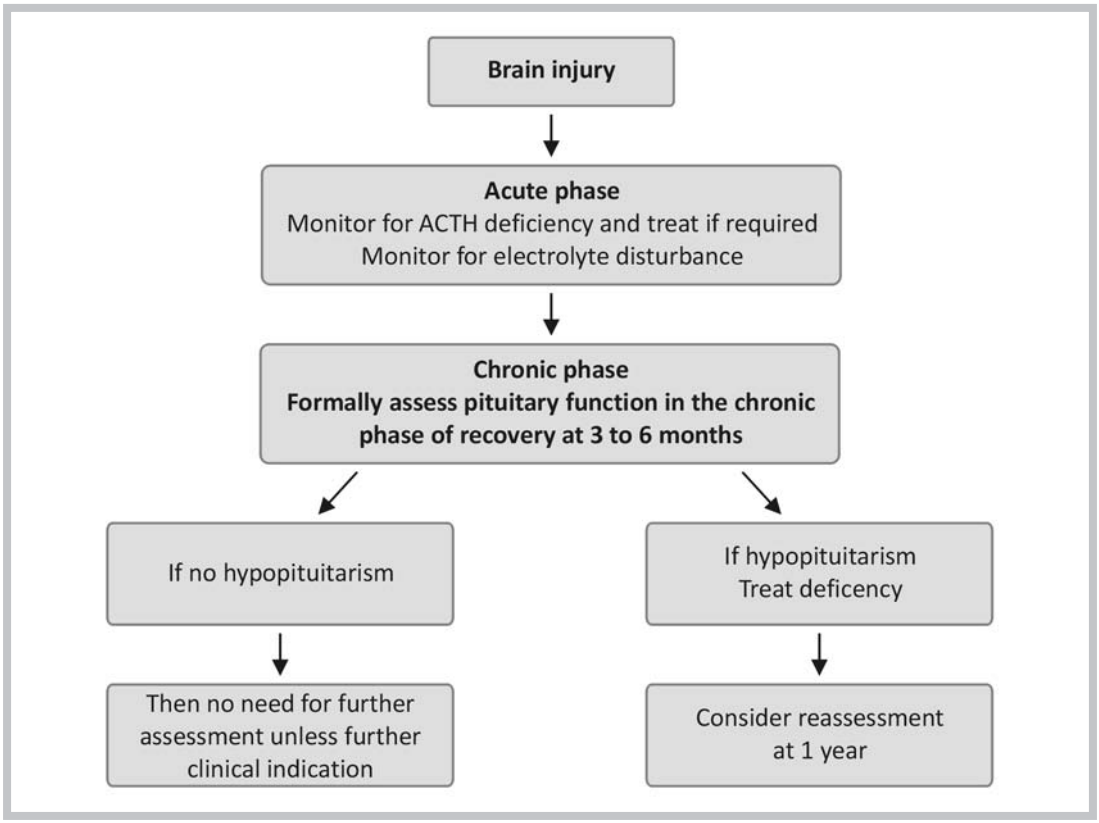

Figure 23.3. Timing of investigation for pituitary dysfunction following traumatic brain injury.

23.2.9 Key Concepts

- Hypothalamic pituitary axis dysfunction is common after acute cerebral injury and many associated features may be protective in nature by redirecting metabolic focus to critical organs.
- "Relative" and "functional adrenal insufficiency" may have important clinical implications. Diagnoses of these conditions can be difficult given the lack of any widely accepted diagnostic criteria. ACTH stimulation tests cannot be used in the early phase of acute cerebral injury to identify adrenal insufficiency.
- In certain subsets of critically ill patients glucocorticoid therapy may be of benefit however treatment of the endocrine dysfunction with GH, sex steroids, thyroxine and DHEA are not recommended at present.
- Increasingly, there is a role for endocrine testing in the recovery phase of acute cerebral injury since new deficiencies can develop months after the initial injury.

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24 Coagulation Disorders in the Neurocritical Patient

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24.1 Introduction

Coagulation disorders in neurocritical or neurosurgical patients is a matter of significant importance. Hypercoagulability states in which intravascular thrombotic activity is increased, as well as deficits in hemostatic mechanisms leading to increased fibrinolysis and bleeding, compromise the evolution of these patients, overshadow the prognosis and worsen the results.
Clotting disorders may be the underlying cause of the neurocritical disease, as in spontaneous bleeding in patients with pre-existing coagulation disorders or in those under anticoagulation treatment. Also, an hypercoagulability state could be the etiology of an ischemic stroke. These disorders can increase secondary insult, promoting both the extent of intracranial bleeding or the development of intravascular thrombosis leading to brain ischemia. The frequency of the association between coagulation disturbances and neurocritical pathologies varies: the highest incidence (60%) is in patients with traumatic brain injury (TBI); 8-12% of cases of spontaneous intracranial hemorrhage (sICH) are related to anticoagulation treatment or coagulopathies; and <5% of patients with ischemic stroke are noted to have an hypercoagulability state.

24.2 Pathophysiology

In healthy individuals, a delicate balance is maintained between coagulation and fibrinolysis mechanisms to counteract excessive bleeding in the context of vascular lesion and inadequate thrombosis activity leading to vascular occlusion. These mechanisms, which include the activation of plasma and tissue factors, are closely regulated and activate only small proportions of clotting factors, since their concentration in a single millilitre of blood is sufficient to clot all the intravascular content within seconds.
In neurocritical patients, these mechanisms are often imbalanced, leading to inappropriate or excessive activation of the coagulation cascade, which results in complications of varying degrees of severity. In this chapter, we will describe the current state of knowledge of disturbances in coagulation-fibrinolysis mechanisms in neurocritical disease.

24.3 Traumatic Brain Injury

In TBI (traumatic brain injury) patients, clotting disorders are described as a combination of hypercoagulability and deficit in hemostasis, occurring simultaneously or successively.

It has been observed that, after the primary insult, tissue factors are released from platelets, white blood cells and endothelial tissue. This is the main trigger of the extrinsic mechanism of coagulation in which, through the triggering of the coagulation cascades, prothrombin is converted into thrombin, culminating in the formation of fibrin with the expected risk of thrombosis. While this "excessive" release of the tissue factor occurs in all trauma patients, the magnitude of this release is related more closely to brain injury than to shock, tissue hypoxia, or other extracranial injuries. It has also been reported that the degree of increase in tissue factor release is directly proportional to the extent of the brain injury. This trend to hypercoagulability triggers the activation of fibrinolysis mechanisms (increase in tissue factor inhibitor, protein C, protein S, antithrombin III, etc.). When fibrin production exceeds the capacity of these physiological mechanisms, an intravascular coagulation ensues in the small and medium-sized blood vessels. This intravascular coagulation can be generalized (disseminated intravascular coagulation leading to the development of extracranial organ failure), as well as localized. In necropsies of animals and patients, the latter has been observed in pericontusional and contusional areas where it leads to an increase in brain damage by extending tissue ischemia. Trauma patients may have a marked reduction in antithrombin III, protein C and S, resulting in thromboembolic or thrombotic complications rather than bleeding.

In TBI patients, coagulopathy may occur parallel with and/or secondary to the depletion of platelets and clotting factors due to hemorrhage, multiple transfusions and/or consumption by disseminated intravascular coagulation (DIC) in a setting of acidosis, hypothermia or hemodilution. Some studies have drawn attention to the occurrence of platelet dysfunction after TBI, more common than in trauma patients without TBI, and that it could have an impact on mortality. Whatever the mechanism involved, the presence of coagulopathy may extend the secondary injury by increasing bleeding in the intracranial lesions.

The incidence of coagulation disorders in TBI patients is related to the severity of the TBI, as categorized by the Glasgow Coma Score (GCS), and is correlated with evolution and prognosis. Various series have described an increase of up to 10 times in the risk of death in patients with coagulation disorders compared with those without such disorders and a greater risk of poor performance in the survivors with such disorders.

With regard to diagnosis, a good practice during the acute phase of TBI is daily assessment of activation partial thromboplastin time, platelet count and prothrombin time to precociously detect these disorders. Under clinical manifestations suggestive of DIC it is good practice to dose plasma concentrations of fibrinogen and fibrinogen degradation products. Specific determinations of clotting factors are not always available in all units, but evaluation is necessary in situations in which standard treatment does not control the coagulopathy state and a more precise assessment is needed.

24.3.1 Treatment

The therapeutic indication for a coagulation disorder in TBI patients should be aimed at controlling the predisposing factors that may have triggered it (hypothermia, acidosis or hypoxemia) and it also should be aimed at replacing the clotting factors. The administration of fresh frozen plasma (FFP) associated with cryoprecipitate solution is used for replacing clotting factors. The latter contains factor VIII and fibrinogen, both absent or at very low concentration in FFP, thus the desirability of their association. Platelets must be simultaneously reinstated, if necessary, according to the analytical.

24.4 Spontaneous Intracranial Hemorrhage

The main relationship between coagulation disorders and sICH is when it is secondary to anticoagulant therapy. This is the most serious and often fatal complication of such treatment. Much less frequently, the etiology of sICH is related to primary hematologic diseases: hereditary coagulation disorders and lymphoproliferative diseases.

The estimated incidence of sICH associated with the use of oral anticoagulants is 1.8% of patients treated with these drugs per year. This association raises the mortality of sICH by more than 10% compared to patients not under oral anticoagulant therapy. According to the 1999 SPIRIT study, those patients with a prior brain pathology and receiving oral anticoagulants have a higher risk of developing sICH. It has also been reported (Smith, 2002) that the presence of leucoaraiosis on brain images was an independent predictive factor for the development of sICH in patients treated with oral anticoagulants.

Gradient echo magnetic resonance imaging (MRI) studies have reported a high incidence of asymptomatic microhemorrhages in aged and/or hypertensive patients. It has been proposed that the use of oral anticoagulants could increase such bleeding events, making them symptomatic. This could be related to the finding that the majority of episodes of sICH, associated with the use of oral anticoagulants, occur within normal international normalized ratio (INR) therapeutic ranges, while higher values increase the risk.

The progression of bleeding of a sICH with expansion of the hematoma within 48 hours of the primary bleeding is seen in about 40% of patients with sICH. In cases associated with the use of oral anticoagulants or coagulopathies, this expansion could be more frequent, larger and extend beyond 48 hours, as has been observed in different published series.

Studies investigating the activation of hemostatic mechanisms in patients with intracranial bleeding have reported that such mechanisms are activated when there is subarachnoid or intraventricular blood. In these cases, there were significant increases in the thrombin-antithrombin and plasmin-antiplasmin complexes as compared to patients without subarachnoid blood and normal controls. According to these findings, there could be an increased risk, at least theoretically, of thrombotic events.

24.4.1 Treatment of Patients With sICH Associated With the Use of Oral Anticoagulants or Associated With Coagulopathy of Other Etiology

In addition to routine therapeutic measures in patients with sICH, in those cases in which it occurs in patients receiving oral anticoagulants or in those with clotting disorders, the treatment should include specific measures to reverse the anticoagulation state. These include the administration of vitamin K and clotting factors. This association is necessary, since the transfused factors have a median life of 5 to 60 hours, depending on each factor; therefore, they exert a rapid but transient effect. To ensure the reversal of anticoagulation over time, concomitant administration of vitamin K is required. Vitamin K begins to exert its effect on K dependent factor synthesis from 6 to more than 24 hours after intravenous infusion (doses of 5 to 20 mg). The intravenous administration of vitamin K solutions can potentially produce allergic reactions of varying magnitude. A slow infusion rate, not exceeding 1 mg per minute, is recommended. The risk of allergic and anaphylactic reactions is 3 in 10,000. Vitamin K given in either subcutaneous or intramuscular form will need longer to take effect.

There are two options in the administration of clotting factor solutions: fresh frozen plasma (FFP) or concentrate of prothrombinic complex (CPC). We will also consider the place of the cryoprecipitates (CP).

Since FFP has a low concentration of factors by volume, it must be administered in high volumes, which may be a limitation in some particular cases. One published study found that the infused volume needed to raise the INR 1.4 points ranged from 800 to 3500 ml. Of note is that the content and concentration of factors in such solutions are highly variable and depend also on storage time. Factor X has the greatest variability. This feature could normalize INR measurements, but it is associated with persistently low plasma levels of factor X and the risk of bleeding. Although this solution does not require compatibilization tests, it is advisable to infuse FFP obtained from donor blood of the same isotype as the recipient. The side effects associated with the use of these solutions include volume overload, allergic reactions, lung injury secondary to transfusion of blood products, and citrate toxicity. The recommend dose is 15-20 ml/kg body weight, but it may be necessary to increase this dose in cases of massive bleeding.

CPC contains K-dependent factors and proteins C, S and Z. It does not require compatibilization tests and, having a high concentration of clotting factors, it allows the infusion of smaller volumes than those needed for FFP.

Cryoprecipitates are solutions which contain factor VIII and fibrinogen, both factors scarce or absent in FFP. They are indicated in treating the specific deficits of these factors and also in cases of massive bleeding in anticoagulated patients, linking them to FFP.

As a recommendation and taking four clinical guidelines as reference, we suggest: vitamin K 5 to 10 mg IV + CPC 30-50 U/kg or FFP 15 ml/kg.

INR measurements are used for the follow-up, always taking into account prevention with respect to the X factor and the use of FFP alone.

Another more recent therapeutic option in the treatment of sICH is the use of recombinant activated VII factor (rVIIa), a potent trigger of the hemostasis cascade. It has been used in patients with hemophilia in intracranial or extracranial bleeding events. Experimental studies have shown that it has a rapid onset of action, mainly at the site of vascular injury. Also, it requires very low infusion volumes and it has good effectiveness and safety profiles. Because of these properties, it has been proposed and tested in patients with sICH to limit persistent bleeding and the growth of the hematoma, both features closely related to poorer outcomes. In a 2005 phase IIB study, rVIIa administration within 4 hours of the primary bleeding correlated with limiting the growth of the hematoma, lower mortality and improved outcome, assessed within 90 days after primary bleeding. But an increase in arterial embolic complications was also observed. According to this study, and the results of the FAST study, a Consensus Committee of experts concluded that the use of rVIIa in sICH limits the growth of the hematoma, but it has no beneficial effects on the survival rate at 90 days. So, rVIIa treatment remains confined to research studies and is not to be used in general practice.

There are few studies on the use of rVIIa in patients with sICH associated with oral anticoagulant therapy; mostly are retrospective with a small series of patients. It was warned that INR values might normalize after rVIIa administration, but, regardless of the persistently low values of other clotting factors, the risk of bleeding remains.

Some published clinical data, which might be confirmed by new studies, showed that reversal of the oral anticoagulant effect with the infusion of FFC or CPC could exacerbate perilesional edema by inducing the release of endothelial growth factor from “leakage” platelets, with an increase in capillary permeability. However, this phenomenon was not observed with the use of rVIIa in experimental studies.

24.5 Ischemic Stroke

A relationship between coagulation disorders and hemorrhagic complications in ischemic stroke is associated with the use of fibrinolytic therapy, but this issue is beyond the scope of this chapter.

Ischemic stroke might result from an hypercoagulability state. Several metabolic diseases or autoimmune disturbances may cause transient ischemic attack (TIA) or venous sinus thrombosis. Numbering among these disorders are: deficit of protein S, antithrombin III, protein C or plasminogen; prothrombin gene mutation; presence in the plasma of anticardiolipin antibodies or lupic anticoagulant factor; high plasma levels of homocysteine or lipoprotein a; and resistance of factor V to protein C. Specific laboratory studies for the detection of each of these disorders are needed when there is some degree of certainty that these mechanisms are involved in certain patients, according to the history and characteristics of the thrombotic event. Younger or pediatric patients with recurrent TIA events, or patients with recurrent venous thrombosis, or those with a family history of venous thrombosis, are likely to be considered affected by some kind of hypercoagulability disorder. Many of these disorders may be treated. A detailed discussion of these pathologies lies outside the scope of this chapter. An interesting and comprehensive review of these aspects was published by Rahemtullah and Van Cott in 2007.

24.6 Subarachnoid Hemorrhage

An increase in the activation of coagulation and fibrinolysis mechanisms has been described in patients with subarachnoid hemorrhage (SAH). It has been observed that the intensity of this activation (reflected in the increase in thrombin-antithrombin complexes, D dimer and fibrinogen concentrations) has a directly proportional relationship with the clinical severity of the bleeding, the amount of subarachnoid blood, the presence of intraparenquimatose hematoma or intraventricular blood. It is likely that these findings may explain what is observed in other studies which found a significant relationship between the magnitude in the elevation of these markers and a poor outcome. Therapeutic approaches to these disorders in patients with SAH have not been proposed.

24.7 Prophylaxis of Pulmonary Thromboembolism in Neurocritical Patients

Among the complications of critical care patients admitted to critical care units, thromboembolic disease and deep venous thrombosis (DVT) should be highlighted because of their high incidence and because they may result in severe consequences. The prophylactic therapy of DVT of the lower limbs is a routine issue in the basic care of all critical patients. Pharmacological therapy has shown greater efficiency for this purpose than mechanical methods such as elastic stockings, bandages or periodical/sequential compression pneumatic boots.

Critical patients with an acute neurological or neurosurgical disease constitute a special category. First, most of them have major risk factors for DVT such as prolonged immobility, coma, old age or associated injuries in the pelvis or lower limbs in trauma patients. On the other hand, pharmacological prophylactic therapy in these patients is reasonable

thought as dangerous because it may impair intracranial bleeding, whether spontaneous or traumatic, and there is a risk of bleeding inside an ischemic stroke lesion.
We will summarize the current state of knowledge about the prevention of thromboembolic disease in neurocritical patients.

24.7.1 Ischemic Stroke and Spontaneous Intracranial Hemorrhage

The reported incidence of symptomatic DVT and/or pulmonary thromboembolism (PTE) in patients with ischemic stroke and sICH is 5-6%. However, the detection of asymptomatic DVT has been found to occur more frequently (from 5 to nearly 50%), depending on the method used for its diagnosis. In 2004, Kelly et al. published a study on 102 ischemic stroke patients who received prophylaxis with aspirin and compression stockings. They reported an incidence of DVT and symptomatic PTE of 3 and 5%, respectively, as diagnosed by MRI. But the incidence of DVT and PTE (symptomatic and more often asymptomatic) was 17.7 and 11.8%, respectively. At multivariate analysis, there was a significantly higher incidence in patients with a Barthel index ≤9 and an increased trend in patients over 70 years of age.
These findings, and those from other studies, underscore that we have to apply measures to prevent such serious complications. In recently published large series of patients, half of them who suffered a PTE event died as a consequence of it.

Prophylaxis

A Cochrane review, which included two randomized trials on the efficacy of compression stockings and pneumatic boots in the prevention of DVT in stroke patients, concluded that their use reduced the incidence of DVT, but the reduction was statistically non-significant. Furthermore, a randomized multicenter European study involving 2518 patients published in 2009 (The CLOTS trial collaboration) reported no significant reduction in the incidence of DVT with the use of elastic compression stockings, but it also reported a 4-fold higher incidence of cutaneous complications, including skin necrosis.
With regard to pharmacological prophylactic therapy, a systematic review assessing the efficacy of the use of antiplatelet drugs for the prevention of DVT/PTE concluded that their use reduces the risk of PTE but not the incidence of DVT.
Studies designed to assess the effectiveness of heparin administration in the acute phase of stroke to prevent stroke recurrence revealed that the incidence of PTE was reduced but with a concomitant significant increase in the risk of intra- and extracranial bleeding. In 2007, Kamphuisen et al. published a systematic review of 17 studies involving 23,043 patients, in which low and high doses of low-molecular-weight heparin (LMWH) were compared with unfractionated heparin. They concluded that the use of low-dose LMWH was the therapeutic strategy that showed the best risk/benefit relationship in reducing DVT and PTE, without an increase in extracranial or intracranial hemorrhage complications.
In 2007 Sherman published the results of the PREVAIL study which included 1762 ischemic stroke patients unable to walk. Patients were randomized to receive, within 48 hours of the primary event, 40 mg of enoxaparin once daily versus 5000 IU of unfractionated heparin twice a day. The enoxaparin-treated group showed a significantly lower incidence of DVT and PTE, with no difference in the incidence of intracerebral bleeding between the two groups (1% in both groups). However, in those who received enoxaparin there was a significantly higher incidence of major extracranial bleeding (0.8 vs. 0%).
Sandercock, in a 2008 Cochrane review (9 studies involving a total of 3137 patients) compared different heparinoids versus unfractionated heparin administered within the first 14 days of an ischemic stroke event. LMWH was associated with a significant reduc-

tion in the incidence of DVT compared to standard heparin; however, Sandercock concluded that the data are insufficient to determine whether the use of this heparinoid reduces the risk of PTE or does not increase the risk of intra- or extracranial bleeding.
The 2007 American Heart Association and American Stroke Association (AHA-ASA) guidelines for the early management of adult stroke patients are based on published levels of evidence. The guidelines recommend: mobilize patients as early as possible; use subcutaneous LMWH in immobilized patients, but the ideal time for initiating therapy is unknown; aspirin is an alternative therapy but it is less effective than heparin; use mechanical compression methods when anticoagulants are contraindicated.
In 2008 Tetri et al. published a retrospective study involving 407 patients with sICH who survived 48 hours after the primary bleeding. They compared those who received 20 mg of enoxaparin once daily with those who did not receive prophylaxis during the acute stage. There were no differences in mortality at 3 months and there were no differences in the degree of growth of the hematoma between the two groups.
The update of the 2007 AHA-ASA guidelines for the management of adults with sICH based on the few articles published about this issue recommends the use of mechanical methods of intermittent compression. In those patients who remain immobilized or with motor deficit in the lower limbs within 3-4 days of the primary bleeding, low-dose LMWH may be used if there is no evidence of ongoing bleeding on the follow-up CT scans.

24.7.2 Traumatic Brain Injury

The incidence of asymptomatic DVT in patients with severe TBI is between 25 and 54%. The use of removable filters in the lower vena cava has been studied in a few trials. The analysis of these studies suggests that its use might be reserved only for those patients with known DVT and in which anticoagulation therapy is contraindicated.
With regard to mechanical or pharmacological prophylaxis, the published data on TBI patients are scarce.
A randomized study of patients with TBI and traumatic spinal cord injury (SCI) compared the use of intermittent pneumatic compression boots versus 40 mg enoxaparin once daily. The study found no significant differences in the incidence of DVT and PTE between the groups. Another retrospective study found that the use of LMWH, initiated within 72 hours of the primary injury, was not related to an increase in the size of intracranial hemorrhagic lesions.
In 2007 Cothren, published an observational study involving 6247 trauma patients (174 of which with TBI), who received 5000 IU dalteparine once a day. Dalteparine administration was begun when the patients showed hemodynamic stabilization and, in those patients with TBI, when the second CT scan at 12-24 hours after the primary injury showed no worsening in intracranial bleeding. The intracranial injury worsened in none of the patients and no death related to PTE or bleeding was recorded.
The 2007 Brain Trauma Foundation Guidelines based on published evidence recommend: use graduated compression stockings; the use of pharmacological therapy is known to potentially increase the risk of intracranial bleeding; there is not enough evidence to recommend any specific agent, doses or time after the primary injury to begin its administration.

24.7.3 Spinal Cord Injury

The incidence of DVT in SCI patients who not receive prophylaxis ranges between 7 and 100%, depending on injury severity, patient age, and the method to diagnosis DVT. Be-

cause of this high incidence, it is an accepted practice to use early prophylaxis in all of these patients. It was stated as a standard, with class I evidence, in the American Association of Neurological Surgeons Guidelines for the Management of Spinal Cord Injury. The guidelines also recommend extending prophylactic measures for 3 months after the primary injury, being reasonable to suspend them before such time if the patient has recovered motor function of the lower limbs.

With regard to which therapy is better, prolonged use of removable lower vena cava filters has been associated with some complications. A 2009 retrospective study suggests that the use of filters could increase the incidence of DVT. They are also indicated in patients under pharmacological prophylaxis who, despite this, underwent a thromboembolic event.

With regard to mechanical devices (graduated stockings, pneumatic boots), the results in some published studies suggest that they could be as effective as pharmacological measures. Others suggest that when associated with pharmacological therapy, their use can enhance its effectiveness. The above-mentioned guidelines recommend the combined use of mechanical devices and low-dose unfractionated heparin. We could add that, in those patients in whom anticoagulation therapy is contraindicated, it might be an indication for its use.

Finally, with regard to LMWH, several studies have found equal effectiveness by comparing the different products available. A 2009 systematic review including 30 studies concluded that LMWH is the best alternative because of its effectiveness and safety, whereas the use of unfractionated heparin has been associated with major bleeding complications.

24.7.4 Elective Neurosurgery

Published series of patients undergoing elective neurosurgical procedures (most of which affected by brain tumour) report an incidence of DVT between 19 and 54% and an incidence of PTE of around 5%. Despite these figures, there is reluctance to use pharmacological prophylaxis therapy in these patients because of the fear of an increased risk of bleeding. Two recently published surveys reported that only 32 to 33% of such patients receive pharmacological prophylaxis, although it is not definitively established whether therapy actually increases the risk of intracranial hemorrhage to any significant degree. Comparing study results is difficult because most studies are non-randomized and because spontaneous re-bleeding after elective neurosurgery has been reported to occur in more than 25% of cases. Also, the rate of reoperation because of post-operative re-bleeding ranges between 1 and 10%, even in patient series in which pharmacological prophylaxis for DVT was not administered.

In 2003, Gerlach published a study of a series of 2823 neurosurgical patients who received 0.3 ml of nadroparine in a single dose within 24 hours of surgery. The incidence of post-operative bleeding associated with clinical deterioration or which required a new operation was 1.5%. Also, Chibaro, in a 2008 study involving a series of 746 neurosurgical patients who received Tinzaparine, reported post-surgical intracranial bleeding in less than 1% of cases.

In 1998 Agnelli published a randomized study of 307 patients undergoing elective neurosurgery (90% involving the brain, 97% of which brain tumours) who received 40 mg enoxaparin once daily + graduated compression stockings versus graduated compression stockings + placebo. Enoxaparin was initiated within 24 hours of surgery and was continued for 1 week. The incidence of DVT and PTE was significantly lower in the enoxaparin group, and there was no increased incidence of major or minor bleeding between the groups.

Coincidentally with this last study, two meta-analyses (Iorio 2000 and Collen 2008), which included 7 and 30 studies, respectively, agreed that the use of LMWH proved effective in preventing DVT, without an excessive increase in the risk of bleeding. According to this evidence, the greatest benefits might be obtained by combining the use of mechanical compression devices with LMWH therapy, but the ideal time when these drugs should be initiated remains unknown.

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Section 4.
Intracranial Hypertension

25 Pathophysiology of Intracranial Hypertension

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25.1 General Concepts

Intracranial pressure (ICP) is one of the key parameters of acute head injury pathophysiology; its knowledge and management are essential to improve the outcome of neurocritically ill patients.

Some basic concepts in intracranial dynamics need to be kept in mind to understand the events that occur during intracranial hypertension (ICH). ICP is classically described as the pressure exerted by the cerebrospinal fluid (CSF). Its normal range in adults in supine position is 5-10 mmHg, measured in the lateral ventricle and taking as zero the foramen of Monro. The normal range in children is 1.5-6 mmHg. ICP results as the interaction between the cranium (inextensible compartment) and its content, which is what will determine ICP variations.

The content is composed of three compartments: the brain (neurons and glia) accounts for 80% (1200 cc); the brain-blood volume (arterial and venous vessels) for 10% (150 cc); and the CSF and interstitial fluid for 10% (150 cc). Although there is no ideal theoretical model that explains every phenomenon in relation to intracranial dynamics, very useful clinical accepted models do exist. Two which play a key role in its understanding are the Monro-Kellie equation and Marmarou's mathematic model.

According to the Monro-Kellie equaltion, intracranial volume is constant as it finds itself in a rigid compartment (uncompressible, but displaceable); therefore, any increase in one of these components or the apparition of a new volume must be necessarily compensated by a decrease in one of the others, otherwise ICP will rise.

$$V_K = V_{CBV} + V_{CSF} + V_{parenchyma}$$

$$1500 = 150 + 150 + 1200$$

It is important to highlight that the Monro-Kellie equation describes volume and not pressure; therefore, even if volume remains constant, this doesn't mean that the system pressure will remain constant. This concept to understand ICH also works in situations where only one of the system's components decreases, as occurs in ICH related to CSF fistula. In such cases, one component of the system must increase its volume to maintain the K, usually the intracranial veins and/or the cerebral blood flow (CBF), which ultimately produces the diagnostic elements of this condition.

Current discussion on defining ICP in measured units from a mathematical point of view has focused on: a scalar magnitude, where there is no direction of the vector that generates the magnitude; a vectorial magnitude, where there's clearly a direction and a sense of the magnitude, or a tensor, and where this magnitude operates in all tridimensional planes. This concept derives from biophysics, given the brain's biomechanical complex characteristics, as a semi solid with complex visco-elastic properties, where ICP must be

defined in the strict sense as a tensor and not as a liquid according to the classical clinical definition (personal communication, Dr. Alonso Peña).
Marmorou's model explains the dynamics of the intracranial system and differentiates: normal conditions (basal state or balanced state); and pathologic conditions, phasic or transitory state.

25.1.1 Normal Conditions (Basal State or Balanced State)

ICP is determined by several factors including the CSF production index, its absorption, venous sinus pressure, and arterial blood flow, as described in the formula:

$$\text{Basal state ICP} = f \times R + Pd$$

where: f (flow) of formation = f (flow) of absorption; f stored (capacitance) = 0; R= flow resistance; Pd = dural sinus pressure
In this situation, CSF formation flow is equal to absorption flow and storage. In other words, a capacitance system where the liquid at any given moment doesn't change and remains at 0. R is the flow resistance and is the sum of all small resistances (r, r′, r′′ …) which the flow encounters. Therefore, the flow resistance (absorption flow or formation flow) plus dural sinus pressure are what maintain the ICP normal or balanced. The dural sinus pressure is the outlet pressure and must be the lowest pressure of the system. Clearly then, the balance between the formation and storage of CSF is critical. If absorption is exceeded, for example, as a result of an elevation in the CSF flow resistance, this will determine, once the CSF storage capacity is exhausted, an elevation in ICP.

25.1.2 Pathologic Conditions, Phasic or Transitory State

This state is produced when the system is subject to an abnormal overload which alters the volume of one or more compartments. To understand this state, we will describe the volume tolerance curve, formerly called the compliance curve. Marmorou showed that the relationship between volume and cranial spinal pressure could be described as a straight line derived from the logarithm of the pressure/volume, which implies a single exponential curve of the volume/pressure ratio that depends on the intracranial compliance grade (Figure 25.1).
The compliance curve was used to describe volume variation over pressure variation; as the curve is exponential, the compliance varies along it.
Three sectors are distinguished:

- Initial: almost horizontal. This is the compensating phase because increasing volume produces minimal changes in ICP, showing the effectiveness of compensating mechanisms.
- Intermediate: (decompensating phase) is the inflection and shows the transition between the two sectors. It corresponds to variable values of ICP (depending on the speed of onset) between 20 and 25 mmHg. This value must be considered as a warning sign because ICP will increase dramatically at higher values.
- Final: almost vertical (cerebral tamponing phase). The increasing volume generates rapid ICP increments because the compensation mechanisms can no longer counteract it. This phase corresponds to ICP values of around 50-60 mmHg, where only systolic flow (ICP=DAP) remains.

These variations in pressure and volume behaviour are determined by intracranial compliance, which is defined as the relationship between volume variations and pressure

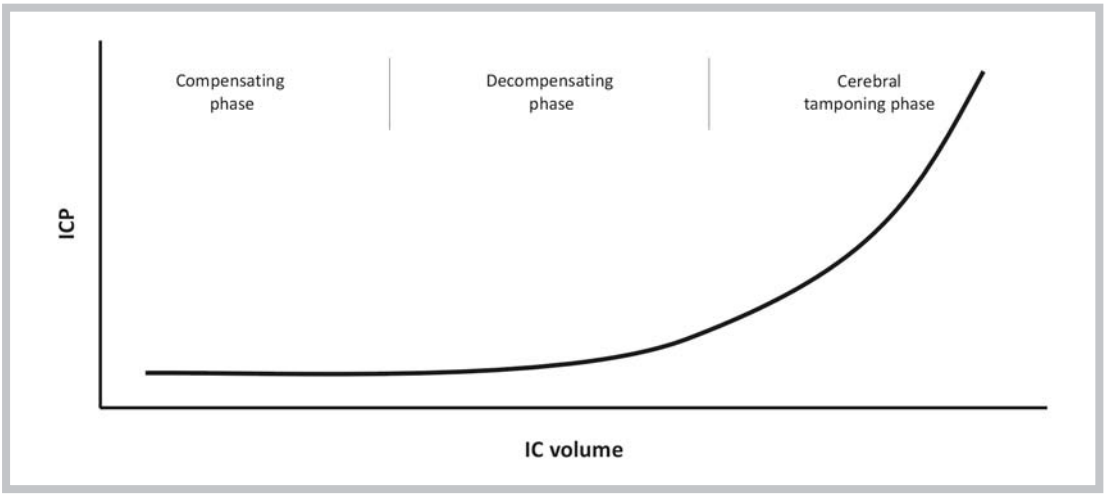

Figure 25.1. **The volume tolerance curve, formerly called the compliance curve.**

variations ((ΔV/ΔP). It is high initially and frankly decreases above 20 mmHg. Its normal range is 0.15 to 0.5 ml/mmHg. Many authors argue that compliance should be referred to as "pseudocompliance" because the intracranial volume is constant. They prefer to refer to it as a volume tolerance curve, referring to the displaced volume more than to the volume variation. Compliance is not homogeneous: it is greater in the supratentorium compartment (80%) than in the infratentorium (20%), in which the compliance curve is displaced to the left, indicating its lower tolerance to volume increments. Some authors prefer to refer to this property as as elastance and not compliance, which would be a more physiological definition, because the brain has a constant volume. Elastance is the opposite of the compliance, i.e., the pressure variations that must be generated to displace a certain volume.

The other important concept is that the compensating system is time-dependent. This means that the slower the volume load, the greater the system's tolerance, ensuing in a lower pressure to a higher volume. This explains why slow-growing tumours can occupy intracranial space, whereas even a slight, sudden increase in ICP with a much smaller volume will generate a much higher pressure. Between this two extremes lie all kinds of intermediate situations, and the physician will need to consider the time factor when making decisions.

So, in short, **the phasic state or transitory state of the intracranial system**, according to Marmorou's model, is described by the compliance curve or elastance. The system works with a non-ideal response with a variable compliance, the pressure/volume ratio is exponential and time-dependent.

25.2 Compliance

There are two ways to measure compliance with the compliance test:

- PVR (Miller): when injecting 1 ml/second it's known that the ICP should be <4 mmHg.
- PVI: it's index of pressure/volume of Marmorou.

This is the volume (normally >20 ml) needed to increase ICP 10 fold.

Commonly used in the 1980s, these indices are now rarely applied but serve to understand the logarithmic relationship between pressure and volume: the higher the volume, the better the compliance and therefore the more tolerant the system to volume loads.

25.3 ICP Waves

ICP waves refer to the study of cerebral pulse curve and periodic waves.

25.3.1 Cerebral Pulse Curve

Another way to understand the compliance curve is to study the cerebral pulse curve, i.e., the ICP instantaneous curve. It normally presents three consecutive peaks, (P1, P2 and P3). The first positive deflection, P1 (percussion wave), corresponds to the arterial pulse wave and represents the arrival of blood to the intracranial cavity. The second wave, P2 (volume wave), is considered a reflex of intracranial elastance. The meaning of the third wave, P3 (dicrotic wave), is still unknown. Normally, the amplitude of P1 is higher than that of P2; however, in situations of greater elastance or decreased compliance, P2 increases in relation to P1. The magnitude of this change is a measure of intracranial compliance, constituting the so-called compliance auto-test.
When we have a space occupying lesion, the arterial pulse constitutes a real volume load. From cerebral pulse wave analysis we can infer in what sector of the compliance curve we are. The normal pulse wave amplitude is 3 mmHg. A high amplitude (10 or 15 mmHg) pulse wave indicates a volume load in the ascending slope of the compliance curve.

25.3.2 Periodic Waves

In the classic description, following Lundberg who described ICP waves (A, B, C) which bear his name, Lundberg A waves, or plateau waves, are the most important from a pathologic point of view. According to its description they were ominous, with duration between 5 and 20 minutes, with an amplitude >50 mmHg, reaching values of 100 mmHg. B Lundberg waves last between 2 and 5 minutes, with an amplitude >20 mmHg, reaching 50 mmHg. Their clinical meaning is less accurate than A waves, but are warning signs that show a decrease in intracranial compliance. Type C waves, (Hering Traube), are of short duration, with low amplitude (<20 mmHg) and show arterial curves; their clinical meaning is unknown. Our current notion about ICP periodic waves follows the concept of Lemaire, which introduced the globalized concept of periodic events separated according to frequency range and taking the B waves as the centre, then subdividing them into infra B, B and ultra B, according to how it's established (Table 25.1).
To detect this type of waves it is important to count with slow ICP recordings. The usual display on most monitors, although they provide a good recording and visualization of the cerebral pulse curve, don't permit these events to be observed. In these conditions, the existence of periodic waves may be sometimes suspected from spontaneous changes in ICP values above the treatment threshold and should prompt doubt about its treatment. What must be emphasized is that as long as the elevation in ICP is not excessive, we must always wait 15 to 20 minutes before starting to treat an increase in ICP so as to avoid unnecessary treatment of reversible ICP elevation caused by these periodic waves.
The phenomenon of periodic waves is essentially a physiological event, as has been demonstrated by transfontanel recording in normal neonates. It is generally of vasogenic origin, emerging from the normal vasomotricity of normal circulation and that of the brain circulation in particular. The most pathological forms would be given by the higher amplitude and slower frequency waves (infra B), which typically show: 1) a sharp drop compliance in all cases; and 2) conservation, but not always, of the autoregulating pres-

Classification	Wave	Oscillation (waves/min)	Aplitude (mmHg)	Frequency band (mHz)
Janny	Type 1	6 to 12	1.5-2.2 (healthy subjects)	66.3-200
	Type 2 or slow cycle "Coup d'hypertension"	0.5 to 3 (dominant 1w/min) Variable occurrence	10.3 (current)	8.33-50
Lundberg	C wave	4 to 8	From discernible to 20	66.3-133.3
	B wave	Variable occurrence (current duration 5-20 min)	From discernible to 50	-
	A wave or plateau wave		50-100 (current)	8.33-33.3
Frequency	UB			>50-200
	B			8-50
	IB			<8

Table 25.1. **Periodic wave classification.**

sure. Detailed study of the chronobiology that initiates a wave of this type is essential for determining its mechanisms. With simultaneous multimodal monitoring and multichannel recording it is possible to determine whether it corresponds to cerebral autoregulating events that normally originate the wave or to a phenomenon of autoregulation loss.

25.4 Factors Which the ICP Depends on

In summary, ICP depends on the following factors: CSF production; CSF flow resistance; venous sinus pressure; and compliance. The first three are balance factors and determine basal ICP. The fourth is the compliance factor. Its behaviour shows with the other variables the volume, i.e., the change magnitude and the time variable, determining ICP by volume load.

For example, head-injured patients with normal ICP have alterations in the balance factors, mainly in the intravascular compartment. At the same time, subarachnoid hemorrhage with normal ICP also has great alterations in balance factors, but mainly the resistance to CSF flow.

25.5 Intracranial Hypertension Compensating Mechanisms

Due to the inextensibility of the cranial enclosure, compensations before elevation of ICP imply displacement of the intracranial structures to tolerate volume loads.

- CSF constitutes the main initial compensatory mechanism. The CSF moves to the subarachnoid space which is distensible and also increases its absorption. Importantly, the spinal fluid accounts for more than 50% of the total CSF and it is the main buffer before ICP starts to rise. Its magnitude is higher in patients with cerebral atrophy and increased subarachnoid space. It can be quantified by computed tomography (CT) to evidence the remaining buffer according to the size of the subarachnoid space, mainly in the basal cisterns and peri-brainstem. The ICP-CT correlation is accurate when both are normal, but an abnormal CT finding could suggest or not

an increased ICP. At the same time, a normal CT finding doesn't necessarily guarantee a normal ICP. Nevertheless, indirect tomographic signs (not pathognomonic) of increased ICP are:
  - Basal cistern and peri-brainstem compression.
  - Unilateral lateral ventricle system compression.
  - Midline deviation.
- Cerebral blood volume (CBV). The decrease in CBV is one of the initial compensatory mechanisms. It involves venous collapse (earliest mechanism) and arteriolar vasoconstriction, which could also be stimulated by hyperventilation, temperature decrease or osmotic agents, besides maintaining adequate cerebral perfusion pressure (CPP). The venous vessels are collapsible structures that displace a considerable volume, decrease their volume, and transfer their pressure to the dural sinus. These two systems, venous and CSF, are very economical for the brain, with fewer clinical repercussions on the patient's final outcome. When these two systems are overwhelmed, however, the ensuing structural changes lead to a major alteration in intracranial physiology: the arteries produce ischemia and the parenchyma is displaced.
- The encephalic mass accommodates ICP elevations at the expense of displacement and distortion of encephalic structures, which constitutes more a second cerebral aggression mechanism than a compensatory mechanism. Likewise, as the compensatory mechanisms depend on the three types of intracranial structures, themselves compromised, ICP ensues:
  - Increased CSF: hydrocephalus (CSF blockage).
  - Increased CBV due to vasodilatation (hyperemia) or hypertension when autoregulation limit is surpassed.
  - Increased encephalic volume due to expansive processes or cerebral edema.

Elevation of ICP depends on:
- Speed of onset of increase.
- Factors concomitant with the initial process caused by increased CBV or cerebral edema, secondary ICP elevation (secondary mechanisms), e.g., seizures, hyperthermia, hyponatremia.

25.6 Effects of Intracranial Hypertension

Intracranial hypertension *per se* is not a structural or functional deteriorative element; instead, it works through two main mechanisms (ischemia and encephalic displacement) to produce brain ischemia by vascular compression. An ICP >20 mmHg generates ischemia initially through venous capillary compression and later by arterial compression. Values of 35 mmHg generate arterial compression; this value is considered as severe ICP. A prolonged ICP of 40 mmHg is correlated with 70% mortality. When ICP equals mean arterial pressure (MAP), CBF ceases. This is called critical cerebral perfusion pressure (CPP) to CPP = 40 mmHg, because CPP <40 mmHg for 2 hours is correlated with a mortality of 100%.

Increased ICP generates severe distortion of anatomic structures. It is this distortion or displacement that determines hernia with occlusion of the compartments. Its clinical manifestation is late and corresponds to the herniary syndrome. When a hernia is accompanied by a compartment occlusion, the total system volume is suddenly reduced, with a significant reduction in compliance and, in general, a pronounced increase in ICP. So we move from an initial exponential curve to its most vertical phase of cerebral tamponing. From the point of view of pressure and flow, this situation occurs when diastolic

pressure equals ICP (ICP = DAP). In such cases, there is only systolic flow to the brain. Later, when ICP equals systolic pressure (ICP = SAP) cerebral fugue flow can occur, i.e., the injected blood returns. We have a detained cerebral circulation which will rapidly lead to brain death. Each of these situations can be clearly identified with a transcranial Doppler study. When ICP >DAP, during the diastolic phase a return of blood after the systole is produced, determining a reverberating diastolic flow, a sign of cerebral tamponing and an indirect sign of brain death.

Displacement occurs earlier than the herniation syndrome, as magnetic resonance imaging studies have shown. Early displacements were found to have a close correlation with neurologic deterioration and deepening coma. The main consequences of displacement are brainstem angulation and distortion, which ultimately define the severity. Also, displacement can cause ischemia by direct vascular compression in diverse topographies, as occurs in transtentorium hernia or in occipital infarction, by compromising the posterior cerebral artery. There's also the notion that several tentorium anatomic variation, 25% of which could be the variations that restrict brainstem displacement, and these patients would have a higher risk of early onset of a herniary syndrome.

25.7 Intracranial Pressure Gradients

The classic concept of ICP measurement based on the system's liquid nature cannot explain the phenomenology of intracranial and cranial-spinal gradients because pressure gradients don't naturally occur inside a liquid. The modern concept that encompasses the system's viscoelastic properties and the conceptualization of ICP as a tensor is the key to understanding the relationship between ICP and deviation of the cerebral parenchyma. Deviation or displacement of the cerebral parenchyma is produced by intracranial pressure gradients. The existence of gradients between the supratentorium and the infratentorium and between the posterior cranial fossa and the subarachnoid spinal space have been observed and confirmed in both experimental models and by clinical assays. There are also gradients inside the supratentorium compartment, between both hemispheres (interhemispheric gradients) and inside each hemisphere (transhemispheric gradients). The gradients originate mainly when there is a space-occupying lesion and depend mainly on its growth rate and they tend to disappear with time. In such cases, the intracranial space acts like two-chamber system in which ICP is unequally distributed for a variable period of time and the higher ICP is always found on the side of the lesion and close to it. That's why ICP monitoring should always be performed ispilateral to the lesion. The reduction and disappearance of the gradients over time could be related to brain relaxation and accommodation to this new volume. (Sahuquillo et al.). In patients with diffuse lesions (midline deviation <3 mm and lesion volume <25 mm) it can be assumed that the intracranial compartment acts like a single-chamber space, with ICP practically equal in both hemispheres (Sahuquillo et al.), so that even a very slight increase in ICP will produce more cerebral distortion, more ischemia and herniation. This occurs because of focal pressure elevations, which possess intracerebral gradients, in the dura mater, which is inextensible, distends inwards. Because the volume change is negligible, ICP doesn't increase greatly. That's why it is important to understand that ICP isn't the panacea in the management of patients with head injury and some other lesions, especially in temporal lobe lesions. In such cases, CT is more reliable for measuring the midline deviation using planimetry as a main factor when taking decisions.

25.8 Herniaton Syndrome

Magnetic resonance imaging (MRI) has revealed that is not necessary that distortions in one compartment lead to changes inside others to produce the herniation syndrome. The herniation syndrome is produced only by cerebral distortions in the horizontal plane or distortions in the vertical plane, without a part of one compartment moving to other to cause hernia, which would be a final event. A close relationship has been identified between consciousness level and midline distortions. Acute distortion >1 cm at the pineal gland and 1.5 cm at the pellucid septum causes coma.

25.9 Elevated ICP

The main events leading to elevated ICP are given below. It must be kept in mind that in many cases more than one process is active in the genesis of ICH, such as: brain edema (congestion or brain edema), hematomas, and hemorrhages.
The difference between hematoma and hemorrhage is that a hematoma arises where there is no pre-formed cavity. Hemorrhage refers to bleeding in a cistern or a ventricle, i.e.: Arteriovenous malformations – giant aneurysms, any kind of collections, tumors, hydrocephalus, osseous causes.
Hydrocephalus results from two mechanisms. At point 1) brain edema and at point 7) hydrocephalus. When hydrocephalus is severe as in hydrocephalic edema which is periependimary edema, then there is a double mechanism through which ICP increases. In hydrocephalus of osseous causes, bone thickening occurs in some hereditary forms of anemia which reduce compliance.

25.10 Hydrocephalus

Before talking about hydrocephalus, we will refer to some basic concepts about CSF physiology and its functions.
Three stages of CSF physiology are distinguished:

- Secretion from the choroid plexus.
- Downstream circulation through the III ventricle, aqueduct of Sylvius, IV ventricle, peri-brainstem cisterns, and from there to the convexity and spinal subarachnoid spaces, ascending up through them to the interhemispheric fissure. This circulation is pulsatile, because that's how CSF is secreted by the choroid plexus, which beats with arterial pulse.
- Absorption by the arachnoid villi in the venous sinus, and extra-villi absorption.

The amount of CSF is about 150 cc (70% from choroid plexus secretion and 30% from interstitial liquid that passes to the ependymal space). The secretion rate is around 20 ml/h, which amounts to a total of 500 cc/day, therefore CSF refill about every 8 hours.
Authors who advocate treatment of ICH by CSF drainage sustain their position by citing two facts: it is the most physiological mechanism and the mechanism through which the clearance is done in interstitial edema and vasogenic edema (due to the communication between the interstitial fluid and the CSF).
CSF functions are many: cushioning of cerebral structures against movement and trauma; transport of neurohormones and neuropeptides; maintenance of the interstitial microhabitat and lymphatic-like effects, elimination of cellular waste through the CSF, which is greater than via the venous sector.

Hydrocephalus is variously defined and no consensus on its definition has been reached. Rekate [Rekate, 2008] proposed a definition to take as a starting point for future debates. He describes it as an active distension of the ventricular cerebral system resulting from an inadequate passage of CSF from its production point in the cerebral ventricles to its absorption point in the systemic circulation. He also poses the existence of a common underlying cause for its different manifestations and for an imbalance between CSF production and absorption.

This definition implies an active process, which excludes cerebral atrophy and hydrocephalus ex-vacuo, and in general implies ventriculomegaly. It can be suspected from the presence of ventriculomegaly but ventriculomegaly isn't synonymous with hydrocephalus. Hydrocephalus can exist without ventriculomegaly and ventriculomegaly without hydrocephalus, as occurs in cerebral atrophy. This form is seen in older patients, in which the spaces where the liquid circulates are dilated. Such patients present a reduction in parenchyma volume and there is no resistance to circulation or liquid absorption. Sometimes it is hard to rule out a hydrocephalus in these situations. A wider definition would be that hydrocephalus represents resistance to the circulation of CSF or a difficulty in its absorption.

Normal resistance is the pressure difference between the CSF pressure and the pressure of the venous sector, i.e. in the venous sinus. The value of the pressure difference between the cortical subarachnoid space and the superior sagittal venous sinus (last CSF absorption point) is approximately between 5-7 mmHg [Rekate, 2008].

25.10.1 Brain Edema

Brain edema is a main factor in most cases of ICH. It constitutes a brain tissue monomorph and a self-response or stereotyped response to multiple forms of acute injury, both structural and metabolic.

Edema refers to an increase of the volume of one or more the tissue components. Strictly defined, it is an increase of water content in the extravascular tissue due to an increase of water in either the extracellular space or the intracellular space alone or both. Clinically, however, brain edema usually refers to an increase in cerebral volume. Therefore, to employ the same terminology, we will use the term brain swelling (or brain bulk enlargement in the English language literature) to describe increased brain volume or brain mass due to:

- Augmented vascular volume: arteriolar dilation or venous obstruction.
- Cellular swelling of intracellular neurons or glia usually caused by cytotoxic edema.
- Extracellular edema or interstitial edema:
  - Vasogenic (altered blood-brain barrier).
  - Osmotic (decreased plasmatic osmolarity).
  - Interstitial, hydrocephalus or peri- ependimary (altered CSF circulation).

Edema may be a focal or a diffuse disturbance.

At the cellular level, several different patterns reflect different etiopathogenic mechanisms.

Vasogenic edema refers to the presence of liquid in the extracellular space caused by loss of blood-brain barrier (BBB) integrity. The BBB is composed of elements between the capillary and the neuron (endothelium, basal membrane, pericytic, astrocytic prolongations). The BBB is less permeable than other capillary membranes of an organism (pores of 6 Ångström vs. 60 Ångström of the general circulation), due to tight endothelial intercellular unions, configuring the so-called continuous capillary type, unlike the other types of capillaries (fenestrated as in the choroid plexus and renal glomerulus, and sinu-

soidal as in organs where cellular passage occurs as in the liver and spleen). Therefore, it is said that systemic circulation is an "oncometer" (it does not allow the passage of proteins but easily allows low-molecular-weight solutes to cross it), while the BBB would be an "osmometer" (the liquid passes through channels according to osmotic pressure differences and the ions by finely regulated transport channels). The movement of liquid is determined by the factors accounted for by Starling's law, wherein: there must be an adequate level between the hydrostatic and osmotic forces to produce edema that tend to move the liquid to the interstitial space. In normal conditions, the BBB is impermeable to the liquid due to tight endothelial unions; however, under pathological conditions, endothelial hydraulic conductivity rises, allowing the passage of liquid through the vascular wall. This increase in vascular permeability also produces plasmatic extravasation, rich in proteins which end up collecting mainly in the extracellular space of the white matter and subsequently in the glia. Vasogenic edema tends to be peri-focal, circumscribed to the initial lesion, but progresses towards unharmed white matter by diffusion and tissue pressure gradient. Although vasogenic edema depends on the permeability of the BBB, the main force is the hydrostatic capillary pressure, which depends on systemic arterial pressure and the RVC. This holds therapeutic importance because increments in the main arterial pressure, even more so when associated with disturbed autoregulation, increase vasogenic edema. However, we think that the hydrostatic pressure by itself is very unlikely to generate vasogenic edema in patients with an intact BBB.
Cytotoxic edema is related to direct neuroglial injury. It's characterized by augmented cerebral cellular volume at the expense of the intracellular space. It mainly affects the gray matter. The underlying mechanisms are complex and include cellular metabolic disturbances, with the accumulation of intracellular sodium due to a dysfunction of the ionic pumps which bring liquid from the extracellular space.
The main causes are: brain ischemia, brain hypoxia, neurotrauma, meningitis, hyperosmolar states.
Osmotic edema is a cellular and interstitial edema linked to a rapid and sharp decrease in serum osmolarity, as occurs in hyponatremia. This results in an important osmotic gradient through the BBB. Normally, the BBB inhibits the passage of liquid excess, but under pathological conditions, its integrity could be affected. In addition, a positive regulation for water channels, aquaporines, could favour its passage through the BBB.
Interstitial-peri-ependimary edema is linked to CSF obstruction as in hydrocephalus, usually with CSF deviation from the ventricles to the interstitial space. It accumulates around the peri-ventricular white matter, assuming a crest form from the frontal and occipital horns.

25.10.2 Classification of Hydrocephalus

The classification of hydrocephalus is controversial. Classically, and since Dandy and Blackfan's work in the early 20th century (1914), hydrocephalus is classified as "obstructive" or non-communicant and "communicant". Later, with the advent of imaging techniques, first CT and then MRI, the exact location of obstruction points to CSF flow was determined with greater precision, leading from the notion of two types of hydrocephalus to multiple types according to the point where CSF is obstructed, with specific treatment techniques for each one [Rekate, 2008]. Non-communicant or obstructive hydrocephalus is produced by an alteration in CSF circulation in the foramen of Monro (passage from the lateral ventricle to the III ventricle), aqueduct of Sylvius (between the III and IV ventricle), the IV ventricle, the basal cisterns (between the spinal subarachnoid space and the cortical space) or between the cortical subarachnoid space and

the venous sinus (final absorption points) [Rekate, 2008]. Communicant hydrocephalus manifests with all cavities dilated, indicating a problem with CSF absorption. Ransohoff described this type of hydrocephalus as "extra-ventricular obstructive hydrocephalus", resulting from obstruction involving the cortical subarachnoid space. The current tendency is to think that most forms of hydrocephalus are obstructive and that the only real communicant hydrocephalus is the one due to CSF overproduction caused by choroid plexus papilloma, which is a rare condition. Another condition considered as hydrocephalus is external hydrocephalus, in which a new space is created, usually in the subdural space, where liquid is secreted and is in communication with the arachnoid space. Several hygromas resemble a real external hydrocephalus.

Hygroma refers to the collection of CSF in the subdural space, between the dura matter and the arachnoid space. Hygroma forms from a lesion in the arachnoid space, where CSF flows from the subarachnoid space to the subdural space. It may or may not be in communication with the CSF circulating system. In the latter case, the hygroma is drained to resolve the problem.

Sometimes an evacuated hygroma will recur; this implies that it is in total communication with the CSF circulation system and is called external hydrocephalus.

25.10.3 Effects of Hydrocephalus

Applying Laplace's law for a liquid inside a recipient:

$$T = 2 (P \times D)$$

where: T = tension; P = pressure; D = diameter.

The tension that produces hydrocephalus depends on pressure and diameter. Therefore, diversion of CFS to treat the hydrocephalus will reduce both pressure and tension. In many situations, however, even if we reduce the pressure, but the diameter is large, the tension will not drop. Therefore, we must wait for the tension to decrease before a proper effect can be obtained. It's the later one that affects the long pyramidal fibres, with the consequent march disorder.

In normotensive hydrocephalus, the pressure is already adjusted at the expense of a larger diameter (larger space) and a subsequently higher tension. Normotensive hydrocephalus was at some point hypertensive. The hydrocephalus must therefore be drained. And this is done by decreasing the pressure while waiting for the tension to fall and the diameter to adjust. Oftentimes the pressure must be reduced to subnormal values or even to negative values to reduce tension and ventricle diameter. When the resistance rises, the ventricle diameter increases, so that it's easy to suspect a hydrocephalus from a ventricle enlargement.

Another effect of hydrocephalus is hypertensive and has a certain evolution in the apparition of a white matter peri-ependimary edema due to an interstitial absorption deficit which is observed as crests around the frontal and occipital horns.

Pseudonormal pattern syndrome with hydrocephalus + cerebral edema: in this case, there are two concomitant processes: cerebral edema (of different etiology) and an alteration in liquid circulation. Therefore, we will have two forces, the centripetal force caused by the brain edema and the centrifugal force caused by the hydrocephalus. And we will have an enormous pressure within the balance state but with normal ventricles because they are two similar forces with different signs, i.e., forces which add up arithmetically but subtract geometrically. This generates a pseudonormal pattern, as shown

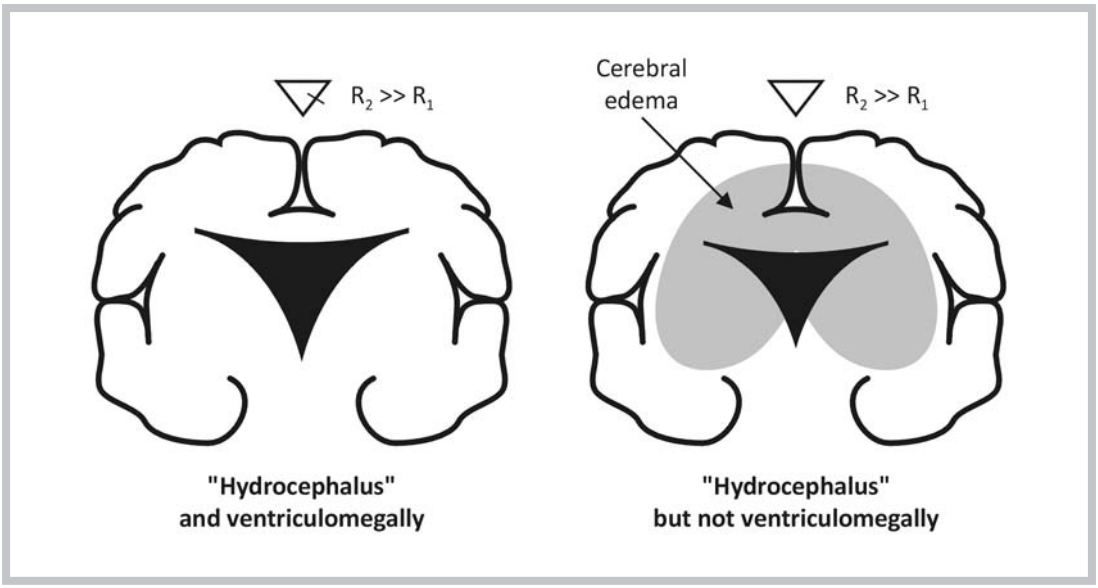

Figure 25.2. Representation of hydrocephalus with and without ventriculomegally.

in the diagram. This phenomenon was described by Levy and Rekate in post-trauma children, but we have observed it in subarachnoid hemorrhage (SAH), post-trauma meningitis, and cerebral cryptococcosis in neuroAIDS.

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26 Cerebral Edema: State of the Art

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26.1 Introduction

While the pathologies that lead to an admission to a neurocritical care are varied, most have in common a natural history of secondary injury. Frequently, the process that leads to secondary injury is cerebral edema, the ubiquitous alteration of normal intracranial fluid and electrolyte balance. In addition to contending with respiratory failure, infection, anemia, and venous thrombosis, the routine treatment of cerebral edema is a common and essential intervention in a specialized neurologic ICU. The focus of this chapter will be to delineate the mechanisms that lead to cerebral edema as well as how it is measured, and its various treatments. Edema can be categorized by the anatomic and physiologic failure that leads to the accumulation of fluid; however, these distinctions may over simplify the reality of the pathology. The understanding of the biochemistry of cerebral fluid balance is in its infancy, but recent investigations into neural water channels have advanced our understanding and will hopefully lead to new interventions. Traditionally, mannitol was the mainstay of osmotic treatment, but now hypertonic salt solutions and renal ADH receptor antagonists have provided new tools for the neurointensivist in modulating cerebral edema by altering water and sodium homeostasis.

The first step in understanding cerebral edema is to explore why its effects are so detrimental. Certainly edema is not a foreign concept to other organ systems. For example, pulmonary edema occurs with impaired cardiac function. Interstitial accumulation of fluid or “third-spacing” is common in liver failure or with sepsis. With these other organ systems, edema can lead to a reversible impairment of normal function which may require intervention; however, in general, the accumulation of fluid does not lead to further injury. Cerebral edema is of an even greater concern in comparison to systemic edema due to the rigid design of the skull. The brain is maintained in a rigid container with minimal compliance. This has obvious survival advantages from traumatic insults; however, it limits expansion of tissue making the brain susceptible to the effects of compression and herniation. Each system has a method to try to compensate for edema. In the case of pulmonary edema, the lungs hyperventilate and the heart increases its output. The brain attempts to compensate for edema by removal of the fluid components of the skull: CSF (cerebro-spinal fluid) and blood.

The limitations of skull chamber compliance were first described in the late 18th and early 19th century and donned the “Monro-Kellie doctrine” or the “Monro-Kellie hypothesis.” The brain is composed of three components: cerebral spinal fluid (approximately 150 ml), blood (both venous and arterial, approximately 150 ml), and brain (parenchyma as well as dura madre and connective tissue, approximately 1400 ml). If there is an intracranial lesion increasing the contents of the skull it must be at the expense of one of its components or an increase in intracranial pressure will occur. Usually this means the entering of CSF or blood. As the intracranial pressure increases, brain perfusion may be compromised leading to global ischemia. Furthermore, the dura and tentorium form

Herniation syndrome	Manifestations
Subfalcine	Cingulate gyus herniates under falx cerebri; may compress anterior cerebral artery and cause contralateral lower extremity paresis
Transtentorial (uncal)	Herniation of mesial temporal lobe/uncus causing ipsilateral third nerve palsy and contralateral hemiparesis
Cerebeller (tonsilar)	Herniation of cerebellar tonsils through foramen magnum, with compression of medulla oblongata
Central herniation	Downward herniation of prosencephalon compressing diencephalon and mesencephalon

Table 26.1. **Manifestations of herniation syndrome.**

functionally separate compartments and pressure differentials caused by mass or edema between these compartments causes herniation of brain tissue and injury. Herniation is described in a set of classic syndromes: subfalcine, transtentorial (uncal), cerebellar (tonsilar), and central herniation (Table 26.1).

26.2 Causes of Edema

Edema is categorized by the dysfunction leading to its formation. Depending on the pathology, the edema may be diffuse (e.g. traumatic brain injury, TBI) or focal (e.g. tumor). While diffuse edema will more often increase global intracranial pressure (ICP) potentially impeding cerebral perfusion, focal edema will cause unopposed pressure differentials, leading to herniation. Edema is an unfortunate companion to most intracranial pathologies, and as disparate are the types of insult as are the ways they may disturb fluid balance. The various etiologies do have in common a similar scheme of inflammatory mediators such as glutamate, free oxygen radicals, kinins, lactate and simple ions exacerbating the edema. Previously, each type of lesion was categorized under a single mechanism; for example, vasogenic edema in tumor and cytotoxic edema in stroke. As can be seen in Table 26.2, recent investigations show that there are elements of both types of edema in both pathologies. Clearly, edema is not as simple as previously thought. As you read the following sections, keep in mind that all of these distinctions are artificial designations for a disease process that we still do not fully understand.

The first category of edema is **vasogenic**. The blood-brain barrier (BBB) is composed of tight endothelial junctions, the zona occludens that preclude the free movement of fluids and solutes. This creates an isolated environment with its own water and electrolyte balance providing protection from systemic disturbances and invading pathogens. If the barrier is disturbed, solute and water can enter the brain parenchyma leading to edema. Exudate is then formed containing plasma proteins and albumin. Often the extent of the barrier disruption is proportional to the amount of edema it causes. Pathologies related to BBB and vascular integrity compromise includes tumor, hemorrhage, trauma, hypertension and cerebral infarction (to a certain extent) and PRES (posterior reversible encephalopathy syndrome). The BBB may be open for weeks after infarction. While traditionally thought to close in a biphasic pattern corresponding with ischemia and reperfusion, the barrier disruption may be monophasic and open for more than a month [1]. With tumor, direct mechanical disruption of the barrier can occur, or production of vasoactive and endothelial factors can lead to edema. With excessive blood pressure, the autoregulatory mechanism of the cerebral vasculature may be overwhelmed and fluid

will leak into the parenchyma due to Starling forces. In posterior reversible encephalopathy syndrome (PRES), also called reversible posterior leukoencephalopathy syndrome (RPLE), cerebral edema occurs with a predilection for occipital and parietal lobes in the setting of uncontrolled blood pressure and leads to headache and visual disturbances. Also included in the vasogenic category is cerebral venous thrombosis associated with hypercoagulable states (including pregnancy and oral contraceptive use as well as intrinsic coagulopathies) leading to a vascular back pressure causing intraparenchymal hemorrhage as well as edema. At high altitudes a special condition can occur as part of acute mountain sickness. As the oxygen partial pressure decreases, hypoxia leads to a decrease in oxidative metabolism of the BBB causing a vasogenic type edema called high altitude cerebral edema (HACE).

The second major category is **cytotoxic edema**. In this category, the sodium/potassium ion exchanger fails leading to an alteration of the normal osmotic balance between the intracellular and extracellular compartments. As cell components degrade and free proteins accumulate, a further increase in intracellular osmolality occurs leading to a water shift termed cytotoxic edema. Diseases usually included under this heading are: cerebral infarction, global hypoxia (such as with cardiac arrest and strangulation), traumatic brain injury as well as tumor and abscess. These pathologies not only cause the direct destruction of parenchyma, but also disrupt the cellular structure or surrounding tissue as they expand and infiltrate worsening the edema.

A third category is **interstitial edema** that occurs with alteration of CSF physiology. CSF is created in choroid plexus, circulates through the ventricular system across the foramen of Monro, Magendie and Lushka and then exudes into the venous circulation via arachnoid villi. If this system is disrupted by an ependymal tumor creating too much CSF or any limitation of its outflow (such as a colloid cyst obstructing the Foramen of Monro or communicating hydrocephalus caused by subarachnoid hemorrhage) hydrostatic pressure will build causing hydrocephalus and flow of fluid into the interstitial space surrounding the ventricles. Traditional therapies for edema can only ameliorate the edema if the underlying cause of the hydrocephalus are not adequately managed.

Toxin exposure, hyperthermia, and systemic disturbances in osmotic balance can also lead to cerebral edema, such as occurs in case of decreased albumin production with liver failure, SIADH (syndrome of inappropriate anti diuretic hormone), psychogenic water intoxication, and beer potamania. Two-thirds of patients develop hyponatremia during hospitalization, but certainly it can occur in non-hospitalized or even in healthy patients, such as long-distance runners who excessively consume water beyond the body capacity to regulate it [2]. SIADH deserves special attention as it is such a frequently encountered problem in a neuro ICU and has been associated with signifi-

Type of edema	Associated pathologies
Vasogenic	• Tumor • Stroke (hemorrhagic/infarct) • Hypertension/PRES • Trauma • HACE
Cytotoxic	• Stroke (hemorrhagic/infarct) • Tumor • Global hypoxia/anoxia • Trauma • Infectious/abscess
Interstitial	• Subarachnoid hemorrhage • Tumor (obstructing outflow) • Tumor (CSF producing)
Systemic/ osmotic	• Liver failure • SIADH (syndrome of inappropriate antidiuretic hormone secretion) • Psychogenic water intoxication • Beer potomania • Overcorrection of hyperosmotic states: hyperglycemia, uremia

Table 26.2. **Type of edema and associated pathologies.**

cant increases in mortality [2]. Common causes of SIADH include drugs, cancer, pulmonary dysfunction, or most of CNS insults. High levels of opiates, angiotensin, endothelian, cytokines, and neurotransmitters can all lead to abnormal production of anti-diuretic hormone (ADH, vasopressin) from the posterior pituitary gland. Even without any CNS pathology, an acute change in ECF osmolality will alter the osmotic balance causing fluid to shift to the intracellular compartment which represents more than the 80% of the brain parenchyma. Excessive hemodialysis of urea can cause an acute decrease in extracellular osmolality leading to marked cerebral edema. Similarly, over rapid correction of hyperglycemia in non-ketotic hyperosmolar hyperglycemia can lead to edema. Regardless of the etiology, a systemic decreased osmolality will cause a shift of fluid from the ECF to the ICF likely leading to cerebral edema.

Cerebral edema was identified early in neurocritical care as a frequent complication of brain insults, but our knowledge about the pathophysiology or even the normal physiology was very limited. While it can be observed macroscopically, it wasn't until this decade that science began to unlock the molecular mechanisms that regulate brain water homeostasis. Clearly diffusion alone is not responsible for fluid management; the brain has very specific mechanisms for maintaining homeostasis creating a privileged, isolated environment. Why would water and salt balance be any different? Indeed, specific molecules controlling the movement of water have been discovered: aquaporins. Peter Agre is credited with beginning an exploration into these transmembrane molecules that are responsible for selective water transport. While working in his lab at Johns Hopkins in the early 1990's on red blood cells and the Rh factor, he identified a molecule responsible for water transport for which he won the Nobel Prize in 2003. This became known as aquaporin-1 or AQP1 and since then 11 different aquaporins have been discovered. The molecule is a small transmembrane protein selective for water with tandem repeats of membrane spanning helices with carboxyl and amino terminals towards the cytoplasmic side containing an aspargine-praline-alanine (APA) motif. Two subtypes are described, the traditional one, transporting water (AQP0, 1, 2, 4, 5, 8) and the aquaglycerolporin, transporting also glycerol (AQP3, 7, 9, 10) [3]. While AQP 1 predominates in the kidney, AQP4 predominates in the brain. It is a 32 kDa protein found in astrocyte end-feet processes close to capillaries. AQP1 is also found in choroid plexus and AQP9 is found in tanycytes [4].

Perivascular astrocytes can increase their volume two to three times in the presence of edema while those not located next to vessels show little change when challenged by free water. As the aquaporins are located mainly in the astrocytes, it is postulated that they are responsible for the change in astrocyte volume [5]. The relationship between aquaporins and cerebral edema has been supported experimentally in transgenic mice that are APQ4 null. Interestingly, The AQP null mice have less edema in cytotoxic edema models while they have more edema in vasogenic models [6,7]. This apparent contradiction may be due to multiple subtypes of AQP4 as well as their role not only in water transport but also in causing astrocyte migration in cerebral edema.

Aquaporin expression likely varies with the current physiologic state. The neural environment has rapid turnover of neurotransmitters and peptides requiring a dynamic system to maintain fluid and electrolyte balance. A growing body of evidence shows upregulation in AQP4 expression associated with edema in cerebral infarction models [8], and interestingly, the upregulation is increased more significantly in the presence of exogenous hypertonic saline [9]. Aquaporin expression is likely not just regulated by local factors but is influenced by systemic signals. For example, liver failure is thought to cause cerebral edema through elevated levels of ammonia and manganese. Astrocytes have been shown to swell in vitro in the presence of ammonia and alteration of aquaporins may be responsible for these changes [3].

26.3 Methods to Measure Edema

When treating cerebral edema it is important to have some way to measure its severity in order to determine whether it is being adequately treated or if a different intervention is needed. Three different methods are usually used: clinical exam, radiographic findings, and invasive monitoring. The choice of a specific exam depends on the location of the insult and the neurologic function of the affected tissue. If the patient has a frontal lobe tumor and shows progression of abulia, impulsiveness, somnolence or language deficit, then the edema may be getting worse. In a temporal subdural with uncal herniation, a pupil becoming fixed and dilated or worsening of hemiparesis may indicate that the cerebral edema is progressing leading to compression of the third cranial nerve.

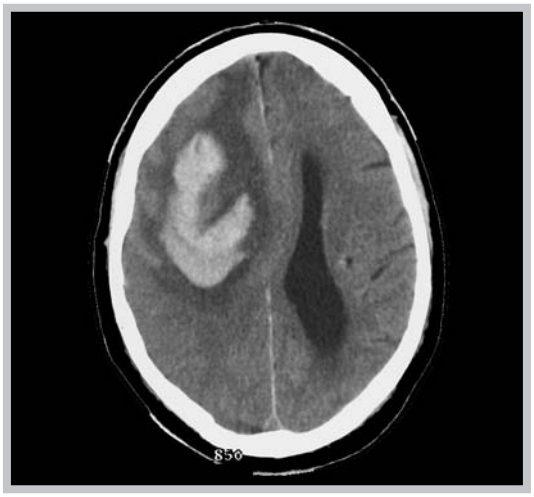

Figure 26.1. Hemorrhagic stroke with cytotoxic edema as indicated by hypodensity surrounding the hemorrhage.

While clinical changes are the most important endpoint of cerebral edema, they indicate an advanced stage and therefore should be coupled with other methods such as radiography. Cerebral edema can be identified by computed tomography (CT) observing low density attenuation around the primary CNS insult (Figure 26.1) causing mass effect. Examining its location and dimension, one can estimate the time of the lesion progression and its effects on the surrounding tissue. The effects of the edema can be identified by the amount of sulcal and cisternal effacement or shifting of tissue out of its normal location (Figure 26.2) such as midline shift or temporal lobe herniation through the tentorum cerebelli. MRI can provide further detail of the location and extent of edema with T2 or FLAIR imaging.

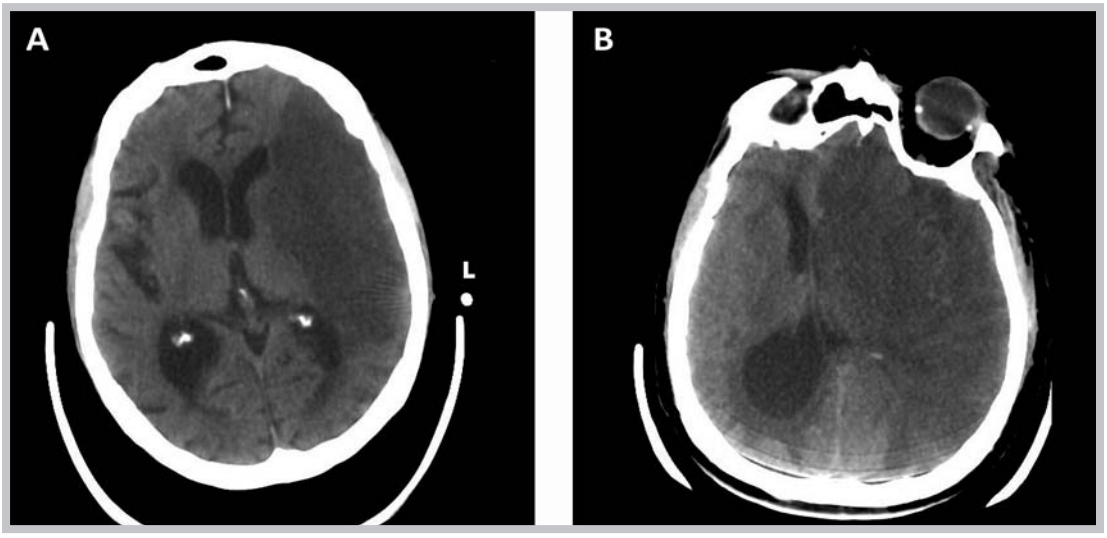

Figure 26.2. Cerebral infarction with edema causing effacement of sulci and ventricles as well as herniation and midline shift of the left hemisphere towards the right.

Cerebral edema can also be measured indirectly by quantifying changes in ICP measured invasively. While the primary insult will have a certain degree of effect in ICP, subsequent changes are more likely due to changes in edema. The intraventricular catheter (ventriculostomy) is a soft tube placed through a burr hole into the lateral ventricle. This not only allows measurement of ICP, but also allows removal of CSF which can relieve pressure caused by edema. The implantable transducer is drilled through the skull with a probe that extends into the parenchyma allowing it to measure ICP but not allowing the removal of fluid. ICP measurement is often the method of choice in diffuse injury such as TBI or global hyponatremia/hyposmolarity caused by metabolic derangements or liver failure, as the CT scan may not show any focal changes. These changes can be followed radiographically in order to determine if an intervention is needed, as well as the response to it.

26.4 Treatment

Now that the causes and methods to measure edema have been explored, we will discuss the treatment of cerebral edema. Several strategies have been developed to treat cerebral edema, both medically and surgically. We'll focus on medical therapies to remove the excess of fluid related to edema. Surgery can effectively treat edema not only by removing the primary insult, but also by removing a large bone flap allowing decompression of edematous tissue. Alternatively, metabolic suppression through induction of hypothermia or drug induced coma can reduce metabolic activity providing protection from edema.

Osmotic therapy has long been the mainstay of medical therapy of cerebral edema. The use of osmotic therapy is based on water diffusion; two solutions separated by a semipermeable membrane will allow the flow of solvent from the compartment with lower solute concentration to the one with the higher concentration. In addition to the barrier created by the vascular endothelium, the BBB will prevent solute from following solvent. The same principle that leads to edema can guide its treatment. Accumulation of osmotically active particles from cell death or leakage caused by membrane breakdown creates an abnormal osmotic gradient which is treated with mannitol to create a new one.

Mannitol is the most commonly used osmotic agent for the treatment of cerebral edema. It is a sugar alcohol with the chemical formula $C_6H_8(OH)_6$. Other examples of sugar alcohols include xylitol and sorbitol. Its properties were first described by Weed and McKibben in 1919 but its use to treat cerebral edema wasn't common until the 1960s. Its role as the ideal osmotic agent is based on the fact that it has a high reflection coefficient, a measurement of how much a substance is excluded by a membrane. The higher the coefficient, the more likely it is to be excluded by the BBB. Sodium chloride has an approximate coefficient of 0.95 (rated 0 to 1) while mannitol coefficient is 0.90. Because it is largely excluded and is not metabolized by the brain or liver, it is an osmotically active particle as long as the cell membrane and BBB are intact. After administrating a dose, it distributes within a few minutes through the extracellular compartment [10]. The effects of mannitol occur in multiple phases. First, it removes excess fluid by creating an osmotic gradient in favor of the ECF over the ICF. Secondly, mannitol acts as osmotic diuretic: as it is excreted by the kidney, it removes free water and thereby reduces overall volume status. Additional postulated effects of mannitol include increasing RBC rheology, thus reducing blood viscosity. As this leads to increased blood flow, cerebral vascular autoregulation may decrease blood volume, potentially assisting in decreasing

ICP. Furthermore, it is postulated that mannitol acts as a free radical scavenger reducing the inflammatory cascade present in cytotoxic edema.

The first question concerning mannitol is, is it effective? The literature clearly shows that it can decrease ICP in TBI [10]. This effect seems to be dose-dependent and higher doses show a more durable ICP control [11]. In respect of cerebral infarction, some animal models show a decrease in peri-infarct edema with mannitol as well as residual deficit, but other models do not show efficacy. The Cochrane review of mannitol in stroke does not find evidence for improvement in outcomes [12]; but the American Heart Association Guidelines still recommends it as a potential therapy based on expert opinion. While osmotic therapy clearly can alter ICP, whether it can cause an improvement in outcome is much harder to demonstrate. In many patients mannitol doesn't seem to affect a patient's sodium level: in one series of 167 patients, 73 (44%) didn't have an increase of sodium greater than 5 mEq/l while 37 patients (22%) didn't have a rise greater than 1 mEq/l [10].

Typical doses of mannitol are 0.5 to 1.5 g/kg given in four to six hour increments. The main limitations of its use are excessive diuresis causing volume depletion which may lead to renal insufficiency, rebound cerebral edema, and renal failure if it obstructs the renal tubules. Within hours to days of mannitol administration, the brain adapts to the higher osmolality by accumulating yet to be described organic osmoles called "idiogenic osmoles" in an attempt to restore normal cell size. This might explain why its effects seem time and dose limited; however, it is likely that this same phenomenon happens with hypertonic saline or other osmotic therapies.

A possible limitation to mannitol therapy is that as it creates an osmotic gradient most effectively across an intact BBB, it may preferentially extract water from the intact brain and not be as effective in the damaged brain. Consequently, it could theoretically exacerbate the intracranial pressure differential and actually aggravate tissue shifts. This complication may be prevented, however, if mannitol is fully eliminated before administering another dose. The complete clearance of mannitol by the kidneys given sufficient time has been well documented, including MRI spectroscopy showing end stage renal patients treated with mannitol that has leaked into the brain parenchyma who demonstrates absence of mannitol after dialysis [13].

In order to ensure proper clearance and prevention of rebound of cerebral edema, mannitol levels need to be monitored. The goal is to ensure proper clearance between doses. Mannitol cannot be routinely measured in a clinical setting. As a surrogate, serum osmolality is directly measured and compared to the calculated osmolality. The calculated osmolality is simplified to the dominate serum solutes sodium, urea, and glucose. The difference between the measured and calculated osmolality will then be composed of the unmeasured osmoles including mannitol and called the "osmotic gap" (OG).

Osmolality is calculated using the following euation:

$$2Na^{+} + (BUN / 2.8) + (glucose / 18)$$

where BUN = bllod urea nitrogen.

This osmotic gap has been validated by studies as an indicator for mannitol levels with a high correlation of OG to mannitol [14]. Historically, some authors recommended to follow a safety level of osmolarity equal to 320 mOsm/l, but such practice is not well founded as it relies on studies where mannitol was given as a continuous infusion, which is not common in clinical practice. It is important that the osmolality and gap are measured before the mannitol is administered as the gap is used to measure the trough of the drug and not its peak. Gap is not used to measure efficacy but to prevent toxicity by ensuring

mannitol is cleared from the blood after each dose. If the current dose is not obtaining the desired effect on the cerebral edema, it can be increased depending on the change of the osmotic gap from its baseline.

The next issue to address is the potential adverse effects caused by inducing a hypernatremic state. To show the extent of the concern, some authors report a mortality of 40% to 60% in those with elevated sodium but this might be do their admitting diagnosis and not the sodium perturberance itself. Hypernatremia can occasionally be found in dehydrated and cognitively impaired patients, but it usually occurs in hospitalized patients. Certainly in a neurologic and neurosurgical ICU hypernatremia is common even in subjects not on osmotic therapies, due to the fact that these patients are obtunded, having central insults causing diabetes insipidus, and central fevers causing insensible fluid loss. Hypernatremia can cause renal failure, gastrointestinal dysfunction, cardiac dysfunction, and worsening delirium. Mannitol itself can be nephrotoxic if it accumulates in the kidneys and shouldn't be used in people with significant renal impairment. Furthermore, patients with poor renal function caused by such things as hypertension and diabetes require careful monitoring. Typically, in our ICU we use a maxiumum sodium level of 160 mEq/l. In a 6.5 year retrospective analysis of more than four thousand patients, sodium over 160 mEq/l was found to have independent increased mortality on multivariative analysis [15]. Once a patient recovers from their primary insult, it is safe to correct the sodium at a rate no faster than 5-10 mEq/l/day to avoid rebound edema. Additionally, magnesium and phosphorous should be followed on a daily basis to monitor for depletion associated with osmotic dieresis.

Hypertonic saline (HS) has become increasing popular as an alternative to mannitol to treat cerebral edema. Skeptics of HS would point out that mannitol might not be solely effective because of the osmotic effects but because of its other actions as described above, but still consider it a reasonable alternative in patients with renal impairment or refractory to mannitol therapy. It certainly has the advantages of being a volume expander, and therefore might be superior in trauma. In addition, patients with subarachnoid hemorrhage may have edema but also be at risk for developing vasospasm if their volume is depleted by mannitol. Insufficient head to head comparison studies have been done, which are largely limited by varying doses used (how much hypertonic saline is clinically equivalent to how much mannitol?) and the heterogenicity of the patient population treated for cerebral edema. Hypertonic saline does have a slightly higher reflection coefficient than mannitol, and therefore less risk of rebound, but it also has other higher risks. For example, more rapid sodium alterations increase the risk of central pontine myelinolysis. Hypertonic saline leads to significant volume expansion which may lead to heart failure and pulmonary edema if not taken into consideration. The excessive chloride with HS increases the risk of hyperchloremic metabolic acidosis. While it does lack of free radical scavenger properties, it has been correlated with decreased ICP in both adults and children [10]. While mannitol is still the first line drug for cerebral edema, there are patient populations for which HS may be an appropriate alternative.

While mannitol is by far the most commonly used osmotic agent, others have been used. **Glycerol** is a sugar occasionally used with the theoretical advantage of being metabolized after crossing the BBB making the likelihood of rebound unlikely. It is hard to comment on glycerol efficacy, because of lack of substantial studies or common clinical experience.

Furosemide is commonly used for control of patient's overall volume status, and its efficacy is certainly well established. **Steroids** such as dexamethasone are the mainstay of vasogenic cerebral edema as they are well established in stabilizing the integrity of the BBB and thereby reducing fluid influx. Pathologies such as tumor-associated edema are commonly treated with steroids, but they have not proven effective in other patholo-

gies such as stroke. Peritumoral brain edema (PTBE) is related to inflammatory mediators secreted by the tumor such as interleukin [16] and growth factors such as vascular endothelial growth factor (VEGF) causing abnormal vascularization with impaired capillary endothelial tight junctions that leads to vasogenic edema [17]. Steroids have not been shown to be effective in cytotoxic edema probably because the integrity of the BBB is not necessarily compromised in these conditions.

As stated previously, SIADH is a common phenomenon in patients with CNS insults. Hyponatremia can worsen cerebral edema; therefore, it's worthwhile to discuss its treatment. A relatively new therapy is the **V1A/V2 (arginine vasopressor) receptor antagonists** such as conivaptan and tolvaptan. They treat SIADH by directly blocking the supraphysiologic ADH at the renal tubule allowing an aquaresis. Previously SIADH was treated with limiting free water intake, hypertonic solutions, and furosemide. Its use requires a careful distinction between cerebral salt wasting and SIADH because in the case of salt wasting syndrome, the further volume depletion with V1A/V2 antagonists would lead to a more severe hypovolemia. Furthermore, its use in subarachnoid hemorrhage patients must be carefully monitored because of the risk of volume depletion contributing to vasospasm. ADH antagonists will cause an aquaresis even in normotremic patients and thereby could be used to treat cerebral edema. Generally speaking, it is better to use ADH antagonists in hyponatremia associated with SIADH, rather than in cerebral edema, but future studies may highlight their role in inducing hypernatremia.

26.5 Conclusions

While cerebral edema seems a relatively simple concept, developments in both clinical medicine and basic science have shown that its causes are as diverse as the disease associated with it and its physiology has complex regulation. We are used to distinguish different types of edema (cytotoxic, vasogenic, hydrostatic, and osmotic); however, most of the diseases encountered in a neurologic ICU show combinations of these types of edema. While many osmotic therapies have been used, mannitol is still the mainstay of treatment, and if used and monitored appropriately it has little risk. The growing use of hypertonic saline will likely continue to increase and in some cases may be a better choice than mannitol. The most exciting development in the science and treatment of cerebral edema is a growing understanding of the role and regulation of aquaporins, whose modulation is already being tested [18] in animal studies and may lead to novel therapies to alter not just the location of fluid by osmotic gradient but augment the brains ability to compensate for edema.

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27 The Treatment of Intracranial Hypertension. Algorithm of Treatment and First Level Therapeutic Measures

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It is quite possible that the phrase "primum non nocere" is more applicable to the treatment of traumatic brain injury in the acute stage than any other pathology. Maintaining an optimal cerebral environment and correctly treating intracranial hypertension are fundamental in avoiding added injury to our patients and achieving the continual decrease in mortality and poor results.

27.1 Introduction

Traumatic brain injury (TBI) continues to be the leading cause of death and disability in people under 45 years of age. Furthermore, incidence is on the increase; at present this disease is considered pandemic, with particular repercussions for less developed countries. However, this pessimistic finding contrasts with a clear, objectively positive observation in recent years: although high-energy injuries involving the severest acceleration/deceleration mechanisms have increased, mortality rates and poor results have decreased significantly. In 1991 the information gathered by the American Traumatic Coma Data Bank (TCDB) indicated that mortality rates were situated at 36%, with an overall percentage of poor outcome (death, vegetative state or severe disability) reaching nearly 60% of patients with severe TBI [1]. Recent analysis indicates that this figure has been reduced very significantly to 40% in centers with extensive experience in the management of brain injured patients [2].

The main explanation for this decrease should be sought in the significant changes in treatment applied to these patients. However, drugs and therapeutic maneuvers used on patients with TBI (mannitol, hyperventilation, barbiturates, etc.) are unchanged in the last 20 years and all attempts to introduce new neuroprotective drugs (glutamate inhibitors, calcium channel blockers, or oxygen-free radical inhibitors, among others) have failed. The causes of this decline in poor outcome may be explained by a combination of factors, including the following: 1) improved understanding of the pathophysiology

of TBI, 2) the multidisciplinary management applied to this condition, 3) the creation of units specialized in the management of these types of neurocritical patients, and 4) the development and following of clinical practice guidelines (CPG) that have advocated the use of standardized and systematic treatment protocols for the treatment of intracranial hypertension (ICH) [3,4]. Nevertheless, the treatment of TBI is still prone to excessive variability in the numerous hospitals that receive and treat such patients. This variability, while justified in some cases, can be a reflection of reluctance on the part of the various medical groups implicated to accept that the systematic treatment of these cases brings about a clear benefit, not only for patients but also for the social environment in which they live.

In the last decade, our center has observed a progressive reduction in mortality and an increase in good outcome in patients with severe TBI. We are convinced that this change is due to the fact that our center was able to carry out the 4 measures described above, especially the systematic, stepwise protocol for the management of these patients optimized on the basis of a multimodal neuromonitoring protocol. This chapter summarizes the series of general measures and the systematic approach used by our hospital for TBI patients admitted to the Neurotraumatology Intensive Care Unit (ICU).

In this chapter, the general measures and specific treatment for ICH given to in-hospital patients with severe traumatic brain injury are outlined. We assume that the foundations of "evidence-based medicine" and other aspects, including multimodal neuromonitoring or the management of specific aspects, such as fluid therapy or nutrition, have been covered extensively in other chapters of this work. In this chapter we focus on general measures and first level measures in the treatment of ICH based mainly on recommendations of the Brain Trauma Foundation (BTF) without ruling out additional sources of evidence, such as the Cochrane Collaboration.

We aim at providing information that is above all practical and concise by supplementing the text with a series of useful tables and algorithms. In addition to theoretical information, we have included an illustrative case report in which we describe the maneuvers used and identify the controversial points or inadequate aspects of patient management.

27.2 Neurotraumatic Patient Treatment in the Hospital

In this section we refer to the treatment of patients once they have arrived at the final hospital. Treatment at the receiving hospital should begin in the emergency department. The therapeutic conduct and the type and number of complementary testing to be carried out must be individualized in all cases. As a general rule, however, once the airway and hemodynamic status is stable, patients should be evaluated according to the Glasgow Coma Scale (GCS), noting whether there are differences at the initial assessment made after resuscitation, during transport of the patient, or at the first reference center. In addition to the GCS score, breathing pattern and the size and shape of the pupils, pupil reactivity to light and the presence of corneal reflexes should all be noted during the neurological examination. In paralyzed patients undergoing mechanical ventilation, prehospital evaluation using the GCS will guide the therapeutic management. In cases where this assessment is unreliable and the CT brain scan shows no obvious injuries, it is advisable to reverse paralysis and re-examine the patient before proceeding to monitoring and aggressive, and possibly unjustified, treatment.

Any associated systemic injuries (pulmonary, genitourinary, abdominal, etc.) should be evaluated and treated in order of priority. At the same time, external craniofacial inju-

ries are evaluated (otorrhagia, head contusions, etc.) and the possible existence of cervical injuries are determined before transferring the patient to the neuroradiology unit for tomography scanning. It is important that the transfer to the CT area is under optimal conditions, which includes ensuring flow of the airway, adequate ventilation and proper functioning of the fluid delivery pathways. Too often, these patients suffer significant deterioration in their neurological status during the periods spent in the hospital corridors waiting for various complementary examinations.

Tomography scans should be performed in a quick and technically correct manner because this first exploration allows existing brain injury to be assessed and classify the patient according to the different groups of pathologies described by Marshall et al. [5]. Based on the volume of the lesions, the status of cistern compression and the degree of deviation from the midline, this classification consists of 4 types of diffuse lesions and the presence of intra- or extra-axial focal lesions requiring surgical evacuation. The Marshall classification also provides initial prognostic information because each of the injury categories is associated with an increased risk of ICH and a poor outcome (Figure 27.1) [6].

Early surgical treatment of space-occupying lesions is essential for the correct treatment of patients with severe TBI. At our center, all space-occupying accesible lesions with a volume exceeding 25 ml are evacuated surgically. In our opinion, the use of the initial levels of intracranial pressure (ICP) in making surgical decisions, while controversial, is helpful in doubtful cases. In general, we can say that regardless of their level of consciousness, patients with focal lesions whose ICP levels are moderately elevated will

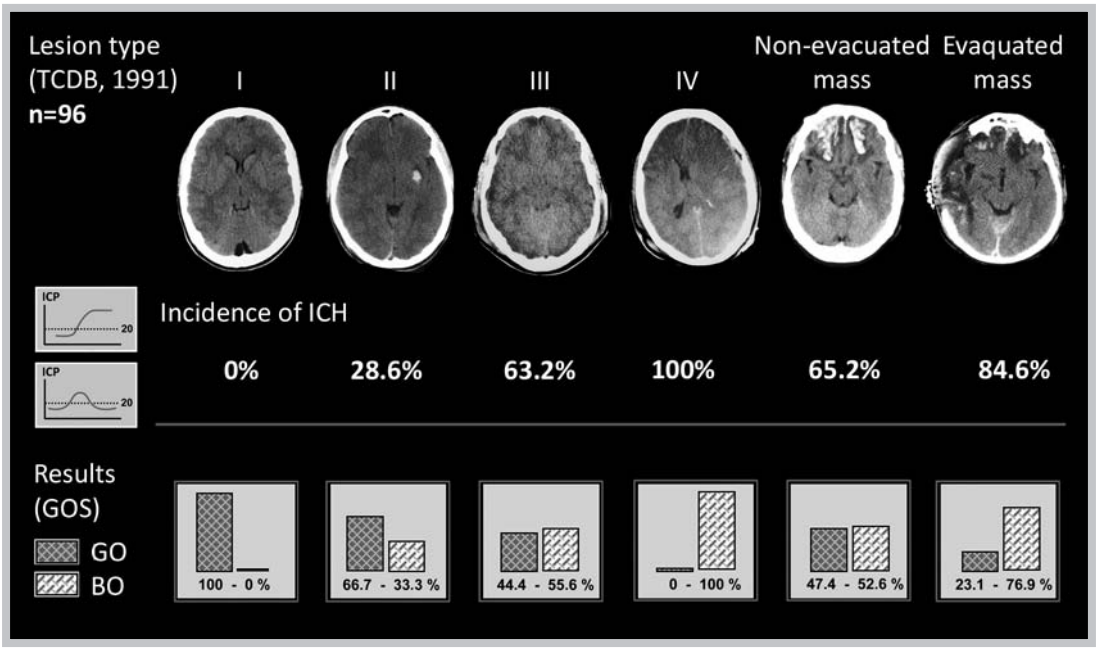

Figure 27.1. **Traumatic brain injury according to the classification system of the American Traumatic Coma Data Bank. (I) Diffuse type I injury (comatose patient with normal CT). (II) Diffuse type II injury (permeable cisterns, midline centered with small lesions). (III) Diffuse type III injury (bilateral brain swelling). (IV) Diffuse type IV injury (midline shift >5 mm with no focal lesions to account for this distortion in the brain). Non-evacuated mass is any intra- or extracerebral lesions with a volume >25 ml that were not evacuated. Evacuated mass is any evacuated focal lesion. The image shows the different percentages of intracranial hypertension incidence and associated poor outcome in the 96 patients included in the study [6].**

GO = Good Outcome

BO = Bad Outcome

present late neurologic deterioration, the result of uncontrolled ICP elevations in a large percentage of cases [7,8]. We feel this point justifies an aggressive therapeutic approach aimed at preventing these situations. The wait-and-see approach in these types of patients, especially those presenting concussions, often has catastrophic results. Although the predominant type of lesion may vary depending on the damaging mechanism, it is generally estimated that 25-45% of patients with severe TBI, 3-12% of those with moderate TBI, and 1 in 500 mild TBI patients present a focal lesion requiring intervention.

27.3 Multimodal Monitoring in Patients With Severe Traumatic Brain Injury

Once the CT scan is performed and any space-occupying lesions are evacuated, patients are transferred to the ICU, where the therapeutic approach should be aimed at creating a means favorable to the recovery from primary lesions and the early treatment and prevention of secondary injuries. The difficulty in carrying out appropriate clinical monitoring in these patients requires the use of a multimodal monitoring protocol that includes neurological and systemic parameters. It is well established that a score less than or equal to 8 on the GCS reflects a risk of ICH. In studies performed by the Traumatic Coma Data Bank during the 1990s, it was shown that between 50-75% of these patients had ICH at some point during the evolution of the injury [9]. At present, we know that this incidence can be adjusted according to the type of brain injury[6] and that it decreases dramatically with an aggressive surgical approach to focal lesions.

The high risk of ICH in severe TBI explains why continuous monitoring of ICP has been implemented almost routinely in the management of these patients, especially since the 1995 publication of the CPG for TBI management developed by the BTF. These guidelines have been updated and endorsed by most international scientific societies. The latest version, published in 2007, reaffirmed with level II evidence that ICP monitoring should be applied in all severe TBI patients with an abnormal CT scan upon admission [10]. The implementation of an ICP sensor is also indicated in TBI patients with an initial CT scan that is normal if a GCS score of less than 8 can be confirmed. This is based on the fact that 1 of every 3 of these patients show new brain lesions in the subsequent CT scan [11]. In recent years, however, we have found that the value of ICP as a parameter alone is insufficient for decision making in complex cases. In addition to the ICP sensor in the latest edition of the BTF guidelines, it is also recommended that additional monitoring systems be included to provide overall or specific information regarding cerebral oxygen availability, such as oxygen saturation in the jugular bulb (SjO_2) or catheters for direct measurement of oxygen pressure at the tissue level ($PtiO_2$) [12].

In our center, all patients with TBI who present a diffuse lesion, or those in whom a focal lesion was evacuated, undergo implantation of an intracranial pressure (ICP), intraventricular, or intraparenchymal sensor. When using an intraparenchymal sensor, the more damaged brain hemisphere is selected [13]. In addition to the ICP sensor, TBI patients are implanted with a retrograde catheter in the predominant jugular vein and/or a catheter for tissue oximetry in the less injured hemisphere. In selected cases, 1 or 2 cerebral microdialysis catheters are also placed in the patient. These new monitoring techniques allow continuous information on various aspects of blood flow and cerebral metabolism to be obtained. At the systemic level, multimonitoring of patients is also recommended. This basically involves the control of diuresis, heart rate, blood pressure (with the transducer leveled at the foramen of Monro), and central venous pressure, in addition to measuring the pressure in the pulmonary artery in cases of hemodynamic instability.

27.4 General Measures for Treating Brain Injured Patients

While in the ICU, severe TBI patients undergo monitoring of both ICP and cerebral and systemic hemodynamics. This is what guides the course of treatment for these patients. Although many of these cases involve associated systemic injuries, we generally refer to the patient with "pure" severe TBI or with associated lesions that do not significantly modify treatment. To simplify, we could define the key therapeutic targets in patients with intracranial hypertension as reducing ICP and maintaining a mean arterial pressure (MAP) sufficient to maintain adecuate cerebral perfusion pressure (CPP). In severe TBI patients, a series of general measures, regardless of the initial value of the ICP, should be taken early on to achieve a correct hemodynamic stability and an adequate supply of nutrients, and to avoid any factors that increase ICP. The latter may include maladaptive breathing, improper positioning of the patient (Figure 27.2), hypoxia, hypercapnia, high fever, seizures, hypo- or hypertension, and hyponatremia.

Maintaining normovolemia and making a correct selection of serums to administer play an essential role in the treatment of these patients. Electrolyte management includes maintaining an adequate circulating blood volume (which helps maintain the correct CPP and availability of O_2), a volume in the brain interstitium that is somewhat lowered, and a discrete serum hyperosmolality. It is recommended that isotonic solutions are administered in TBI patients. A NaCl solution at 0.9% is considered the crystalloid of choice. A 5% albumin or hydroxy-ethyl starch of low molecular weight are the more widely accepted colloids. The administration of glucose solutions is not advised unless there is a risk of hypoglycemia because this condition may exacerbate ischemic injury. In addition, glucose causes an osmotic drag of water in the transport, which may contribute to the formation of cerebral edema.

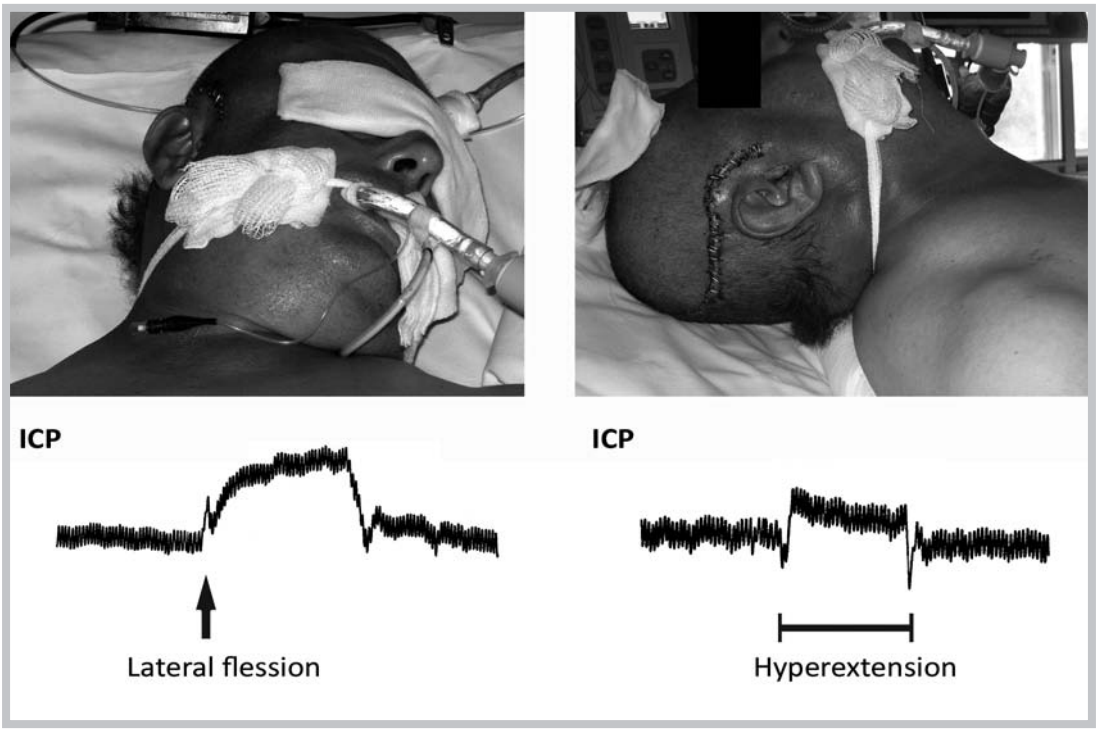

Figure 27.2. **Image showing the effect of cranial position on intracranial pressure (ICP). Both hyperextension (right) and lateral flexion (left) in moderate amounts cause evident increases in ICP.**

Ideally, the objectives of this set of comprehensive measures are aimed at: 1) evacuating lesions with a volume >25 ml occupying intra- or extracerebral space, 2) maintaining normothermia, with a core temperature (rectal, esophageal or bladder) <37 °C, 3) maintaining an ICP below 20 mmHg, 4) maintaining levels of MAP >90 mmHg that allow CPP values ≥ 60 mmHg [14], 5) maintaining a total content of hemoglobin and a level of PaO_2 to ensure proper transport of oxygen to the brain (recommended: hemoglobin >10 g/dl and PaO_2 of 100-110 mmHg), 6) maintaining values of SaO_2 >95% associated, if possible, with normocapnia and 7) maintaining values for SjO_2 above 60% [15].
General measures also include proper analgesia and sedation of the patient. Analgesics and sedatives should be used in combination to enhance their effects and thereby reduce the individual doses. Given the depressant effect of these drugs on the respiratory system, mechanical ventilation should be used. To address their cardiovascular impact, doses may be adjusted according to the patient's hemodynamic status. At present, **midazolam** is considered the sedative of choice due to its short half-life in comparison to other benzodiazepines. Other sedatives, such as **propofol**, may cause arterial hypotension, an important drawback. **Morphine hydrochloride** and **fentanyl** are the more adequate analgesics because a conventional dose not increase cerebral blood flow (CBF) or ICP.

27.5 Specific Treatment of Intracranial Hypertension

In cases where ICP >20 mmHg and the abovementioned maneuvers have been carried out correctly while ensuring that there are no new space-occupying lesions requiring surgical evacuation, a stepwise, additive treatment for ICH should be initiated. From the

Measurement	Recommendation	Level of evidence
Muscle relaxants	There are no specific recommendations	-
Evacuation of CSF	There are no specific recommendations	-
Mannitol	Without monitoring ICP, mannitol may only be given if signs of transtentorial herniation or progressive neurological deterioration are observed	III
	Mannitol is effective in controlling ICH when used at doses of 0.25-1 g/kg. When used, decreases in systolic arterial pressure (SAP) to below 90 mmHg should be avoided	II
Hypertonic saline solution	There are no specific recommendations	-
Hyperventilation (HV)	HV should not be used prophylactically ($PaCO_2$ <25 mmHg)	II
	HV should be used intermittently for ICH	III
	HV should be avoided during the first 24 hours of injury, when CBF is reduced	III
	If using HV, monitoring the availability of brain oxygen using SjO_2 or $PtiO_2$ is recommended	III

Table 27.1. **Table of evidence of the Brain Trauma Foundation (2007 edition) for the treatment of intracranial hypertension in patients with severe traumatic brain injury.**

CBF = cerebral blood flow
CSF = cerebrospinal fluid
ICH = intracranial hypertension
ICP = intracranial pressure
$PaCO_2$ = arterial pressure of carbon dioxide
$PtiO_2$ = brain tissue oxygen pressure
SAP = systolic arterial pressure
SjO_2 = jugular bulb oxygen saturation

time of the publication of the first version of CPG (1995) by the BTF, our center designed a treatment algorithm largely adapted to the recommendations of these guidelines. After almost 15 years, this algorithm remains essentially unchanged because the latest versions of these guides have not produced significant changes in most of the therapeutic measures used. However, this algorithm included, and includes, differential aspects, such as a less frequent use of barbiturates (this is discussed extensively in the chapter on second level measures in the treatment of ICH), additional maneuvers, such as hypertonic saline, as well as specific considerations for certain injuries obtained from other sources of evidence.

For patients with persistent intracranial hypertension, first level measures for the treatment of ICH, as outlined in the first 2 editions of the BTF CPG, will be initiated in addition to reviewing previous general measures. These measures include muscle relaxation, the evacuation of cerebrospinal fluid (CSF), the administration of hyperosmolar solutions, and hyperventilation. Almost all are based on type I or II levels of evidence (Table 27.1). In the sequence of application for treating ICH, the administration of muscle relaxants follows the evacuation of CSF, if possible. This therapeutic maneuver is only possible in cases in which ICP monitoring is done using an intraventricular catheter. Hyperventilation and/or the administration of hyperosmolar solutions are the subsequent therapeutic stages. When all these measures are insufficient, the BTF recommends the administration of barbiturates at doses sufficient to induce a burst-suppression pattern [16]. However, based on the controversies generated by the dissemination of the results of the Cochrane Collaboration on the real effectiveness of this drug [17], our center does not routinely consider using this therapeutic measure.

27.6 Muscle Relaxation

Despite the controversy that still exists in the literature on the use of muscle relaxants in the treatment of patients with severe TBI, it is generally accepted that the first specific maneuver to treat ICH should be muscle relaxation [18-21]. The periodic tracheal aspirations performed on these patients may incur significant elevations in ICP despite the additional administration of sedatives and analgesics. When the patient is given muscle relaxants continuously, these changes in ICP are reduced significantly. As an additional advantage, muscle relaxants reduce elevations in ICP that may occur during habitual movements of the patients (daily hygiene, postural changes, clapping, etc.), and facilitate mechanical ventilation. Despite the fact that the BTF do not include a specific chapter on muscle relaxants in its CPG, in its previous version and in the chapter on the early management of patients, the panel recognized that muscle relaxants facilitate the ventilation and treatment of ICH, although they do not address its use on specific patients [22]. For children, there are no specific recommendations for these drugs [23].

While the use of muscle relaxants during the prehospital phase or hypothermia treatment is unquestionable [24], a continuous infusion of muscle relaxants during hospital treatment has been associated with longer stays in the ICU and a greater dependence on the ventilator, both of which increase rates of septic complication in the patient [19,25]. Other problems associated with the prolonged administration of relaxants are the impossibility of making an appropriate neurological assessment, drug accumulation and the appearance, in some cases, of secondary myopathy [26]. The latter is enhanced by the co-administration of aminoglycosides and corticosteroids [26]. Despite these drawbacks, recent studies have not associated the use of muscle relaxants with a worse patient outcome [24].

Response*	Cause	Recommendation
TOF=0	Excessive muscle relaxation	Dose reduction or temporary suspension of relaxant administration
TOF=1	Appropriate level of muscular block	None
TOF=2-4	Inadequate level or absence of muscular block	Increase dosage of the drug

Table 27.2. **Monitoring the effectiveness of muscle relaxants using the "Train of Four" (TOF).**
TOF = 0: no muscle response by electrical stimulus
TOF = 1: muscular contraction by electrical stimulus
TOF = 2-4: two to four muscular contractions by electrical stimulus

Current recommendations on the use of muscle relaxants indicate that they should always be administered simultaneously with sedatives and analgesics. The dose should be the lowest possible amount, with monitoring of its effect using the train of four (TOF – peripheral nerve stimulator), and should be stopped at an early stage [22]. Adequate relaxation should cause a contraction by electrical stimulation. The administration of relaxants should be optimized according to the responses obtained in the TOF [15] (Table 27.2). Of the drugs emerging on the market, vecuronium at a dose of 0.01 to 0.05 mg/kg/hour is recommended because it allows for more hemodynamic stability [15]. Other alternatives continue to be pancuronium or cisatracurium. In the absence of contraindications, preventative measures for deep vein thrombosis and bedsores should be taken [22].

27.7 Evacuation of Cerebrospinal Fluid

When ICP increases, there is a physiological tendency toward the displacement of CSF from the cranial cavity to the spinal canal and an increase in elimination, mainly via the venous compartment. This phenomenon is one of the main mechanisms for compensating for increased volumes in a "closed" system like the cranial cavity and explains why patient ICP initially remains stable despite this increase (the "flat" area of the pressure-volume curve). In contrast, CSF formation is relatively constant and independent of ICP values. A slight but noticeable decrease in CSF production is observed only at very high levels of ICP. From a therapeutic standpoint, we can enhance the elimination of CSF by diverting it to outside of the cranio-spinal system using a ventricular or lumbar catheter. The implantation of a ventricular catheter is a routine maneuver in neurocritical patients, but the placement of a lumbar drain should be reserved as an alternative measure in the treatment of ICH, only applicable to certain patients and never in the initial phase of trauma.

Intracranial pressure monitoring via ventricular catheter permits not only the evacuation of CSF but also access to the CSF for sampling and/or drug administration. It is recommended that the catheter is open intermittently if needed, limiting the evacuation to 2-5 ml without exceeding 20 ml/h [15]. The ventricular catheter reservoir should be located about 20 cm from the external auditory canal (EAC), an anatomical reference for locating the foramen of Monro. In this position, CSF drains against a pressure of 20 cm of H_2O (15 mmHg). The need to evacuate CSF volumes >20 ml/h should be regarded as a treatment failure and requires an additional therapeutic measure, such as hyperosmolar solutions and/or moderate hyperventilation. Taking into account that the treatment of ICH is additive and not a substitutive, CSF drainage in these patients should not be dispensed with *a priori*, unless the ventricular system collapses. Ventricular drainage should

not be left open permanently because it distorts the ICP readings [27] (Figure 27.3) and subjects the patient to unnecessary risks. The only exception to this rule is in patients who present a dilated ventricular system secondary to trauma. In these cases, post-traumatic hydrocephalus plays a key role in ICH and requires a continuous opening in the system. In this subgroup of patients, it is advisable to measure ICP with a device separate from the ventricular catheter.

The implementation of a ventricular catheter is a relatively simple maneuver and is associated with a reduced complication rate, even when placed in a TBI patient with nor-

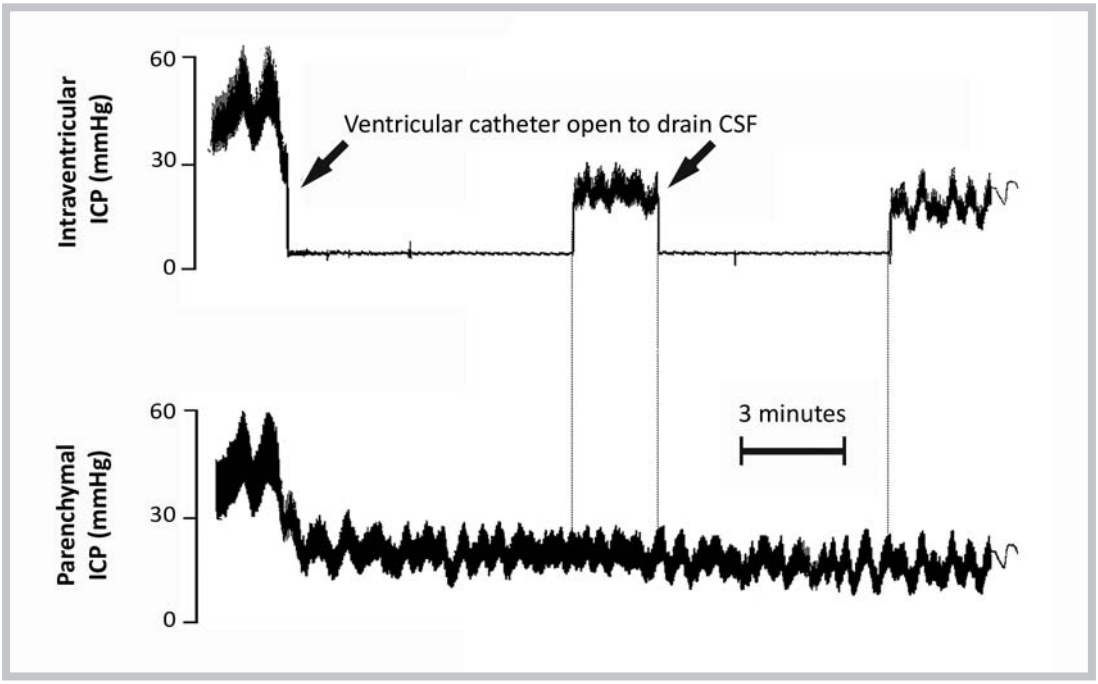

Figure 27.3. **Recording of simultaneous intracranial pressure (ICP) monitoring in parenchymal and intraventricular compartments. Observe how when the ventricular catheter remains closed the recordings match. However, when the ventricular catheter is opened to drain CSF, the intraventricular ICP recording is lost.**

A) Insertion of the catheter	• Avoid hyperextended cervical positions for prolonged periods of time • Avoid the sudden loss of large quantities of CSF • When using a fluid-coupled system, the ventricular catheter should be tunneled through the subcutaneous brain tissue (this maneuver is avoided if the ventricular catheter is inserted through a screw implanted in the cranial vault) • Initial position of the space 20 cm above the foramen of Monro (EAC)
B) Maintenance of the catheter	• Protect direct access to the ventricular catheter (silicone element) • Protect and prevent tampering of the 3-step keys • Biochemical and microbiological analysis of CSF every 48-72 hours • Intermittent opening of the system through the clamp (Figure 27.3) • Regular control of the volume of CSF being drained
C) Removal of catheter	• Suture the catheter exit point to prevent leakage of CSF • Send the removed catheter tip to the microbiology lab

Table 27.3. **Methodological recommendations to consider during the implementation, maintenance, and removal of ventricular catheters.**

CSF = cerebrospinal fluid

EAC = external auditory canal

mal or reduced ventricles [28]. Despite the advantages offered by new intraparenchymal devices, the BTF continues to recommend the use of a ventricular catheter to measure ICP because of the therapeutic potential and cost-benefit ratio [29]. However, the use of these devices increases the workload for nurses and exposes the patient to a series of potential complications, including: 1) infection, 2) catheter obstruction, usually by hematic content, 3) migration of the catheter, 4) CSF leakage through the space surrounding the catheter or from the residual hole after removal, and 5) over-drainage due to poor handling of the system. All these complications have been reported variably in the literature, although frequency is reduced with experience and rigorous protocols for the insertion and maintenance of ventricular catheters (Table 27.3). In patients with a collapsed ventricular system in the initial stage or those with a deviated midline, a ventricular catheter to measure ICP should not be inserted. In these patients, the sensor of choice is intraparenchymal and the treatment of ICH should be started with the administration of hyperosmolar solutions and/or moderate hyperventilation.

27.8 Hyperosmolar Solutions

For over 30 years hyperosmolar solutions have been central in the treatment of ICH. Mannitol has replaced other osmotic diuretics, which in some cases had increased side effects or were less effective in reducing ICP (urea, glycerol or sorbitol). Mannitol is considered one of the most useful drugs in the neurosurgical therapy arsenal and is the only hyperosmolar solution currently recommended by the BTF for the treatment of ICH [30]. However, there is evidence that hypertonic saline solutions are more useful than mannitol in some patients, therefore these solutions are also used in certain patients with TBI and ICH. To understand the fundamental mechanism of hyperosmolar solutions, the pathophysiology of the blood-brain barrier (BBB) must be recalled.

Under physiological conditions, the BBB limits the flow of substances from brain capillaries into the brain parenchyma. This consists of a moderately water-permeable membrane that is relatively impermeable to small solutes and proteins, and thus it maintains a balance between the transcapillary hydrostatic pressure gradient and the osmotic pressure gradient, which determines the flow. However, in areas with a disrupted BBB this balance does not exist and thus the passage of proteins and electrolytes through the membrane is permitted. The hydrostatic pressure in this case becomes the dominant force and favors the movement of fluid from the intravascular space to the brain tissue. This movement of solutes and fluid produces cerebral edema, increases ICP, and decreases CPP, favoring the development of secondary brain injury.

Initially, it was thought that the beneficial effect of osmolar substances on ICP was exclusively due to the dehydration produced at the brain tissue level. It has now been confirmed in animal models that osmolar substances cause a reduction in brain volume, although this occurs only in the non-injured areas of tissue with the BBB intact. At the same time, the decrease in ICP persists for some time after the plasma concentration of the osmotic substance has declined to below the level considered osmotically active. These findings suggest that hyperosmolar solutions act by additional mechanisms of action other than mere tissue dehydration.

At present, we know of two distinct mechanisms of action of mannitol: rheological effects and osmotic action [31]. Mannitol, given in bolus form, produces an expansion of circulating blood volume, decreases hematocrit levels, reduces blood viscosity (hemodilution), and increases CBF [32]. Secondary to the hemodynamic effects, a reflex vasoconstriction of cerebral vessels is produced, with a consequent drop in cerebral blood

volume and therefore a reduction in ICP [33]. These mechanisms of action may explain the rapid effect of mannitol on ICP (mere minutes) and the demonstrated fact that this drug is particularly effective in patients with a CPP under 70 mmHg.

The best known mechanism of action of mannitol is osmotic activity. This effect occurs between 15 and 30 minutes after administration, when an osmotic gradient between plasma and cells is established [32]. In the brain, mannitol does not cross the normal BBB, but remains in the cerebral vascular bed. In this situation there is a "pull" of water from the interstitial compartment to the intravascular compartment. When the BBB is injured, mannitol can penetrate the brain tissue, worsening the edema. Regarding additional mechanisms of action, it has also been found that mannitol reduces CSF production and the rigidity of red blood cells, facilitating their passage through small vessels and tissue areas with precarious perfusion.

It has been shown that the response to mannitol depends on the type of lesion, the values of the ICP, and the state of cerebral autoregulation [33,34]. Muizelaar et al. [33] showed that mannitol reduced ICP by 27% in patients with TBI and intact autoregulation, without changing CBF. However, when autoregulation was impaired, ICP decreased by only 4.7% and CBF increased. This suggests an individualized response to mannitol for each patient. In the treatment of ICH, mannitol should be the therapeutic measure of choice in situations of normal or reduced CBF.

Despite numerous studies, there are no defined protocols in relation to how this drug should be administered [35]. The dosage of mannitol required for the treatment of ICH differs depending on the author. In terms of its effect on ICP, the rate of infusion plays as important a role as the dose administered. At a higher rate of infusion, the decrease in ICP is more significant, but the duration of this effect is also shorter [36]. Doses of 0.5 g/kg of mannitol at 20% in 60 minutes is recommended in non-emergency situations or when prolonged treatment is expected. In emergency situations, a dose of 1 g/kg at a faster rate (30 minutes) can be administered. The decrease in ICP starts at 5-10 minutes, with a maximum effect at 60 minutes and a duration of 3-4 hours.

The association of mannitol and furosemide in the treatment of ICH is controversial. Clinical and experimental studies show that when combining the 2 drugs, the osmotic gradient induced by mannitol is prolonged [37]. In this partnership, furosemide inhibits the reabsorption of H_2O and electrolytes at the ascending limb of Henle's loop, delaying the restoration of the normal osmotic gradient across the BBB [37]. However, for some authors there is no clear evidence that the mannitol-furosemide association is more effective than the administration of mannitol alone. The addition of furosemide should be reserved for cases of fluid overload or pre-existing heart disease in which it is necessary to use mannitol.

Following administration of mannitol, diuresis must be replaced to prevent dehydration, volume depletion and hemoconcentration, factors that tend to create a situation of low cerebral perfusion because they act as vasodilator stimuli that produce secondary increases in ICP. Electrolyte replacement should aim to keep osmolality below 320 mOsm/kg, maintaining a normal circulating volume and cardiac output. At the same time, the maximum daily dose of 6 g/kg mannitol ahould not be exceeded because higher amounts increase the risk of hyperosmolality.

Side effects of mannitol have been reported to include acute volemic overload (hypervolemia) followed by volume depletion and dehydration, a rebound effect on ICP, hyperosmolality, and electrolyte disturbances (hyponatremia, hypokalemia, hypocalcemia). The use of mannitol is contraindicated in cases of severe dehydration, anuric renal failure, heart failure, hepatic decompensation and osmolality exceeding 320 mOsm/kg.

Several authors have demonstrated the efficacy of hypertonic saline solutions (HSS) as a therapeutic alternative to mannitol in the treatment of ICH. Vialet compared 20% man-

nitol with HSS at 7.5% in patients with severe TBI and ICH despite sedation, CSF drainage and optimal systemic management [38]. The objective was to reduce ICP to below 25 mmHg or increase CPP to above 70 mmHg. The authors found an increased mortality in the group treated with mannitol. However, equimolar doses of either drug were not used and the study was not designed to test the effect of osmotic agents on mortality or the functional outcome of patients [38].

Administering HSS produces a rapid expansion of intravascular volume due to the high osmotic gradient established between this compartment and the extravascular space [39]. Volume expansion depends on the concentration of sodium administered. These solutions have been shown to be ideal in the resuscitation of hypovolemic patients, with the administration of small volumes achieving rapid hemodynamic stabilization. Furthermore, they also produce a decrease in peripheral vascular resistance, which improves perfusion in various organs. HSS also improve myocardial contractility in patients with shock and promote lung and kidney function. When the BBB is intact, the infusion of HSS creates an osmotic gradient that decreases cerebral edema. In the context of TBI, these solutions have proved particularly effective in patients unresponsive to mannitol or furosemide.

The action of HSS is short-lived and can be extended with the addition of a hyperoncotic agent such as dextran 70 at 6%. Continued use requires comprehensive monitoring of the hemodynamic state, the osmolality and the serum electrolytes. Regarding adverse effects, administering large doses HSS can result in states of severe hyperosmolality and hypernatremia. Rapid volemic expansion can also cause hypokalemia and arrhythmias. In addition, the significant administered concentrations of chlorine can cause hyperchloremic metabolic acidosis [40]. However, a prospective study of 106 patients, designed to detect potential risks for the administration of NaCl at 7.5%, showed no notable adverse effects [40]. Due to potential side effects, its use is contraindicated in patients with hypervolemia or heart, liver or kidney disease, as well as those patients in states of hyperosmolality and hypernatremia.

According to the latest revision of the BTF, there is currently insufficient evidence to recommend the use, concentration and method of administration of HSS in patients with TBI (Table 27.1). In our center, the hyperosmolar solution of choice is mannitol. However, in situations of serum sodium <135 mEq/l, CPP <60 mmHg or hemodynamic instability, the hyperosmolar solution of choice is HSS at 7.2%.

27.9 Hyperventilation

For years, moderate hyperventilation (HV) (pCO_2 at 31-35 mmHg) or severe HV (pCO_2 <30 mmHg) has been one of the main pillars of treatment of endocranial hypertension. It is a therapeutic measure that is easy to apply and fast acting, producing a significant influence on ICP (Figure 27.4). Although the mechanism of action of hyperventilation is not well known, one of the most accepted theories is that the decrease in pCO_2 causes a decrease in the concentration of hydrogen ions in the extracellular medium, which produces an arteriolar vasoconstriction. Vasoconstriction that provokes hypocapnia decreases cerebral blood flow and volume and, consequently, ICP. Furthermore, studies have shown that most severe TBI patients maintain cerebral reactivity to CO_2 until very advanced stages of neurological deterioration. This allows therapeutic HV to be used throughout the evolution of the brain injured patient.

In contrast, the vasoconstrictor effect induced by HV, apart from reducing ICP, may also contribute to the development or aggravation of ischemic lesions (findings common in

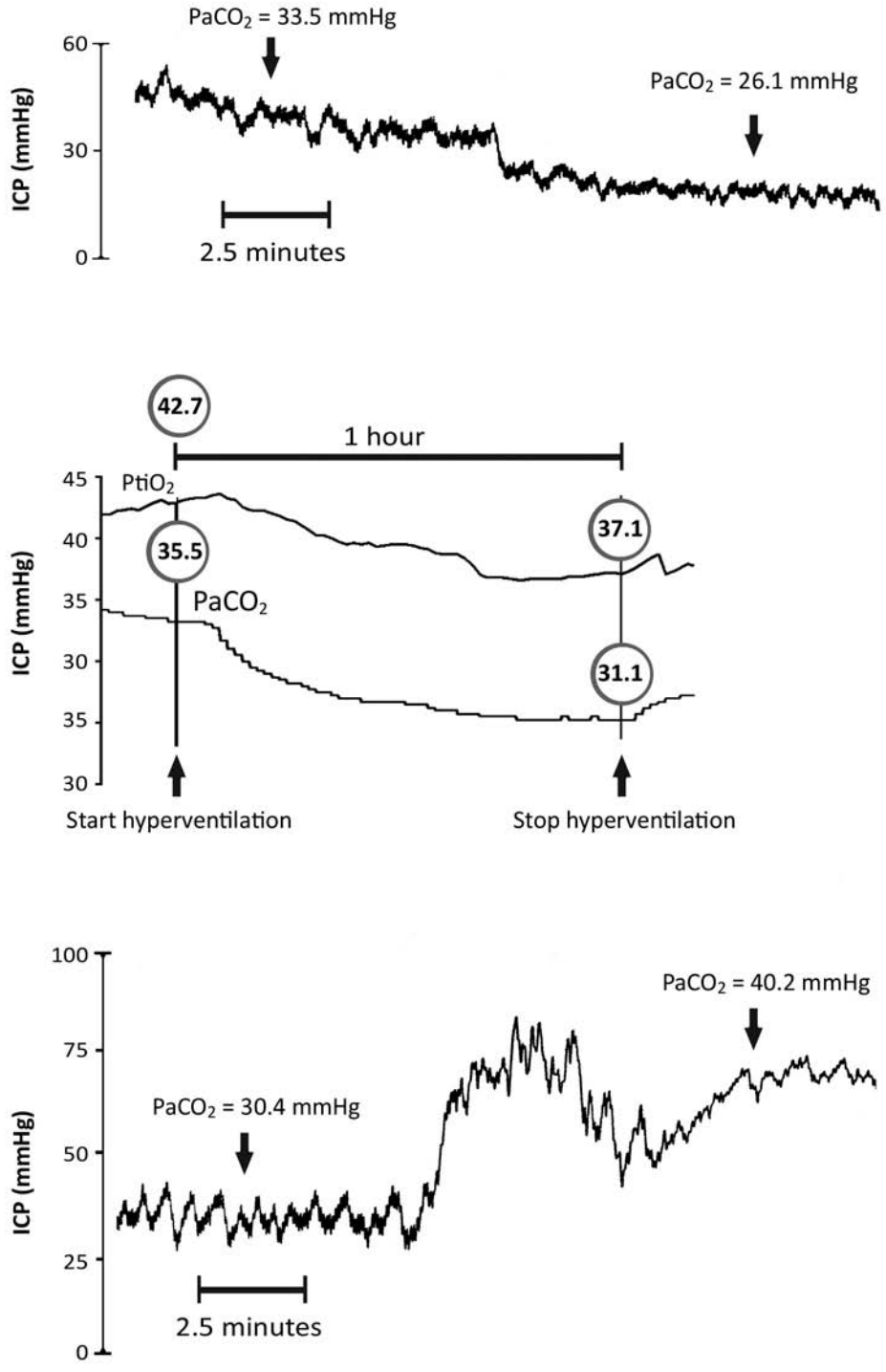

Figure 27.4. **The effect of hyperventilation ($PaCO_2$ reduction) on intracranial pressure (ICP) and tissue oxygen pressure ($PtiO_2$). Note below the "rebound" in ICP when the values of CO_2 normalize after a change in ventilatory parameters.**

the evolution of these patients). This has been the source of considerable controversy in recent years. Several authors have shown that TBI generally involves a situation of low CBF in the acute phase of trauma [41,42]. In some cases, CBF is found to be below the threshold of irreversible ischemia or tissue infarction [43]. In patients with focal lesions, HV leads to precarious metabolic situations that affect the injured brain and the surrounding areas (the "traumatic penumbra") in particular ways [44]. Figure 27.4 shows the parallel decline, caused by the drop in CO_2, in the brain tissue oxygen pressure. These findings demonstrate that the indiscriminate use of HV in certain patients could cause or exacerbate underlying ischemic lesions [45], making this a contraindicated therapeutic maneuver.

An additional problem or difficulty in the use of HV that should be taken into account, given that changes in interstitial pH tend to cancel in time, is the potential loss of efficacy of maintined HV affirmed by some authors [46]. In healthy volunteers, Raichle showed that the maximum decrease of CBF (40%) occurred within 30 minutes from the start of HV. After 4 hours of maintaining HV, CBF had reached 90% of the baseline value [47]. When restoring the initial arterial level of $PaCO_2$, an increase in CBF occured that exceeded the baseline value by 31% [47]. Figure 27.4 shows the rebound effect on ICP produced by normalizing $PaCO_2$ after a period of marked hyperventilation. At the same time, Muizelaar showed in a prospective study of randomized patients that the prophylactic use of HV for severe TBI worsened neurological outcome when assessed at 3 and 6 months after injury [48].

Because of these potential adverse effects, the recommendations of the BTF in 2000 clearly indicated (level I recommendation) that this therapeutic measure should be avoided within the first 24 hours of injury, and as a level II recommendation that moderate HV ($PaCO_2$ at 31-35 mmHg) should not be used prophylactically. In cases in which levels of $PaCO_2$ need to be maintained below 30 mmHg (intense HV) to control ICP, this maneuver should be used under the control of parameters that provide information on blood flow or cerebral oxygen availability (level III recommendation) [49]. In the most recent guidelines (2007) all of these recommendations remain, albeit with a lower level of evidence (Table 27.1) given the absence of randomized studies that demonstrate the relationship between HV used to treat ICH and patient outcome [12]. The BTF guidelines [12] recommend the use of SjO_2 or $PtiO_2$, as instruments for cerebral oximetry monitoring to detect potential adverse effects from using HV, and the avoidance or suspension of this measure if the values fall below 50% or 15 mmHg, respectively ("optimized hyperventilation," a term defined in 1992 by J. Cruz [50]).

Despite the drawbacks mentioned and the very specific recommendations on the use of this therapeutic measure published before 2000, the use of HV today is still very liberal and does not follow the BTF recommendations. In a recent study, Neumann et al. [51] described how 22 European BrainIT member centers (http://www.brainit.org) routinely used this therapeutic measure in tertiary hospitals known for their extensive experience in treating brain injured patients. Information collected on the use of HV in 202 patients with TBI treated in these centers between 2003 and 2005 showed alarming data:

- There is a tendency to use HV indiscriminately. Prophylactic HV (for patients without ICH) was used during 40% of the ventilation time. Intense HV ($PaCO_2$ <30 mmHg) was used in a high percentage of patients during and after the first 24 hours of injury, even with ICP values <20 mmHg. At some centers severe TBI patients were never normoventilated.
- In situations of ICH, intense HV was frequently administered before mannitol.
- Monitoring SjO_2 or $PtiO_2$ was carried out with a frequency of only 4 or 5%, respectively, in the cases involving ventilation analyzed by the authors.

Based on the above, the following recommendations for use of HV have been made [12]: 1) HV should not be used prophylactically and HV within the first 24 hours of injury should be carried out with caution; 2) HV can be used in a timely manner in cases of persistent ICH despite the previous and adequate use of sedation/analgesia, muscle paralysis, CSF drainage, and the administration of hyperosmolar solutions; 3) HV use should be "optimized" through the simultaneous monitoring of CBF or tissue oximetry, especially when $PaCO_2$ levels <30 mmHg are required. In cases in which ICH persists and the measures described have been carried out properly, the intensity of HV may be increased based on the values of SjO_2 or $PtiO_2$.

27.10 Therapeutic Alternatives in the Treatment of Intracranial Hypertension. Second Level Measures: How Often do We Use Them?

The high morbidity and mortality associated with ICH refractory to treatment (>90% of these patients die, are left in a persistent vegetative stage or are severely disabled), has prompted the search for alternative therapeutic options. The BTF refer to second level therapies for ICH as a series of measures to be used as rescue therapy in these patients. Among the measures most commonly used today are barbiturates, more intense hyperventilation ($PaCO_2$ <30 mmHg), decompressive cranial surgery and moderate hypothermia (32-33 ºC). These measures are considered second line therapies because there is less support from evidence-based medicine. At present their use is based on small series of patients, case reports or expert opinion (level III recommendation). Depending on the clinical and radiological characteristics of each patient, our center tends to opt for more intense hyperventilation, decompression techniques or moderate hypothermia when first level measures are exhausted. Regarding alternative drugs to the abovementioned measures, some authors recommend the use of lidocaine, indomethacin, THAM, or dihydroergotamine, among others. However, none of these measures are widely accepted at the moment. Today, this set of therapeutic options should be considered experimental treatments. The practice of controlled clinical studies with randomized patients is essential for determining if they constitute real therapeutic alternatives for ICH refractory to standard measures.

An important aspect to consider is when and in what percentage of TBI patients is it necessary to implement second level measures to treat ICH. Figure 27.5 summarizes the general algorithm for treatment of ICH in our center and includes the criteria for starting the use of second level measures in the treatment of refractory ICH. In centers with extensive experience in treating brain injured patients, there has recently been a clear reduction in the percentage of patients requiring second level therapeutic measures to treat ICH, no doubt due to the rigorous application of stepwise therapeutic protocols and a greater tendency to remove focal lesions early. In 2000, the European multicenter study published by Citerio et al. indicated that at that time the percentage of patients in whom any second line therapy was used was around 19%, with severe hyperventilation or barbiturates being the most commonly used therapeutic measures [52]. In 2008, the same study was carried out and found that the percentage of second line measures used for refractory ICH was reduced from 19 to 13% [53]. This percentage coincides with our center (13.1%), with decompressive craniectomy as a second line therapy currently being most frequently used treatment for our patients.

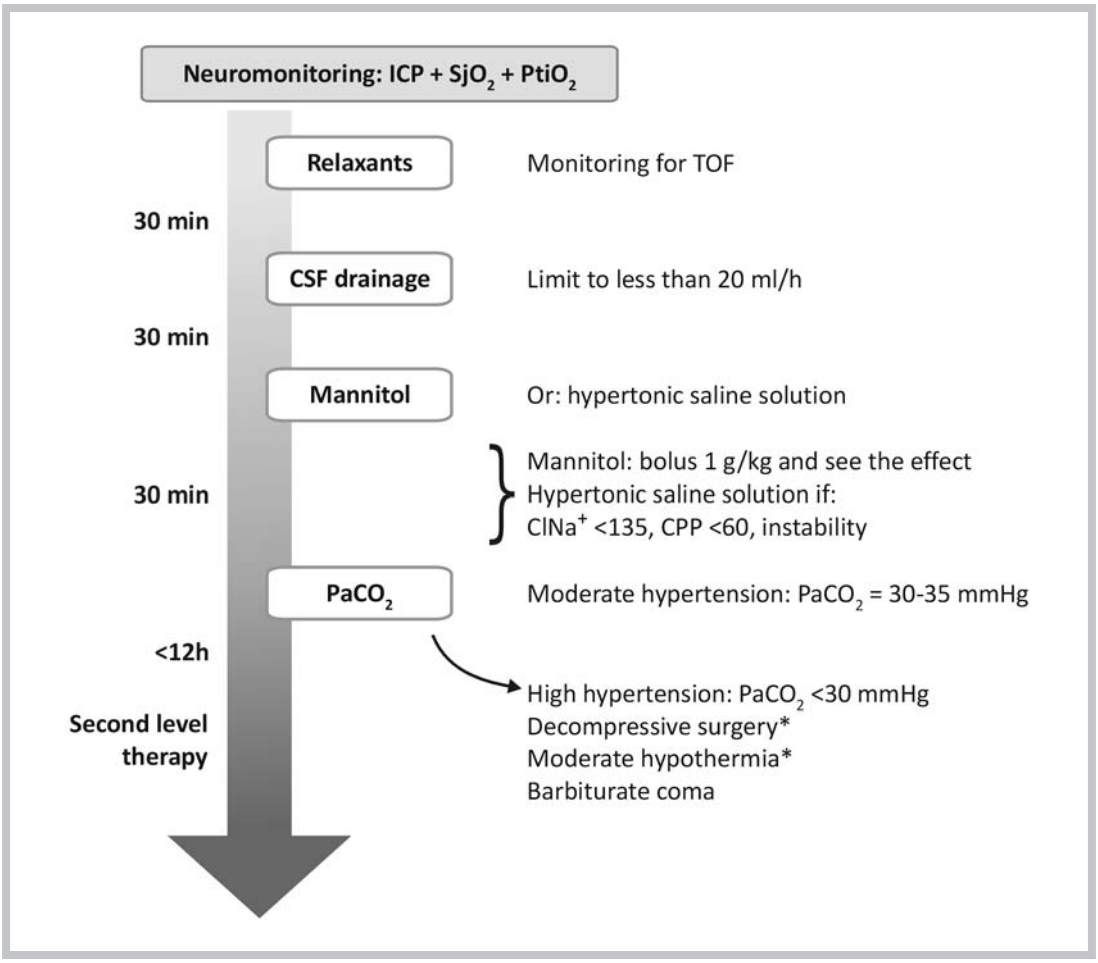

Figure 27.5. **Algorithm for hospital treatment of intracranial hypertension in patients with severe traumatic brain injury admitted to the neurotrauma ICU at Vall d'Hebron University Hospital. The image shows the minimum monitoring required for these patients, the time period allowed between the different therapeutic measures, and the criteria used for the practice of decompression craniectomy.**

* Inclusion criteria: ICP >25 mmHg, refractory to level I measures; age = 1-60 years; Glasgow = 4-8, reactive pupils; absence of focal lesions >25 ml, multiple or devastating trunk injuries

27.11 Quantification of Intensity of Treatment Applied to Control Intracranial Pressure: The Extended Therapy Intensity Level Scale

Two patients with similar injuries as seen in the brain CT scan and similar ICP values may involve difficulties in management and very different outcomes if only the maintenance of basic sedation and analgesia were required, or if the administration of all drugs and therapeutic measures previously mentioned were needed, in order to maintain ICP levels. In order to quantify the intensity of treatment required for these patients, we propose the use of a scale that addresses each therapeutic measure. The scale we propose is a modification of a version presented in 1987 by Maset et al. (TIL: Therapy Intensity Level Scale) [54] and includes the various possibilities that we use today in the treat-

ment of the ICH: the E-TIL scale (Extended Therapy Intensity Level Scale) [55].

For the use of this scale of treatment, one must remember that the general management of these patients in the acute stage of trauma always includes the maintenance of sedation and analgesia, usually through a continuous administration of midazolam and morphine. Specific treatment of ICH includes muscle relaxation, CSF drainage, moderate hyperventilation, and the intermittent administration of a bolus of mannitol or hypertonic saline solution. When these measures do not sufficiently control ICH, second line treatments, such as greater hyperventilation, moderate hypothermia (32-33 °C), or surgical decompression techniques, are used. In our center, barbiturates are used only when all of the above measures fail.

In the E-TIL scale, a minimum score of 1 is given if the patient only receives sedation and analgesia. A maximum score of 62 corresponds to a maximal therapeutic application (Table 27.4). When the patient is not hyperventilated ($PaCO_2$ >45 mmHg) or does not require muscle relaxants, CSF drainage, or the administration of hyperosmolar agents, a score of 0 is given for these items. Regarding the application of level II therapies, 15 points are assigned to moderate hypothermia and the administration of barbiturates at doses sufficient to achieve burst-suppression, and 20 points to decompression craniectomy. Included in hyperosmolar treatment is the administration of mannitol or hypertonic saline. In CSF drainage, no difference in score is obtained if a ventricular catheter (standard technique) or a lumbar drain is used. The latter is indicated only in selected patients in a subacute phase of injury.

Therapeutic measure	Score
Decompressive craniectomy	20
Moderate hypothermia (32-33°C)	15
Barbiturates	15
Mannitol	
• >1g/kg/h	6
• ≤1g/kg/h	3
• Do not administer	0
Hypertonic saline solution (7.2%)	
• >140 ml/h	6
• 1-140 ml/h	3
• Do not administer	0
Drainage of CSF	
• >10 ml/h	2
• 1-10 ml/h	1
• Do not perform drainage	0
Hyperventilation	
• Intense ($PaCO_2$ <30 mmHg)	2
• Moderate ($PaCO_2$ 30-44 mmHg)	1
• $PaCO_2$ <45 mmHg	0
Muscle paralysis	
Yes	1
No	0
Sedatives and analgesics	
Yes	1

Table 27.4. Extended Therapy Intensity Level Scale (E-TIL) for treatment of ICH. The minimum score on this scale is 1 (patient sedation and analgesia) and the maximum score 62, which corresponds to the application of all therapeutic measures described to maximal intensity.

ICH = intracranial hypertension

$PaCO_2$ = partial pressure of carbon dioxide.

27.12 The Withdrawal of Treatment: A Reverse Stepwise Process

One of the aspects with fewer protocols in the treatment of severe TBI patients is the withdrawal of therapeutic measures. In patients with severe TBI, the withdrawal of treatment should be gradual and should not be initiated until the patient maintains ICP values <20 mmHg for at least 24 hours (48 hours is recommended). Withdrawal follows

the reverse order of therapeutic measures implemented, meaning the withdrawal of the second level measures takes place first while first level measures are continued. If ICP remains below 20 mmHg, the phasing out of first level measures can begin, followed by a withdrawal of sedation and analgesia if the patient's condition allows it.

McKinley et al. propose a period of 6 hours between removing each of the therapeutic measures administered to the patient, provided that this withdrawal is not followed by a further increase in ICP [56]. The increase, or "rebound", of ICP after removing one of the measures justifies the immediate reinstatement of the measures that were effective in their control.

After the first week of injury, the decision to treat ICP values >20 mmHg should be done case by case based on the control CT scan findings and clinical variables. It must be taken into account that in the final phase of waking, nociceptive stimuli generated by intubation, nasogastric tubes/probes or other elements may cause increased ICP. However, the compliance of the craniospinal system in this period should already be improved enough so that the patient adapts to these transient increases in ICP. During this process, maintaining the sensor and treating periodic increases in ICP will prolong the process of extubation and may lead to iatrogenia from unnecessary "overtreatment".

27.13 Case Report

The following is a didactic description of the evolution and treatment of a patient with severe TBI. The description begins at the scene of the accident and includes the acute phase after admission to the ICU. The purpose of this case report is to highlight some of the aspects mentioned in this chapter and to analyze controversial issues in the management of this patient.

A 33-year-old woman with no known prior pathologies was involved in a traffic accident (2-car collision) at 5 p.m. on a Tuesday in December (temperature 10 °C) and became trapped in the vehicle. Forty-five minutes after the onset of injury she was assisted by firefighters and evaluated at the scene. A GCS score of 4 (EO 1 + VR 1 + MR 2) was assigned and anisocoria (right pupil: 6 mm; left pupil: 4 mm) with both pupils non-reactive was observed, along with arterial hypotension (70/36 mmHg) and a heart rate of 68 bpm. After cervical stabilization and oral-tracheal intubation, the patient was sedated and myorelaxed. She was then taken to the nearest hospital, which in this case was a level II hospital. Due to pupillary changes during transfer, the patient was administered a bolus of mannitol and underwent hyperventilation. Following a 20-minute trip by ambulance, the patient arrived at the destination hospital, where the following tests were performed: general blood analysis, electrocardiogram, chest radiography, and arterial blood gas analysis. Thirty minutes after arrival at the hospital, the patient presented bradycardia (<35 bpm) and hypertension (220/110 mmHg), which required her transfer to a Trauma Center (arrival time: 11 p.m.).

Upon arrival at the level III hospital, the patient was re-evaluated and given a GCS score of 6 (EO 1 + VR: intubated + MR 5). Normoreactive and isochoric pupils, normal blood pressure and heart rate, and normal cardiopulmonary examination results were observed. A few minutes after admission, the patient was transferred to the neuroradiology unit to undergo a cerebral CT scan. During this exploration, an absence of basal cisterns, a midline deviation to the right measuring 12 mm, and diffuse hemorrhagic spots (petechiae) in both brain hemispheres were detected (Figure 27.6). The total volume of these lesions was <5 ml, corresponding to a diffuse injury type IV according to the Marshall's classification [5]. With these findings in mind, the patient was admitted to the

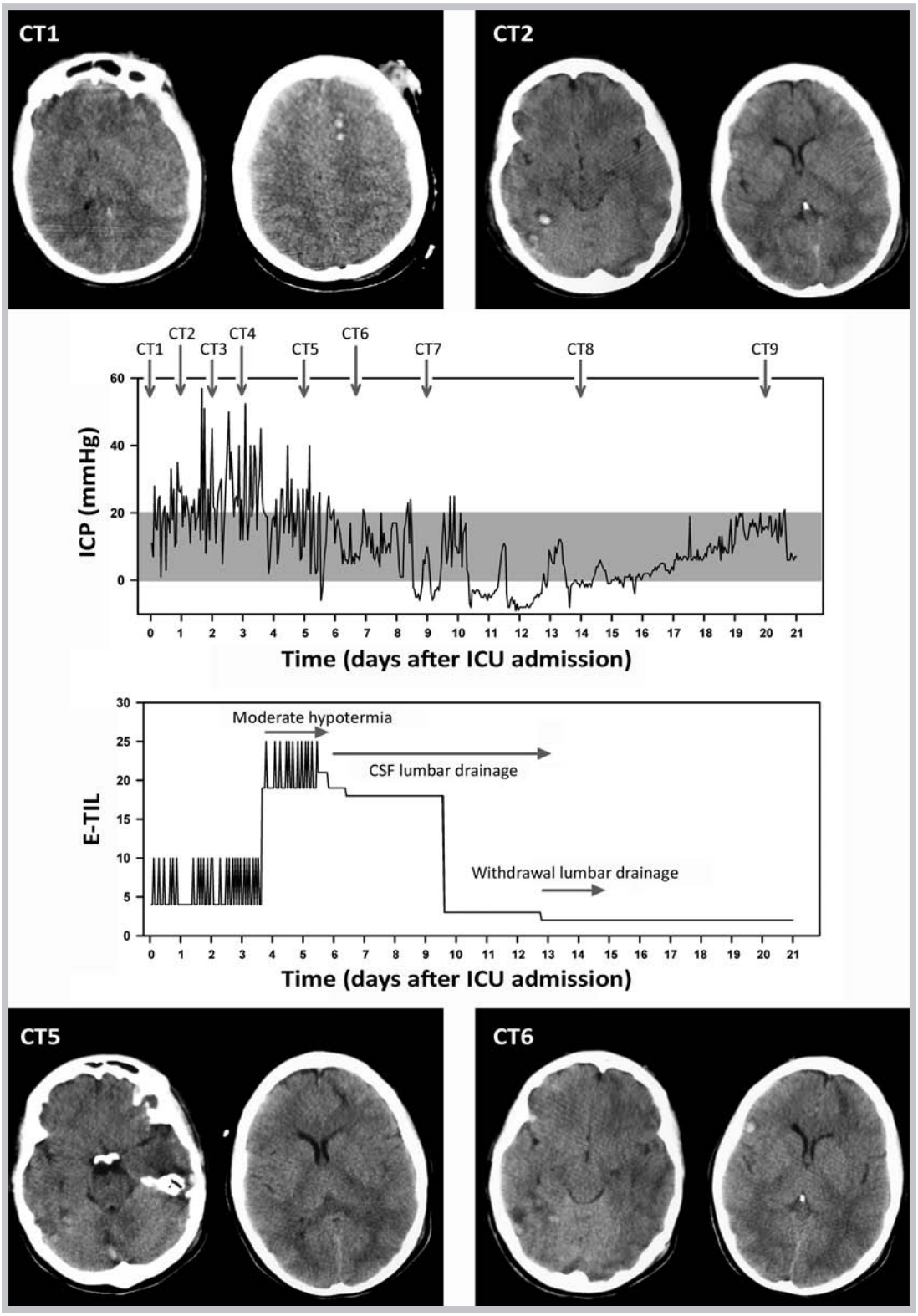

Figure 27.6. CT brain scan, intracranial pressure values, and a recording of the intensity of treatment required for this patient (E-TIL) to control ICP. For detailed explanations, see text (case report).

ICU and administered multimodal neuromonitoring, which included an intraparenchymal ICP sensor implanted in the left hemisphere, a retrograde jugular catheter placed in the right side, and a $PtiO_2$ sensor and a microdialysis catheter implanted in the right hemisphere.

At 24 hours from the time of injury, and 14 hours after ICU admission, a new CT scan was taken that showed an improvement in the parameters when compared to the initial CT (visible basal cisterns, midline displaced <5 mm and no increase in the volume of the hemorrhagic lesions, corresponding to a Marshall type II injury). Despite the radiological improvement (Figure 27.6) during the first 24 hours of admission and the correct maintenance of myorelaxation, sedation, and $PaCO_2$ values of approximately 27 mmHg, the patient required 5 boluses of mannitol and hypertonic saline solution in order to keep ICP at <20 mmHg and CPP at >60 mmHg. Over the next 72 hours, the patient continued to present slightly elevated ICP values, requiring the periodic administration of hypertonic saline and mannitol, despite the results of control brain CT scans performed at 48 and 72 hours that did not show significant changes (diffuse injury type II) (Figure 27.6). During this period SjO_2 levels were always >60%.

On the fourth day of admission, ICP was refractory to first level measures. After performing a new brain CT scan that showed no changes compared to the previous scans, the decision to apply a second level therapeutic measure was taken. In this case, moderate hypothermia (32 °C) was the chosen technique. With this maneuver, ICP values initially improved. However, these levels increased once more after a few hours. On the sixth day of ICU admission, ICP returned to a refractory state despite first level measures and hypothermia therapy. This led to the addition of a new bailout measure. After a new control brain CT scan was taken, a lumbar drain was implanted in the patient in order to drain CSF. This maneuver controlled ICP almost immediately and allowed the patient to begin gradual warming (0.5 °C/24 h). All other therapeutic measures were also withdrawn one by one, with the exception of lumbar CSF drainage, which remained in place for 7 days (removed on day 13 of ICU admission) (Figure 27.6).

27.13.1 Points to Consider

- The level of consciousness presented by the patient at the accident site could have been an artifact produced by the hypothermia and hemodynamic instability that occured at the time of evaluation. The GCS score and pupillary examination were more reliable when recorded on arrival at the definitive medical center.
- In this patient, the left hemisphere was selected for the implementation of an ICP sensor because it corresponded to the more swollen hemisphere, where ICP values were most likely to be higher. Based on the characteristics of the initial injury, an intraparenchymal ICP sensor was selected. A retrograde jugular catheter was inserted into the dominant jugular vein. The remaining cranial monitoring devices were implanted in the less-injured brain hemisphere.
- During the evolution of the injury, the patient required several control brain CT scans to rule out the emergence of new space-occupying lesions. These scans also showed how the patient went from presenting a type IV diffuse injury to a type II, illustrating the dynamic nature of neurotraumatic injuries.
- After the poor response to moderate hypothermia in order to control ICH, the decision to place a lumbar drain was taken at 7 days post-injury based on the following: 1) the patient presented cerebellar tonsils in an intracranial position, 2) the basal cisterns were visible, and 3) no deviation from the midline was observed. The existence of apparently benign radiological images in this period contrasted with the difficul-

ty in controlling ICP, suggesting an alteration in CSF dynamics. This was confirmed after inserting a lumbar drain, CSF drainage being the most effective therapeutic measure in this patient.
- The figures illustrating the evolution of the ICP levels and the intensity of treatment required to control ICP (E-TIL) show how both the application and withdrawal of treatment were stepwise.

27.13.2 Points of Controversy and Inadequate Therapeutic Maneuvers

- At present, there is sufficient evidence to conclude that this patient should have been transferred directly to a Trauma Center, defined as a center equipped with CT scanning, a neurosurgeon on duty, and all human and technological resources required by patients with severe TBI. The intermediate transfers and "superfluous" exploratory tests in the early stages of injury adversely affected the outcome of the patient.
- In patients with TBI and clinical signs of ICH before ICP monitoring (in our patient, anisocoria and pupillary reactivity failure), initial hyperventilation should be administered. Mannitol should be administered in cases of hemodynamic stability only, and was contraindicated in this patient.
- The CPG of the BTF indicate that first level measures to control ICH should include moderate hyperventilation ($PaCO_2$ >30 mmHg). In this patient, it was administered prematurely before exhausting other first level therapeutic measures.
- The effectiveness of lumbar drainage of CSF in this patient suggests that more aggressive therapeutic techniques, such as hypothermia, could have been avoided. The adequate moment for this maneuver occurs after the third control brain CT scan showing a non-deviated midline and normal ventricular size.

27.14 Key Concepts

Resuscitation and treatment carried out in the acute phase of trauma are vital to the outcome of TBI patients. Arterial hypotension and hypoxia, in addition to intracranial hypertension, should be avoided throughout the evolution of injury in these patients.
Action algorithms for these patients should be standardized as much as possible, in addition to being well-directed and started early on post-injury.
Because TBI is highly dynamic, periodic exploration using cerebral CT scans are required before initiating specific therapeutic measures for intracranial hypertension.
The early evacuation of focal cerebral lesions of sufficient volume further facilitates the clinical management of patients with TBI.
Correctly applying the general measures indicated for patients with TBI reduces the percentage of patients requiring specific treatment for ICH. At the same time, applying first level measures correctly would allow an incidence of only 10-15% for TBI patients who require second level measures to treat refractory ICH.
The use of a ventricular catheter for ICP monitoring also permits the drainage of CSF, which can reduce the number of additional therapeutic maneuvers needed for such patients.
Hyperventilation should be used in moderation in accordance with BTF recommendations and, if possible, optimized in combination with the monitoring of parameters that are used to estimate CBF or cerebral oxygen availability.

Quantifying the intensity of treatment required provides additional information about the level of severity and the management difficulties of these patients.
Although the general treatment algorithm outlined in this chapter is designed for most cases of TBI, it should be noted that there are specific therapeutic maneuvers that should be reserved for specific injuries or select patients (e.g. anticonvulsants, steroids). The treatment of these patients concludes with the withdrawal of the administered drugs or maneuvers, which should be carried out in the reverse order in which these therapies were administered.

27.15 Acknowledgements

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28 Second Level Measures for the Treatment of Intracranial Hypertension in Traumatic Brain Injury

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I have yet to see any problem, however complicated, which, when you looked at it in the right way, did not become still more complicated.
Poul Anderson (1926-2001)

28.1 Introduction

Intracranial hypertension (ICH) is still the leading cause of death in patients with acute brain damage and especially in those with severe traumatic brain injury (TBI) (Glasgow Coma Scale [GCS] score ≤8).

The normal range of intracranial pressure (ICP) measured in any compartment (intraventricular, in the brain parenchyma, subdural space, etc.) does not exceed 10-12 mmHg in the supine position. However, high ICP or intracranial hypertension (ICH) is defined when the absolute values of ICP exceed 20 mmHg during a defined period of time (5-10 minutes) and all those causes that can increase it have been ruled out (poor patient adaptation to the ventilator, inadequate sedation or analgesia, postural changes, nadequate head and neck position, high blood pressure, hyponatremia, fever, etc.). However, this threshold should always be considered relative, and it can vary depending on the etiological factors responsible for ICH, the location of the injury, and other circumstances such as when the skull is partially open in patients with decompressive craniectomy or semiclosed as in infants and children. There is now widespread agreement, endorsed by the Clinical Practice Guidelines of the Brain Trauma Foundation (BTF), that the threshold of 20 mmHg is acceptable, with a level II recommendation to initiate therapeutic measures [1]. However, ICP values should be individualized for each patient and for each clinical situation in particular [2].

Traditionally, it was claimed that between 50-75% of patients with severe TBI developed ICH during the first week after injury. This incidence has been verified in nearly all studies since the publication of the results of the Traumatic Coma Data Bank (TCDB) published in 1991 [3,4]. In this study, 72% of patients had an episode of ICH (>20 mmHg) during their stay in intensive care [3]. Since then, we know that in the natural evolution of patients with severe TBI the risk of ICH is highly variable and will depend on the type of injury according to the classification proposed by Marshall et al. [5]. However, the

analysis of recent multicentre studies questions this widely-accepted premise. The results of a phase III controlled study to demonstrate the neuroprotective efficacy of dexanabinol (synthetic cannabinoid), showed that in both the treated and the control group the percentage of time in which ICP remained above the 25 mmHg threshold was only 10% [6].

The results of this study are striking and may be explained by the following reasons: 1) the 861 patients included were treated in highly specialized neurotrauma centres with a standardized and homogeneous medical and surgical treatment; 2) half of the patients (48% in the placebo group and 49% in those treated with dexanabinol) had type II lesions on the Marshall classification while in the TCDB study only 24% of the patients were included in this category, and 3) in most participating centres the Brain Trauma Foundation recommendations were followed (to evacuate the space-occupying lesions with a volume >25 cc).

In our opinion, the significant reduction of ICH reported in this study was mainly due to an early management of systemic complications and a more proactive behaviour in the evacuation of focal lesions with a relevant volume in most of the participating centres.

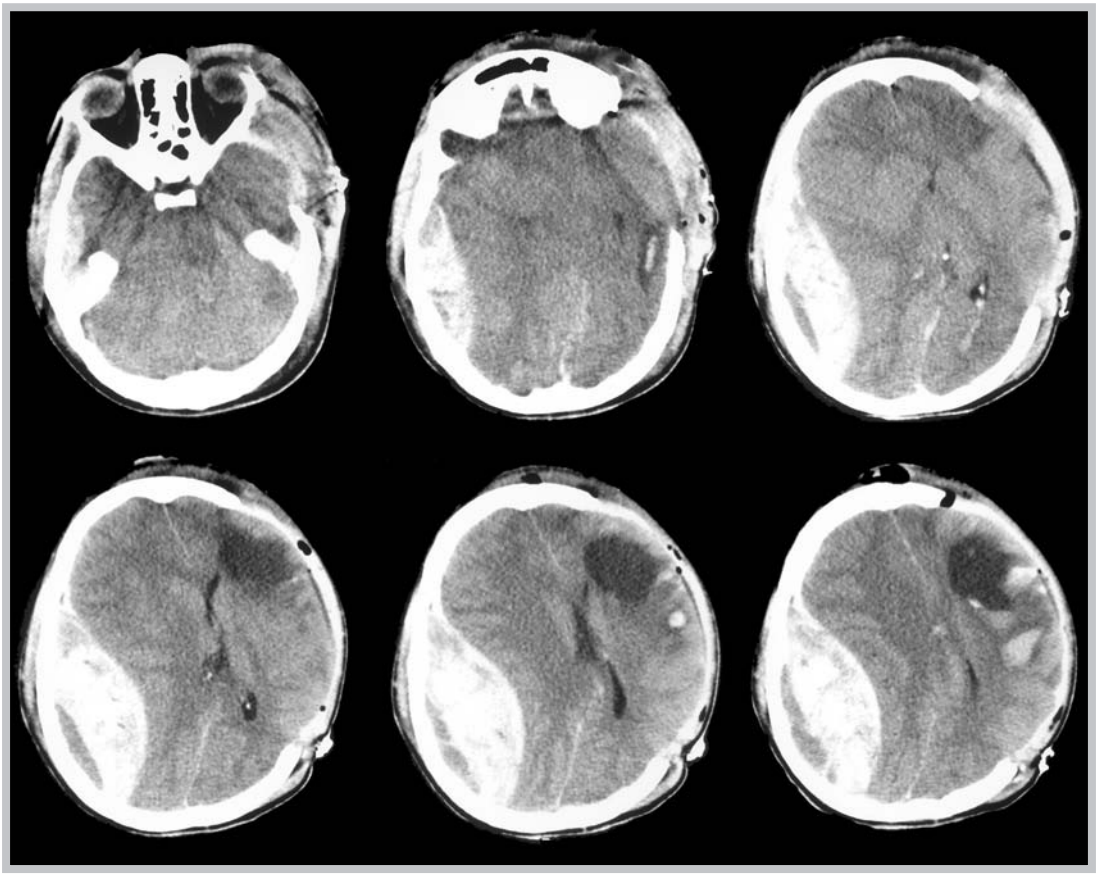

Figure 28.1. **CT scan of a 19-year-old woman who underwent evacuation of an acute left subdural hematoma. In the immediate postoperative period she developed a contralateral anisocoria with a mydriatic right pupil. A new control CT scan showed the appearance of an extensive right epidural hematoma which caused severe brain herniations (subfalcial, uncal and tonsillar), with the complete absence of the basal cisterns. Although the latter hematoma was also evacuated, the patient remained in a vegetative state for several months after injury. She then regained a minimally conscious state; 3 years after trauma, she remained in a state of severe disability, with total dependence for activities of daily living and very limited communication.**

28.2 Etiology of Intracranial Hypertension

To better understand the implementation of the second level measures, it is useful to recall the traumatic lesion classification introduced by Gennarelli et al. in the 1980s [7-9]. Pragmatically, these authors differentiated between two types of lesions: focal and diffuse. The inclusion of a patient in one of these two groups is determined from the findings observed in the computed tomography (CT). This classification, although apparently simple, allows to differentiate groups of patients with different mechanisms of injury, clinical presentation and outcome. Focal lesions (cerebral contusions, lacerations and hematoma) cause neurological deficits due to tissue destruction and perilesional ischemia and cause coma when they reach a size big enough to cause brain herniation and secondary compression of the brainstem (Figure 28.1).
Diffuse injuries are those that do not occupy a well-defined volume within the intracranial compartment (axonal injury, brain swelling, etc.). This latter group of patients is clinically and neuroradiologically heterogeneous, and in most cases coma is a consequence of the diffuse involvement of axons in the cerebral hemispheres and deafferentation of subcortical structures and the brainstem. In these cases, anatomopathological study fairly consistently demonstrates diffuse axonal injury of variable severity [10].

28.3 Intracranial Pressure Monitoring

The only reliable way to confirm whether or not a patient has ICH is with the continuous monitoring of ICP. Estimates from neuroradiological signs have a high margin of error. Continuous ICP monitoring has become routine in the management of severe TBI since the publication of the Brain Trauma Foundation's Clinical Practice Guidelines for the management of severe TBI in adults in 1995 [11]. These Guidelines have been updated and endorsed by most international scientific societies. The latest version, published in 2007, reaffirms with level II evidence, that ICP monitoring should be conducted in all patients with severe TBI who have an abnormal CT scan on admission [1]. However, in recent years we have learned that the absolute value of ICP, although the mainstay in the management of severe TBI, as an isolated parameter is not sufficient for decision making in complex patients. Monitors for recording ICP, signal processing, its value as a diagnostic method and its importance in the clinical management of many patients with acute neurological diseases have been substantially modified over the last two decades. There are two main reasons for this change: first, a much better understanding of the pathophysiological factors that regulate the response of the craniospinal axis in situations of volume increases, and second, advances in the technology available for recording and analyzing the ICP signal and other physiological variables associated with it (cerebral perfusion pressure, cerebral blood flow, etc.).
The introduction in the last two decades of global and regional methods to monitor cerebral metabolism and oxygen supply (jugular bulb oxyhemoglobin saturation, brain tissue pressure of oxygen and microdialysis) has provided valuable information that allows us to better understand the complex pathophysiology of high ICP.

28.4 Clinical Significance of the Pressure-Volume Curve

Often, new technologies let people forget basic pathophysiological fundamentals. In the late 19th century, Monro and Kellie were the first to define the relationship between

pressure and volume in the intracranial space. In the neurosurgical arena, Burrows and Cushing introduced their theories, which remain valid today with almost no significant changes.

According to the Monro-Kellie theory, in the adult – in whom the fontanelles and cranial sutures are completely closed – the volume of intracranial space must remain constant due to the physical characteristics of its components. These characteristics are: the incompressibility of the three intracranial components – brain parenchyma, blood and cerebrospinal fluid (CSF) – and the indeformability and inextensibility of the intracranial space in the adult. For these reasons, a volume increase at the expense of any of the three intracranial components or adding a new volume (tumour, hematoma, etc.) must necessarily be accompanied by a simultaneous decrease in one or all of the other components can be distingusihed. The mathematical equation which relates the variables pressure and volume in the intracranial space is not comparable to that of a perfect elastic body, but two distinct components. In a first phase, the volumetric increases do not change the absolute value of ICP, suggesting an intracranial compartment with high compliance (low elastance) [12]. However, when the physiological buffers of the intracranial space (circulating blood volume and CSF, mainly) are depleted, even a minimal increase in volume causes large increases in ICP (low compliance or high elastance phase). The pressure-volume curve is mathematically described by an exponential function and its mathematical description is based on both clinical and experimental studies. The pressure increase is always more pronounced as the patient moves to the right part of the curve. This right part of the curve, which draws an almost vertical segment, is called the space decompensation phase and is associated with a higher risk of neurological deterioration (Figure 28.2).

The mathematical relationships between pressure and volume allow to assess by means of injecting a known volume in the intracranial space, the patient's tolerance to the ad-

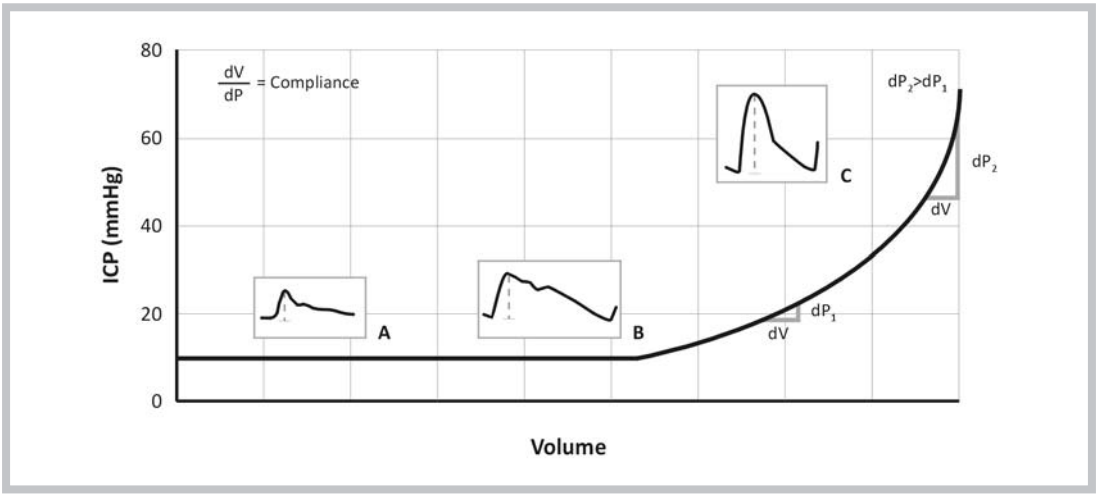

Figure 28.2. **Pressure-volume curve. The horizontal segment of this curve (A) corresponds to the compensation phase. In this phase, the physiological compensatory mechanisms (venous drainage, displacement and increased absorption of CSF, etc.) allow, despite the progressive increase in volume, the maintenance of intracranial pressure (ICP) within the normal limits. As compensatory mechanisms are exhausted, i.e., the more we move to the right of the pressure-volume curve, small increases in volume generate significant increases in ICP. From the point of inflection (B), we enter what is called the decompensation period of the curve or period of high elastance (low compliance) (C). This figure also shows how, as we move to the right the curve, there is a progressive increase in the amplitude of the cardiac component of the ICP. This increase can be used as an indirect information on the intracranial compliance.**

dition of new volumes into the cranial cavity or the elastance of the craniospinal axis. Czosnyka proposed, as a noninvasive method for continuous monitoring of the elastance, the use of a computerized system to assess continuously the Pearson's correlation coefficient (R) between the amplitude of the arterial wave and the intracranial pressure wave. The periodic increase in the blood volume entering the intracranial space with each cardiac cycle induces a synchronous change in the amplitude of ICP, which allows to estimate the intracranial volume reserve [12].

An R value close to zero between the amplitude of the arterial wave and the amplitude of the cardiac component reflects the lack of synchronization between the pulse wave and ICP and therefore indicates an adequate reserve volume. A high index close to 1 indicates an almost linear transmission of the pulse wave to the intracranial space and therefore a low volume reserve (low compliance or high elastance status) [12].

The volumetric compensatory mechanisms in the intracranial space require a variable period of time to be effective. Therefore, slow increases in volume (brain tumours) are always compensated for much more effectively than the abrupt increases that occur in acute situations, such as in spontaneous intracerebral hematoma or acute hydrocephalus.

28.5 Where to Monitor ICP? The Problem of Intracranial Pressure Gradients

The traditional concept assumes that the intracranial space behaves as a single chamber where the pressure is distributed evenly and is, therefore, identical at all points. The immediate consequence that follows from this premise is that ICP monitoring in any compartment (epidural, subdural, etc.) should reflect similar results both in absolute values and in its evolution. The existence of gradients between the supra- and infratentorial space and between the subarachnoid space of the spinal cord and the posterior fossa has been confirmed in different animal species. However, the existence of gradients between the two cerebral hemispheres has always been questioned. Experimental studies have objectified the presence of significant interhemispheric gradients in space-occupying lesions. However, the few clinical studies on interhemispheric gradients in head-injured patients ended with conflicting conclusions.

Our group studied this subject in 50 patients with moderate or severe TBI in whom ICP was monitored in both cerebral hemispheres [13]. The monitoring results were stratified according to the predominant type of lesion into two groups: focal or diffuse lesions. Within the diffuse injury category, patients were included in whom the focal lesion volume was <25 ml and the midline shif was ≤3 mm. In the focal lesion cathegory we included patients in whom the sum of the lesion volumes of a hemisphere was >25 ml and/or the midline shif was greater than 3 mm.

Our study showed that in 25% of patients with a focal injury there were clinically significant differences in ICP (>5 mmHg) and hence in cerebral perfusion pressure (CPP) calculated in the two hemispheres. However, in none of the patients with a diffuse injury the differences observed were clinically relevant. It is therefore possible to assume that in patients with a diffuse injury the intracranial space behaves as a single unicameral chamber without a compartmentalized space and, therefore, the pressure transducer can be implanted interchangeably in either of the cerebral hemispheres. However, since volumetric increases may occur in initially small focal lesions, it is always advisable to monitor ICP on the side where lesion volume is greater. In focal lesions with or without

midline shift, monitoring must always be performed on the side with the greater lesional volume. If ICP is monitored on the side contralateral to the lesion, treatment will be inappropriate and calculation of CPP inaccurate and overestimated.
The clinical management of patients with increased ICP is complex and often differentiated into several stages. The Brain Trauma Foundation Guidelines (1995) proposed a staged protocol wherein a distinction was made between first and second level therapeutic measures. Many clinical protocols have been based on this scheme. In the first Guidelines version, the classes of evidence (Class I, II and III) defined recommendations called standards, guidelines and options. In the latest Guidelines version published in 2007, the same classification of the evidence is followed, but the initial terminology is replaced with the most commonly used in other clinical guidelines: Level I, Level II and Level III [14]. Class I evidence is a result of controlled studies of high methodological quality. Controlled but methodologically questionable studies (systematic biases, significant losses, etc.) may give support to a lower level of evidence (II or III).
Class II evidence usually derives from well-designed prospective or retrospective studies where two or more treatment options are compared. The lowest level of evidence (Class III) corresponds to retrospective studies, case series or expert opinion, among others [14]. In the new 2007 Guidelines, although the standard terms and options are abandoned, its meaning remains.

28.6 Stepped Versus Individualized Treatment

In the 1990s many units, including ours, attempted to use individualized treatment of high ICP based on CT sacn criteria and parameters obtained from the monitoring of hemodynamics and cerebral oxygenation. At present, we believe that this kind of management is not successful, since it is difficult to systematize and is subject to great variability in both its application and its effectiveness. Moreover, the success of these personalized treatments often depends on uncontrollable factors such as the physician's experience, protocols which are difficult to implement and the availability of complex and not widely-available neuromonitoring methods. Therefore, since the early 2000s, the use of structured and uniform protocols applied systematically to all patients with severe TBI and ICH has become general. These protocols tend to be minor modifications from the recommendations published by the different versions of the BTF Guidelines. There is no need to stress that these protocols should not be rigid, but flexible enough to allow their adaptation to specific clinical situations [15].

28.7 Types of the Therapeutic Measures

The original version of the Guidelines for the clinical management of patients with severe TBI defined three main levels to manage ICP: 1) general measures which should be applied to all patients, with and without ICH, 2) first-level measures for the treatment of high ICP and 3) second-level measures for the management of patients who do not respond to the first-level measures.
General and first-level measures have already been discussed in previous chapters of this book. This chapter will discuss the second-level measures. Note that the 2007 Guidelines present no treatment algorithm, so in this section we have followed the systematics of the initial BTF guidelines release updated in 2000. It is essential to empha-

size that evacuation of volumetrically significant (>25 ml) space-occupying lesions or those with a lower volume but located in high-risk anatomic locations, as in the temporal lobe, should be included within the general or first-level measures. When there is a focal lesion, extending medical measures to extremes without evacuating the lesion is the wong way to go. This premise is especially important in the treatment of brain contusions, a field traditionally abandoned by the neurosurgeon and where early surgery allows to obtain excellent results in patients with high GCS scores. Recently Servadei et al. have completed a comprehensive review on the role of surgery in the management of TBI [16].

In all patients with severe TBI, a set of general measures should be initiated early in order to achieve hemodynamic stability, adequate nutritional support, and to avoid any factors that can increase ICP [15]. Among the last are the mismatch between the patient and the ventilator, improper patient position, hypoxia, hypercapnia, fever, seizures, arterial hypo-or hypertension and hyponatremia. Maintaining normovolemia and the proper choice of replacement solutions play a vital role in the management of the neurotrauma patient.

28.7.1 First-level Measures

These are initiated when the ICP values are >20 mmHg. The first version of the BTF Guidelines recommended treating thresholds above 20-25 mmHg, but it should be underlined that this recommendation was based on expert consensus rather than in any strong evidence. In a previous work, we emphasize that, in our opinion, the lower threshold suggested by the Guidelines (20 mmHg) is preferable because in this way treatment is started earlier improving the chances of achieving a correct control of ICP [2]. The last version recommends a threshold of 20 mmHg (level II evidence) although the text mentions the threshold of 20-25 mmHg as proposed in the 1995 version [17] makin this issue misleading. In patients with a bone decompression greatet than 5 cm and with an open duramater, it is recommended to lower the treatment threshold to 15 mmHg [4]. Also, this threshold should be also reduced in patients with focal lesions in one or both temporal lobes.

28.7.2 Second-level Measures

In the first version of the BTF guidelines these measures were defined as treatments which should be initiated when the first level measures (muscle paralysis, hyperosmolar solutions, moderate hyperventilation, etc.) were unable to control ICP below the established thresholds. In the 2007 update, this term and the whole algorithsm of treatment has disappeared. As a result of the collaboration between the Brain Trauma Foundation and a group of methodology experts, the methodology on the latest release has changed significantly compared to the first two editions. However, the lack of a clear proposal as to when and how to apply the various measures has generated some confusion. The latest version lacks a common thread and loses clarity. At the time of writing this chapter, the Brain Trauma Foundation has appointed an expert committee to update the algorithm proposed in the first version of the guidelines that should be upgraded in 2013.

In the earlier editions, the “second-level” measures formed a broad category which included many therapeutic manoeuvres considered strictly first-level or even general manoeuvres such as the use of the Lund therapy or a CPP increase above accepted thresholds (Rosner therapy).

To avoid misunderstandings, we have selected for discussion three therapeutic options: 1) barbiturates, 2) moderate hypothermia and 3) decompressive craniectomy.
These second-level measures should be introduced early after the threshold of 20 mmHg has been passed and under a stepwise treatment protocol. Some authors have suggested modifications in the indication and timing to introduce these measures, using other monitoring parameters such as the CPP, tissue oximetry and/or the jugular bulb oxyhemoglobin saturation. It should be emphasized that there is no evidence that any of these alternatives is superior to the classical thresholds of ICP. In addition, it must be emphasized that high ICP itself is harmful and that brain herniations may occur at relatively low ICP thresholds. Our recommendation is to apply these measures following a set of pre-established rules agreed between neurosurgeons and intensivists. The degree of collaboration between different specialists in the multidisciplinary management of these patients is probably the "non-measurable" and hidden factor which more strongly modifies the outcome of the patient with severe TBI.
Our recommendatios is second-level measures implementation shloud be based on the evolution of the ICP and serial neuroimaging tests. A new CT must always be obtained before instituting any of these measures and to rule out evacuable space-occupying lesions. Once the decission has taken, these measures should be implemented quickly applied in a complementary and not exclusive way. The association of barbiturates and hypothermia has been reported, as has the association of hypothermia and decompressive craniectomy. It is important to empasize that the use of these rescue measures makes sense only if the patient is considered neurologically viable.

28.8 Barbiturates

Barbituric acid was first synthesized in 1864 by von Bayer and is obtained from the condensation of malonic acid with urea [18]. From the chemical substitution of this primordial molecule a series of barbiturates are obtained which have a depressant action on multiple cellular functions in all organs, including the central nervous system (CNS).
The first barbiturates introduced into clinical practice were barbital in 1903 and phenobarbital in 1912 [18]. Since then, numerous derivatives has been introduced in the therapeutic armamentarium as sedatives, hypnotics, anticonvulsants or anesthetics. The most important ones from a neurological point of view are phenobarbital, pentobarbital and thiopental. At high doses, these drugs diffuse across all cell membranes and concentrate preferentially in certain tissues depending on their blood supply and the lipid solubility of the molecule, its affinity for plasma proteins and its degree of ionization [19]. Barbiturates are highly lipid soluble substances with a relatively uniform distribution in the CNS, are metabolized in the liver by oxidation, and are mostly eliminated with the urine [20]. However, there are pharmacokinetic differences depending on the type of barbiturate and its lipid solubility [20]. Moreover, individual factors such as body weight, fat compartment volume, muscle mass and other variables modify their pharmacokinetic characteristics. The main mechanism of action of barbiturates on the CNS is through the GABAergic system, the major inhibitory system in the mammalian CNS, mediated by GABA and its receptors (GABAA and GABAB). Barbiturates block GABAA receptors, a receptor involved in the mechanisms of action of benzodiazepines and substances with convulsive capacity such as picrotoxin [21]. In addition, barbiturates also inhibit AMPA glutamate receptors. This dual mechanism explains the deep depression that these drugs cause on the CNS metabolism.

28.8.1 Effects of Barbiturates on ICP: Recommendations

The effect on ICP of barbiturates was first reported by Horsley in 1937 [22]. However, it was Shapiro et al. in 1973 who first introduced barbiturate coma as treatment for patients with severe TBI and increased ICP [23,24]. In the beginning, this therapy created, as often happens with new treatments, excessive optimism owing to its potential neuroprotective effect. Over time, the use of these drugs has raised significant controversy and has also shown that their use requires considerable pathophysiological knowledge for their precise and individualized application [25]. In the 1995 Guidelines version, barbiturates were covered in a single paragraph [11]. In the last update of 2007, barbiturates are included in a larger section called "Anesthetics, analgesics and sedatives" [26]. In this section, two drugs are considered for the treatment of ICH, barbiturates and propofol. In our view, the inclusion of barbiturates in this broad section blurs the issue, because both analgesia and sedation are part of the general management of severe TBI, while high-dose barbiturates are used only as a second-level measure in the treatment of refractory ICP.

The 2007 Guidelines state that "High-dose barbiturates are recommended (level II evidence) to treat ICH refractory to medical or surgical measures. Hemodynamic stability is essential before and during the administration of barbiturates".

Propofol is recommended with a level II evidence for ICP control but its efficacy in improving mortality or functional outcomes has not been proved. In addition,

high doses of propofol (>5 mg/kg/h) can cause serious side effects and the so-called "propofol infusion syndrome" [26].

In reviewing the evidence on the use of barbiturates there are only three controlled studies. The first multicentre study on the use of barbiturates in the treatment of TBI was published by Schwartz et al. in 1984 [27]. However, its design left unanswered the most important questions because it compared barbiturates versus mannitol in patients with severe TBI [27].

In a study by Ward et al. pentobarbital was administered prophylactically to a group of patients with intradural hematoma or diffuse lesions and a GCS score ≤5 [28]. In the analysis of the results there were no significant differences in the group assigned to pentobarbital compared with the control group or in the incidence of increased ICP, in the duration of these elevations or in its response to treatment [28]. Only the study published by Eisenberg et al. in 1988 studied the effect of pentobarbital in patients with refractory ICP [29]. In this prospective, multicentre controlled trial, barbiturates were used as a last resort to control refractory ICP. It included 73 patients aged between 15 and 50 years and with GCS score ≤7 [29]. The treatment protocol started early when ICP was above 15 mmHg, using hyperventilation, mannitol, muscle relaxation and other first-level options. When ICP was not controlled according to preset criteria – 25 mmHg in patients without bone defect and 15 mmHg in those with a bone defect >25 cm2 –, patients were randomized to treatment with pentobarbital or continuation with conventional measures. The success or failure of treatment was evaluated by assessing the control of ICP but not the patient's functional outcome. The findings showed that the probability of controlling ICP in the group treated with pentobarbital was twice that in the control group. This probability remained after controlling for prognostic variables (GCS score, accident-inclusion period, etc.). In those cases without cardiovascular complications before inclusion into the study, the effectiveness of barbiturates was four times higher in controlling ICP than in the control group.

This study is the one which supports the Brain Trauma Foundation recommendation to assign a level II evidence to these drugs. However, this study presents some problems that prevent its analysis. Among others, 11 patients who did not respond to conven-

tional therapy were allowed to cross over. When the "intention to treat" methodology was applied to the analysis of the results, the effect of barbiturates on mortality was lost [26]. In the latest Guidelines version, the results match those of the systematic review conducted by the Cochrane Collaboration that concluded that even though barbiturates may be useful to reduce ICP, their effect is moderate. In Eisenberg's study the relative risk (RR) for the control of ICP was 0.81 (95% CI, 0.6-1.06)[30]. In addition, there was no evidence that barbiturates improve either mortality or functional outcome and in one out of four patients treated with pentobarbital hypotension was a clinically relevant adverse effect.

28.8.2 Thiopental or Pentobarbital?

The effects of barbiturates on ICP are attributed to their ability to reduce the brain functional metabolism and the consequent coupled reduction of cerebral blood volume (CBV). This CBV reduction causes decreased ICP. An important issue for clinical practice is which barbiturate is preferred to treat refractory high ICP. The most commonly used barbiturates have been pentobarbital in the United States and thiopental in Europe. In a pilot study Pérez-Barcena et al. have suggested that thiopental may be better than pentobarbital [31]. However, because of its design, this study does not allow draw any definitive conclusions. As a general recommedation, barbiturates should be selected based on pharmacokinetic considerations and the lower frequency of their side effects. Although thiopental is more widely used in Europe, pentobarbital theoretically offers some advantages that facilitate its use.

The metabolism and pharmacokinetics of thiopental are more complex than those of pentobarbital [20,32]. Part of thiopental administered parenterally becomes pentobarbital [20,32], making it difficult to control plasma levels and their correlation with therapeutic effects. Thiopental is more lipid soluble than pentobarbital and its action faster, although its half-life is shorter due to rapid redistribution into fat, muscle and other tissues [20,32]. The extracerebral distribution of pentobarbital is lower and its excretion slower, as it is eliminated mainly by metabolism. In obese patients or those with a large volume of adipose tissue, thiopental accumulates more than pentobarbital and after prolonged treatment, thiopental is eliminated more slowly than pentobarbital [20,33]. Moreover, thiopental has a significant depressant effect on the immune system by inhibiting the phagocytic activity of lymphocytes. This effect has not been observed with pentobarbital [20,34].

For these reasons, and in the absence of controlled studies on the subject, our recommendation is to use pentobarbital when treating patients with increased ICP.

28.8.3 Dosage and Controls in Barbiturate Coma

The main problem with the use of barbiturates is that they make the patient completely inaccessible to neurological examination. Continuous ICP monitoring and sequential CTs are the primary methods for controlling the clinical of the patients in induced coma. The last version of the BTF guidelines recommend starting with a loading dose of 10 mg/kg pentobarbital administered over half an hour followed by three consecutive doses of 5 mg/kg/h [26]. The load should be continued with a continuous infusion of 1 mg/kg/hr [26]. The frequently observed hemodynamic instability should be treated with colloids and/or vasoactive drugs (dobutamine, dopamine or phenylephrine). It has been shown, however, that when intravascular volume is properly preserved and drug administration is slow, the hemodynamic effects are significantly reduced [19]. Daily barbituremias

should be performed, trying to maintain plasma pentobarbital levels between 35 and 45 µg/ml. It has been shown, however, that there is often a dissociation between the degree of suppression observed on the electroencephalogram (EEG) and plasma barbiturate levels [20]. EEG is the best way to monitor barbiturate coma and the "burst suppression" EEG pattern is the best indicator of the maximum metabolic reduction achievable with barbiturates. The usefulness of the BIS or entropy in monitoring the depth of induced coma is still poorly defined.

28.9 Moderate Hypothermia

Moderate hypothermia, defined as a core temperature of 32-33.9°C [35], has been used sporadically since the 1940s in both experimental models of TBI and in non-controlled clinical studies for its potential neuroprotective efficacy [36,37]. The neuroprotective effects of hypothermia are manifold and some still poorly understood. Traditionally, it is assumed that its effect is closely linked to its ability to reduce cerebral metabolism, especially the basal metabolism. It is clear that brain metabolism, and cerebral oxygen and glucose consumption ($CMRO_2$, CMRgl), are temperature-dependent and that hypothermia reduces both. However, experimental studies show that this effect is only one of the many mechanisms by which hypothermia modulates the abnormal neurochemical cascades triggered by TBI [38,39,40].
In healthy subjects, moderate hypothermia induces a linear reduction of CBF in a temperature range between 18 and 37°C. An interesting phenomenon is that physiological metabolic coupling is preserved intact across this temperature range [41].

28.9.1 Basal Metabolism and Functional Metabolism

To understand the beneficial effects of hypothermia on the CNS, it is important to remember some basic physiological concepts. Basal metabolism of an organism is the basic metabolic requirements below which the body is unable to survive [42]. Howerver, certain animals are able to reduce their metabolism for prolonged periods of time and enter in a self-induced state of prolonged reduction of their metabolism to protect themselves against adverse environmental conditions such as lack of heat, water or oxygen [42].
In the cerberal metabolic rate of oxygen ($CMRO_2$), we must distinguish two compartments: functional metabolism and basal metabolism. Functional metabolism is the fraction of $CMRO_2$ dedicated to maintaining electrical brain function, an the electrical activity reflected in the electroencephalogram (EEG) [43]. Basal metabolism is dedicated almost exclusively to sustain the functions necessary to maintain cell structure [43]. The basal metabolism in mammals is organ-dependent, so that each organ contributes differently to the total basal oxygen consumption. Skeletal muscle, abdominal organs and the brain are the three organs which, in this order, consume most of the basal oxygen. However, when $CMRO_2$ is considered in relation to weight, the brain has the highest basal metabolism of any organ in the body.
Vise, using the comparison with a computer defined functional metabolism simply as the metabolic requirements needed to give support to the "brain software", while basal metabolism is responsible for maintaining the "hardware" [44]. Michenfelder reported that 50-60% of $CMRO_2$ is dedicated to maintaining the brain's electrical activity [45,46]. This functional metabolism is the one that decreases when barbiturates are adminis-

tered at doses sufficient to induce the so-called “burst suppression”. An important fact to consider is that hypothermia is only able to cause an isoelectric EEG when reaching 17 to 18°C core temperature.

28.9.2 Therapeutic Use of Hypothermia

In the early 1990s several researchers reported encouraging results in phase II and III clinical trials in which moderate hypothermia was used—prophylactically or to treat patients with increased ICP— in patients with severe TBI [47-51]. The turning point that rekindled interest in hypothermia was the study of Marion et al. published in 1997 where moderate hypothermia was used prophylactically [50]. The excitement caused by this study was largely due to the substantial media coverage that it received outside the medical field. However, the hopes that moderate hypothermia was able to improve the outcome of patients with severe TBI were aborted prematurely and probably hastily, after reports of the results of two large multicentre trials conducted in the United States and Japan [52-55]. In these two studies, early induced moderate hypothermia was not effective in improving mortality and functional outcome of patients with severe TBI. The two studies were questioned for various reasons but we will not discuss them in detail in this chapter. However, it must be emphasized that these results put a moratorium on further research into this powerful but complex treatment.
A few years later, a controlled single-centre study published by Zhi et al. involving 396 patients showed that hypothermia was able to significantly reduce mortality and increase the percentage of patients with a favourable neurological outcome [56]. Due to the uncertainty of its effectiveness, the complexity of its use and its side effects, hypothermia has been virtually abandoned in recent years in the management of patients with TBI. However, in the opinion of many, hypothermia deserves a second chance in the management of neurotrauma patients. At present, a European multicentre study is being designed, aimed at demonstrating the effectiveness of moderate hypothermia in patients with severe TBI.
In a recent systematic review, Sydenham et al. [57] found 22 randomized clinical trials on hypothermia in severe TBI. These studies included 1409 patients. The study showed that mortality was significantly lower in the group treated with hypothermia than in the control group (odds ratio [OR] = 0.76, 95%CI, 0.60-0.97).However, the eight studies considered methodologically the most robust showed no significant differences in mortality (OR 0.96, 95%CI, 0.68-1.35) or in the probability of a favourable functional outcome [57]. The review also reported a greater tendency to pneumonia, but with a narrow odds ratio and a wide confidence interval (OR 1.06, 95%CI, 0.38-2.97).
Recently, Sahuquillo et al. in a pilot study have demonstrated the feasibility, speed and effectiveness of this measure, induced by intravascular cooling in reducing increased ICP refractory to first-level therapeutic measures [58]. These results are consistent with those of other authors who demonstrated in open and non-controlled studies that hypothermia is effective in reducing ICP.
In addition, the results of the six systematic reviews carried out to date do not allow to definitively exclude the neuroprotective efficacy of prophylactic hypothermia. For this reason, moderate hypothermia can be considered a reasonable alternative to barbiturates in a selected group of patients when first-level measures have failed to control ICP. However, we recommend that moderate hypothermia be used only in centres with experience in its management and a sufficient number of patients to maintain a minimum level of expertise, without which the complications of moderate hypothermia can mask its clinical utility [58].

Traditionally, methods to induce moderate hypothermia in patients with severe TBI were surface methods (by convection or conduction) associated or not with adjuvant measures such as gastric lavage with cold saline, infusion of cold intravenous fluids, ice applied to the skin surface, and so on. The main disadvantage of these methods is that they require skilled nursing staff to reach the target temperature within a reasonable time, which is almost always more than 6-8 hours. On the other hand, after reaching the target temperature with these methods, the stability of the core temperature is highly variable and can range from 0.5 to 1.5°C in either direction. These temperature variations result in a suboptimal temperature management. Another additional disadvantage of the surface methods is the significant workload it posses to nurses.

Moderate hypothermia may have some complications which can be grouped into four broad categories [59]:

- Cardiac, including bradycardia, arrhythmias, reduced myocardial contractility and hypotension;
- Immune, mainly immunosuppression with consequent increased infectious complications, especially nosocomial pneumonia and bacteremia;
- Hematologic, primarily thrombocytopenia and coagulopathies; and
- Metabolic.

The last include metabolic stress induced by shivering , hyperglycemia, hypokalemia, paralytic ileus and cold-induced polyuria and their associated electrolyte disturbances.

We can conclude that although the role of moderate hypothermia is not yet well established, the variability in clinical outcomes may be the result of the different methods and protocols used to reach the target temperature. Further studies are clearly needed to establish the criteria for selecting patients with severe TBI who may benefit from this treatment, the optimal time for moderate hypothermia induction, the optimal target temperature with a better risk-benefit ratio, the optimal duration of treatment, and the best way to avoid complications. The new European multicentre study funded by the European Society of Intensive Care Medicine (EuroTherm3235) may help in the near future to better define the indications for moderate hypothermia in TBI [60].

28.10 Decompressive Craniectomy

A rescue alternative to medical treatment when ICP is not controlled is decompressive craniectomy. In essence, this technique seeks to increase the cranial volume by removal of a more or less large part of the cranial vault and by opening the dura mater (Figure 28.3).

Decompressive has been reinstated for the treatment of severe TBI after many years of almost complete abandonment. Despite the lack of Class I evidence to justify its routine use in adults, decompressive craniectomy is often used in many specialized neurotrauma centres. In the last decade, both neurosurgeons and intensive care physicians have shown a renewed interest in decompressive craniectomy for the management of high ICP refractory to first- and second-level measures. These patients have a catastrophic result if ICP is not controlled. We recently updated a systematic review for the Cochrane Collaboration, upon which we base much of the content of this section [61].

Even if it remains unclear who was the first neurosurgeon to practice decompressive craniectomy, the first known publication was by Annandale in 1894. For an excellent historical review of the initial stages of this technique, we recommend the work by Spiller and Frazier, 1906 [62]. Nearly all pioneers in neurosurgery occasionally performed this surgical procedure as a palliative measure in inoperable tumours, although it was Kocher in

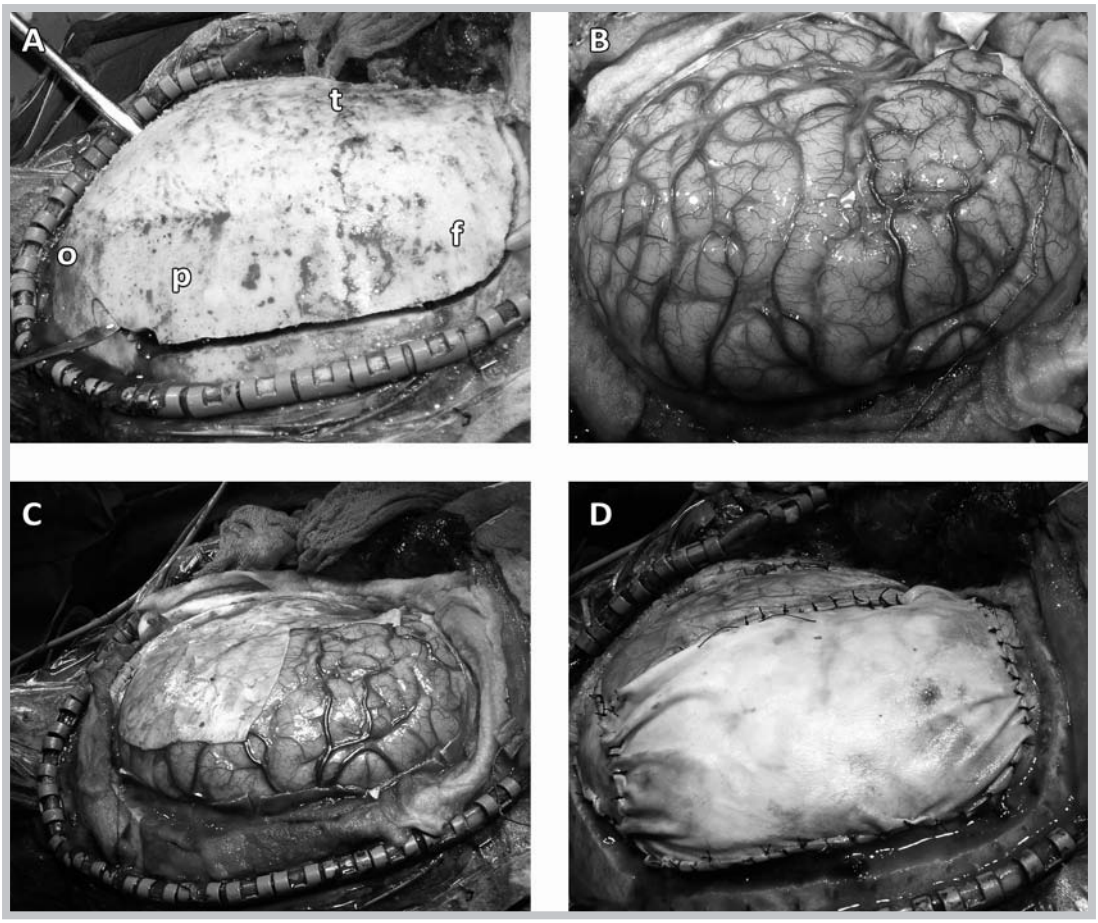

Figure 28.3. **Decompressive hemicraniectomy in a patient with unilateral brain swelling. The image (A) shows the bony limits of the craniectomy, which includes part of the frontal (f), temporal (t), parietal (P) and occipital (o) bones. The decompression is not effective until wide dural opening has been done (image B and C). Although the duramater of the patient can be used for duraplasty, there is need to augment it with a duraplasty which allows better tissue closure in the acute phase and facilitates reimplantation of the bone graft or cranioplasty in a later period (D).**

1901 who first proposed decompressive craniectomy as a technique for the treatment of high ICP. In 1905, Cushing made the first detailed description of subtemporal craniectomy to relieve ICP in patients with brain herniation secondary to inoperable brain tumours [63].

Historically, resection of a bone area of the cranial vault with or without opening of the dura mater has been used sporadically by many neurosurgeons. The first formal publications on this technique dates back to the late 1960s. It must be emphasized that in TBI, decompressive craniectomy does not change the primary lesion – established at the time of impact – but it can be very useful to reduce secondary injuries caused by ICH.

28.10.1 Types of Decompressive Craniectomy

In our systematic review, we distinguished between two types of decompressive craniectomy: prophylactic or primary decompressive craniectomy and secondary decompressive craniectomy [61]. We defined primary decompressive craniectomy the decom-

pression technique which is practiced in patients undergoing any intervention for the removal of an intradural lesion and in whom the purpose of removing the bone flap is to prevent postoperative increases in ICP. In these procedures, the decision is made during the surgical procedure and it is usually based on neuroimaging tests and/or intraoperative findings (brain swelling or difficulty with replacement of the bone flap). "Secondary" decompressive craniectomy is the one practiced in patients in whom ICP control is not achieved with maximum medical treatment. This therapeutic option is generally used when the first- or second-level measures have failed to control ICP.

A systematic review was performed with the objective of assessing the effectiveness of secondary DC in patients with severe TBI and ICP refractory to maximum medical treatment and the functional outcome at 6 and 12 months after injury. For this, randomized or quasi-randomized studies published in any language were included which included patients aged over 12 months, a GCS score ≤8, and ICP refractory to medical treatment (analgesia, sedation, muscle relaxants, hyperosmolar solutions, hyperventilation, barbiturates, etc.) [61].

The review detected only one Australian study aimed to test the effectiveness of DC in increased ICP refractory to medical treatment in the pediatric population (<18 years). The study by Taylor et al. included a total of 27 patients over a period of 7 years and was suspended by the authors because they thought it was unethical to continue enrolling patients after having demonstrated the effectiveness of this technique in an interim analysis. The quality and design of the study were high and the lack of blinding of patients was compensated by evaluation of outcome by an independent evaluator [64]. In this study the relative risk (RR) of death in the DC group was significantly lower than in those treated with medical therapy (RR = 0.54, 95%CI 0.17-1.72). The risk of an unfavourable outcome (death, permanent vegetative state or severe disability) was also lower than in the control group (RR 0.54, 95%CI 0.29-1.01).

Despite the numerous publications on this technique in the last decade (retrospective, prospective nonrandomized studies, etc.) suggesting the effectiveness of secondary DC, no studies were found in adults that met the criteria set by the review. Therefore, in adults, we must strictly conclude that there is insufficient evidence to substantiate the efficacy of decompressive craniectomy in reducing mortality or improving neurological outcome in patients with severe TBI and high ICP. It should also be emphasized that DC may have potential adverse effects, such as increased edema, the appearance of subdural collections, hydrocephalus or stroke.

28.10.2 Indications for Decompressive Craniectomy

Despite the lack of robust evidence, many small series consistently indicate the potential benefit of DC in reducing mortality and improving functional outcome in adults with severe TBI and increased ICP refractory to medical treatment. However, these studies have important methodological limitations, so it is difficult to extract any conclusion because of the heterogeneity of patients and the wide variability in the surgical techniques. Therefore, and although decompressive craniectomy cannot be strictly recommended as routine treatment in patients over 18 years of age, in our opinion it is reasonable to include this procedure as a rescue therapy in patients in whom maximal medical treatment has failed to control ICP.

In pediatric patients, the only study carried out so far showed that decompressive craniectomy—even without the opening of the duramater— is effective in reducing ICP, mortality and improving functional outcome. We would like to emphasize that leaving the duramater closed should be considered a suboptimal procedure in children and not indicated

in adults. Currently, there are two randomized controlled trials (RESCUEicp and DECRA) which will set the indications of decompressive craniectomy in adult patients. In fact, evidence-based guidelines, protocols and recommendations from both European and North American societies consider DC acceptable as a rescue procedure when medical treatment fails to control ICP and intracranial lesions surgically evacuable are ruled out.

28.11 Acknowledgements

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29 Non-conventional Therapeutics for the Treatment of Elevated Intracranial Pressure: Indomethacin and THAM

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29.1 Indomethacin

Indomethacin, a non-selective fatty acid cyclo-oxygenase inhibitor, is a potent cerebral vasoconstrictor and decreases cerebral blood flow (CBF) without affecting cerebral oxygen metabolism in experimental and clinical studies. Indomethacin's action on cerebrovascular physiology is unique and does not appear to be shared by other cyclo-oxygenase inhibitors.
Published clinical experience with indomethacin in the management of elevated intracranial pressure (ICP) in head-injured patients is limited to six small uncontrolled studies. In order to provide the clinician with sufficient information on the use of indomethacin as a treatment option, the following section presents a short review of the literature on clinical experience with indomethacin in controlling ICP.

29.1.1 Literature Review

Jensen et al. treated five patients with severe head injury and elevated ICP. Indomethacin was administered as bolus of 30 mg IV, followed by infusion of 30 mg/h for 7 hours when ICP was >20 mmHg despite treatment with hyperventilation, pentobarbitone and mannitol [1]. Intracranial pressure decreased within 5-10 seconds after administration and reached a minimum 1-5 minutes after indomethacin administration; and within 15 minutes, the mean ICP decreased from 28 to 17 mmHg. This decrease in ICP lasted about 4 hours and was followed by an increase in ICP after 7 hours. The reduction in ICP was accompanied by a non-significant increase in cerebral perfusion pressure (CPP) and an average decrease in CBF from 34 to 29 ml/100 g/min, measured 15 minutes after initiation of treatment. The pronounced effect of indomethacin in lowering ICP was later confirmed in an uncontrolled study by Biestro et al. who treated 10 patients with severe head injury and elevated ICP refractory to treatment with mannitol, hyperventilation and barbiturates [2]. Indomethacin was administered as a bolus dose of 50 mg IV over 20 minutes, followed by continuous infusion of 21.5±11 mg/h over 30±9 hours. Mean ICP was reduced from 34.4 to 16.4 mmHg and associated with an increase in CPP. Intracranial pressure (average, 23.1 mmHg) remained decreased during the infusion. Subsequent discontinuation of indomethacin treatment resulted in a significant rebound of ICP to pre-treatment levels. The authors did not measure CBF or cerebral metabolic rate of oxygen ($CMRO_2$) [2].

In another study of patients with severe head injury, Dahl et al. found that the decrease in ICP following an indomethacin bolus dose of 30 mg was comparable to the ICP decrease observed during a 0.88 kPa decrease in partial pressure of carbon dioxide in arterial blood ($paCO_2$) [3]. However, as compared to hyperventilation, the authors reported that indomethacin administration was accompanied by a more pronounced decrease in CBF and a significant increase in both mean arterial blood pressure (MABP) and CPP.
Imberti et al. demonstrated in 9 patients with severe head injury or intraparenchymal hemorrhage that indomethacin (bolus of 15-20 mg) is effective in extinguishing plateau waves (sudden and steep increases in ICP due to cerebral injury) [4]. They found that ICP decreased from an initial average of 58 to 21.2 and 25.8 mmHg after 5 and 10 minutes, respectively. Also, they found an increase in brain tissue oxygen partial pressure (PO_2), CPP and arteriojugular venous difference of oxygen ($AVDO_2$) without changes in MABP.
Recently, Puppo et al. demonstrated in 16 patients with severe head injury that indomethacin significantly reduced ICP and CBF and increased CPP. Their study also suggested that indomethacin may improve dynamic cerebral autoregulation [5].

29.1.2 Dose Considerations

The bolus dose of indomethacin used in clinical studies ranges from 0.1 to 0.5 mg/kg. Infusion rates range from 22 over 30 hours to 30/h mg over 7 hours.

29.1.3 Adverse Effects

The vasoconstrictive effect of indomethacin may increase the risk of cerebral ischemia in head-injured patients with compromised CBF. No studies have evaluated the risk of indomethacin-induced cerebral ischemia in patients with head injury. Currently, no adverse effects have been reported. However, reductions in CBF after indomethacin administration were reported in the above-mentioned studies and it is possible that some of these patients suffered from cerebral hypoperfusion.
Indomethacin does extend bleeding time but not beyond the normal range in healthy volunteers. It is possible that indomethacin may increase the risk of bleeding in coagulapathic patients.
Care should be taken with the use of indomethacin in patients with compromised renal function, and the drug may also have an adverse effect on renal function in hypovolemic patients.

29.1.4 Summary and Recommendations for the Use of Indomethacin

Evidence for the use of indomethacin in the treatment of elevated ICP is scarce. In a small number of uncontrolled studies, indomethacin has been demonstrated to effectively reduce ICP and improve CPP in patients with severe head injury. Therefore, we only recommend it as a therapeutic option to reduce increases in ICP when conventional therapy has failed. We suggest the following treatment protocol in the sedated, mechanically ventilated patient with severe head injury (Glasgow Coma Scale [GCS] <8):

- Elevated ICP >20 mmHg for 1-2 hours despite conventional ICP-reducing therapy. Surgical explanations for persistent high ICP should be eliminated.
- Administer indomethacin as a bolus dose of 0.1 mg/kg followed by infusion of 0.1 mg/kg/h. Monitor ICP if possible and repeatedly re-evaluate the patient and reconsider the need for indomethacin. We suggest that indomethacin infusion be terminated after a maximum of 30 hours.

- A central venous catheter should be placed in the jugular bulb to monitor the effect of indomethacin on CBF. Jugular bulb oxygen saturation ($SjVO_2$) <50 % may indicate cerebral hypoperfusion and increase the risk of cerebral ischemia.

29.2 Tromethamine (THAM or TRIS)

In our experience, THAM is a alternative option for the treatment of refractory intracranial hypertension (ICH). The drug acts on the main mechanisms of ICH: 1) derangement in cerebrovascular reactivity; and 2) lowering of spatial buffering.
Like indomethacin, it is a low-cost, easily managed drug with a good benefit/risk ratio.

29.2.1 Pharmacological Properties

THAM is a stable, hydrophilic alcohol amine that behaves as a weak base and can buffer metabolic and respiratory acidosis (formulas 1 and 2, respectively). Along with carbicarb, it is the only compound in clinical use with the property to reduce carbon dioxide content in the blood.

$$\text{THAM-R-NH}_2 + H^+ + La^- \leftrightarrow \text{THAM-R-NH}_3^+ + La^- \text{ (Formula 1)}$$

$$\text{THAM-R-NH}_2 + H_2O + CO_2 \leftrightarrow \text{THAM-R-NH}_3^+ + HCO_3 \text{ (Formula 2)}$$

The formulation currently used is a 0.3 molar solution of THAM acetate (mol/l) with the following properties:

- Molecular weight = 121 Da.
- Osmolarity = 380 mOsm/kg of H_2O.
- pH = 8.6.
- Both properties (osmolarity and pH) make peripheral venous administration safe.
- pK 7.82 very close to the plasma pH range, which is why THAM is a more efficient buffer than sodium bicarbonate, which has 6.1 pK. THAM also maintains unchanged its buffering capacity in hypothermia, which is why it is also preferred in this condition.

THAM is rapidly distributed in the approximate volume of the extracellular space. Very little penetrates into the cells and its passage across the intact blood-brain barrier (BBB) is negligible [8,9] unless the BBB is injured.
THAM is eliminated renally in a protonated form, with a clearance similar to creatinine. In healthy subjects, 25% of the intravenously administered drug is excreted in 30 minutes and over 80% after 24 hours.

29.2.2 Mechanism of Action

The mechanisms of action of THAM in lowering ICP in the brain are not fully elucidated. Some explanations have been postulated:

- Reduction of cerebral blood volume (CBV). Despite its poor passage across the BBB, THAM alkalizes the brain interstitium and the intracellular fluid at a distance from the capillaries. At this level, THAM induces a decrease in CO_2, with a CO_2 offsetting increase, highly diffusible from the cell into the extracellular medium, to form HCO_3. The resulting alkalinisation of the extracellular medium induces vasoconstriction and reduces CBV, improving cerebral hemodynamics and the pressure-volume ratio, and lowering ICP. This is thought to be the drug's mechanism of immediate action in controlling specific rises in ICH.

- Effect on intracellular brain edema. Alkalinisation of the intracellular fluid gives rise to "saving" of sodium entry into the glia where the ion is accumulated in order to expel protons (generated in abundance during injury) and maintain electroneutrality thanks to the membrane H^+/Na^+ exchanger. This sodium "drags" water and consequently swelling is the price the cell pays to maintain intracellular acid-base balance. Thus, THAM operates as a "proton vacuum pump" from the capillaries, as confirmed by animal models of acute brain injury which showed a decrease in sodium and water content (edema) of both cerebral hemispheres in the THAM-treated group [10]. This drug-mediated action would provide the rationale for THAM's prophylactic use in continuous infusion.
- Recently, a differential action on cerebral microvascular reactivity between hypocapnia and THAM has been reported. While both produce alkalinisation of the brain interstitium, only THAM activates the extracellular signal-regulated kinase (ERK) pathway of the interstitium, which is believed responsible for a further increase in

Study design	Nr. of patients	ABI type	Dose	Initial ICP	ICP	Other effects
Rosner, 1989 [14]						
Prospective Controlled	37 C: 20 Th: 17	Severe TBI GCS <8 (M: 5)	B: 2 cc/K 1 h CI: 1 cc/K/h	Variable	↓ compared with control/ day* Prevented increase in ICP	↓ CSF lactate
Gaab, 1990 [10]						
Prospective Controlled? Th vs. OSM	21 202 doses Th: 80 Ma: 82 S: 40	TBI swelling	18-36 g/100-200 ml/1-2h	ICP ≥ 25	↓ (max. 33%) Same power as osmotherapy Longer lasting effect (79 vs. 69 min.)	↑CPP Early improvement of EEG ↓ cerebral edema (animals)
Muizelaar, 1991 [13]						
Prospective Controlled Randomized	113 C: 41 IHV: 36 IHV + Th: 36	Severe TBI GCS ≤8 (M: 6)	B: ml = kg x base deficit at 2 h (reach pH 7.6) IC: 1 ml/k/h 5 days	Variable Control Groups 14% ICP >20 (n = 41) IHV 14% ICP >20 (n = 36) IHV + THAM 5% ICP >20 (n = 36)	IHV + Th: establish hourly variations of ICP no ↓ hourly average ICP	<mannitol requirement (compared with controls) ↓ CSF drainage (compared with controls) Absence of cerebral ischemia (ΔajO_2)
Wolf, 1993 [15]						
Prospective Controlled Randomized	149 C: 76 Th: 73	Severe TBI GCS ≤8	B: 4.27 cc/k/h in 2 h CI: 1 cc/k/h for 5 days	Variable (Crit. Prof.)	↓ ICP time >20 in first 48 h* ↓ as cause of death: uncontrollable ICH*	↓ BBT requirements

Table 29.1. **Major clinical studies with THAM in the control of the ICH.**

ABI = Acute Brain Injury
B = bolus
BBT = brain-based therapy
C = control
CPP = cerebral perfusion pressure
IHV = intense hyperventilation
CI = continuous infusion
CSF = cerebrospinal fluid
GCS = Glasgow Coma Scale
M = mean
Ma = mannitol
OSM = osmotherapy
S = sorbitol
T = treatment group
TBI = traumatic brain injury
Th = tromethamine

vascular resistance and inhibition of endothelial-related relaxation [11]. This could impair cerebral autoregulation due to the action of THAM, an event not demonstrated in our own studies, however [12].

29.2.3 Clinical Studies

Several clinical studies (Table 29.1) have demonstrated the efficacy of THAM in lowering ICP. The results of randomized prospective trials conducted by Muizelaar [13], Rosner [14] and Wolf [15] provide a higher level of evidence and should be considered. These studies reported a decrease in ICP in the THAM-treated groups and a decrease in therapeutic intensity as evaluated by the need for cerebrospinal fluid (CSF) drainage, mannitol doses and use of barbiturate. ICP decreased as reliably as with osmotherapy, and its effect was more durable. In Muizelaar's study [13] it was observed that THAM offset the negative effect on the outcome obtained with intense hyperventilation alone (<30 mmHg $paCO_2$), even better than in the control group (moderate hyperventilation). The THAM group also showed more stable ICP. Although this was confirmed by Wolf's study [15], no final improvement in patient outcome was evident because a type alpha or II error may have had an impact owing to the small sample in this study.

29.2.4 Practical Aspects

THAM [8] can be administered in two ways:

- 500 cc to 1000 cc bolus of 0.3 molar solution over 30-60 minutes, followed by 0.3-0.6 mmol/kg/h.
- Bolus similar to the first one, on demand, according to ICP values.

The recommended daily maximum dose is 15 mmol/kg.

In prolonged infusion, arterial pH should be monitored, without exceeding pH 7.5. Otherwise, infusion should be reduced.

There are three recommended specific indications for the use of THAM in neurocritical patients with ICH:

- When $paCO_2$ can't be manipulated by mechanical ventilation because of severe respiratory impairment, THAM can be given to reduce capnia and thus reduce secondary ICH.
- Sequential alternation of osmotherapy with hypertonic saline (synergistic effects on ICP while regulating the acid-base status, theoretically counteracting the effect of hyperchloremic acidosis) to control refractory ICH.
- Correction of accidental severe hyperventilation ($paCO_2$ <30 mmHg). Dose (150-300 ml/h over 3-6 hours) can be repeated after achieving moderate hyperventilation. THAM should be given during prolonged intense hyperventilation, as it improves clinical outcomes, as Muizelaar's study showed.

During its use, the plasma K level and daily intake of the ion should be monitored, because of the possibility of THAM causing hyperkalemia.

Contraindications:

- Renal failure.
- Spontaneous breathing (THAM requires mechanical ventilation); and c) pH >7.5.

29.2.5 Conclusions

This is a very interesting drug, with unique actions not shared by other therapies (complementary). Its use is common, especially in Europe; however, the most relevant stud-

ies are from the United States, though it is not cited in the more widespread guidelines. We have gained experience in its use over the past ten years and believe that has been studied insufficiently, so that new studies are needed to identify its right place in the management of neurocritical patients.

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30 A Different Point of View in Intracranial Hypertension Management: the Lund Therapy

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30.1 Introduction

Traditional treatments of severe head injury have mainly followed the protocols formulated by the U.S. Brain Trauma Foundation [1], the European Brain Consortium (EBIC) [2] and some local protocols such as the Addenbrook algorithm from Cambridge [3]. These protocols are based on meta-analytic overviews, combined with consensus and expert opinions. The protocols have been variously modified since their introduction, but they all comprise essentially the same components and have informed the dominating guidelines worldwide during the last 10 to 15 years.

An essential goal in the treatment of severe brain injury is to minimize the secondary injuries that develop soon after trauma. For this purpose, traditional treatments have advocated the maintenance of cerebral perfusion pressure (CPP) above a certain level in an attempt to squeeze enough oxygenated blood through the swollen brain. Vasopressors such as noradrenalin have been used more or less routinely and often in relatively high doses. Traditional treatment can therefore be characterized as a mainly "CPP-targeted" therapy. Mortality rate and poor outcome after severe head injury remain high. Two recent British database surveys showed that overall outcome after severe head injury has not improved during the decade after 1995 in spite of significant advances in general intensive care [4,5]. This and the lack of convincing scientific support for most measures in the treatment of severe head injury have cast doubt on the effectiveness of traditional treatments. The introduction of a different point of view in the management of intracranial hypertension, such as the Lund therapy, is therefore warranted.

The Lund therapy [6] was introduced about 20 years ago at the Lund University Hospital, Sweden. The Lund therapy was controversial from start as it differed considerably from traditional protocols, both in theory and in clinical approach. Its main characteristics are based on hypotheses derived from basic physiological principles of the control of brain volume and cerebral perfusion. The Lund therapy can be characterized as a combined "ICP-targeted" and "perfusion-targeted" therapy. In the normal brain there is a wide margin for cerebral perfusion before adverse hypoxia will occur, as in the less injured areas of the injured brain. Accordingly, the perfusion-targeted part of the therapy aims to optimize perfusion of the pericontusional areas, normally denoted the penumbra zone. As with traditional treatments, we still lack randomized clinical studies proving the effectiveness of the Lund protocol. However, its principles rest on a strong physiological basis and are supported by experimental studies and non-randomized clinical outcome studies from five different neurotrauma centres [6]. Most of the hospitals that have adopted the Lund concept have shown a marked reduction in mortality compared to historical control data [6,7].

This chapter will present the main principles of the Lund therapy and its use in clinical practice. A more detailed overview of the basic principles of the Lund therapy and its clinical application has been presented previously [6].

30.2 Pathophysiology After Brain Trauma

There is a general view that not only primary injury but also secondary injuries, developing over a period of hours and days and ensuing in a further loss of potentially salvageable cells, is of importance for outcome. Secondary injuries may be triggered by the release of neurotoxic factors such as excitatory amino acids and free radicals. Cell apoptosis is further aggravated by hypoxia around the hemorrhagic and ischemic contusions. Hypoxic pericontusional areas (penumbra) may expand due to further compromised microcirculation resulting from vasoconstriction, endothelial cell swelling, blood cell aggregation and wall adhesion. This may cause the release of inflammatory and neurotoxic substances and trigger more cell damage, including opening of the blood-brain barrier (BBB) and more brain edema.

Brain edema after head trauma may be intracellular due to energy failure (cytotoxic edema). It may also be interstitial due to increased hydrostatic and decreased plasma oncotic pressure, combined with disruption of the BBB (vasogenic edema), in addition to increased interstitial osmotic pressure from cellular and molecular disintegration. As we still lack any neuroprotective substance shown to improve outcome, we have to focus our therapy on reducing the secondary insults by improving microcirculation around the contusions and by reducing brain edema. Vasogenic edema can be counteracted by modulating transcapillary hydrostatic and oncotic pressures. Modulating the transcapillary Starling forces (hydrostatic and oncotic transcapillary pressures) and improving microcirculation around contusions are keystones in the Lund therapy, as will be described below. Improved microcirculation will not only spare brain cells from hypoxia but also counteract the vasogenic edema by reducing the breakdown of the BBB and ultimately save hypoxic brain cells.

30.3 Measures to Reduce Vasogenic Brain Edema

Normal control of brain volume is based on an intact BBB. This means that passive transport of even the smallest solutes – sodium and chloride ions – across the cerebral capillaries is highly restricted and only water passes the capillary membrane passively. At steady state, the transcapillary hydrostatic pressure of 20-25 mmHg is balanced by an equal plasma oncotic pressure. Any imbalance between these pressures favours filtration, however, it will not induce transcapillary fluid exchange because fluid filtration of pure water will be immediately counteracted by dilution of the high interstitial crystalloid osmotic pressure of about 5500 mmHg. In the normal brain, these mechanisms protect it against variations in brain volume following alterations in intracapillary hydrostatic and oncotic pressures.

In the injured brain with a BBB permeable to small solutes, the normal dilution mechanism counteracting filtration will be much weaker, as the filtrate will contain small solutes owing to an imbalance between the hydrostatic and the oncotic pressure. The filtration will continue until it reaches a new steady state at a higher ICP. It can be calculated that, in the worst case, the increase in intracranial pressure (ICP) may be up to 8 times higher than the imbalance between the hydrostatic and the oncotic pressures triggering the fil-

tration [8]. The hypothesis that ICP is highly dependent on arterial pressure at a state of increased cerebral capillary permeability has been confirmed experimentally in the cat [9]. The gaining relation between the Starling forces and ICP is a consequence of the fact that the brain is enclosed in a rigid shell, allowing ICP to be higher than extradural venous pressure. This is in contrast to other body tissues where tissue pressure is close to atmospheric pressure or even negative. The supra-atmospheric intracranial pressure is created by a sophisticated balance between the production and absorption rates of cerebrospinal fluid (CSF) and the fact that the brain lacks a lymphatic draining system. The hemodynamic principles for the brain being enclosed in a rigid dura/cranium are presented in Figure 30.1.

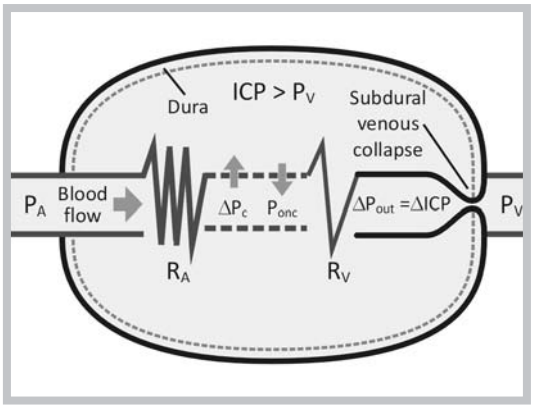

Figure 30.1. **A schematic illustration of the brain enclosed inside the dura/cranium. ΔP_c denotes transcapillary hydrostatic pressure; P_{onc} plasma oncotic pressure; P_A arterial inflow pressure; R_A arterial resistance; R_V venular resistance; P_{out} pressure just retrogade to the venous collapse; and ICP intracranial pressure. The magnitude of subdural venous collapse depends on the difference between ICP and P_V. The existence of a venous collapse means that the change in ICP in any direction is greater than the imbalance between P_c and P_{onc} creating the change in ICP, and that the brain is protected hemodynamically from P_V variations (see text for details).**

According to these principles, vasogenic brain edema can be counteracted by reducing hydrostatic capillary pressure and by normalizing the lowered plasma oncotic pressure. The first can be accomplished by reducing arterial pressure from the commonly raised levels towards normal values (see below) and, the second, by increasing the plasma oncotic pressure by colloid infusions. Note that the limit for adequate arterial pressure is lower in the sedated patient in a horizontal position than in the awake mobile patient. The hydrostatic capillary pressure will vary more with the arterial pressure in the injured brain with depressed autoregulation than in the normal brain.

Reducing arterial pressure with antihypertensive treatment should only be initiated from a normovolemic state (see below) and only with drugs which do not induce cerebral vasodilation, which *per se* will increase intracranial blood volume and ICP. Drugs with $beta_1$-selective antagonistic, $alpha_2$-agonistic and angiotensin II antagonistic effects are therefore recommended. Moderate head elevation can be used, if necessary, to reduce the hydrostatic capillary pressure from the arterial side. Plasma oncotic pressure can be normalized with albumin infusions (see below). In contrast to the hydrostatic transcapillary filtration effect, the oncotic absorbing effect is independent of the brain's autoregulatory capacity. Note that the reduction in brain edema following a shift in the balance between the hydrostatic and the oncotic pressure towards absorption is slow, and it may take several hours before any signs of ICP reduction will appear.

As mentioned above, normal ICP (about 10 mmHg) is always higher than extradural venous pressure, creating a passive venous collapse just inside the dura (venous outflow resistance, Figure 30.1). The magnitude of the collapse depends on the difference between ICP and the extradural venous pressure. By an automatic passive adaptation of the degree of venous collapse to the difference between ICP and extradural pressure, the brain is protected hemodynamically against venous pressure variations [6,8]. For example, it is because of this passive mechanism that brain circulation is not influenced on the venous side by head elevation or the use of positive end-expiratory pressures (PEEP) in the ventilator. Therefore, PEEP has no side effects on venous drainage and should always be used

in head-injured patients to prevent atelectasis. The initial reduction in ICP following head elevation can be explained by a blood volume reduction on the arterial side and to some extent from the gravitational force in the spinal canal, but not by an increase in venous drainage. A more long-term ICP-reducing effect of head elevation can be explained by the reduction in hydrostatic capillary pressure when arterial inflow pressure to the brain is reduced, analogous to the effect of antihypertensive treatment.Osmotherapy given in a single bolus dose of hypertonic saline can be used as a life-saving means to prevent an incipient brainstem herniation, while awaiting the effect of other ICP-reducing measures. Mannitol should not be used due to its adverse rebound effect on brain edema.

30.4 Decompressive Craniotomy and Other Surgical Measures

Evacuation of hematomas and focal lesions may reduce the release of inflammatory substances and result in less edema. Decompressive craniotomy will offer extra space to the brain, reducing the risk of herniation. Decompressive craniotomy, however, also causes a loss of transcapillary counterpressure when ICP is reduced which, in the injured brain with a disrupted BBB, will result in transcapillary filtration with the risk of herniation through the cranial opening. Transcapillary filtration may also explain the slow recovery in ICP from the lowered value often seen soon after the operation. These adverse effects can be counteracted by preventing unnecessarily high arterial pressure and by maintaining normal plasma oncotic pressure. Also, the ventricular collapse sometimes seen after CSF drainage can be explained by the induced imbalance between transcapillary hydrostatic and oncotic pressures, and the loss of CSF will be replaced by brain edema with an increased risk of brainstem herniation. Continuous CSF drainage, therefore, must be done with great caution and, when performed, done under computed tomography (CT) control of the ventricular volumes.

30.5 Microcirculation Around Contusions

According to the analogy to Ohm´s law, tissue perfusion relies on perfusion pressure and vascular resistance. The vascular resistance of the penumbra zone depends on several factors, such as the vasoconstrictor state of vessels, degree of micro-occlusion and wall adherence of various blood cells. This means that blood flow to the penumbra zone can be improved by increasing CPP and by decreasing its vascular resistance. According to the fourth power relationship between radius and resistance as formulated in Poiseuille's law, even small variations in vessel radius may result in large variations in vascular resistance in areas with increased resistance, such as the penumbra zone. It follows then that a relatively small decrease in the radius of a vessel or an increase in the degree of micro-occlusion/adherence in the penumbra zone will result in a large decrease in perfusion. Therefore, it is much more important for the perfusion of the penumbra zone to minimize vascular resistance than to maintain a high CPP. The paragraphs below deal with different measures to improve penumbra zone perfusion.

30.6 Maintenance of Normovolemia to Improve Cerebral Microcirculation

Hypovolemia compromises cerebral circulation via an alpha-mediated effect secondary to activation of the baroreceptor reflex. As shown experimentally in piglets, hypovole-

mia has a great adverse impact especially on the traumatized brain [10]. Prevention of excessive baroreceptor reflex activation, and the concomitant catecholamine release by keeping the patient normovolemic, is probably the most important measure to preserve microcirculation of the penumbra zone. Preservation of normovolemia under a generally increased permeability is, however, a sophisticated task, as explained below.

Unless adequately treated with intravascular volume substitution, head trauma patients will develop hypovolemia due to increased permeability in most body organs and a reduced recirculating capacity of the lymphatic system in the unconscious immobile patient. The transcapillary escape rate (normal, 5-7% of total plasma volume per h) may increase significantly above the level of the lymphatic capacity, which will increase the interstitial protein concentration in combination with tissue edema.

When using a crystalloid solution as plasma volume expander, the infused volume must be much greater than that when using a colloid solution, as crystalloids are distributed quickly throughout the whole extravascular space, resulting in general tissue edema. More importantly, the crystalloid solution will also be distributed to the interstitial space of the injured brain with a disrupted BBB, aggravating the brain edema. Furthermore, plasma oncotic pressure cannot be maintained when crystalloid solution is used as plasma volume expander.

Normal endogenous plasma protein albumin has become the dominating colloid in severe head injury because of the potential risk with synthetic colloids of coagulation disturbances and increased intracranial bleedings, and because albumin is the only colloid that allows measurement of its plasma concentration. Plasma concentration also gives a measure of plasma oncotic pressure. Like other colloids, albumin also improves a compromised microcirculation. As will be described below, albumin has side effects mainly related to transcapillary leakage. But when used in combination with an otherwise proper therapy, protein leakage can be limited to the extent that normovolemia can be maintained with the use of moderate volumes of albumin without inducing severe side effects.

30.7 Arterial Pressure and Plasma Volume Expanders

A crucial component in the Lund therapy is to avoid hypertension with the use of antihypertensive drugs and the avoidance of vasopressors, so as to prevent or counteract brain edema. According to the 2-pore theory for transvascular fluid exchange [11], the magnitude of transcapillary leakage at increased microvascular permeability in the rest of the body depends on the hydrostatic capillary pressure – the larger the hydrostatic capillary pressure, the larger the leakage of plasma to the interstitium and vice versa. The principles of the 2-pore theory are illustrated in Figure 30.2 and will be described below. The capillary membrane has small pores permeable only to small solutes, while there are a few (about 20,000 times fewer) large pores also permeable to proteins at the venous side of the capillary network and in the venules. This means that the hydrostatic filtration force is the only force inside the large pore. In brief, the higher the hydrostatic pressure, the greater the loss of plasma fluid to the interstitium. Accordingly, the need for plasma volume substitution to maintain normovolemia will be lower in situations of low than of high arterial pressure, also resulting in less interstitial edema. It is known that vasopressor-induced increases in arterial pressure will increase the transcapillary loss of plasma fluid and proteins. This effect was confirmed in a recent study on the rat which showed a drastic increase in plasma volume loss following treatment with noradrenalin at a state of increased permeability [12].

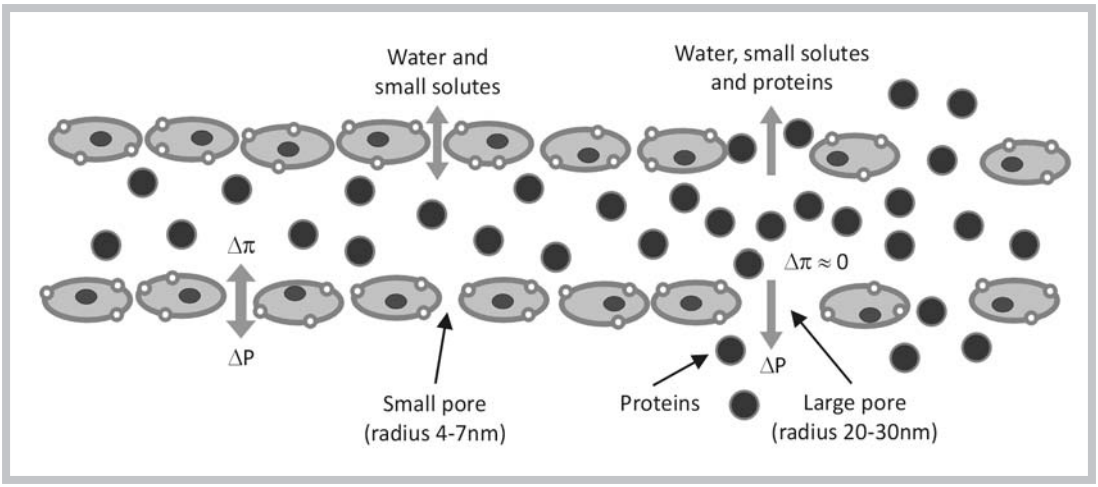

Figure 30.2. **The principles of the 2-pore theory for transcapillary fluid exchange in the body (not the brain). The capillary membrane with its numerous small pores and its few large pores at the venous side of the capillary network. While the transcapillary hydrostatic and the oncotic pressure balance each other across the small pores according to the Starling fluid equilibrium, the hydrostatic filtration force is the only force acting across the large pore, as the oncotic pressure is equal on both sides of the membrane for the large pore. Plasma proteins are lost mainly via convection following the fluid stream through the large pore. This means that an increase in hydrostatic capillary pressure will increase the loss of plasma proteins (see text for details).**

Most likely, due to its effect on hydrostatic capillary pressure, overtransfusion will increase the loss of plasma fluid to the interstitium, as shown experimentally in the rat, and should therefore be avoided [13]. The need for albumin transfusions can also be reduced by increasing the recirculating lymphatic capacity of proteins with a more effective physiotherapy and by keeping a relatively normal hemoglobin concentration (see below).

30.8 Albumin and Erythrocytes as Blood Volume Expanders

There are no studies evaluating the effect of blood transfusion to maintain normovolemia in patients with severe head injury. The need for plasma substitution, however, will be lower when the hemoglobin concentration is normal than when it is low, because a low hemoglobin concentration indicates that the loss of red blood cells must be replaced by a similar large volume of plasma to avoid hypovolemia. A low hemoglobin concentration raises the risk of larger transcapillary leakage of plasma to the interstitium. It has also been shown in the dog [14] and the rat that the loss of plasma volume to the interstitium is larger at a low than at a normal hemoglobin concentration. This is in accordance with our clinical experience where we noted less need for albumin at normal than at low hemoglobin concentrations and that the frequency of undesired hypotensive periods were markedly reduced. Modern research has also shown that optimal oxygenation of the brain occurs when the hemoglobin concentration is close to normal [15]. Most likely, net oxygen delivery to the brain is higher at a normal than at a low hemoglobin concentration in spite of the higher blood viscosity. There are arguments for the use of red blood cell transfusions to achieve normal hemoglobin values, and the Lund therapy recommends erythrocyte transfusions up to a lowest hemoglobin concentration of 12 g/dl. To reduce the side effects associated with blood transfusion, leukocyte-depleted blood and a short storage time of the blood are strongly recommended.

According to the principles described above, normovolemia cannot be achieved in spite of large volumes of albumin infused under acceptance of low hemoglobin concentrations and acceptance of a high arterial pressure, and especially when using vasopressors. Large volumes of albumin infusion do have side effects, which most likely can be related to an increased loss of plasma to the interstitium as a result of vasopressor therapy. This may explain, at least partly, why outcome with albumin was not better than with 0.9% saline [16]. However, when used correctly as a part of the Lund therapy, albumin is most likely the best plasma volume expander available today for severely head-injured patients. This is not only because of its endogenous nature or that the volumes of albumin needed are relatively small to maintain normovolemia, but also because it preserves a relatively normal oncotic pressure. Serum albumin levels were recently shown to be a favourable predictor of outcome after severe head injury [17]. Therefore, albumin is recommended as the main plasma volume expander in the Lund therapy. Higher concentrations of albumin (20-25%) are to be preferred, as higher concentrations have a relatively better plasma volume expanding effect and smaller transcapillary leakage. Furthermore, the peak concentration of albumin following a fast infusion will cause a larger transcapillary leakage of albumin than when albumin is given more slowly over a longer period of time.

30.9 How to Determine Whether Intravascular Volume is Adequate

No doubt, the probability of maintaining normovolemia is much higher with normal hemoglobin and albumin values than with low values – in fact, there are great difficulties to maintain a normovolemic condition with low hemoglobin/albumin concentrations. It is no guarantee, however, that the patient is normovolemic even when hemoglobin and plasma albumin (protein) concentrations are normal. A blood pressure below acceptable values in spite of relatively normal hemoglobin and albumin concentrations indicates that the patient is still hypovolemic. In an isolated head injury, this rarely indicates the need for vasopressors. In such a situation, normalization of blood pressure with further infusion of erythrocytes, perhaps in combination with albumin infusion, will confirm whether the patient is hypovolemic or not. Hypovolemia is the main cause of hypotension in most head-injured previously healthy patients. It must be stated from the principles described above, however, that we cannot fully normalize the intravascular volume whatever the blood volume expander given without inducing side effects such as interstitial accumulation of fluid and proteins, but the side effects will be minimized with use of the therapeutic principles of the Lund therapy. In this respect, avoidance of vasopressors and the use of antihypertensive therapy and transfusion to a relatively normal hemoglobin concentration hold special importance.

30.10 Other Measures to Improve Cerebral Microcirculation

Vasoconstrictors may compromise perfusion of the penumbra zone in analogy with baroreceptor reflex activation during hypovolemia, and they may also compromise microcirculation in other body organs such as the intestine, the kidney and the lung, triggering the development of the acute respiratory distress syndrome (ARDS). The use of noradrenalin, a proinflammatory drug, to increase arterial blood pressure under a hy-

povolemic condition may have severe adverse effects not only on brain circulation, but also on the perfusion of other body organs. Unless otherwise motivated by specific reasons, as in patients with paraplegia or those with severe sepsis, the Lund therapy does not include vasopressor therapy, vasoconstrictors or inotropic support. Beta-stimulating inotropic drugs may increase ICP through their cerebral vasodilating effects and their hydrostatic capillary pressure-increasing effect. The veno-vasoconstrictor drug dihydroergotamin was previously a component of the Lund therapy to reduce intracranial blood vlolume and ICP, but is no longer recommended due to its potential peripheral circulatory side-effects [6].

Stress-induced increases in sympathetic discharge and concomitant catecholamine release may compromise cerebral circulation of the penumbra zone. Antistress therapy is therefore an important part of the Lund therapy. Antistress therapy can include the use of sedatives and analgetics and the avoidance of awakening tests. Also, recommended antihypertensive treatments with $beta_1$-antagonists and $alpha_2$-agonists may have antistress properties, and $beta_1$-antagonists may protect the heart against stress-induced microinfarctions.

Besides its metabolically-induced vasoconstriction and ICP-reducing effects, barbiturate treatment is also effective as antistress therapy. However, the traditional use of barbiturate therapy in high doses up to a burst suppression electroencephalographic (EEG) pattern and over several days leads to severe cardiovascular, electrolyte and pulmonary complications. High fever is also a common sequela of this therapy perhaps due to pulmonary complications. Barbiturates given in lower doses and over a limited period of time, however, are safe and are accepted in the Lund therapy as antistress and ICP-reducing therapy.

It is a well-established recommendation that hyperventilation should be avoided in order to avert hyperventilator-induced vasoconstriction. Short-term hyperventilation can still be of value to break a persistent ICP plateau wave or an incipient brainstem herniation while waiting for other ICP-reducing measures to take effect.

30.11 Arterial, Plasma Oncotic and Cerebral Perfusion Pressure

The optimal arterial pressure is the pressure at which transcapillary hydrostatic and oncotic forces are balanced (no transcapillary filtration). But, simultaneously, there must be an acceptable perfusion of the brain. The higher the plasma oncotic pressure, the higher the arterial pressure (CPP) can be used without transcapillary filtration. A normalized plasma oncotic pressure will allow a higher arterial pressure without filtration, resulting in better perfusion of the penumbra zone compared to a low plasma oncotic pressure.

The lower the vascular resistance of the penumbra zone, the better the perfusion and the oxygenation at a specific CPP. Therefore, a lower arterial pressure can be accepted for preventing the development of vasogenic brain edema under normovolemia and normal hemoglobin concentrations than under hypovolemia and low hemoglobin concentrations. The coupling between ICP, arterial pressure and CPP (CPP = mean arterial pressure – ICP) means that a low arterial pressure does not necessarily imply a low CPP, as a lower arterial pressure means a lower ICP.

The Lund protocol is not a CPP-targeted therapy. In principle, any CPP values in the range of 50-75 mmHg in an adult are acceptable, providing the principles of the Lund therapy are followed. Our experience is that CPP stays in the range of 60-70 mmHg in most adult patients treated according to the principles described in this chapter. CPP values

in the range of 50-60 mmHg may appear and it may be necessary to reduce a markedly raised ICP; such values are acceptable only if cerebral perfusion is optimized as described above. In children, CPP is lower since arterial pressure is lower in children, and CPP values as low as 38-40 mmHg can be accepted in small children but, once again, only with use of the ICP and perfusion-targeted therapy presented in this chapter. A significantly raised ICP in a state of high CPP values despite antihypertensive treatment can be reduced by intensifying antihypertensive treatment and/or by head elevation.
In a large series of adult head-injured patients treated according to the Lund protocol, the interstitial milieu of the penumbra zone was analyzed with the microdialysis technique [18]. The study showed that the interstitial lactate/pyruvate ratio and the glycerol and glutamate concentrations decreased after initiation of the Lund therapy, and this in spite of a simultaneous reduction in CPP following antihypertensive therapy. A reduction in the lactate/pyruvate ratio reflects improved oxygenation, a reduction in glycerol and glutamate reflects less cell damage. In this study, CPP was reduced to 60-70 mmHg in the majority of patients, and the microdialysis results strongly indicated that perfusion of the penumbra zone was improved in spite of the lowered CPP.

30.12 Body Temperature Control

There is a general consensus that fever worsens outcome after severe head injury and that active cooling has neuroprotective effects. This has resulted in the marketing of equipment for active cooling. However, we still lack any randomized studies showing beneficial effects of active cooling after severe head injury. The two randomized studies performed so far, one in adults and one in children, instead showed a trend toward worse outcome in the patient groups treated with active cooling [19,20]. It may be that active cooling has adverse effects in addition to beneficial neuroprotective effect and that the net effect is not predictable.
Lowering of body temperature via active cooling below the thermostat level in the brain induces increased stress and shivering, with increased sympathetic discharge and release of catecholamines to restore the temperature back to its previous level. This may further compromise penumbra zone perfusion. Active cooling to temperatures below normal will also induce coagulation disturbances, with the risk of aggravating contusional and other intracranial bleedings. It has been suggested that the adverse effects of active cooling can be referred to the warming period. The reasons may be related to an increase in intracranial blood volume and an increase in hydrostatic capillary pressure due to a vasodilator effect induced by the increase in temperature. Unlike the situation after cardiac arrest, there are potential negative effects of active cooling after severe head injury, and especially cooling to temperatures below normal, which may explain the lack of improved outcome in the studies performed so far. Physiologically, a better alternative than active cooling would be to normalize a persistently raised body temperature by acting on the thermostat pharmacologically. A bolus dose of steroids can be used for this purpose. Due to the documented side effects of long-term treatment of severe head injury with steroids (the MRC CRASH study), steroid treatment should be limited to a single dose. Paracetamol can also be used, but its temperature-reducing effect is small, and it may have adverse prostacyclin-inhibiting effects.
The best way to prevent fever is to counteract its causes. Fever can be avoided or reduced by lowering the risk of pneumonia by minimizing atelectasis with general lung support and recruitment, the use of PEEP, inhalation and bagging. Furthermore, avoidance of proinflammatory vasocontrictors and high-dose barbiturate therapy are impor-

tant measures to prevent fever in head-injured patients. Fever can also be reduced with the use of enteral instead of parenteral nutrition and by avoidance of overnutrition.

30.13 Nutrition

Nutrition should be adapted to provide the basal energy need without overnutrition, as too much energy supply cannot be utilized in these highly catabolic patients and results in an adverse increase in body temperature. From measurements of the metabolic rate in deeply sedated head-injured patients we have estimated an energy demand of 15-20 kcal/kg/day in the adult. The nutritional requirement per kg body weight in head-injured patients varies with age: it is higher in children than in adults; therefore, it should be adapted to age.

30.14 Clinical Application

A short summary of the main guideline principles is given in Table 30.1.

A more detailed summary of the clinical application of the principles presented in this chapter to reduce brain edema and improve microcirculation of the brain are summarized in the Appendix following this chapter. The treatment components are applicable to all ages, but drug doses must be adapted to the age of the patient. The Lund therapy has no adverse effects – in fact, its principles are beneficial to both less injured patients with normal ICP and to more severely injured patients with elevated ICP. It can be used in both patients with depressed and those with more normal autoregulation. The Lund therapy should start as early as possible after the trauma to prevent ICP from rising to dangerous levels. ICP measurement is of great value in such patients. The Lund therapy can still be used even if ICP cannot be measured. The Lund therapy also seems to be beneficial for other body organs. Almost no severe ARDS, intestinal ischemia or renal insufficiency with the need for dialysis has occurred in patients with an isolated head injury treated at our neurointensive care unit since the introduction of the therapy. This in spite of the fact that the Lund therapy includes antihypertensive therapy. Most likely, this can be explained by better general perfusion obtained with optimal volume therapy, including erythrocytes to normal hemoglobin concentrations, avoiding vasoconstrictors and stress, and with the use of effective lung recruitment including PEEP. When treating a severe head injury according to the Lund therapy, all components presented in the Appendix should be considered. The Lund therapy can also be used to reduce elevated ICP in meningitis.

- Surgical evacuation of contusions and hematomas
- Normoventilation using mechanical ventilation and effective lung recruitment including PEEP
- Maintenance of normovolemia and a normal plasma oncotic pressure with albumin and erythrocytes
- Antihypertensive therapy ($beta_1$-blockade, $alpha_2$ agonist, angiotensin II inhibitor
- Antistress therapy
- Low energy, preferably enteral nutrition
- Avoid vasopressors (neither vasoconstrictors nor substances for positive inotropic support)
- Craniotomy may be life-saving in refractory high ICP
- A single bolus dose of hypertonic saline (not mannitol) can be used to prevent incipient brainstem herniation

Table 30.1. **Short summary of the most important guiding principles of the Lund therapy. See the Box in the following page for details on its clinical application.**

Clinical Guidelines for the Lund Therapy in Severe Head Trauma

- Surgical evacuation of available hematomas and contusions. Placement of an ICP device.
- Mechanical ventilation to normal $paCO_2$ (4.6-5.2 kPa, 35-39 mmHg) and normal paO_2 (12-14 kPa, 90-105 mmHg). Use PEEP (6-8 cmH_2O), intermittent moderate bagging under ICP control, and inhalation to prevent atelectasis. Reduce doses of β-stimulating inhalation drugs (e.g., salbutamol) if they increase ICP and decrease blood pressure (vasodilation). Short-term moderate hyperventilation (<2 min) can break intermittent ICP peaks. Do not extubate until ICP has been stabilized to a normal level.
- In persistent high fever (>38.5°C), the temperature can be reduced with paracetamol or one bolus dose of Solu-Medrol IV (5-7 mg/kg). Do not use active cooling.
- Use low-energy, preferably enteral, nutrition (15-20 kcal/kg/24 h in adults, relatively more energy in children). Enteral nutrition can be complemented with intravenous glucose 5% with electrolytes 1000-1500 ml/24h in the adult. Keep blood glucose levels normal (5-8 mmol/l) with insulin, if necessary. Avoid hyponatremia.
- Effective sedation and stress reduction can be achieved with sedatives (midazolam, thiopental, propofol) combined with α_2-agonist and β_1-blockade (see below). Thiopental should only be used in low doses (2-3 mg/kg in bolus + 0.5-3 mg/kg/h IV), and for 2 days at most to avoid the side effects of barbiturates (e.g., pneumonia, ARDS, fever). Due to uncertainty about long-term treatment with propofol, this drug should be limited to the weaning period.
- Normovolemia is mandatory and is achieved with erythrocyte infusions (leukocyte-depleted blood) to normal S-Hb (120-140 g/l) and albumin transfusions to normal S-alb (33-40 g/l), also normalizing plasma oncotic pressure. High concentrations of albumin solution (20-25%) are to be preferred. Limit the use of crystalloids as plasma volume expanders. Physiotherapy may reduce the need for albumin infusions by activating the lymphatic system. The need for plasma volume expanders is lower in normal than in raised arterial blood pressure (see below), and may be lower when given at a slow than at a fast infusion rate. Avoid overtransfusion. Diuretics can be used (not mannitol). Low doses of an ADH analogue can be used in marked polyuria.
- ICP can be controlled by normalizing plasma oncotic pressure (see above) and blood pressure, the latter with antihypertensive and catecholamine-reducing therapy with β_1-antagonists (e.g., metoprolol 0.04-0.08 mg/kg x 6-8 IV, or corresponding doses continuously, or 50-100 mg x 2 per os) and α_2-agonists (e.g., clonidine 0.3-1.0 μg/kg x 4-6 IV, or corresponding doses continuously or per os) and angiotensin II inhibitor (e.g., losartan 50 mg x 1-2 per os). Clonidine may have adverse α_1-agonistic vasoconstrictor effects at higher doses.
- Optimal CPP is individual. In most cases, it is 60-70 mmHg in the adult and, depending on age, 38-55 mmHg in children and adolescents. Transient, relatively low CPP values (50 mmHg in the adult) may be necessary in selected cases to reduce a critically elevated ICP. Such low CPP values can only be accepted if the perfusion-targeted therapy recommended here is used. Too low a CPP may be corrected by: (a) correcting latent hypovolemia; (b) no extra head elevation; (c) discontinuing thiopental; and (d) reducing antihypertensive therapy. Vasopressors should not be used.
- Moderate head elevation (max 20°) can be used to reduce ICP and provide an acceptable CPP. Additional head elevation may have the adverse effect of reducing venous return to the heart.
- CSF drainage should not be used routinely. It may be used intermittently via a ventricular catheter in small volumes to break an incipient Cushing reflex or a critically high ICP. Drainage at a fairly high level may help to control ICP at a later phase of therapy if CSF absorption is insufficient.
- If ICP increases to higher persistent values despite the interventions described above, a large uni- or bilateral craniotomy may be a life-saving measure to reduce ICP, break a Cushing reflex, and reduce arterial pressure. Optimal ICP-reducing pharmacological and fluid therapy (points 1-9 above) must be continued to reduce strangulation and herniation in the craniotomy. A bolus dose of hypertonic saline (not mannitol) can be used as osmotherapy to break an incipient brainstem herniation.

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31 A Critical Point of View in the Management of Intracranial Hypertension: Are All Therapeutic Tools Evidence Based?

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31.1 Introduction

Most TBI patients with cerebral lesions on cerebral computed tomography (CT), such as hematomas, swelling, contusions or herniation, will develop ICH in the days ensuing injury. A recent observational study showed that the mean intracranial pressure (ICP) will peak within the first 3 days after injury in half of such patients and after 5 days in 25% [1]. An uncontrolled rise in ICP is probably the most common cause of death in TBI patients. For these reasons, ICP monitoring is strongly recommended in TBI associated with abnormal cerebral CT findings. Intracranial pressure monitoring allows to continuously monitor ICP, manage cerebral perfusion pressure (CPP), and withdraw cerebrospinal fluid if an external ventricular drainage is inserted. Elevated ICH is strongly associated with poor outcome in patients with severe TBI. Indeed, elevated ICP may lead to decreased CPP, cerebral ischemia and/or herniation. The ICP threshold above which treatment should be initiated is still debated. A large, prospectively collected database study published in 1991 by Marmarou et al. [2] reported a strong correlation between the number of hours with an ICP >20 mmHg and outcome. Similar results have been recently reported by Balesteri et al. in a retrospective analysis involving 429 TBI patients [3].

Does treatment to decrease ICP improve outcome in TBI? Few data exist regarding this question, and no controlled randomised trial is available, but it seems that patients in whom ICP could be controlled have a much better outcome than those with in whom ICP remained uncontrolled [4,5]. More recently, two retrospective studies showed similar results, suggesting an improved outcome with aggressive ICP therapy [6,7].

In the treatment of ICH, one of the key issues to consider is that TBI is more likely a syndrome than a disease. After trauma, the traumatised brain is characterised by a marked pathophysiological heterogeneity: ischemic areas (cytotoxic edema) coexists with areas with blood-brain barrier disruptions (vasogenic edema), contusions, and normal brain parenchyma. The proportion of each of these areas likely depends on the etiology of TBI. Intracranial pressure-lowering therapies may have some systemic or cerebral differential effect according to the TBI presentation. For example, one can consider that in blood-brain barrier disruption, treatment such as hypertension-induced high CPP and osmotherapy could worsen contusional areas of the traumatised brain.

31.2 Sedation as a Therapy

Sedatives and anesthetics are commonly given to prevent agitation, minimize noxious stimuli, and adapt TBI patients to mechanical ventilation. Benzodiazepines, especially midazolam, are administered in combination with morphine or derivatives such as sufentanil. While they are particularly suitable in the neurological intensive care unit, they are unable to depress brain electrical activity even at high doses, present a long duration of action and a plateau effect.

Propofol administration has been proposed as an alternative in TBI patients. Propofol decreases ICP by reducing brain metabolism [8], which explains its potential neuroprotective effect. Only one double-blind controlled randomised trial was conducted to compare propofol infusion with another sedative regimen in TBI patients. Kelly et al. [9] evaluated the clinical safety and multiple clinical and radiological endpoints in 23 patients in the propofol-morphine group and 19 patients in the morphine sulphate group. The authors found a lower incidence of ICH at day 3 in the propofol group, without any difference in adverse effects between groups. The combined use of midazolam and propofol allows the control of ICH and the possibility to obtain burst-suppression at high doses. Such a combined strategy reduces the use of barbiturates. However, the potential risk with using propofol is the feared propofol infusion syndrome. This syndrome, characterized by multiorgan failure, has a high incidence in sepsis or septic shock, which are therefore contraindications to propofol administration. It is mandatory to stop propofol in case of metabolic acidosis (with or without lactates), hyperkalemia, renal insufficiency, rhabdomyolysis or triglyceride level >5 mmol/l [10]. A daily dosage of blood triglycerides is a common practice in our unit. Hypertriglyceridemia is a warning symptom in this context.

The occurrence of refractory brain hypertension during the first days following the onset of head trauma often requires therapeutic escalation with such therapeutics as neuromuscular blockers, hypothermia and thiopental, all of which have a high potential to deteriorate lung status further through mechanical effects or direct immunosuppressive effects. Barbiturate therapy reduces cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) and it increases cerebral vascular resistance in patients with severe head injury [11]. Barbiturates, particularly pentobarbital and thiopental sodium, have been used effectively in brain-injured patients with increased ICP refractory to sodium management, cerebrospinal fluid drainage, and moderate hyperventilation. The first published series of head-injured patients receiving this therapy in 1979 [12] found that high-dose barbiturate administration reduced elevated ICP in most patients refractory to a rigorous regimen of ICP management. Several studies in the 1970s suggested that barbiturate therapy had a major impact on the prognosis of patients with intractable ICH. Marshall et al. [12], for example, found that 19 of 25 (76%) patients with severe, intractable ICH responded to treatment with high-dose pentobarbitone therapy and that 10 of the 19 responders made a good functional recovery. The authors concluded that barbiturate therapy significantly improved clinical outcome on the assumption that their patients would have otherwise died.

Other studies showed that high-dose barbiturate, when added to a routine of conventional management, could be useful for the reversal of ICP. Barbiturates seem to provide the brain with some protection against anoxia, ischemia, and cerebral edema by decreasing the brain's oxygen consumption, reducing CBF, and stabilizing the membranes. However, barbiturates have a number of serious adverse effects. Cordato et al. [13] reported that prolonged barbiturate infusion induces respiratory complications in 76%, lung infection in 55%, arterial hypotension in 58%, hypokalemia in 82%, hepatic dys-

function in 87%, and renal dysfunction in 47% of the treated patients. Continuous barbiturate infusion is also known to produce immunosuppression by inhibiting lymphocyte function [14], affecting neutrophil function and depressing humoral immune response through a decrease in immunoglobulin production [15]. The use of barbiturates is, by itself, a statistical predictor of an increased risk of pneumonia [11].

31.3 Hyperventilation

The simplest way to decrease ICP is to reduce arterial partial pressure of carbon dioxide ($PaCO_2$). Reduction in ICP is secondary to a decrease in cerebral blood volume. The impact of a sudden change in blood volume on ICP depends on brain compliance and the position of the patient on the Langfitt curve. Accordingly, a given change in $PaCO_2$ and cerebral blood volume will markedly decrease ICP in a non-compliant brain and induce nearly no change in pressure in a compliant brain. Such a decrease in cerebral blood volume also occurs when the mean arterial pressure is increased. However, both therapies have opposite effects on CBF.

Cerebral arteries respond to highly localized perivascular alterations of $PaCO_2$ and pH. During chronic hypocapnia, the CBF remains constant, suggesting that carbon dioxide itself does not control cerebral vascular cerebral tone. It is likely that local pH rather than local carbon dioxide is the mediator of tone regulation. The mediator cascade that links extracellular pH to cerebral vascular tone is complex and interrelated, the final mediator being intracellular calcium. Most studies report a change in global CBF of 1 to 2 ml/100 g^{-1} min^{-1} for each mmHg change in $PaCO_2$. Acutely reducing $PaCO_2$ to 25-30 mmHg decreases the global CBF by 40 to 50%.

Payen et al. [16] studied by contrast-enhanced magnetic resonance imaging the relationship between the change in ventilation and CBF in rats. The authors demonstrated that hypercapnia results in a significant increase in CBF in the brain-studied regions, although there was no direct correlation between the change in cerebral blood volume and flow. Carmona Suazo et al. [17] investigated the effect of hyperventilation on cerebral oxygenation by means of continuous monitoring of brain tissue oxygen pressure ($PbrO_2$). Acute hypocapnia significantly decreased $PbrO_2$, indicating the risk of secondary ischemic damage during hyperventilation in severely head-injured patients. These conclusions agreed with those of Imberti et al. [18] who observed similar results, clearly suggesting that hyperventilation can compromise cerebral oxygenation. The most recent guidelines of the Joint Committee on Trauma and Critical Care of the American Association of Neurologic Surgeons indicate that aggressive or prophylactic hyperventilation must be avoided in patients with severe head trauma [19].

31.4 Drainage of Cerebrospinal Fluid

Drainage of cerebrospinal fluid (CSF) is frequently performed in TBI patients. The external ventricular drain (EVD) connected to an external strain gauge allows to continuously measure ICP and to calculate CPP (when the drainage line is externally clamped), or to withdraw CSF (when the drainage line is open). In low cerebral compliance due to cerebral edema, the evacuation of a few ml of CSF may be sufficient to decrease ICP dramatically. Kerr et al. showed that a 3-ml withdrawal of CSF resulted, on average, in a 10% decrease in ICP and a 2% increase in CPP, which were sustained for 10 minutes [20]. This

therapy is simple, cost effective and overrides the often serious systemic complications related to drug or physical therapies, especially those induced by barbiturates and hypothermia. Drain placement might be technically difficult, and can be complicated by cerebral contusion or ventriculitis [21]. Two studies have shown that the difference in pressure gradient induced by intracranial CSF drainage facilitates the transfer of cerebral edema to the ventricles, thus improving its clearance [22]. Continuous drainage of CSF against a zero pressure via an EVD, combined with continuous ICP monitoring with an intra-parenchymal catheter, is a common practice in our unit. This technique likely increases the volume of drained CSF as compared to discontinuous drainage, although there are no hard data to support this clinical observation.

31.5 Osmotherapy

In TBI, increased ICP is most often due to cerebral edema. Hyperosmolar agents are widely used to control edema formation after TBI. There is abundant literature supporting the use of mannitol to decrease ICP, increase CPP, and enhance CBF (23) without affecting cerebral oxygenation [24]. Hypertonic saline used at various concentrations (from 3% to 23.4 %) has been consistently shown to decrease ICP and cerebral water content in TBI patients [25]. Hyperosmolar agents were shown to decrease water content in non-traumatised brain tissue by osmotic mobilisation of water across an intact blood-brain barrier (BBB). However, there is the possibility of an opposite effect of the osmotic agent in the areas of a disrupted BBB. This was observed by Saltarini et al. [26] using magnetic resonance spectroscopy to assess cerebral water content in a patient with refractory ICH. One recent CT-based analysis showed an increase in contusion volume after hypertonic saline infusion, suggesting a leak of electrolyte and plasma from the extracellular compartment into the contused area through a disrupted BBB [27]. These results argue for the differential effects of hypertonic saline according to the state of the BBB in various brain areas. As a result, it could be proposed to reserve the use of osmotic agents for patients presenting a small volume of contusion.

31.6 Cerebral Perfusion Pressure

Management of cerebral perfusion pressure (CPP) in TBI is still debated. In 1995, Rosner et al. developed a management paradigm that focused on maintaining CPP >70 mmHg. This strategy, based on BBB integrity and preserved cerebral autoregulation, seemed to improve outcome in an uncontrolled series of TBI patients [28]. An alternate approach has been described and popularized by the Lund group [29]. The Lund theory hypothesises that the BBB is mainly disrupted after head trauma and that cerebral autoregulation is lost. Increasing CPP or using osmotic agents is therefore regarded as a potentially dangerous therapy which can increase edema formation. The Lund protocol therapy has two main goals: 1) to reduce or prevent an increase in ICP (ICP-targeted goal); and 2) to improve perfusion and oxygenation around contusions (perfusion-targeted goal). There is current evidence to support the concept that hypotension is deleterious for the traumatised brain. In contrast, increasing CPP up to 70 mmHg was associated with an increased incidence of pulmonary failure [30].

A recent prospective observational study compared the 6-month outcome of two groups of TBI patients: one group (n=67) treated in Sweden with the aim of keeping

ICP <20 mmHg and CPP >60 mmHg, and a second group (n=64) treated in Scotland with a Rosner-derived strategy protocol in which the goal was to reach a CPP of at least 70 mmHg while keeping ICP <25 mmHg [31]. The authors noted that CPP management therapy seemed to be more efficacious in the patients with intact cerebral autoregulation. In contrast, patients with loss of cerebral autoregulation appeared to benefit from Lund CPP management. This discrepancy could be linked to the presence of contusions: preserved autoregulation is more frequently observed in patients with few contusions [32]. Taken together, the results suggest that patients with numerous contusions (BBB mainly disrupted and loss of autoregulation) would benefit from a Lund-based therapy. Conversely, in patients with only a few contused areas, a CPP-targeted therapy associated with osmotherapy would be logical from a pathophysiological point of view.

31.7 Hypothermia

Prophylactic hypothermia is effective in improving outcome in cardiac arrest [33]; however, it remains controversial in other indications such as brain injury. Nevertheless, the results of different studies, and meta-analyses in particular [34-37], did not demonstrate that hypothermia was associated with a reduction of mortality in TBI. However, the systematic use of hypothermia, independently of ICP, may have underestimated its usefulness. Polderman et al. assessed the efficacy of hypothermia therapy (32-34°C) as part of a step-up protocol to detect and treat side effects [35]. They found that artificial cooling could improve survival and neurological outcome, especially in the patient group with low Glasgow Coma Scale (GCS) scores (GCS=5-6). According to these results, it seems logical to reserve hypothermia for patients with increased ICP. Outcome after hypothermia can be optimised when proper indications, techniques for implementation, as well as management procedures and their enforcement are followed. A rigorous and effective application cannot be conceived outside specialized units with experienced teams. After a minimum duration of 24 hours and after controlled ICP, very gradual warming can be started with the possibility to interrupt it when ICP increases [38]. A decrease in brain metabolism associated with anti-inflammatory effects is the main mechanism of action attributed to hypothermia treatment. Kalemia must be strictly controlled during the ascending and descending changes in body temperature. Of note is that the implementation of hypothermia has been recently facilitated with the availability of automatic cooling blankets and specially designed catheters.

31.8 Steroids

Steroids are particularly effective to treat ICH secondary to cerebral tumoral processes and bacterial meningitis. The bulk of available evidence indicates that steroids do not improve outcome or decrease ICP in TBI patients. The randomised controlled CRASH trial [39] involving 10,008 patients showed no effect of corticosteroids on ICP and a higher mortality was observed in the steroid-treated groups. The study demonstrates that systemic corticosteroids are detrimental to TBI patients. However, the inclusion criteria were very broad and the population of TBI patients was extremely heterogeneous.
The use of steroids in TBI patients with severe contusions could be effective in managing ICH owing to their acting on pericontusional edema, which usually markedly increases ICP between 24 and 72 hours after trauma (clinical experience). Their use under these

Emergency care	**1. Mannitol 20% (0.7 to 1.4 g/kg) or hypertonic saline (20%, 40 ml) if pulsatility index >1.4 and/or mydriasis** **2. Immediate correction of hemostasis disorders** • Fresh frozen plasma if prothrombin time <70 % and platelets if <70,000/mm^3 • Prothrombin concentrate complex (PPSB) if patient chronically treated with oral anti-coagulant therapy **3. Surgical treatment** *3.1 Categorical indications* • Extradural hematoma >10 mm on CT • Temporal polar hematoma with ipsilateral anisocory and disappearance of the basal cistern on the same side • Open skull fractures *3.2 To be discussed on an individual basis* • Subdural hematoma with a midline shift >5 mm if: ▪ Mydriasis duration <30 min or reversible with mannitol whatever its duration, ▪ Parenchymal lesions compatible with short-term survival and long-term relational life • Closed skull fractures • Drainage of an intraparenchymal hematoma • Contusectomy **4. Delay non-vital surgery** • Contraindication to volatile anesthetics • Surgery performed only after stabilization and under strict monitoring of ICP
LEVEL 1 **Mandatory in all patients**	**Homeostasis control (all items must be controlled)** • Head 30°, neutral neck alignment without impeding venous return • CPP between 65 and 75 mmHg • Normovolemia • Normalization of left ventricular function • Sedation for adaptation to mechanical ventilation (combining sufentanil + midazolam) • $PaCO_2$ between 35 and 40 mmHg • SaO_2 >97 % • Temperature between 36.5 and 37.5°C with paracetamol and/or automatic cooling blanket • 5.5 <glycemia <7.5 mmol/l • Maintain natremia between 140 and 155 mmol/l • Diagnostic and treatment of cerebral salt wasting • Prevention of seizure (levetiracetam 500 mg every 8 h) • Transfusion to maintain hemoglobin level >8 g/dl **External ventricular drainage for cerebrospinal fluid drainage and ICP measurement**
LEVEL 2 **if ICP >20-25 mmHg and/or IP >1.4 after level 1 completion** **Go to the next item if ICP is not controlled with the previous one** **Cerebral CT scan obtained to exclude new surgical lesion**	**1. Nursing without mobilisation** **2. Intraparenchymal catheter for ICP monitoring and continuous CSF drainage via EVD** **3. Increase sedation and add propofol** (measure pH daily and serum triglycerides every 48 h – stop propofol infusion if metabolic acidosis, hyperkalemia, renal insufficiency, rhabdomyolysis or triglyceride level >5 mmol/l). **4. Contusion volume** *4.1. Contusion volume <20 ml* • hypertonic saline • and/or increase CPP >70 mmHg *4.2. Contusion volume >20 ml* • Methylprednisolone 120 mg every 12 h (3 days) • Consider albumin administration **5. Hypothermia between** 35°C and 36.5°C **6. Transfusion** to maintain hemoglobin level >10 g/dl
LEVEL 3 **If ICP not controlled at level 2**	• Decrease temperature step by step according to ICP response (control kalemia every 6 h) • Pharmacologic coma with barbiturates (EEG monitoring) • Consider surgical therapy (lobectomy, decompressive hemicraniectomy)

Table 31.1. **Algorithm for the treatment of intracranial hypertension. Neurosurgery-neurointensive care, Pitié-Salpêtrière Hospital, Paris France.**

conditions is possible should all other conventional therapies fail to reduce ICP. A treatment duration of 2 to 4 days is often enough in these circumstances. In our unit, methylprednisolone is administered (dose of 120 mg twice a day for 3 days) if ICP increases in a patient with major brain contusions despite maximal medical therapy and temperature control.

31.9 Albumin

There are some experimental findings showing that albumin reduces pericontusional edema. In a model of ischemia-reperfusion in an isolated guinea pig heart model, albumin more effectively prevented fluid extravasation than crystalloid or artificial colloid. This effect may be attributable to an interaction of albumin with the endothelial glycocalyx also present on the endothelial layer of the BBB. In humans, the results of systemic albumin administration are disappointing. A post-hoc analysis of the SAFE study showed deleterious effects of systemic albumin administration [40]. The main flaws of this study were the *a posteriori* analysis and the slight imbalance between the two groups. Albumin use should be restricted to this sub-population of patients with severe TBI.

31.10 Conclusions

One of the key issues to consider is that TBI is more likely a syndrome than a disease. After trauma, the traumatised brain is characterised by pathophysiological heterogeneity. One and the same therapy for the various different types of brain trauma is not efficient. This could partly explain why systematic use of an increased CPP approach, hypothermia, corticosteroids or albumin failed to demonstrate any positive effect in large multicentre trials. Indeed, the volume of contused brain seems to reflect the state of the BBB and the preservation of cerebral autoregulation, which are the determinants in the choice of therapies. The algorithm in Table 31.1, used in our institution, illustrates therapeutic strategies delineated according to both the side effects of the therapies and the presence or not of a high contusional volume.

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Section 5.
Traumatic Injury

32 Mild Traumatic Brain Injury

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32.1 Introduction

Traumatic brain injury (TBI) is a major health problem and a leading cause of death or disability in persons aged under 45 years. TBI has social and economic implications with a direct impact on healthcare resource utilization. Despite decisive changes in the diagnosis and management of head-injured patients in the last 25 years, prevention remains the most effective treatment. In reference to a disease, the term "mild" implies "not severe or dangerous; benign" (*Webster's Third New International Dictionary*). But within the context of TBI this definition falls short of describing the totality of cases, since the initial condition may worsen in some and will require further diagnostic procedures and therapeutics. Over the medium and long term, the adjective "mild" loses relevance in such cases, given that physical and neurocognitive sequelae after an acute "mild" traumatic event have been variously reported.

We find often ourselves attending head-injured patients, either intoxicated or with a previous pathology, in whom the initial management must be appropriate. Although very few will need therapeutic manoeuvres and still fewer will require surgery, an error in the initial diagnosis can lead to lengthy – and worst of all, unnecessary – hospitalization, as well as dilatory interventions that can be fatal in the prognosis of the disease.

Various different strategies for the management of mild traumatic brain injury (MTBI) are based on the availability and/or accessibility of resources for its diagnosis and treatment. Any approach adopted, however, requires a working algorithm adapted to the complexity and diversity of the local or regional healthcare system. The objective in case management thus consists in identifying those brain injuries involving greater risk and then selecting the appropriate therapy or intervention. the focus of this chapter is the management of mild traumatic brain injury.

32.2 Epidemiology

The incidence of TBI varies between 229 and 2000 cases per 100,000 inhabitants per year in Europe, constituting the primary cause of death in persons aged under 45, with the highest occurrence in the 15-to-25-year age group. About 95% are MTBI, 6.3 to 21% of which can exhibit abnormalities on computed tomography (CT), while injuries possibly needing surgery account for between 0.2 and 3.1% of cases.

In the United States, the incidence of MTBI is 128 cases per 100,000 inhabitants per year, with similar age-group distributions, CT findings, and frequency of surgical interventions as reported for Europe.

In Argentina, Marchio et al. (2006) reported, based on a series of 1540 patients hospitalised in a trauma hospital in Buenos Aires, an incidence of 300 cases of MTBI per 100,000 inhabitants, with a trimodal distribution according to age group from 20 to 24, 40 to 44, and more than 75 years. Of a total of 108 CT scan, only 3 (2.7%) showed hemorrhagic lesions that required surgical drainage.

32.3 Classification

32.3.1 Risk categorization

The risk for neurologic deterioration or the presence of potentially surgical intracranial lesions is predicted on the basis of the Glasgow Coma Scale (GCS) score after the patient has been resuscitated, the presence of neurologic symptoms and risk factors, together with neuroimaging evaluation for deciding a possible hospitalization.

Glasgow Coma Scale

The GCS, devised by Teasdale and Jennet in 1974, is a physiological scale that evaluates the level of consciousness according to three components: motor, ocular, and verbal. While easy and quick to use, interobserver variability and difficulties in recording certain of the scale's components have documented, e.g., the ocular in facial injury, the motor in injury of the extremities, discrepancies between pre-hospital services and in-hospital emergency departments in recording GCS components.
GCS upon hospital admission after TBI has great prognostic value for outcome. But since the time elapsed between the moment of injury and arrival at hospital can influence categorization, various authors have established that the measurements are valid for 24 hours after the injury. Alterations in the state of consciousness exponentially increase the possibility of encountering lesions on CT. For example, patients with 14 points on the GCS have double the risk of developing intracranial hemorrhage than those with 15 points, while those with 13 points are at four times the risk of having CT abnormalities.
Continuous evaluation of the state of consciousness is of utmost importance for noting clinical improvement in cases with favourable evolution or clinical deterioration which requires more aggressive therapeutic interventions. This approach is necessary above all in a medical centre where the diagnostic resources (e.g., neuroimaging services) or treatment facilities (e.g., emergency neurosurgery and/or a critical care unit) are limited.

Neurologic Alarm Symptoms

Loss of consciousness. In a patient who has suffered a TBI, it be must established whether or not loss of consciousness (LOC) has occurred, and if so, its duration. The occurrence of LOC represents a ten-fold increase in the risk of cranial fracture and brain lesions, although the absolute risk of the latter still remains low.
Establishing the duration of LOC is difficult if no witness of the event is available for questioning. Although different time limits can be cited for determining the relevance of LOC, the clearest interval applies to pediatric patients in whom LOC longer than 15 minutes necessitates CT in order to discard the possibility of an intracranial lesion. In adults, a LOC for 15 to 30 minutes is believed valid by some authors, while others hold that the occurrence of LOC is sufficient for ordering a CT scan.
Posttraumatic amnesia. Posttraumatic amnesia (PTA) is defined as the difficulty in acquiring and/or recalling new |sensory or cognitive information after the moment of injury, i.e., a lack of remembering daily activities. PTA is a functional expression of focal anatomical damage in the frontal and/or temporal lobe secondary to diffuse axonal injury or contusions. PTA may be associated with spatiotemporal disorientation – especially in persons with attention disorder, retrograde amnesia, confabulation, agitation and uninhibited behaviour – depending on the extent of injury. The duration of PTA is one of the most useful prognostic factors for the eventual recovery of cognitive functions in TBI patients. According to the American Academy of Neurology guidelines, a lesion is considered mild when PTA lasts for less than 30 minutes.

Risk Factors

Risk factors include predictive variables independent of the presence of an intracranial hemorrhagic lesion such as age over 60 years, coagulopathy or antithrombotic treatment, very recent use of illicit drugs or alcohol, previous neurochemical treatment, history of epilepsy, a high-energy trauma mechanism, or evidence of injury above the clavicle. Depending on the literature consulted, the principal causes of traumatic injury are vehicle collisions, falls, and physical aggression. Stiell (2001) reported that the most frequent situations involved a pedestrian run over by a car, a driver or a passenger thrown out of a moving vehicle or off a motorcycle, and a fall from a height of 1 meter or 5 steps.

32.3.2 Definitions

The World Health Organization (WHO) classification distinguishes three categories of brain trauma: mild, moderate, and severe, according to the severity of the alteration. In accordance with this scheme, we can clearly determine what we consider to be MTBI.
In 1981 Rimel applied the term **light** to designate head-injured patients with a score between 13 and 15 on the GCS. In 1996 Culotta published a paper illustrating a pronounced difference between patients with a GCS score of 13 and those with score of 14 or 15 with respect to CT findings, cranial fractures, and the need of |neurosurgery. On the basis of these observations, along with the differences in the extent of brain damage and the risk of death, a distinct differentiation among patients with MTBI must be made.
Certain authors define **concussion** as being that form of cranial trauma where the victim exhibits LOC or amnesia, but the skull is not fractured and no lesions are radiolographically demonstrable. This definition, however, we regard as rather broad and risks blurring the initial categorization.
In accordance with the Neurotraumatology Committee of the World Federation of Neurosurgical Societies classification, we prefer to define MTBI as the presentation of a patient with a GCS score of 14 to 15. Within this classification and according to the incidence of hemorrhagic lesions, we would define three risk levels.

- **Low risk:** GCS of 15 with no history of LOC, amnesia, vomiting or diffuse headaches; the risk of presenting with a hematoma requiring neurosurgery is <0.1%.
- **Moderate risk**: GCS of 15 with one or more of the above-mentioned symptoms, including recovery from concussion; the risk of presenting with a hematoma requiring neurosurgery is between 1 and 3%.
- **High risk**: GCS of 14 or 15 along with cranial fracture or a neurologic deficit**;** the risk of a finding that requires neurosurgery is from 6 to 10%.

To finalize this classification we must determine whether or not the patient presentation includes the associated risk factors cited above. These risk factors include elements from the patient's medical history that increase the incidence of lesions potentially requiring surgery. The inclusion of any one of these risk factors would place the patient in the high-risk group with respect to the occurrence of surgically relevant findings.

32.3.3 Initial Management

All patients with a traumatic injury to the brain or the cranium must be admitted to the emergency service for evaluation. According to the severity of the injury, the symptoms, and the associated lesions, a decision is made following a treatment algorithm.
The first step in the treatment plan is to document the means of trauma, the nature of the presenting symptoms, the risk factors involved, and the extensiveness of the objective data. Finally, the evaluation on the basis of the norms for all trauma patients – in

Group	Clinical condition	Skull radiography	Brain CT without contrast with bone window	Management
0 Low-risk	GCS 15/15 Without neurologic deficit With or without pain at the point of impact or temporary vertigo	No	No	Discharge with instructions about warning symptoms
1 Moderate-risk	GCS 15/15 No neurologic deficit Headache, vomiting, loss of consciousness, amnesia, or major trauma [ATLS]	Yes	No fracture on skull radiography Optional (availability)	Clinical observation for 24 h (if CT unavailable)
			No intracranial lesion or fracture	Observation for 6 h
			Intracranial lesion or fracture	Hospitalization for at least 24 h Neurosurgical consultation
2 High-risk	GCS 14/15 Confusion, stupor, or disorientation With or without neurologic deficit With or without headache, vomiting, loss of consciousness, amnesia, or major trauma [ATLS]	No	No intracranial lesion or fracture	Hospitalization until symptoms resolve Repeat CT at 24 h with coagulopathy or use of anticoagulants
			Intracranial lesion or fracture	Hospitalization until symptoms resolve Neurosurgical consultation
0, 1, 2 Plus risk factors	GCS 14/15 GCS 15/15 + risk factors	No	No intracranial lesion or fracture	Hospitalization until symptoms resolve Repeat CT at 24 h with coagulopathy or use of anticoagulants
			Intracranial lesion or fracture	Hospitalization until symptoms resolve Neurosurgical consultation

Table 32.1. **Algorithm for the management of mild traumatic brain injury. Risk factors: coagulopathy or antithrombotic or anticoagulant treatment, alcoholism, drug addiction, epilepsy, previous neurosurgical treatments, age >60 or risk factor, advanced age with some degree of disability.**

addition to an assessment of the state of consciousness, pupil diameter, and neurologic foci – will assist in making an initial categorization of the patient's condition, including a definition of that victim's risk situation.

Table 32.1 illustrates our proposed systematic approach to decision-making in patients with MTBI. This table is based on 1996 Italian guidelines and on the 2001 Neurotraumatology Committee classification.

32.3.4 Special Situations

MTBI in Patients Under the Effect of Depressants or Toxicants

Alcohol intoxication is involved in 35-50% of head-injured patients. The effect of alcohol is dose-dependent, with a minimal effect at blood concentrations <80 mg/dl, but caus-

ing coma at concentrations >200 mg/dl. The authors of a recent study were unable to find a linear relationship between the level of alcohol intoxication and the initial GCS score (unintoxicated, 10.1±4.8 *vs*. intoxicated, 10.3±4.7; p=0.5). This would imply| that a lower GCS should not be attributed to alcohol intoxication alone and that the attending physician should not wait until a patient has metabolized the ethanol load before making a diagnostic decision.

MTBI in Patients With Coagulopathy

Since TBI patients are part of the general population, a certain proportion may be under medication with warfarin or acenocumarol or may harbour hepatic lesions or hematologic alterations. Accordingly, this patient subset will constitute a group at higher risk for bleeding and with larger and more rapidly growing hematomas.

Cohen et al. found that in patients with a GCS <8 the International Normalized Ratio (INR) in more than 50% was >5.0 and that the mortality rate was 91.5%. In this group the most frequent brain CT finding was subdural hematoma, and progression was furthermore documented by CT for up to 18 hours after the first scan. The combination of coagulopathy, age >65 years, and TBI should be regarded as a potentially lethal circumstance. Working with this patient group requires caution in admitting a patient; CT studies in accordance with established criteria; and if surgical treatment has been elected, the provision of vitamin K, freshly obtained frozen plasma, and concentrated coagulation factors in order to ensure proper homeostasis during the intervention.

MTBI in Sports

The incidence of MTBI during a sports event – and especially contact sports such as boxing, rugby or American football – is an interesting subject for discussion. Athletes presenting after a high-contact sports accident should be examined with the same criteria in mind as for MTBI under any other circumstance regardless of the trauma's having occurred during competitive event. The pressure to "get back into the game" should in no way jeopardize the patient's health by influencing the decision-making process; and the persistence of symptoms should be carefully evaluated, if necessary, advising the athlete against returning to competition or practice in the days to weeks after the accident. Another point to stress is that although more than twenty sets of guidelines have been issued on this subject in recent decades, the level of available evidence for definitive recommendations for the timing of resumption of physical activity is low.

The U.S. Academy of Neurology defines **sports-related concussion** as an alteration in mental state following an injury that may or may not be accompanied by a change in the level of consciousness and further emphasizes that the state of confusion that characterizes this circumstance can appear either immediately or some minutes afterwards. The Academy classifies concussion into three grades: **grade 1**, where symptoms persist for <15 minutes; **grade 2**, where the symptoms persist for >15 minutes; and **grade 3**, where LOC occurs. In the initial evaluation (at the place of competition), the state of consciousness (orientation, concentration, and memory); response to external stimuli; and degree of| motor ability, acuteness of sensation, and pupillary reflexes are all assessed. Individuals presenting with grade 1 are fit to return to competition if no further symptoms persist after 15 minutes. Those with grade 2 are recommended to discontinue the sport for at least 24 hours, provided that the symptoms (headache or others) resolve; but if the latter continue or worsen during the first 7 days, neuroimaging evaluation and neurologist consultation are recommended. In LOC (grade 3) the patient should be taken immediately to the emergency department of the nearest hospital for appropriate evaluation and a brain CT with a bone window to rule out possible spinal cord injury. The patient must refrain from participation in sport for 7 to 14 days, during which he/she will undergo sequential monitoring by a specialized neurologic team.

32.4 Radiological Diagnosis

32.4.1 Skull Radiography

Between 3 and 18% of radiographed MTBI patients exhibit a cranial fracture with an ample margin owing to the heterogeneity of the indication. The risk of harbouring a lesion requiring surgical drainage after skull fracture is 4%; and if accompanied by a deterioration in consciousness, it increases to 25%. Conversely, some 95% of patients with epidural hematoma will also be found to have an associated skull fracture. Skull radiography, however, is not sufficiently sensitive or specific to warrant its recommendation as a routine procedure, especially since the reading of radiograms is difficult and on occasion incorrect.
Nevertheless, the technique can play a role in centres lacking brain CT services. The recommendation is that skull radiography be reserved for the moderate-risk group. The absence of fractures on skull radiography will still require clinical observation of the patient for 24 hours, while the presence of skull fractures will necessitate a CT in order to discard the possibility of lesions requiring surgical drainage.

32.4.2 Brain CT Without Contrast Material

Neither the clinical history nor the neurological findings – and not even the GCS – can predict with certainty the presence of lesions within the cranial cavity. A CT with normal findings can indeed ensure that a discharged patient has no dangerous lesions; but the volume of patients with MTBI makes this generalization difficult to apply to the general population, especially in countries without optimal resources.
Not all tomographic findings require neurosurgery; nevertheless, the physician must not rule out the possibility that skull fracture on an early initial CT will not necessarily eliminate the possibility of the later development of epidural hematoma [Poons, 1992; Riesgo, 1997; Matsuda, 2008].
On the basis of the proposed algorithm, CT would be appropriate in patients with a GCS score of 14, a GCS of 15 with a skull fracture, or a GCS of 15 with a high-risk factor.
Whether or not the availability of a resource or device should influence management guidelines is a subject of debate. The norm should perhaps be to improve the use of the technical resource through the application of algorithms or clinical guidelines before using the technology either in a defensive manner or excessively. More specifically, the question is whether or not to carry out a series of CT studies in such patients. The literature proposes as a good option the assessment of the severity of the initial CT and clinical findings as a criterion for deciding upon the necessity for ordering a second image.
A routine second CT in patients whose primary lesions are considered to have no risk of progression is not recommended. Nevertheless, in patients with associated risk factors such as coagulopathy or coagulant use, clinically observed neurologic deterioration, or hemodynamic alterations, a second image would aid in ruling outing the possibility of late lesions that would compromise the evolution.

32.4.3 New Radiologic Modalities

The evaluation of the brain structures by magnetic resonance imaging (MRI) in the acute stage of MTBI has disadvantages compared to CT. For example, MRI is less useful for identifying bone lesions, needs patient cooperation in order to minimize movement-associated artifacts, requires lengthy time periods for image acquisition (less so with last

generation machines), involves the cost of the imaging study, and is hampered by the irregular availability of MRI machines and trained personnel for correct image interpretation. This would relegate the use of MRI to situations where CT services are unavailable and the degree of patient risk be such that the potential presence of surgically operable lesions or the need for hospitalization be discarded. The imaging sequences of spin-spin relaxation time (T2) and fast-fluid inversion-attenuated recovery (FLAIR) have greater sensitivity than CT for the detection of contusions, diffuse axonal lesions or edema and also enable differentiation between acute hemorrhagic and other types of subacute or chronic lesions. The technique termed susceptibility-weighted imaging (SWI) shows higher sensitivity in detecting hemosiderin deposition in the acute stage of TBI; but although this modality is highly promising, the technique is not widely available for use.
In the post-concussion syndrome, MRI during the follow-up period exhibits a good correlation with neuropsychological-testing results – for which reason we consider the technique as a support modality in such patients – and is able to detect minimal frontal and temporal lobe lesions at up to 3 months after injury.
Very recent studies have shown ever-increasing accuracy between image findings and clinical findings, as, for example in MRI and the modality called diffusion-tensor technique or tractography. The latter is an extension of the sequence employed by diffusion and allows reconstruction of the white matter tracts; in so doing, it constitutes an assessment of axonal integrity. In acute TBI, tractography can identify small alterations in the white matter that are consistent with a diffuse axonal lesion of the corpus callosum and the internal capsule not evident on CT. In chronic lesions, generally those associated with high-contact sports such as boxing, the degree of alteration in the diffusion of water within the white matter is related to motor sequelae and long-term neurocognitive alterations.
In a 2008 paper published by a group from Baylor University, abnormalities in the tractography of patients with mood changes or the post-concussion syndrome indicating cytotoxic edema were readily visualized. These findings can now serve to redefine the long-term management of this patient group in order to select different, more appropriate modalities of therapy and neuropsychological support.
Single-photon-emission computed tomography (SPECT) employs a tracer to indicate by indirect means changes in cerebral metabolism by measuring blood flow through the brain. In MTBI or moderate TBI, the authors found alterations in 40-70% of patients followed for up to 3 months after the injury – the affected zones being areas local of hyperperfusion within the frontal and temporal lobes and the gray basal nuclei. The persistence of these findings was correlated with the duration of the post-concussion syndrome. An initial SPECT study is a reliable indicator of good functioning at the end of 3 months. Despite these characteristics, SPECT application remains limited because of its low resolution, high radiation dosage, and difficulties in obtaining quantitative data, in addition to its higher cost.
Perfusion CT enables the quantification of cerebral blood volume, the transit time for the clearance of a contrast marker, and the cerebral blood flow rate, though only within a limited area of the brain. Nevertheless, perfusion CT reveals hemodynamic alterations within the regions near a hemorrhagic lesion which, because undetectable by CT without the use of contrast material, would constitute a potential target for treatment.

32.5 Timing of Hospital Discharge

Patients with a normal neurologic examination and without associated symptoms can be discharged if accompanied by another person and given an instructions sheet informing

them about warning symptoms which, if they occur, the patient must return to the hospital immediately. An analysis by Servadei and colleagues indicated that, among 1480 patients discharged in this way to home care, no new lesions were detected. On the basis of this evidence, a hospital discharge policy under such criteria can be considered safe. Table 32.2 illustrates a hospital discharge instructions sheet for the caregiver or the patient. These instructions would be adequate for any healthcare facility or institution utilizing them.

By contrast, if a patient does present symptoms, the following patterns of timing must be borne in mind. Clinical deterioration associated with an epidural hematoma occurs within the first 6 hours, while a delayed hematoma may have its onset up to 24 hours after the injury. Therefore, in the moderate-risk group if only a fracture without hematoma is demonstrated on skull radiography or CT or some risk factor is determined, in-hospital observation should continue for at least 24 hours.

In high-risk patients, i.e., with a GCS score of 14 or 15 and neurologic findings, the timing of discharge should be determined by resolution of the symptoms.

- You were examined for a mild head injury for which at the present time no findings suggest neurologic effects or that the injury was severe. If you show any of the following symptoms over the next hours or days, you should return to the hospital for a follow-up examination (We strongly recommend that you be watched by someone for the next 48 hours):
  - Sleepiness or difficulty in waking up
  - Nausea or vomiting
  - Dizziness
  - Severe or persistent headaches
  - Confusion
  - Convulsions
  - Changes in your normal behavior
  - Loss of strength or numbness in any part of your body
  - Visual alterations such as double vision or blurred vision
  - Buzzing in your ears
- Do not drink alcoholic beverages or take any medications for going to sleep

Table 32.2. **Hospital discharge instructions for mild traumatic brain injury.**

32.6 Post-traumatic Sequelae

Although MTBI has a low probability of poor functional outcome or death – with the incidence of such sequelae in patients with GCS of 1 and 2 being 1.0 and 0.5%, respectively – the occurrence of PTA, memory lapses or headache are frequent reasons for a follow-up visit and sick leave from work.

Unfortunately, the prognostic usefulness of biochemical markers for neural damage (e.g., the glia-specific protein S100B and other S100 regulatory proteins) utilized in severe TBI has not yet been established for MTBI, though such markers are, in fact, present but at insignificant levels. Certain laboratories have attempted to determine a relationship between the presence of APOEe4 after initial injury and the possibility of substantial neurocognitive deterioration. Basic research, however, has not established the significance of the presence of the allele in the short- and long-term outcome of MTBI.

Post-concussion or Post-MTBI Syndrome

The post-MTBI syndrome refers to a constellation of common symptoms in MTBI patients, e.g., headache, irritability, neurocognitive deficit, depression, insomnia, and that persist for 60 days or more in >50% of such patients. Although a systematic follow-up is not felt to improve the development of their case, the communication of information forewarning the patient of the possibility, or even likelihood, of experiencing these symptoms does improve their acceptance of such an eventuality. The persistence of symptoms, however, would necessitate re-examination using orientation and neuropsychological tests.

32.7 Key Concepts

A classification system and management algorithm should be established for patients with MTBI since such an approach would avoid misdiagnosis and excessive costs, and the availability of technology *per se* provides no guarantee for the proper management of MTBI.

Even with accurate classification, however, careful initial management is essential to determine whether or not a patient will require further observation for the detection of lesions that might require surgery.

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33 Moderate Traumatic Brain Injury

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33.1 Introduction

Traumatic brain injury (TBI) may be rated as severe, moderate or mild according to the Glasgow Coma Scale (GCS). Severe and mild TBI have been extensively reviewed in the last few decades and international consensus documents, management guidelines and papers supported by various degrees of scientific evidence have been published. Moderate TBI positions somewhere between the two, probably because this patient category is much more heterogeneous, with ends-of-range bordering on mild and severe TBI where far different management guidelines apply. Such variability within the same category may carry a higher risk of inadequate medical procedures, through medical actions or lack thereof, in the ends-of-range of severity in patients with GCS scores 13 and 9, respectively.

33.2 Epidemiology

The incidence of TBI is between 250 and 600 new cases per 100,000 people/year, depending on the geographical area considered. It has been estimated that about 12.5% of TBI cases are severe and 75% are mild. Though no confirmatory data are available, we could very well estimate that about 12.5% of cases are moderate TBI, or roughly 10,000 cases per annum in our country.

Between October 1997 and October 2000, 412 TBI patients were admitted to our service (Intensive Care Unit, Dr. Clemente Alvarez Emergency Hospital [HECA], Rosario, Argentina) (HECA ICU Database), 137 (33.2%) of which were moderate and mostly involved young men.

33.3 Baseline Evaluation

TBI severity is evaluated on the basis of neurological response according to the GCS criteria: severe TBI (GCS ≤8); moderate (GCS 9-13); and mild (GCS ≥14). Even when patients with GCS 13 are initially evaluated as having mild TBI, we rate them as moderate, in line with other authors. This practice is partly based on prognostic considerations and partly on the higher risk of negative progression.

Concomitant conditions such as alcohol or drug intoxication that hinder the outcome need to be ruled out. Respiratory or circulatory instability must be monitored to determine the TBI score (GCS score after non-surgical life support).

Moderate TBI patients may deteriorate while under observation. Deterioration may be defined as a reduction in GCS of 2 or more points and/or understood from the onset of focal neurological deficits. Such patients will eventually be rated as severe (10-20%).

A major problem is predicting which patients will require early intervention and how to identify them. But what are the clinical or prognostic variables (age, mechanism of injury, temporary loss of consciousness, focal neurological deficit, GCS, computed tomography [CT] lesions, etc.) that have the sensitivity and specificity sufficient to help pinpoint the risk of neurological impairment or the need for early intervention? Perhaps the lack of clear responses explains the paucity of reliable data that describe the evolution of TBI in this patient subset. Therefore management recommendations will ultimately depend on data extrapolated from other groups.
In brief, moderate TBI patients need to be approached as a heterogeneous group having different, identifiable variables which evolve over time, where medical intervention needs to anticipate the natural history of head injury.

33.4 Management Issues

All moderate TBI patients will require medical care, hospitalization and full life support provided according to the Advanced Trauma Life Support (ATLS) guidelines. Also the mechanism of trauma, the time since the injury, and the clinical events that occurred before hospital admission (hypotension, hypoxia) will need to be taken into account.

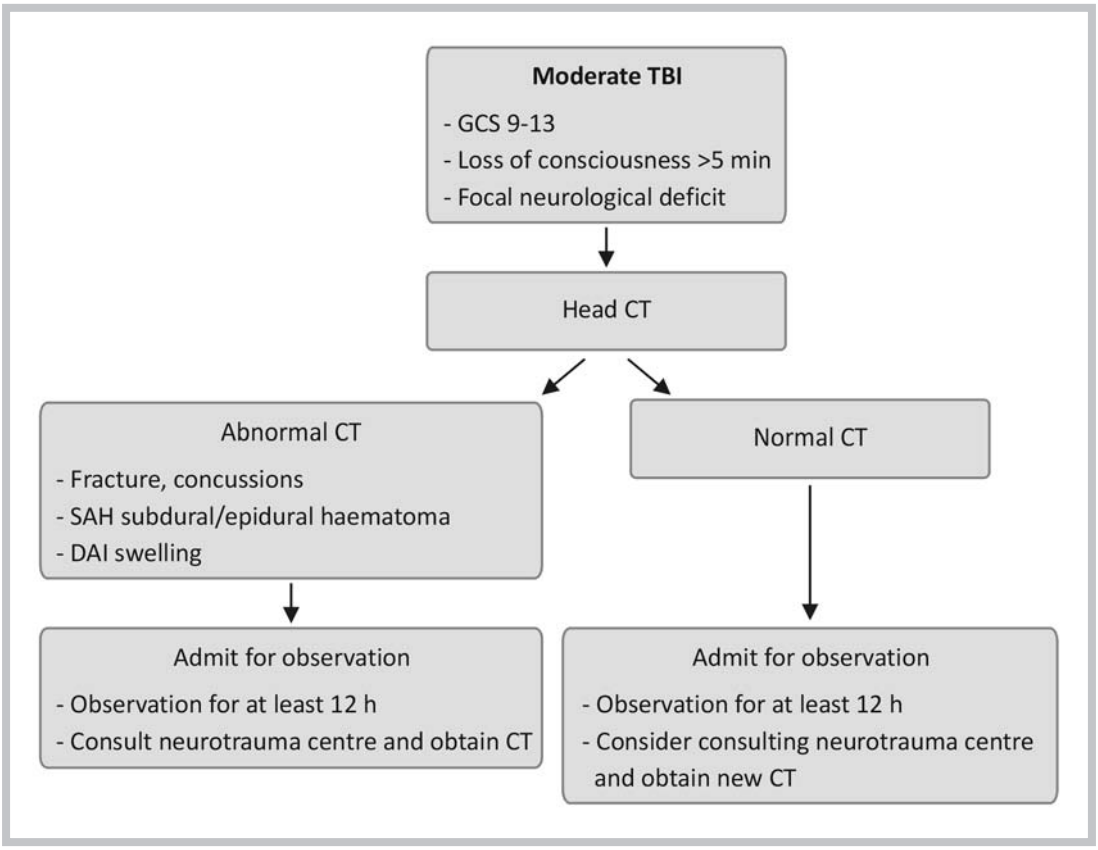

Figure 33.1. **Algorithm for the management of moderate TBI patients recommended by the Scandinavian Neurotrauma Committee**.
DAI = diffuse axonal injury
SAH = subarachnoid hemorrhage

Added to these are the assessment of extracranial lesions (chest, abdomen, limbs, etc.) and a "mini-neurological examination" including the GCS, motor focal deficit, pupils (symmetry and reactivity), difficulty breathing, and loss of consciousness.
Since focal neurological deterioration is the most powerful predictor of poor outcome, patient management should be carried out in a facility that can ensure continuous clinical surveillance.

33.5 Computerized Tomography

A head CT scan without contrast material is recommended in all moderate TBI patients due to the high incidence of acute intracranial lesions (Figure 33.1). Some 40% of patients have CT scan abnormalities and 4-8% of these will require a surgical procedure.
There is an exponential relationship between a GCS score from 13 to 15 and the frequency of CT abnormalities: the frequency of CT abnormalities is four-fold higher in patients with a GCS score 13. The frequency of surgical injuries shows the same trend (5% for GCS-13 patients).
Head CT should be repeated in patients where recovery is less or slower than anticipated and in those with evidence of worsening neurological status.
Skull fractures, cerebral concussions, history of loss of consciousness and worsening consciousness level on admission are major risk factors. A small decrease in the consciousness level on admission increases the risk of an abnormal head CT as well as the risk of a surgical lesion. Cerebral concussion or subarachnoid bleeding following trauma increases the risk four-fold of a hematoma or swelling. Other additional risk factors to be considered are: anticoagulant or hemophilia therapy; alcohol abuse; posttraumatic seizures; multiple injuries; and skull-base fracture.
Many patients have an altered state of consciousness after TBI, as well as secondary neurological sequelae with relevant CT findings throughout their evolution. Cranial magnetic resonance imaging (MRI) is a sensitive test for detecting non-hemorrhagic lesions in the posterior fossa and could therefore play a major role in evaluating these patients. MRI detects diffuse axonal lesions with a much greater sensitivity and should thus provide a higher prognostic capacity.

33.6 Intracranial Pressure Monitoring

Intracranial pressure (ICP) monitoring is not indicated on a routine basis in moderate TBI. The physician, however, may opt to monitor ICP in certain patients with mass lesions.

33.7 Results

This heterogeneous patient group is remarkably variable in relation to long-term neurological recovery and outcomes. Early predictive factors of poor outcome include: GCS score, CT findings, coagulopathy, subarachnoid bleeding, and skull-base fracture.
While technological progress has improved patient survival in the last two decades, it has also lead to multiple disabilities in survivors. The Glasgow Outcome Scale (GOS) is

widely used to globally assess TBI patient outcomes. Some limitations (wide categories, scarce sensitivity to subtle recovery changes, excessive worth attached to physical disability *vis-à-vis* cognitive and behavioural alterations, etc.), however, have been described. Several authors recommend the Disability Rating Scale (DRS) or the Extended Glasgow Outcome Scale (GOS-E) to assess delayed (6-month) outcomes in moderate TBI patients because of the higher sensitivity these tools have.

Many moderate TBI patients show some degree of neuropsychological impairment, memory, fine coordination or speech alterations. Even when cognitive functions improve in the first few years, memory deficits can persist.

33.8 Final Considerations

Moderate TBI patients are a heterogeneous group whose evolution and outcomes are almost impossible to predict, making it difficult to set up clear intervention guidelines. Hospitalization and baseline life support are universally accepted procedures, as is CT on admission. Predicting which patients will require intervention (ICP monitoring, neurosurgery, or both), however, has not been possible, except in the event of deterioration. A large multicentre trial is needed to improve the management of this group of patients.

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34 Medical Treatment of Severe Traumatic Brain Injury

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34.1 Introduction

Traumatic brain injury (TBI) is a serious public health problem in both developed and developing countries. In the developed countries it is the leading cause of death and permanent disability in young people. Globally, it is one of the main reasons for hospital admission, with a high mortality rate and an aftermath of enormous social and economic impact. TBI patients are most often the victims of traffic, sports and workplace accidents, unexpected falls, and violent assaults. The distribution of TBI incidence varies across different world regions. While prevention measures and strict enforcement of traffic laws have notably reduced the occurrence of TBI in the developed countries, its incidence in the developing countries has increased because of the greater use of motor vehicles and more frequent workplace accidents associated with growing industrialization and building construction. Conversely, increased longevity in the richer nations has led to a rise in the number of high falls and road accidents involving the elderly. TBI secondary to violent assault, however, continues to rise worldwide in connection with terrorist or criminal attacks.
The mechanisms underlying TBI produce a wide variety of brain injuries which, together with the possible association of extracranial lesions, make it a heterogeneous entity in pathology, pathophysiology, classification, and probably in its therapeutic approach as well, despite the development of clinical treatment guidelines to improve its management. In this chapter we outline current knowledge and methods in the evaluation and treatment of the acute phase of TBI.

34.2 Epidemiology

The annual incidence of TBI ranges between 200 and 500 new cases per 100,000 inhabitants. As in the rest of the European Union, the incidence in Spain is estimated at around 200/100,000 inhabitants, a rate below that observed in other parts of the world, including Argentina (323/100,000) and the United States (403/100,000). Fairly uniformly throughout the world, TBI patients are predominantly male (male-to-female ratio 3-4:1). About 80-85% of the total are considered mild TBI, and only about 15% require hospitalization for the treatment of severe or moderate TBI. In spite of advances in evaluation and treatment, the 6-month mortality rate for severe and moderate TBI is 24% and 15% of TBI patients remain severely disabled. However, there is wide geographic variability in outcome, being worse in low-income countries where mortality is twice that of rich countries.
Added to these discouraging figures is the ensuing psychological impairment: 10% of patients will suffer memory deficits, inattention, disorganized thinking, disinhibition, irri-

tability, depression, hyperkinesia, impulsivity, and 25% will be unfit to resume work or maintain social or family life. Measured against a country's level of medical development and income, mortality associated with severe TBI may reach around 50%. While the impact of TBI on personal and family relationships is unquantifiable, its social and economic burden is enormous. The United States spends more than $60 billion per year; in Spain the economic cost of hospital stay alone was estimated at 180 million euros in 2002. Added to healthcare expenditures is the loss in years of productive work and revenue from taxable income.

34.3 Classification

The difficulty in defining objective criteria for classifying TBI has been a major obstacle to comparing different series or therapeutic approaches, evaluating the real benefit of new drugs in clinical trials, and designing benchmarking programs in health care quality. TBI has been variously classified: mechanism of injury; presence (or not) of associated traumatic injuries; clinical severity according to level of consciousness; age; and magnitude of structural damage on head computed tomography (CT). Each of these factors weighs differently on outcome and should therefore be taken into account to describe an individual patient or to categorise them. For example, age ≥40 years in a patient with the same clinical severity or anatomic lesion as a younger one may influence decisions on whether or not to monitor intracranial pressure (ICP).

Traditionally, the level of consciousness as assessed by the Glasgow Coma Scale (GCS) score has been the keystone of classification. According to the GCS (Table 34.1), TBI is considered severe in patients with a score ≤8 and moderate in those with a score between 9 and 13. Higher scores indicate TBI will be mild. The widespread use of the GCS as a primary classification in the initial phase of TBI has not been questioned. The GCS debate centres on its subjective criteria, artifacted at the most acute stage by intoxication (alcohol or illegal drugs), drugs (analgesics, sedatives or relaxants) or associated medical complications (hypotension, hypoxemia) or difficulties in evaluation due to eyelid injury, endotracheal intubation, etc. And because the final score is the sum of three components, these must be scored independently, since it has been shown that the motor scale is best classified and related to prognosis. TBI is considered severe in all patients with a GCS score ≤5 on the motor component.

Response	Score
Verbal response (V)	
Orientated	5
Confused	4
Inappropriate	3
Incomprehensible	2
None	1
Eye opening (E)	
Spontaneously	4
To speech	3
To pain	2
None	1
Motor response (M)	
Obeys commands	6
Localizes to pain	5
Withdraws to pain	4
Flexion to pain	3
Extension to pain	2
None	1

Table 34.1. Glasgow Coma Scale.

Unless influenced by other factors, the head CT scan can fairly accurately assess the extent of structural damage, which is related to TBI severity. Thus, CT allows for a more objective categorization of patients than the level of consciousness. The

Injury type	Features
Diffuse injury type I	No visible lesions on CT
Diffuse injury type II	Cisterns are present with shift <0-5 mm; no high or mixed density lesions >25 ml; may include bone fragments and foreign bodies
Diffuse injury type III	Cisterns compressed or absent; shift 0-5 mm; no high or mixed density lesions >25 ml
Diffuse injury type IV	Shift >5 mm; no high or mixed density lesions >25 ml
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High or mixed density lesions >25 ml; non-surgically evacuated

Table 34.2. **CT Marshall classification categories.**

classification proposed by Marshall et al. (Table 34.2) has become a universal system for classifying anatomical lesions. The aim of the scheme is to quantify the risk of intracranial hypertension (ICH), which derives from the presence or absence of mass lesions and the compression or absence of the basal cisterns, as well as to predict poor outcome in relation to previous findings. However, it is not devoid of certain limitations.

One is the overly sharp distinction between mass and diffuse lesions, when many patients have both types simultaneously; it does not differentiate between expansive lesions (subdural, epidural, intraparenchymal), though recognizing the different prognosis each implies. Another is the difficulty in choosing the reference CT: in 50% of cases new lesions can appear or pre-existing ones seen on the first scan may increase in size within hours or days following trauma.

The Rotterdam scale proposed by Mass in 2005 better standardises CT scan findings and could overcome some of the limitations inherent to the Marshall scale. However, the Rotterdam classification has not been fully validated. Currently, although it is not something completely innovative, the risk of death and poor outcome at 6 months is predicted with the use of prognostic models such as derivatives of the IMPACT CRASH registry. These models include simple factors present at hospital admission, including: age; motor response scored on the GCS; pupil reactivity; presence of hypotension or hypoxia; biological parameters such as blood glucose and hemoglobin; and injuries considered in the Marshall CT classification, in addition to the presence of epidural hematoma and subarachnoid hemorrhage.

34.4 Pathology of Brain Damage

TBI is characterized by lesion heterogeneity. However, what all lesions share is that they are produced by external forces: either by direct impact, sharp objects (knives or guns), heavy machinery, or rapid acceleration/deceleration. Recently, head-blast injury during armed conflict has gained clinical relevance. The nature, intensity, duration and area of impact of external forces all determine the extent and predominant type of damage. Although lesions evolve and overlap with time and are schematically arranged along a continuum, they may be classified into two basic types: primary and secondary damage.

34.4.1 Primary Brain Injury

Primary brain injury occurs immediately after the impact and may develop at the cellular level during the first hours after trauma, leading to functional or structural damage,

some of which is reversible or irreversible. Microscopically, primary injury is characterized by cell damage, tearing and retraction of axons, and vascular rupture and torsion. These changes lead to two types of macroscopic lesions: focal and diffuse. Focal lesions, produced by forces transmitted directly through the skull, can be single or multiple and usually occur in the frontal and temporal lobes or also on the lower surfaces of these lobes, where the nerve tissue lies in contact with bony prominences. They are found in 25-35% of severe TBI and in 5-10% of moderate TBI, and are more frequent in elderly patients. This type of injury encompasses skull fractures, lacerations, contusions, subarachnoid hemorrhage, and intracerebral and extracerebral hematoma (subdural and epidural). Focal lesions produce neurological deficits ensuing from tissue destruction and compression of neighbouring brain tissue and ischemia. Alterations in consciousness result when the lesion reaches a volume sufficient to produce a shift and herniation of the intracranial contents and subsequently affects the brainstem reticular formation. All these types of injuries can be easily demonstrated on a CT scan.

Diffuse axonal injury (DAI) refers to diffuse brain damage and includes hypoxic or ischemic brain damage. DAI is caused by rotation of the gray on the white matter, with the effect of forces acting on the axons in a linear or angular direction, producing a physical breakdown (primary axotomy), which occurs in <6% of the fibres affected, or a functional breakdown (deferred axotomy).Delayed axotomy is due to increased permeability to extracellular calcium in the nodes of Ranvier and the cytoskeleton itself. The accumulation of intracellular calcium initiates a process that leads to axon destruction after a few hours or days. Both primary axotomy and deferred histopathological changes are progressive and, sometimes contrary to what was previously thought, they are reversible. Microscopically, they manifest initially as abalone forms of axonal retraction, with the accumulation of microglial cells weeks later and, after a few months, the presence of long tracts with phenomena of Wallerian degeneration. Macroscopically, delayed axotomy is characterized by the presence of multiple small lesions in various different brain areas, including the centrum semiovale of the subcortical white matter of both cerebral hemispheres, the corpus callosum in the dorsolateral quadrant of the midbrain, the cerebellar peduncles, and even in the bulb. Patients with DAI fall into a deep coma from the time of injury because axonal involvement interrupts the signals ascending the reticular activating system, not usually present with increased ICP, and its prognosis is more unfavourable.

In the early phase of TBI, DAI is difficult to observe on a CT scan which may display an almost normal image. In the subacute phase, a magnetic resonance imaging (MRI) scan is very demonstrative in both fluid attenuated inversion recovery (FLAIR) and T2-weighted gradient-echo sequences. Since the FLAIR sequence may overestimate the true extent of damage, acute and diffusion sequences should always be added to reveal pre-existing pathological conditions.

Ischemic brain damage commonly accompanies or is superimposed on DAI; at times it may be extensive or limited to the perilesional area. This type of aggression may result from cerebral hypoxia, increased brain oxygen requirements, altered regulation of cerebral blood flow (vasoplegia), obstruction of microcirculation or excitotoxicity. It usually manifests as diffuse brain swelling; the CT scan will show obliteration of the basal cisterns and ventricles which causes increased ICP.

34.4.2 Secondary Brain Injury

Because there is no specific treatment for the primary lesion, early recognition and treatment of secondary injury is of paramount importance in TBI. This type of damage occurs

in response to the primary injury and is parallel in intensity to the severity of the primary lesion, the brain (Table 34.3) and systemic factors (Table 34.4) being involved in its genesis. It manifests with the presence of new lesions or an increase in previous injuries appearing within minutes, hours or days after TBI. Bleeding due to previous concussions or new contusions, cerebral infarction, brain swelling, cerebral edema, and hydrocephalus are all easily identifiable on a CT scan.

Among the secondary causes of intracranial injury, elevation of ICP is the most frequent and severe. It is seen in more than 50% of cases and has a negative effect on prognosis. A close relationship has demonstrated between elevated ICP and increased mortality and permanent sequelae. Similarly, the longer the duration of ICH, the worse the outcome. In the initial phase of TBI, although there may be other factors, the presence of intracranial hematoma or large contusions is the most common local cause of ICH. Regardless of the mechanisms leading to ICH, the latter exerts its deleterious effect through two mechanisms which may co-exist in the clinical setting: 1) cerebral pressure cones provoking herniation and brain death unless the situation is reversed; 2) development of ischemic cerebral hypoxia due to decreased global cerebral perfusion pressure (CPP).

- Arterial hypotension
- Hypoxemia
- Hypercapnia
- Anemia
- Hyperthermia
- Hyponatremia
- Hyperglucemia
- Hypoglucemia
- Acidosis
- Systemic inflammatory response syndrome

Table 34.3. **Secondary brain insults of extracranial origin.**

- Intracranial hypertension
- Mass lesions, ischemia/anoxia
- Cerebral edema
- Vasospasm
- Hydrocephalus
- Convulsions
- Carotid or vertebral arteries dissection

Table 34.4. **Secondary brain insults of intracranial origin.**

Cerebral edema is one of the most common mechanisms of secondary injury in TBI. Whether focal or diffuse, virtually all types of cerebral edema (vasogenic, cytotoxic, neurotoxic, interstitial, hydrostatic, osmotic) can be observed at some point in the evolution of TBI. However, in the initial phase (first 24 hours), it is neurotoxic and cytotoxic edema that accompany the most common primary lesion, followed by vasogenic edema after the blood-brain barrier has been damaged.

Hypertension and increased intracapillary hydrostatic pressure contribute to exacerbate this complication. In cerebral edema, intracranial volume and ICH are increased, cerebral compliance is decreased, and brain metabolism is altered. Altered permeability of the blood-brain barrier allows the passage of certain metabolites that damage cell membranes and create a vicious circle, given the high edematogenous capacity of these substances. Another way edema damages the brain is by cerebral hypoxia due to disperfusion in which edema fluid separates the capillaries carrying nutrients to the brain cells.

In most cases of TBI, and at any point in its evolution, another factor of secondary injury is cerebral hypoperfusion. Many circumstances may arise in the acute phase of TBI, the most common being a global or regional decline in CPP due to an increase in ICP or a decrease in mean arterial pressure (MAP). However, other mechanisms co-exist such as extrinsic stenosis of the cerebral arteries, especially of the posterior cerebral artery and anterior cerebral artery, generated by pressure cones that lead to brain herniation. Stenosis can provoke or exacerbate previous ischemia which appears on the CT scan as hypodense lesions of vascular distribution unrelated to cerebral contusions.

Another possible cause of ischemia, usually regional, is cerebral vasospasm. Cerebral vasospasm is seen on transcranial Doppler sonography in approximately 25% of patients with

traumatic subarachnoid hemorrhage, with a close relationship between vasospasm severity and the amount of blood visible on the CT scan. Besides causing direct damage due to ischemia, cerebral vasospasm can provoke reperfusion injury when the ischemic period has been reserved. Reperfusion injury induces ischemic foci outside the initial area. Some studies have demonstrated a higher incidence of stroke when cerebral vasospasm is associated with low CPP, and an improved prognosis of TBI when nimodipine is used to treat it. Also, reperfusion injury was observed, as our group has demonstrated, when extra-axial hematoma ischemia occurred in a brain that was decompressed very quickly.

During the acute phase of TBI, generalized or focal seizures may appear, with an estimated incidence of 6% in adults and 8% in children under 5 years of age. Penetrating injuries, cortical contusions or intracranial hematoma, and increased depth of coma are risk factors for early post-traumatic seizure. Early seizures exert their harmful effects via several mechanisms, primarily through increased cerebral blood flow (CBF) and cerebral oxygen consumption, which are associated with the release of excitatory amino acids. The increase in CBF, especially in a setting of decreased cerebral compliance, increases ICP as evidenced by sustained elevation or Lundberg A waves.

There is also the possibility of arterial dissection, mainly extracranial (carotid or vertebral) (up to 17% of cases) when TBI is associated with trauma to the neck area or skull base fractures in proximity to the carotid canal or the entry of the vertebral artery. Arterial dissection causes ischemia through the interruption or reduction of carotid or vertebral flow or by generating embolic phenomena, whose incidence has been estimated to be close to 60%. While not preventing its consequences, the CT scan shows signs consistent with ischemic stroke. Today, though disputed by the risks and lack of clear evidence, the careful use of heparin and mesh placement to restore flow and prevent emboli have been advocated.

Among the causes of secondary damage of systemic origin, arterial hypotension is the most common and arises not only in the pre-hospital phase but most often in the operating room during surgery for space-occupying lesions or in the ICU itself. Moreover, up to 8.5% cases of TBI do not show external causes that justify the onset of shock, being attributed to neurogenic origin in the context of severe diffuse lesions or to the massive use of diuretics. Although its frequency is high, more alarming is the impact it can have on outcome. CPP is decreased in hypotension, leading to cerebral ischemic hypoxia. It was observed that even brief episodes of hypotension raise the death rate of severe TBI from 27 to 50%. Because cerebral autoregulation is impaired and the coupling of cerebral blood flow and cerebral oxygen consumption is altered in the acute phase of TBI, any fall in MAP caused by a decline in CPP will result in global cerebral ischemia.

Finally, the effect of hypotension is exacerbated by co-existing hypoxemia, which is commonly encountered in clinical practice. Thus, while isolated hypoxemia increases the mortality rate by around 2%, mortality is more than 25 times higher when associated with hypotension. Extreme anemia (hemoglobin <7 g/dl), prolonged hyperthermia, and septic states, by decreasing the cerebral oxygen supply or increased metabolism, can aggravate situations of cerebral ischemia and hyponatremia, inducing cerebral edema and worsening the prognosis; however, as independent variables, the effect of these factors on the end result is not well established.

34.5 Pathophysiology

Regardless of the type of damage, primary or secondary, and the origin of the latter, intracranial or systemic, TBI develops over hours or even days if further secondary attacks

occur, triggering harmful biochemical processes responsible for increased ICP, disruption of the blood-brain barrier, genesis of cerebral edema, alteration of cerebral self-regulation, mitochondrial dysfunction, brain damage and late apoptosis. Current research into new drugs is aimed to stop or minimise this pathophysiologic cascade of events which, in simplified form, sequentially and synergistically involves the release of excitatory amino acid, cellular entry of calcium, production of free oxygen radicals, gene activation, activation of pro-inflammatory molecules, and so on.

Initially, the mechanical aggression of cell membranes and subsequent secondary attacks such as increased ICP or the presence of hypoxia/ischemia facilitate the excessive release of glutamate and other neurotransmitters (e.g., aspartate or glycine). These act on specific receptors and provoke intense cellular depolarization that results in: 1) the massive influx of sodium and water leading to cytotoxic edema and even cell death by explosion; and 2) the increase in sodium favours the influx of calcium into the cell. The accumulation of intracellular calcium exerts many negative actions and is the fundamental mechanism in the genesis of diffuse axonal injury. The cellular influx of calcium promotes the activation of inducible nitric oxide synthase (iNOS), and through it large amounts of NO. NO-induced vasodilatation, with abolished or altered cerebral self-regulation, produces vasoplegia and cerebral ischemia and elevates ICP.

During the ischemic period, the intracellular calcium overload induces the production of xanthine oxidase, which is inactive in the absence of oxygen. When reperfusion occurs, oxygen induces hypoxanthine, an intermediate DNA degradation product, to produce xanthine and uric acid, generating in the course of these reactions large amounts of oxygen-free radicals such as superoxide anion. This radical reacts with NO and generates peroxynitrite. These free radicals destroy the membranes by lipid peroxidation and cell nuclei, causing necrotic cell death. Also, free radicals injure the endothelial cells, producing a breakdown in the blood-brain barrier and vasogenic edema. Excess intracellular calcium also induces immediate and late axonal destruction by increasing the activity of specific proteases, i.e., the calpains that disorganize microtubules and neurofilaments. The calpains are now considered one of the factors responsible for traumatic brain atrophy through retrograde axonal degeneration.

The early activation of genes is another cause of delayed cell death by apoptosis. These genes induce the synthesis of molecules such as caspase 1 that suppress the inhibitory mechanisms of apoptosis. However, whether apoptosis in TBI is a harmful or a repair mechanism is still debated. Also, early gene expression (e.g., *c-fos*) following TBI may exert beneficial effects for the formation of nerve growth factor (NGF) and neuroprotective activity. Specifically, such gene expression would defend the brain against ischemia.

Today, the inflammatory component is recognized as a common pathophysiological element of TBI, essentially accompanying focal lesions such as contusions or subdural hematoma. Although its maximum expression occurs at 48 or 72 hours post-trauma, there is a release of pro-inflammatory cytokines, mainly IL 1, IL 6 and IL 18, from microglia, astrocytes, and polymorphonuclear cells. As with apoptosis, while excessive inflammation is detrimental because it stimulates the opening of the blood-brain barrier and the apoptotic pathway of complement activation, it is necessary for the removal of cellular debris and cell repair.

Expressed by the fall in ATP and oxygen consumption by about 50%, mitochondrial dysfunction has been implicated in apoptotic and necrotic cell death. It also appears to be involved in axonal disruption, which explains the modern concept of possible axonal regeneration and repair if mitochondrial function is restored within the first 72 hours. Several factors cause mitochondrial dysfunction: intracellular calcium overload that decreases the selective permeability of the membrane into the interior of ions that cause swelling; substances such as hydrogen cyanide, nitric oxide or carbon monoxide

interacting with the electron transport complex chain; hypoxia damage to mitochondrial structures; and certain genetic alterations which modify the phenotype of mitochondrial complexes.

34.6 Diagnosis of TBI

34.6.1 Systemic Injury

Various series have shown that between 25 and 80% of severe TBI cases involve multiple trauma or extensive trauma. Likewise, the co-existence of these associated injuries is considered a variable in forecasting models that predict the outcome of TBI. Therefore, the diagnosis and treatment of associated injuries, especially life-threatening injuries, are of paramount importance and should never be relegated, despite the severity of brain injury.

Advances in imaging techniques (latest generation multislice CT, MRI and ultrasonography) have facilitated the safe and prompt recognition of these lesions. Previously, we highlighted the association of cervical lesions and intracranial and extracranial vascular pathology; however, one must keep in mind injuries of the cervical spine and other regions of the spine, depending on the mechanism of injury, to recall that improper patient handling may cause or aggravate spinal cord injury.

There are two frequent and serious situations that can accompany TBI: 1) oxygenation or ventilation disorders ranging from minor alterations to gasometric parameters of acute life-threatening respiratory failure. The most common thoracic injuries are rib fractures, pulmonary contusions, and hematoma, hemo- and pneumothorax, and bronchoaspiration of blood or gastric content; and 2) hemodynamic alterations ranging from hidden hypoperfusion to refractory shock due to severe exsanguination. The causes include spinal shock, cardiac pump failure, or cardiac tamponade-bruising, lacerations and ruptures of the great arteries or solid organs, usually the liver and spleen, or pelvic fractures.

34.6.2 Neurological Exam

The neurological exam entails rapid but rigorous assessment of the level of consciousness, focal signs, brainstem reflex, pupillary examination and initial CT scan findings. The level of awareness reflects global brain dysfunction as a result of trauma. Despite the drawbacks outlined above, the GCS evaluation obtained after resuscitation remains the basic method to assess the level of consciousness. Along with its ability to classify TBI, the GCS is useful for clinical decision-making (monitoring, emergency surgery, etc.) and helps to predict the prognosis of TBI. The benchmark score is achieved on the side with better response, remembering that the most valuable of the scale's three components is motor score unaffected by difficulties in the verbal (intubation, tracheostomy) or ocular components (eyelid lesions).

The presence of focal signs, including in addition limb paresis or plegia, focal seizures and dysphasia, guides the classification of TBI severity and the likelihood of injury immediately amenable to surgical intervention on the side opposite the sign. Assessing the state of the pupils (pupil size and asymmetry) permits the assessment of the severity of traumatic injury and its topographic location and prognosis. In general, pupillary abnormalities reveal very severe TBI; and when there is bilateral fixed mydriasis, the injury is in the midbrain and the prognosis dims.

In patients with bilateral pupililary abnormality, the risk of mortality is >80%, which may be <15% if both pupils remain normal throughout the acute phase. The most frequent pupillary abnormalities are paralytic mydriasis of one or both pupils. Unilateral mydriasis occurs when the third cranial nerve is injured in its journey through the fissure of Bichat, the most common cause being herniation of the hook of the hippocampus, with transtentorial wedge pressure which compresses the ipsilateral oculomotor nerve and midbrain peduncle. Occasionally, orbital trauma associated with optic nerve damage causes anisocoria, which requires exploring the consensual reflex. By not reversing uncal herniation it would produce bilateral mydriasis due to injury against the free edge of the tentorium of the contralateral oculomotor nerve. Also, unilateral or bilateral mydriasis originates (dilated medium pupils), depending on the size of the lesion in dorsal midbrain lesions (quadrigeminal), where the nucleus of the oculomotor nerve has its origin, and in the ventral midbrain (cerebral peduncles). In this latter case, the pupils are at maximum dilation.

Miosis is observed less frequently in TBI, given as the cause of unilateral or bilateral lesions of the sympathetic fibres originating from the hypothalamus. Respiratory rhythm disorders are commonly seen in intense bilateral miosis with pontomesencephalic dorsal lesions (red nucleus). When miosis is unilateral, it usually indicates the development of transtentorial herniation and precedes paralyzed anisocoria. In case of bulbar symptoms, injury may occur in complete or incomplete Horner syndrome.

Hypodense space-occupying lesions	• Simple contusions • Hemispheric swelling • Hypodense vascular distribution
Hyperdense space-occupying lesions	• Epidural hematoma • Subdural hematoma • Intraparenchymal hematoma • Hemorrhagic contusions
Signs of diffuse axonal injury	• Corpus callosum injury • Mesencephalon-brainstem injury • Injury to basal ganglia • Subarachnoid hemorrhage • Intraventricular hemorrhage • Of the posterior cerebral artery • Other
Signs of increased cerebral volume	• Compression of base cisterns • Compression of fourth ventricle • Compression of third ventricle • Decrease in size of lateral ventricles
Vascular compression	• Of the anterior cerebral artery
Signs of intracranial hypertension	• Injury occupying large volume space • Signs of increased cerebral volume
Disturbances of clinically significant structures	• Subfacial hernia • Uncal hernia • Tonsilar herniation • Midline shift ≥5 mm • Bilateral injuries • Centroencephalic lesions • Diffuse axonal injuries

Table 34.5. **Guide to computed tomography interpretation. Modified from [Domínguez Roldán, 1997].**

Before the advent of CT, clinical examination of brainstem reflex (oculovestibular oculocephalic and reflexes) was an essential part of the neurological examination because of its prognostic implications, as it foreshadowed a negative outcome and a topographic location of the lesion (pontobulbal region). Today, it has lost value, as have other neurological signs because they are late. When altered or abolished, they reveal highly developed lesions that should have been previously diagnosed for more effective patient management.

Head CT scan is essential in the initial phase to determine the extent of structural damage and to detect surgical lesions. It also helps to classify the patient, predict final outcome, estimate the risk of ICH and response to therapy. For these purposes, and to establish a comparison between different series, the CT scan classification proposed by Marshall in 1991, despite the limitations mentioned above, is the most widely used scheme. The highest incidence of ICH and poor functional outcomes are observed in diffuse injury type IV and in non-evacuated space-occupying lesions >25 cc (type VI), followed by diffuse type III lesions and evacuated space-occupying lesions (type V). The incidence of ICH ranges from 10% in type I lesions to 40-60% in lesion types III, IV and VI.

Our group recommends adding the Marshall classification systematic reading of the CT (Table 34.5) to obtain valuable information for clinical decision-making and better classification of patients. Recent studies show a progression of structural damage within the first 9 hours, so it is advisable to repeat the initial CT after this period of time. Independently, CT should always be repeated whenever there are major injuries, neurological deterioration, or there is an unexplained increase in ICP.

In the initial or ICU phase, MRI does not provide useful information for immediate surgical decision-making. Furthermore, obtaining an MRI involves moving patients, interferes with resuscitation measures and is time-consuming. After this initial period, however, it can be very useful to show white matter lesions unexplained on the CT and may explain the clinical course of some patients. The most useful MRI techniques are T2-, FLAIR- and susceptibility-weighted imaging (SWI), and diffusion tensor imaging (DTI).

34.7 Treatment of TBI

34.7.1 Pre-hospital Management

At this stage, the main objective is to prevent and treat hypoxemia and hypotension because the brain is very vulnerable in these situations. Some studies have demonstrated a rate of hypoxemia (hemoglobin saturation <90%) between 45 and 55%, and hypotension (systolic blood pressure <90 mmHg) between 20 and 30%. Classical studies have shown that hypoxia is associated with poor outcome (OR 2.1) and hypotension (OR 2.7). In contrast, more recent studies have argued that normalisation of oxygenation (hemoglobin saturation >92%) and blood pressure improves the outcome.

- TBI with Glasgow Coma Score (GCS) ≤8
- Shock (systolic arterial pressure <90 mmHg)
- Airway obstruction
- Combative patient requiring sedation
- Prior to general anesthesia
- Chest trauma with hypoventilation
- Hypoxemia (PaO_2 <60 mmHg or pulse oximetry hemoglobin saturation <95%)
- Cardiac arrest
- Severe maxillofacial injury

Table 34.6. Indications for endotracheal intubation.

Current debate on tracheal intubation centres on the composition of the prehospital emergency team. In countries where emergency medical services involve paramedics, especially if not properly trained, intubation has been associated

with worse outcomes than in countries where emergency doctors perform intubation. Table 34.6 shows the criteria for tracheal intubation for airway protection and maintenance of hemoglobin saturation >95%.

Treatment of arterial hypotension entails surgically controlling the visible hemorrhage foci and restoring blood volume with colloid and crystalloid solution. Hypertonic sodium has not been shown to achieve greater benefits than isotonic saline, while the use of albumin to resuscitate patients may worsen the prognosis. TBI patients should be transferred to a medical centre with adequate clinical services and facilities (CT, MRI, ICP monitoring, etc.) and a neurosurgeon on duty. During transport, the patient should be placed in supine neutral position with a cervical collar and a nasogastric tube connected to a vacuum bag. Once the airway is secured and ventilation is effective, the use of analgesics (narcotics) and sedatives (benzodiazepines) can be very helpful.

34.7.2 The Emergency Room

At this stage, the aim is to stabilize hemodynamics and respiration and carry out diagnostic evaluation according to the recommendations of the American College of Surgeons Advanced Trauma Life Support (ATLS) protocol (Table 34.7). From a neurosurgical point of view, the priority is to detect and treat the most removable mass lesions. Therefore, TBI management relies on a multidisciplinary organization with pre-planned actions that can provide early treatment and quality. While there is consensus on the need to maintain hemoglobin saturation >92%, there are no studies that establish the optimum MAP in TBI. In >50% of patients with TBI, ICP levels are 20 mmHg above the target. When ICP is unknown, it is advisable to keep MAP >90 mmHg to preserve CPP at or above 60 mmHg.

Crystalloids and colloids allow rapid infusion of volume, taking into account that hypotonic fluid to plasma such as 5% dextrose and Ringer solution can induce osmotic swelling and increase ICP. As in pre-hospital resuscitation, the use of hypertonic solutions of 3% or 7.5% sodium alone or in combination with low-molecular-weight dextran does not improve neurological outcome. When, in spite of a rapid increase in volume, crystalloids and colloids do not achieve adequate MAP or CPP persists at <60 mmHg, the administration of vasopressors, usually norepinephrine or phenylephrine, should be considered.

Once hemodynamics and respiratory function are stabilized, a neurologic examination should be performed according to the guidelines given above. If during neurological clinical exploration there are warning signs of neurological impairment (GCS score ≤2, signs of cerebral herniation, unresponsive mydriasis such as unilateral or bilateral motor posturing, etc.), mannitol should be administered at a dose of 20% 1 g/kg, the patient hyperventilated to bring $PaCO_2$ to 30 mmHg, and CT and surgery performed, if needed.

Although >50% of patients with TBI present with associated traumatic lesions of varying severity, time should not be wasted on a thorough assessment of all possible traumatic injuries during this phase, but only to discard and to treat those that are life-threatening. As discussed above, modern scanners allow quick and safe imaging of all body areas where significant injuries are assumed, not to mention ruling out cervical spine injury. Up to 15% of TBI patients can have an injury at this level. Once a head CT scan is obtained, the neurosurgeon will decide the necessity of a surgical procedure. The surgical treatment of TBI is presented in another chapter of this book.

- Airway maintenance with C-spine control
- Breathing (oxygenation and adequate ventilation)
- Circulation and hemorrhage control
- Disability: neurologic status
- Exposure: completely undress the patient

Table 34.7. Interventions in the resuscitation phase.

34.7.3 The Intensive Care Unit

Cerebral Monitoring

During the ICU stay, the goal is to continue the prevention of secondary injury and provide the best physiological conditions for brain recovery. We do this by monitoring ICP and cerebral homeostasis and we prevent and treat brain swelling, cerebral intracranial hypertension (ICH), and hypoxia. Table 34.8 presents the key systemic and cerebral therapeutic objectives to obtain. In TBI, as in any other critical illness, surgical and medical complications may arise which will require care and general treatment that the ICU provides.

Although recent studies have questioned ICP monitoring, there is no doubt that a GCS score ≤8 portends a risk of IHC. Present in up to 77% of cases, this complication overshadows vital and functional prognosis. Moreover, it was found that in addition to increased ICP, cerebral hypoxia is the factor most often implicated in poor outcome. Cerebral hypoxia may co-exist with normal ICP and not all episodes of cerebral hypoxia are associated with increases in ICP. Therefore, in addition to ICP and CPP, other variables such as SjO_2 and cerebral oxygen partial perfusion pressure ($PtiO_2$) should be monitored and corrected.

According to the Braun Trauma Foundation's clinical guidelines, ICP monitoring is indicated in all patients with TBI who present a GCS score ≤8 and abnormal CT findings on admission, i.e., findings that do not qualify as diffuse brain injury type I according to the Marshall classification. The guidelines also state that ICP should be monitored in patients with TBI and a normal head CT scan who present at admission with two or more of the following characteristics: age >40 years; decerebrate posture; and unilateral, bilateral or systolic blood pressure <90 mmHg. The ICP will inform about the presence or absence of ICH (numerical value) and the exhaustion of the reserve of volumetric brain waves (abnormal recording) ICP is considered normal or "normalized" by active treatment when >20 mmHg with a closed skull or 15 mmHg with an open skull. In children, ICP is somewhat lower in both situations. The normal chart recording should be flat and present no spontaneous or induced oscillations. Pathological waves, primarily A and B, immediately signal a warning for the presence of neurological impairment in the presence or absence of high ICP, and indicate that the brain's compensation mechanisms have been overwhelmed by volume.

SjO_2 monitoring is the most common method to measure cerebral oxygenation, although $PtiO_2$ monitoring has been gaining acceptance, given its far greater stability and reliability and fewer technical complications. The only drawback of this method is the higher cost of catheters and the need for a specific monitor for recording. Although both methods explore cerebral oxygenation, the SjO_2 expresses purity in the balance between cerebral blood flow (CBF) and cerebral oxygen extraction or is redrafted if the CBF is sufficient, excessive, or insufficient to satisfy cerebral metabolic oxygen needs. Normal SjO_2 values range between 50 and 75%, considering hypoperfusion when SjO_2 is <50%, and contrary to absolute or relative hyperemia (luxury perfusion) when SjO_2 is >75%.

$PtiO_2$ monitoring, which has become the reference method to detect cerebral hypoxia, provides the value of the partial

SaO_2 >92%	Mean arterial pressure 90-120 mmHg
$PaCO_2$ 35-40 mmHg	Hemoglobin ≥9 g/dl
ICP <25 mmHg	CPP ≥60 mmHg
SjO_2 55-70%	$PTiO_2$ ≥20 mmHg
Mean velocity in MCA	60±10 cm/sec
Pulsatility index	<1.2

Table 34.8. Systemic and cerebral goals in TBI management.
MCA = Middle cerebral artery

	Hyperemia	Vasospasm
Increased velocity	Bilateral	Unilateral
MCA velocity >3 times ICA (LI)	No	Yes
Lack of dicrotic notch on the sonogram	Yes	No

Table 34.9. **Difference between hyperemia and vasospasm on TCD.**
ICA = Internal carotid artery
LI = Lindegaard Index
MCA = Middle cerebral artery

pressure of oxygen at the end of the capillary loop, reflecting mainly the balance between oxygen supply and consumption at the cellular level. The reference range of $PtiO_2$ is 15-40 mmHg (moderate cerebral hypoxia); 15 mmHg is defined as low hypoxia and values below 10 mmHg as critical hypoxia. Values >40-50 mmHg, by extrapolation from SjO_2, are considered luxury perfusion, although there is no absolute consensus on the latter.

Pattern	Value
Normal pattern	MCA mean velocity 60±10 cm/sec and PI <1.2
Hypoperfusion	MCA mean velocity <50 cm/sec
Hyperemia and vasospasm	MCA mean velocity >120 cm/sec
Circulatory arrest	Systolic spikes or sonogram absent

Table 34.10. **TCD hemodynamic patterns in TBI.**
MCA = middle cerebral artery.
PI = pulsatility index

Finally, transcranial Doppler ultrasound (TCD) monitoring provides valuable data to refine the treatment of severe TBI. TCD measures the flow rate in the large arteries at the base of the skull. Because the flow rate is directly proportional to CBF and inversely proportional to vessel radius, if the diameter is unchanged, any change in speed will translate into a change in CBF. Conversely, if the CBF seems stable, velocimetric changes will indicate modifications in the vessel radius as occurs, for example, in vasospasm. Cerebrovascular resistance is closely related to changes in ICP and CPP and is reflected by the pulsatility index (PI), an index automatically provided by the TCD device. In the acute phase of TBI, hemodynamic states are primarily normal, hypoperfusion, hyperemia, vasospasm and circulatory arrest. The TCD is normal when the values in the middle cerebral artery are about 60 cm/sec and the PI <1. Table 34.9 shows the data for the classification of hemodynamic states and Table 34.10 compares the differences between hyperemia and vasospasm.

Other methods such as continuous electroencephalogram (EEG) can be useful in identifying occult epileptogenic activity, present in 15% of cases, or cerebral microdialysis which indicates the presence of cerebral ischemia or hyperglucolysis. However, these methods are not available in most clinics. The interested reader is referred to other chapters of this book for a discussion of these topics.

General Measures

In patients with severe TBI, regardless of the ICP value, a set of general measures (Table 34.11) should be initiated immediately upon admission: to control or prevent elevation in ICP; prevent diffuse cerebral swelling; and to provide the metabolic substrates that will meet the consumptive demands of cerebral tissues. Essential steps are to ensure adequate oxygen delivery by means of adequate hemoglobin saturation and proper maintenance of blood volume by fluid replacement. As in the previous phases, the administration of isotonic crystalloid is recommended, essentially, 0.9% saline solution and

- Head 30° above the horizontal line
- Effective analgesia (opiates)
- Sedation (propofol/benzodiazepines)
- Normothermia (<37.5°C)
- Normovolemia (arterial lactate <2.2 mmol)
- Pulse oximetry (O_2 saturation >92%)
- Hemoglobin ≥9 g/dl
- Mean arterial pressure 90-110 mmHg
- Glucemia 140-180 mg/dl
- Plasma osmolarity >290 mOsm/l
- Seizure prophylaxis within 7 days of injury

Table 34.11. **General measures for treatment of TBI patients.**

colloids such as hydroxyethyl starch (HES) or gelatin. Unless there is hypoglycemia, one should avoid the use of glucose solutions as they can induce or aggravate hyperglycemia, which has been associated with worse outcomes in neurocritical patients. Furthermore, hypotonic solutions of 5% glucose may contribute to the formation of cerebral edema.

In cases where the administration of high replacement volumes is contraindicated (e.g., co-existing hyponatremia or ICH), an alternative is the use of hypertonic 7.5% sodium solutions at a dose of 4 ml/kg bolus weight. Also, to maintain a CPP of at least 60 mmHg, norepinephrine or phenylephrine in continuous infusion can be used when this objective is not achieved with volume replacement. Although the ideal hematocrit of these patients has not been established, the transfusion of packed red cells can be considered to maintain adequate oxygen delivery when hemoglobin levels are <9 g/dl.

In general, a combination of measures with sedation, and analgesia should be included. The most commonly used sedative agents are midazolam and propofol. The preference of one over another depends exclusively on the discretion of the attending physician. Propofol is inconvenient in that it tends to provoke arterial hypotension if the circulating blood volume is suboptimal and it requires adjusting the administration of lipids in the diet. The most common painkillers are opiates, especially morphine, and fentanyl, which in analgesic doses does not increase CBF or ICP.

Mechanical ventilation also forms part of the general measures, ensuring that $PaCO_2$ does not fall below 35 mmHg during the first 24 hours in order to prevent hypocapnia and cerebral ischemia. $PaCO_2$ <35 mmHg should be reserved exclusively for the active treatment of ICH, monitoring its effect on CBF through SjO_2 or $PtiO_2$.

While it is undisputed that silent or apparent seizures should be treated, anticonvulsant prophylaxis continues to be debated and views on its value are changing. For some time it was thought that it was effective in controlling early epilepsy (onset within the first week) and late epilepsy. There is currently no scientific evidence to support the use of anticonvulsants to prevent late post-traumatic epilepsy, and their use is indicated only during the first week. The most widely used agents are phenytoin, carbamazepine, and levetiracetam.

34.7.4 Treatment of Intracranial Hypertension

The specific treatment of IHC should be started when ICP exceeds 20 mmHg in an adult and 15 mmHg in both children and adults with an open skull for ≥30 minutes, and after having dismissed or surgically removed an expansive lesion. Figure 34.1 shows the treatment algorithm recommended by the Brain Trauma Foundation guidelines and adapted by our group. This guide is a step-by-step algorithm, structured in first and second level measures, reached by expert consensus with a generally low evidence level, but which are widely accepted and have demonstrated improved TBI results according to recent studies.

Although we argue that the best approach would be personalized treatment of a patient's cerebral hemodynamics, we refer to the Brain Trauma Foundation's clinical guide-

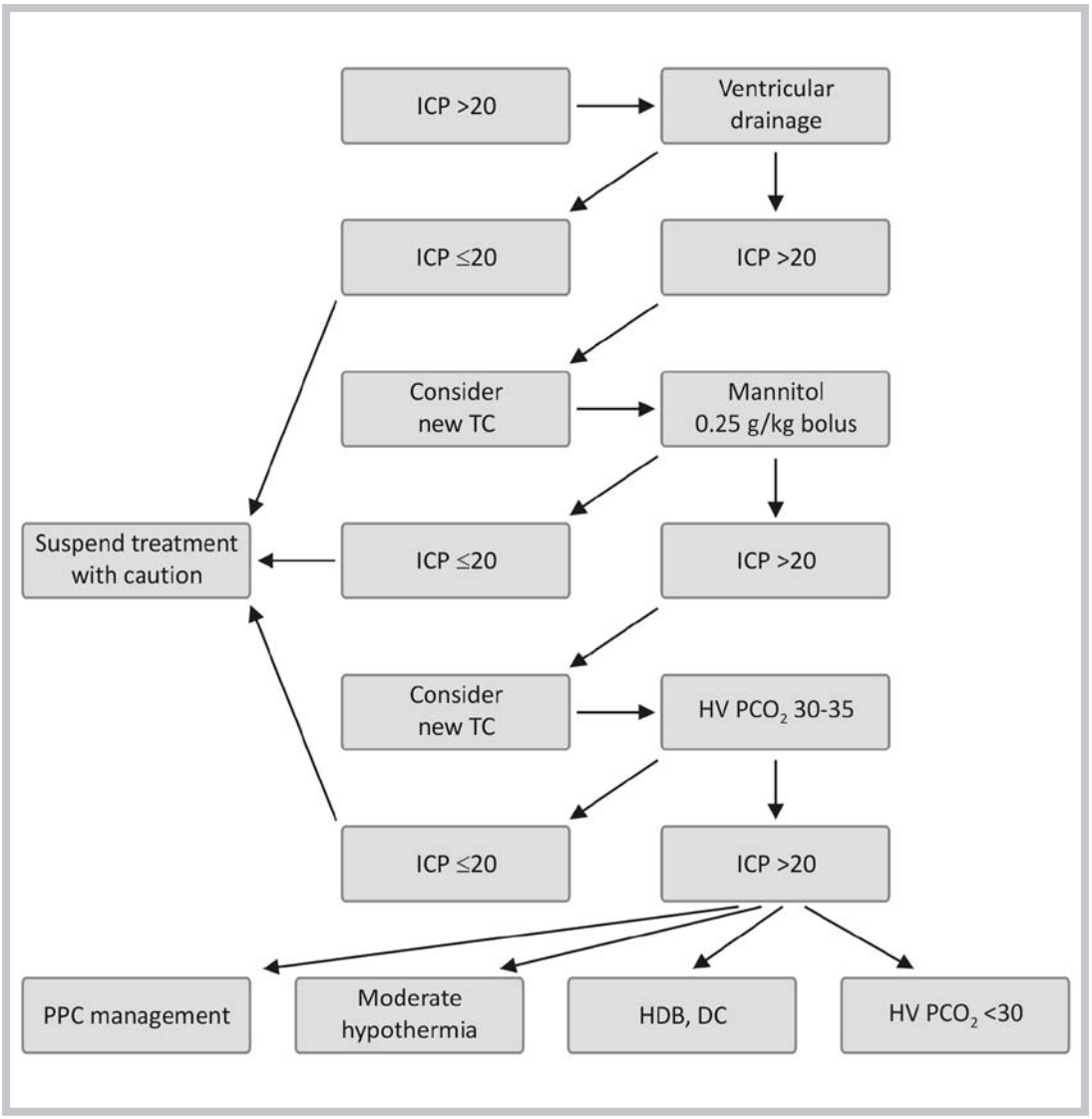

Figure 34.1. **Algorithm for the treatment of intracranial hypertension.**
HDB = Barbiturates in high doses
DC = Decompressive craniectomy
HV = Hyperventilation

lines. It should be noted that each successive therapeutic step is taken only if a previous step has failed (no control of ICP within 30 minutes of onset), without suspending the former agent but adding a new measure.

Accepted, although not unanimously, is the use of muscle relaxants as a first step to control ICP. The advantages to the use of muscle relaxants in continuous infusion are the control of ICP during tracheal suction manoeuvres, hygiene and patient repositioning, and easier adaptation to mechanical ventilation. The disadvantages are increased length of ICU stay, increased risk of ventilator-associated pneumonia, failure to maintain contact with the patient's neurological development and, sometimes, neuropathy and myopathy. Juul et al. in a study involving 326 patients failed to demonstrate longer time without ICH in patients who had received muscle relaxants. Therefore, muscle relaxants

(e.g., as pancuronium, vecuronium, rocuronium, cisatracurium, etc.) should be reserved for very specific occasions, advising the use of vecuronium by increased hemodynamic stability that its use entails.

First Tier Measures

When ICP is monitored with an intraventricular catheter, drainage of 2-3 ml of CSF through the ventriculostomy catheter reduces ICP, which on many occasions permits the control of ICP without the need to move on to other therapeutic steps. For this purpose, the drain should not be kept open continuously but for as long as required to normalise ICP. In other cases, especially in diffuse lesions with absent cisterns and/or compressed ventricles, this manoeuvre can be useless to normalise ICP. However, its major drawbacks are technical (i.e., inability to insert the catheter into the ventricle if there is displacement of the medial axis) and possible complications: infectious, since the operation and maintenance of the catheter over 4-5 days is associated with a high rate of infection and to a lesser extent (<1.5%) bleeding in the catheter line.

Osmotherapy represents the next therapeutic step. Mannitol is the most widely used agent, followed by hypertonic saline 3%, 7.5% and 24%. Few studies have compared these agents; however, according to some, hypertonic saline can provoke a more intense fall and lasting resolution of ICP, and would therefore be effective when ICH is refractory to other agents, while mannitol would more sharply increase CBF. However, the available evidence is still insufficient to recommend hypertonic saline over mannitol. The agents act through two different and complementary mechanisms. The first and immediate one is hemodynamic, which results in an increase in MAP, CPP and CBF. According to Rosner, it reduces ICP by activating the vasoconstrictor cascade. Another beneficial outcome in relation to its hemodynamic action is the improvement of cerebral microcirculation by reducing blood viscosity.

The second and most studied effect is the creation of an osmotic gradient that causes water to flow across the intact blood-brain barrier. Dehydration of the brain parenchyma facilitates the maximum reduction of ICP observed around 20 minutes post-infusion. When the blood-brain barrier is altered, worsening of edema has been reported with the use of mannitol, as well as an increase in bruises with the use of hypertonic saline. Favourable possible effects of mannitol are the decrease in CSF production and oxygen uptake of free radicals, while hypertonic saline has been reported to decrease endothelial edema and increase cerebral oxygen transport.

Mannitol 20% should be administered in bolus doses from 0.25 to 1 mg/kg as often as needed to be effective, but at least every 4-6 hours to maintain the osmolar gradient and avoid the rebound effect, not to mention that mannitol doses are higher (1 g/kg) when elevated ICP causes brain herniation. The dose of hypertonic saline is not well established, but it is recommended to be sufficient to maintain serum sodium >145 mEq/l. Our group employs bolus 4 ml/kg of 3% sodium, which is repeated as needed and osmolarity does not exceed 320 mOsm/l.

Osmotherapy, particularly when used for long periods, is associated with complications such as dehydration with subsequent hypovolemia, a complication that would buffer the hemodynamic and rheological effects and electrolyte abnormalities, especially hypernatremia, with the use of hypertonic saline, heart failure, bleeding diathesis, and phlebitis. Mannitol also has a toxic effect on the renal tubules, an effect that is greater in hypovolemia, use of nephrotoxic drugs, sepsis or previous kidney disease. Although the toxic action of mannitol is reversible, it is sometimes difficult to manage the patient.

When previous measures have failed, hyperventilation will be initiated, maintaining PCO_2 at 30-35 mmHg. Hypocapnia induces a decrease in CBF and thus cerebral blood

volume responsible for the decrease in ICP. PCO_2 levels below those recommended are dangerous because of the risk of producing ischemia due to both the vasoconstrictor effect of hypocapnia and the leftward shift that tissue alkalosis determines on the hemoglobin dissociation curve (Bohr effect). In our experience, one of the leading causes of cerebral hypoxia, $PtiO_2$ is evidenced by the decrease in $PaCO_2$, which currently prevents the routine use of hyperventilation. Moreover, a study on the effectiveness of prophylactic hyperventilation in TBI showed poorer outcomes in patients at 3 and 6 months after head injury. We must insist on the need to monitor SjO_2, or better $PtiO_2$, when hyperventilation is used for sustained treatment of ICH.

Second Tier Measures

The best overall management of TBI has led to a decrease in the number of patients with ICH refractory to conventional medical and surgical measures used to lower ICP. However, in approximately 12% of patients it´s necessary to proceed to second level measures, as refractory ICH is associated with a mortality of 84-100%. Since there is no scientifically established hierarchy in the use of these measures, we will describe them according to our own experience. Although its usefulness was questioned in a systematic review, high-dose barbiturates (HDB) are continuing to be administered now that numerous case studies have shown that these drugs can reduce mortality and decrease ICP in refractory ICH.

The main effects of HBD seem to lie in their property to couple CBF to metabolic demands, so that the drop in metabolic requirements in TBI would be accompanied by a parallel decrease in CBF and cerebral blood volume, thereby inducing a reduction in ICP and an improvement in CPP. Besides their effect on ICP, HDB have been attributed with neuroprotective properties which cause cerebral vasoconstriction which could decrease cerebral metabolism and inhibit lipid peroxidation mediated by oxygen-free radicals.

The most widely used HBD are pentobarbital and thiopental, which must be administered with a loading bolus and an hourly maintenance dosage. The usual loading dose for thiopental is 1.5 mg/kg over 30 minutes and 10 mg/kg over 30 minutes for pentobarbital. The maintenance dose is 1-6 mg/kg for thiopental and 5 mg/kg for pentobarbital. It was once advised to monitor plasma HDB levels to adjust the maintenance dose. However, monitoring HDB levels has not been helpful to avoid side effects nor to optimise their therapeutic effects. Currently, EEG monitoring is the preferred way to adjust the dose, mainly by bispectral index (BIS) monitoring; as they appear in bursts of EEG suppression, the greatest effect on metabolism and CBF is achieved.

Among the adverse effects of HDB the most pernicious is arterial hypotension, which occurs almost normally and should be prevented and treated vigorously, vasoconstriction (or cerebral vasoplegia), and decreased T lymphocyte activity. Arterial hypotension is more frequent in elderly patients with a history of cardiovascular diseases and in patients with hypovolemia, acidosis, hypoalbuminemia or infection. In patients treated with HDB it´s therefore necessary to carry out periodic analysis of plasma albumin, pH, blood gases and continuous MAP monitoring.

A further problem posed by HDB is the difficulty in the early diagnosis of infection because the patient may be hypothermic due to the action of HDB and peripheral leukocytosis may not be detectable. As a general guide, HDB can be more useful in patients with higher ICH when the CT scan shows signs of diffuse brain swelling, moderate hyperventilation reduces ICP, SjO_2 >70 mmHg or $PtiO_2$ >20 mmHg, and before a high-velocity TCD exam.

As second-tier therapy in refractory ICH, after the first 24 hours of TBI, and an absence of global ischemia or regional cerebral hypoxia as measured by oximetry ($PtiO_2$ or SjO_2), profound hyperventilation can be used ($PaCO_2$ 27±2 mmHg). As with HDB, hyperventilation is most useful when the CT shows signs of diffuse brain swelling, CPP >60 mmHg, SjO_2 >70 mmHg or $PtiO_2$ >20 mmHg, and TCD ultrasound shows high average velocity flow.

Although performed for over a century for treating ICP, decompressive craniectomy (DC) has attracted renewed and growing interest from groups that advocate it as a first- level procedure. However, controversy persists about its appropriateness. First, not all published series of adult patients have shown improved the results. The only prospective study conducted to date was positive but not statistically significant and involved in 13 pediatric TBI patients and 14 controls: It showed that ICH was reduced and that outcome was better in the patients who had received DC. The prospective, controlled Australian DECRAN study, which has recently been completed, has failed to demonstrate better outcome in the DC-treated group. We are awaiting the results of the European ICP Rescue study to know whether they contradict or otherwise confirm the DECRAN results.

Adding to the controversy over DC is the high rate of substantial complications: hematoma, intracranial cerebral hyperemia with or without associated edema, hydrocephalus, subdural hygroma, secondary heart attack, fungus cerebri and neurological deficits related to bone removal. Furthermore, mixed series can create confusion, since primary DC is not identical or prophylactic after surgery performed on an injury mass and cannot be compared with a secondary DC performed when other measures fail to control ICP.

Nonetheless, there is consensus that craniectomy in the treatment of refractory ICH should take place within the first 48 hours, with wide resection (15 cm x 15 cm), followed by duroplasty, bilateral in diffuse lesions and unilateral in mass lesions, and that the beneficial effect will depend on the amount of bone removed from the temporal base when the total size equals that of the mass lesion. Young patients without extremely elevated ICP, not at risk of dying or poor outcome, could benefit more from DC.

Increasing MAP, or the CPP-oriented strategy, is another second level option. It is based on the theory advanced by Rosner (Figure 34.2) that in TBI self-regulation is never lost but rather is shifted to the right, the critical point on the autoregulation curve, requiring, therefore, greater MAP to induce vessel narrowing. According to the author, the decrease in CPP initiates a cerebral vasodilator cascade that increases the cerebral blood volume, which, in turn, leads to an increase in ICP, thus closing a vicious circle.

In contrast, an increase in CPP through a decrease in ICP or an increase in MAP would trigger a beneficial vasoconstrictor cascade that reduces cerebral blood volume and controls ICP. To lower ICP, MAP should be gradually increased to a value that occurs in the fall of ICP. MAP values may sometimes be as high as 150-160 mmHg and sometimes do not lead to such a reduction in ICP, despite having exceeded these values. This expands the intravascular volume with saline. If MAP does not increase despite good vascular filling with fluids or its value is insufficient to trigger the vasoconstriction cascade, the infusion of vasoactive agents such as norepinephrine or phenylephrine may be an option for the stated objectives.

Renal failure is the most common complication when high-dose vasoactive drugs are administered to increase MAP. At this point, increasing MAP is usually reserved for patients with space-occupying lesions in which previous options have failed and there are no systemic contraindications to increasing MAP.

Another measure that appears and reappears as an option in second level treatment is controlled hypothermia. Its interest resides in the neuroprotective effect of controlled hypothermia. At the most studied temperatures (32-34°C) a reduction in systemic and cerebral demands of oxygen is reportedly coupled with a decrease in CBF and ICP, de-

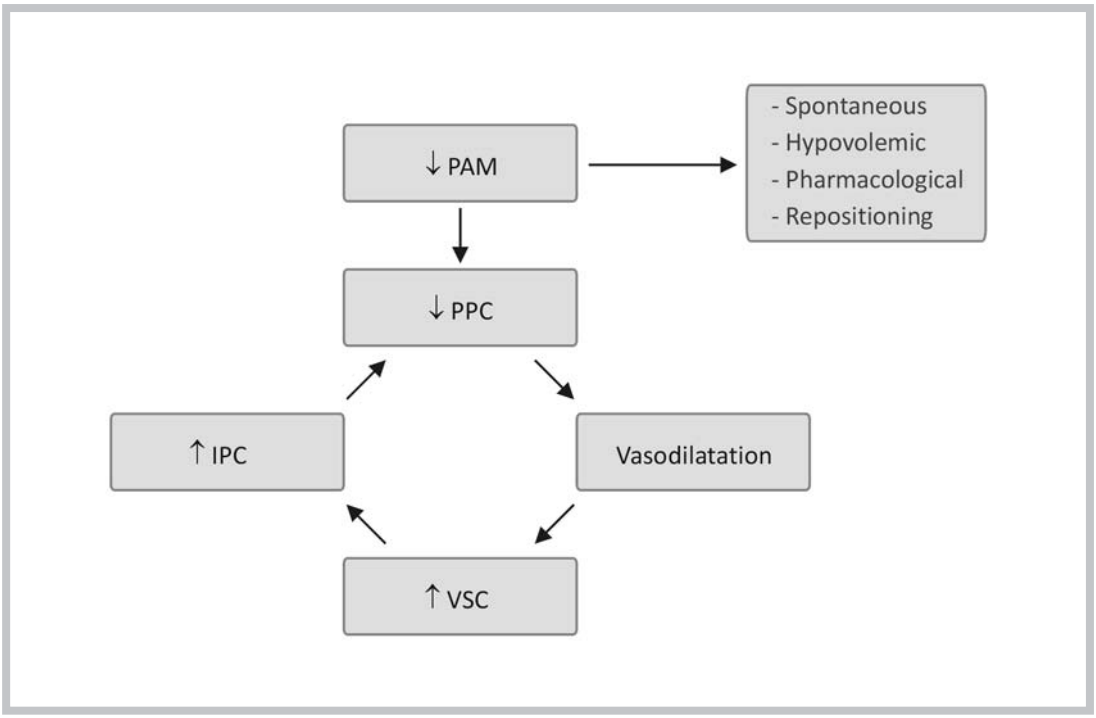

Figure 34.2. **Rosner vasodilator cascade.**

creasing the release of excitatory amino acids and protecting against free radicals. At lower temperatures (<32°C), however, hypothermia has been associated with immunosuppression, hypokalemia (with severe hyperkalemia during overheating that can result in cardiac arrest) and severe coagulation disorders. Studies involving small TBI populations, especially those by Marion in 1999, reported beneficial effects of hypothermia on outcome; however, a well-designed prospective and controlled study by Clifton in 2001 failed to demonstrate efficacy. Recently, the good results in neurological recovery obtained in patients resuscitated after sudden death from ventricular fibrillation has rekindled interest in hypothermia.

A recent meta-analysis of 13 studies involving more than 1300 patients with TBI, although mixing dishomogeneous data sets and procedures, reported a modest reduction in mortality and a slightly higher percentage of favourable outcomes. However, complications, especially pneumonia, may outweigh the neurological benefit. Therefore, pending the availability of new controlled studies, cautious use is recommended in centres with expertise in selected cases, with temperatures no lower than 33°C, with slow heating (>48 hours).

A different approach to the clinical guidelines issued by the Brain Trauma Foundation and the European Brain Injury Consortium is advocated by the school in Lund (Sweden). Its main objective is to control ICP, assuming that any increase results from vasogenic edema caused by an impaired blood-brain barrier and loss of cerebral autoregulation. The increase in MAP would be the force that in these pathophysiological conditions produces cerebral edema. To abort this cascade, MAP must be reduced, oncotic plasma increased and the venous vascular space collapsed with dihydroergotamine. Despite the good results reported by the Swedish authors, the shortness of the series and the lack of a control group currently make this therapeutic strategy unacceptable to the scientific community. Table 34.12 illustrates the Lund therapy protocol.

General measures	• Moderate head elevation (maximum 20°). Surgical evacuation of available hematomas and contusions. Insertion of ICP monitoring device • Avoid hyperthermia. At persistent high fever (>38.5°C) the temperature can be reduced with paracetamol or one bolus dose of methylprednisolone (10-15 mg/kg). Avoid active cooling • Mechanical ventilation to normal $PaCO_2$ (35-39 mmHg) and normal PO_2 (90-100 mmHg) • Effective sedation and stress reduction by using sedatives (midazolam, propofol, thiopental) combined with α_2-agonist. Thiopental should be used only at low doses (2-3 mg/kg bolus + 0.5-3 mg/kg/h IV) and for a maximum of 2 days • Normovolemia is mandatory. Use erythrocyte infusion to maintain normal hemoglobin (125-140 g/l) and albumin infusions to normal serum albumin concentration (35-43 g/l). Achieve normal plasma oncotic pressure by albumin infusion and diurectics (avoid mannitol). Minimize use of ADH analogue in polyuria • Use low-energy nutrition (15-20 kcal/kg/24 h) If possible, mainly enteral nutrition. Keep blood glucose normal (5-8 mmol/l) with insulin if necessary. Avoid hyponatremia • ICP can be controlled by normalizing plasma oncotic pressure and blood pressure, the latter by anti-hypertensive and catecholamine-reducing therapy with β_1-antagonist (e.g., metoprolol 0.04-0.08 mg/kg×6-8 IV, or corresponding doses continuously, or 50-100 mg × 2 PO) and α_2-agonist (e.g., clonidine 0.3-1.0 μg/kg×4-6 IV, or corresponding doses continuously or per os) and angiotensin II inhibitor (e.g., losartan 50 mg × 1-2 PO)

Treatment of raised intracranial pressure. Objectives: ICPC ≤20 mmHg + CPP=60 mmHg	• If ICP increases to a life-threatening level, despite the interventions described above, large unilateral or bilateral craniotomy may be life-saving by reducing ICP (decompressive craniectomy)
	• Dihydroergotamine at minimum necessary doses. Not indicated if: long bone fractures; subarachnoid hemorrhage, renal failure:
	  ▪ Day 1 maximum dose 0.6-0.8 mg/kg/h
	  ▪ Day 2 maximum dose 0.6 mg/kg/h
	  ▪ Day 3 maximum dose 0.4 mg/kg/h
	  ▪ Day 4 maximum dose 0.2 mg/kg/h
	  ▪ Day 5 maximum dose 0.1 mg/kg/h
	• CSF drainage should be avoided but drainage via ventricular catheter may be used to break an incipient Cushing reflex or a critically high ICP

Table 34.12. **Lund therapy protocol.**

When and How Should Treatment of ICH Be Discontinued?

Active treatment of ICH should be withdrawn in stages, beginning with the last measure initiated and leaving for last the general measures of treatment of TBI, i.e., analgesia and sedation. Treatment withdrawal should not begin until the following conditions are met: normalized ICP for at least 24 hours, CPP >60 mmHg; absence of abnormal ICP waves; midline centred on the CT scan, no vasospasm on TCD.

34.7.5 Evaluation of Results in TBI

The evaluation of treatment of TBI involves several objectives. First, to know our reality and compare it with accepted standards for our level of economic resources and technological complexity and training. This should lead, if not favourably compared, to establish an improvement plan, investigating our pockets of inefficiency in the integrated

treatment of TBI. Second, to design a neurocognitive rehabilitation plan and neurophysiotherapy program individualized to each patient. Finally, it is useful to evaluate the results of clinical trials of new drugs or procedures.

Conventionally, it's accepted that 6 months after the accident is an adequate time point to establish the result, given that in around 80-85% of patients marked changes will not occur after this time. In young people, however, particularly in those undergoing holistic rehabilitation, it is possible, and our experience corroborates this, can improve in cognitive areas beyond that period.

For these purposes, we have devised a simple global assessment scale, globally accepted as the GOS (Table 34.13), which is yielding ground in favour of a more elaborate version that will allow an intermediate number of categories such as the Extended Glasgow Outcome Scale (Table 34.14). However, more complex scales that measure quality of life and degree of recovery of higher brain functions are required, especially in intensive rehabilitation plans. Numbering among these latter scales are the Disability Rating Scale, currently widely used in clinical trials, the Barthel scale, and the QOLIBRI (quality of life in brain injury) scale. It is important, implying the possibility of some recovery, to neatly differentiate vegetative states from states of minimal response, since in the latter cases positive developments have been occasionally observed. Functional studies with MRI can help differentiate these situations.

Score	Response
1	Dead
2	Vegetative state (meaning the patient is unresponsive, but alive; a "vegetable" in lay language)
3	Severely disabled (conscious but the patient requires others for daily support due to disability)
4	Moderately disabled (the patient is independent but disabled)
5	Good recovery (the patient has resumed most normal activities but may have minor residual problems)

Table 34.13. Glasgow Outcome Scale Score.

Score	Response
1	Dead
2	Vegetative state
3	Lower severe disability
4	Upper severe disability
5	Lower moderate disability
6	Upper moderate disability
7	Lower good recovery
8	Upper good recovery

Table 34.14. Extended Glasgow Outcome Scale.

Any scale that we use must meet the following requirements:

- Easily completed by doctors or nurses with a minimum level of training.
- Validated in face-to-face use or by telephone.
- Good interobserver reproducibility.
- Integration of all domains related to functional recovery (activities of daily living, quality of life, neurocognitive function).

34.8 Conclusions

Despite marked progress in the diagnosis and pathophysiology of brain damage in recent years, proper treatment of TBI relies on:

- Knowledge of local TBI epidemiology to establish plans and rigorous prevention policies.
- Regional rapid-response systems with trained multidisciplinary teams able to handle all injuries associated with TBI.

- Regionalization of TBI care in hospitals with appropriate services and facilities (diagnosis, treatment and neuromonitoring) for the delivery of comprehensive treatment from the time of the accident until rehabilitation, including complications of critically ill patients.
- Adherence to clinical guidelines for TBI management.
- Rigorous assessment and plans to improve our results, after comparing them with the finest hospitals.

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35 Surgical Management of Severe Traumatic Brain Injury

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35.1 Introduction

The incidence of morbidity and mortality after severe traumatic brain injury (STBI) is high, particularly among the young, many of which will suffer life-long disability. STBI demands urgent neurosurgical treatment since brain injury begins at the moment of the trauma and damage may worsen with time. STBI is a dynamic entity which can change within hours, which is why it requires continuous monitoring and multidisciplinary management. Early identification of patients who may need surgical treatment is critical because delays can result in poor outcome or even death. The objectives of this chapter are to describe the different types of lesions in STBI, differentiate which may need surgical or medical treatment, and provide some guidelines for STBI management.
Intracranial hematomas may be classified into intra-axial and extra-axial and all of them appear as hyperdense areas on the computed tomography (CT) scan in the acute phase. Because it is often a concomitant event, damage to adjacent parenchyma should also be ascertained. Treatment will usually be instituted in the acute phase, but we must differentiate which lesions to treat and when to treat them.
An extra-axial lesion refers to an intracranial hematoma located outside the brain in the epidural or subdural space. This is one of the most common neurosurgical emergencies related to head injury. Although similar in location, its prognosis is different.

35.2 Epidural Hematoma

Epidural hematoma is generally caused by a blunt injury but with enough energy to fracture the skull and disrupt the meninges. It is associated with a skull fracture in 30-90% of cases. Skull fracture or deformation following impact disrupts the meninges around the fracture; blood accumulates in the space created between the bone and the dura, usually due to laceration of the medial meningeal artery or the diploic veins or the dural sinuses. In young patients, the dura can be easily detached, especially in the temporal region known as Marchant's zone (the area on the sphenoid and occipital bones at the skull base from which the dura mater is readily detached). A temporal location is seen in up to 70-80% of cases and is often unilateral. In 50-68% of cases, epidural hematoma is associated with intradural lesions, subdural hematomas or cerebral contusions. The association with other injuries carries a poorer outcome.
Clinic presentation depends on the location and cause of bleeding (arterial or venous), tolerance of brainstem compression and elevation of ICP: 30-60% of patients may suffer loss of consciousness and 20% may be unconscious from the time of trauma. The classical "lucid interval" is seen in only one third of cases.

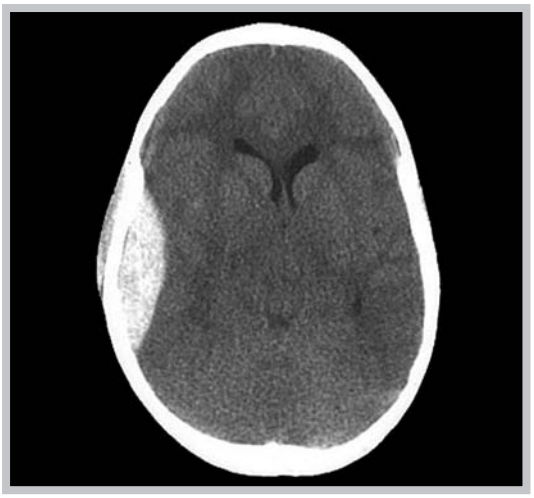

Figure 35.1. Temporal epidural hematoma displaying the typical biconvex lens appearance.

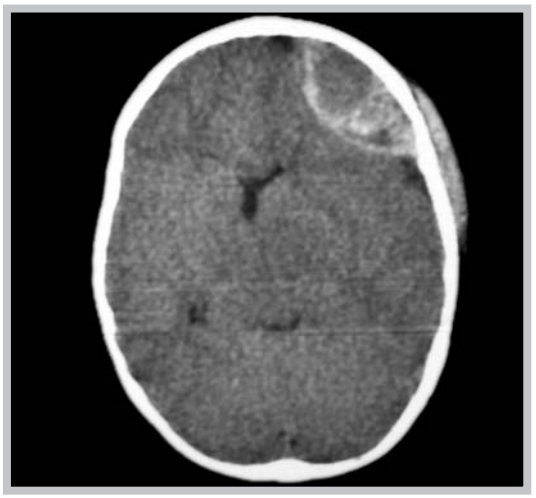

Figure 35.2. Frontal epidural hematoma in the hyperacute phase; note the hypodense areas inside the collection of blood typical of the hyperacute phase.

35.2.1 Diagnosis

CT scan without contrast and with bone window view is the study of choice for diagnosis. The hematoma appears as a hyperdense homogeneous lesion with the shape of a biconcave lens (Figure 35.1) in the temporal region and associated with a bone fracture. In a hyperacute state the appearance is heterogeneous with areas of hypodensity (Figure 35.2) suggestive of active bleeding. Hematoma enlargement is generally limited by the adherence of the dura to the bone sutures, which gives the lesion its typical appearance on the CT scan. It is important to examine the vertex because a hematoma may develop there in some cases.

35.2.2 Surgical Treatment

Most epidural hematomas must be treated surgically (Figure 35.3 A and B). Critical is the initial management in the emergency room and at the scene of the accident, as well as rapid specialist evaluation once the patient is stabilized. In patients presenting with progressive neurological deterioration it is very important to avoid secondary damage and to provide adequate brain resuscitation when needed. If the patient cannot be adequately stabilized and no other reason is found that justifies the neurological condition, or another studies are delayed as may happen in centres lacking available clinical services, urgent surgical evacuation as a salvage manoeuvre may be indicated [1].

We can use the side of pupil dilatation, the side opposite the motor deficit or even the side of the fracture on the x-ray film to determine hematoma location in 85% of cases. In stabilized patients, or those without progressive neurological deterioration, all necessary studies should be completed. Bone resection for hematomas in the temporal region should be performed up to the floor of the medial fossa if it is necessary to gain access to the proximal portion of the medial meningeal artery when bleeding cannot be controlled. Intracranial pressure monitoring is not necessary if there are no associated parenchymal lesions. There are reports of medical management for epidural hematoma. In most of these patients not treated surgically without clinical manifestations or any neurological deficit, the lesion volume is <40 ml. Such management entails prolonged hospitalization and serial CT scans to evaluate lesion resolution.

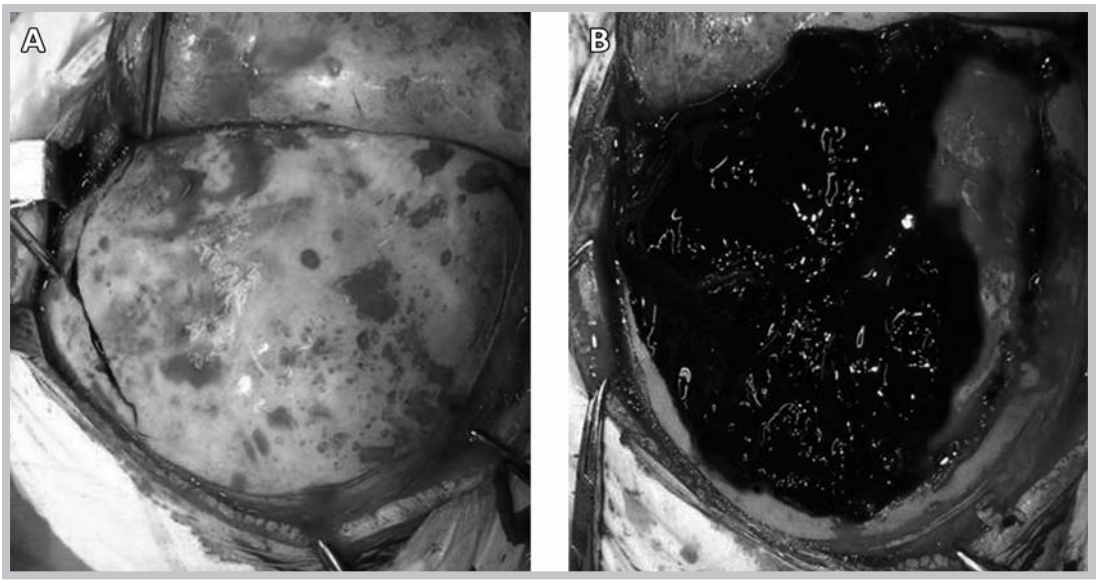

Figure 35.3. **Intraoperative image of an epidural hematoma. The fracture on the posterior temporal region can be seen, with protrusion of the hematoma through the fracture (A). A huge epidural hematoma in the same patient after craniotomy (B).**

Indications for surgery	• An epidural hematoma (EDH) >30 cm^3 should be surgically evacuated regardless of the patient's Glasgow Coma Scale (GCS) score • An EDH <30 cm^3 **and** with <15 mm thickness **and** with <5 mm midline shift (MLS) in patients with a GCS score >8 **without** focal deficit can be managed non-operatively with serial CT scanning and close neurological observation in a neurosurgical centre
Timing	• It is strongly recommended that patients with an acute EDH in coma (GCS score 9) with anisocoria undergo surgical evacuation as soon as possible
Type of surgery	• There are insufficient data to support one surgical treatment method. However, craniotomy provides a more complete evacuation of the hematoma

Table 35.1. **Guidelines for the surgical management of epidural hematoma.**

Prognosis is related to the level of consciousness, the presence of other neurological deficits and the severity of associated intracranial lesions. In patients admitted not in coma the outcome is favourable in 90-100% of cases and the mortality is 0-5%. In patients with a Glasgow Coma Scale (GCS) score <8 the outcome is favourable in 38-73% of cases and the mortality is 11-41%. The risk of mortality is three times higher if there are associated lesions (subdural hematoma or contusions).
Prompt diagnosis and surgical evacuation are key to achieving a good outcome if there are no associated lesions and neurological deterioration is related only to hematoma expansion. Guidelines for the management of these lesions are summarized in Table 35.1.

35.2.3 Non-surgical Management

There are reports of spontaneous resolution of epidural hematoma. This has been explained by reabsorption of the hematoma by the fibrovascular membrane over a period of 13 days. An epidural hematoma may increase in size during this time. Epidural hematomas that can be successfully managed with this criterion are those with a volume <44 cm^3. Special care must be taken if the lesion is located in the posterior fossa or the

middle fossa owing to the possibility of temporal lobe herniation due to brain swelling and brainstem injury. Any sign of neurological deterioration or signs and symptoms of increased intracranial pressure is an indication for surgical evacuation.

35.2.4 Prognosis

Global mortality is 0-10% but depends on the neurological state at the time of surgery. The mortality rate for comatose patients at surgery is 14-70%. Outcome is usually worse in patients older than 40 years or with lesions >150 cm^3 in volume

35.3 Subdural Hematomas

Subdural hematoma is an accumulation of blood between the dura and the brain. Road accidents are the most common cause. A subdural hematoma may be simple or complex. The simpler ones are not accompanied by parenchymal lesions and are usually caused by laceration of the bridging veins between the brain and the dural sinuses. Urgent evacuation is associated with good prognosis. Complex subdural hematoma is associated with parenchymal contusions and high intracranial pressure. Generally, it is located on the temporal, frontal or orbitofrontal lobe and the convexity in the interhemispheric space. The external margin is determined by the skull and the internal margin by the brain, which lends the margin its irregular shape. The volume may increase because of the lack of adherences on the subdural space.
But blood accumulation is not the only cause related to poor prognosis. Brain swelling and ischemia usually associated with subdural hematoma may be related to blood derivates and their neurotoxic action. This ischemic condition may not change with hematoma evacuation. The presence of this lesion justifies urgent surgical evacuation.

35.3.1 Clinical Manifestations

Signs and symptoms result from the mass effect of subdural hematoma, elevated intracranial pressure, location, size, association with another space-occupying lesions, and secondary insults. Early seizures are frequent (24%). Pupillary abnormalities may be seen, as well as motor deficits (<50% of patients); when present they may help localize the side of the lesion. But it should be kept in mind that in 25-30% of cases pupillary signs and in 38% of cases motor signs may give a false localization, which is why CT scan is of vital importance in the management of these patients.

Figure 35.4. **Fronto-temporo-parietal subdural hematoma, also known as hemispheric, with the shape of a biconcave lens and hyperacute content characteristic of a hyperacute lesion.**

35.3.2 Diagnosis

CT scan without contrast and with bone window view is the study of choice. The

CT scan will show a concave-convex lens next to the skull (Figure 35.4) generally over the parietal, temporal and frontal lobes and usually unilateral or occasionally bilateral (15% of cases). Subdural hematomas extend beyond the bone suture line, which helps to differentiate them from epidural hematoma. In 66-80% of cases subdural hematoma is associated with other intracerebral lesions (contusions, hematomas); it may be seen in a hyperacute state with characteristics resembling those of epidural hematoma and it may also be related to coagulation disorders. Interhemispheric subdural hematoma is uncommon.

35.3.3 Surgical Treatment

Factors to be weighed before operating on a subdural hematoma are the size, timing (time since the CT scan was performed and time elapsed since the trauma), presence of associated lesions and brain swelling [2].
Subdural hematoma carries a poorer prognosis than epidural hematoma. Prompt evacuation in the first 4 hours seems to be related to better outcome. The delay in surgical

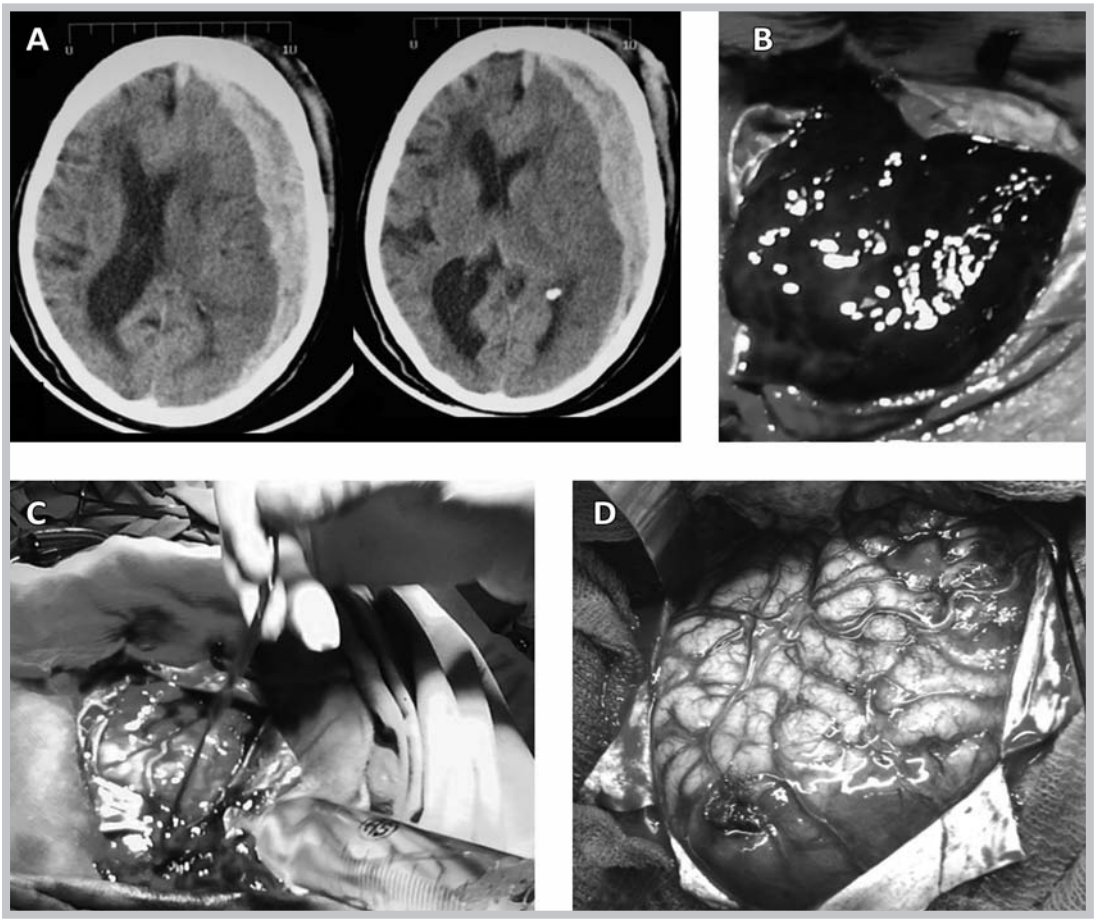

Figure 35.5. CT scan showing an acute hemispheric subdural hematoma with mass effect, midline shift and collapse of the subarachnoid space (A). Intraoperative image showing the large hematoma immediately after dural opening (B). Manoeuvres of washing and aspiration to achieve complete removal of the hematoma (C). Swelling, areas of contusion, and traumatic subarachnoid hemorrhage (TSH) of the brain after lesion evacuation (D).

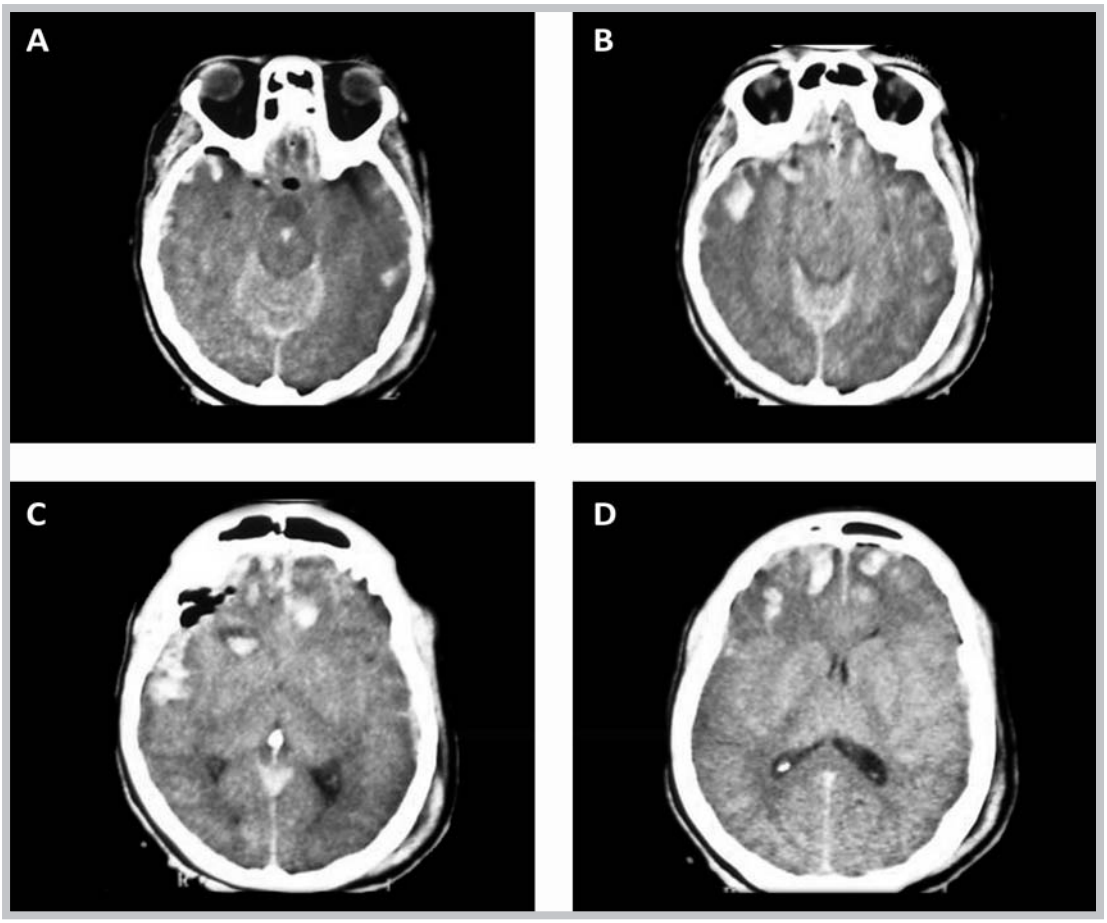

Figure 35.6. Multiple bifrontal contusions and left temporal with TSH.

evacuation once the decision is taken to operate does not offer any advantage, which is why the procedure should be done urgently (Figure 35.5).
Subdural hematoma <3 mm in diameter could be observed; but in patients with a GCS score <8 ICP monitoring is indicated with continuous follow-up by the neurosurgical team.

Indications for surgery	• An acute subdural hematoma (SDH) with a thickness >10 mm *or* a midline shift >5 mm on computed tomographic (CT) scan should be surgically evacuated, regardless of the patient's Glasgow Coma Scale (GCS) score • All patients with acute SDH in coma (GCS score <9) should undergo intracranial pressure (ICP) monitoring • A comatose patient (GCS score <9) with an SDH <10-mm thick and a midline shift <5 mm should undergo surgical evacuation of the lesion if the GCS score decreased between the time of injury and hospital admission by 2 or more points on the GCS and/or the patient presents with asymmetric or fixed and dilated pupils and/or the ICP exceeds 20 mmHg
Timing	• In patients with acute SDH and indications for surgery, surgical evacuation should be performed as soon as possible
Type of surgery	• If surgical evacuation of an acute SDH in a comatose patient (GCS = 9) is indicated, it should be performed using a craniotomy with or without bone flap removal and duraplasty

Table 35.2. Guidelines for the surgical management of subdural hematoma.

Unquestionable indications are those with clear neurological deterioration, presence of mass effect on the CT scan, intracerebral bleeding, compression of basal cisterns or midline shift >5 mm. There are patients in which the midline shift is considerably greater than expected as compared to the hematoma width. This should prompt us to consider the possibility of brain swelling or adjacent brain injury (infarction). Mortality increases the greater the difference between midline shift and hematoma width. Guidelines for the management of acute subdural hematoma are summarized in Table 35.2.

35.3.4 Postoperative Complications

The most common complications are hematoma recurrence, infection and intracerebral hematomas. The recurrence may be subdural or epidural or combined, the last of which is associated with coagulation disorders. Infections develop in <5% of cases. Increased ICP may be present in 50% of cases, which is why ICP monitoring is indicated.

35.3.5 Nonsurgical Management

Surgical evacuation is suggested for treating hematomas >4 mm in width. Smaller collections may resolve spontaneously. It is believe that the slow and progressive spread over the brain surface may help the hematoma to dissolve or to mix with the cerebrospinal fluid. In comatose patients with a midline shift <5 mm and a hematoma width <10 mm, conservative management with ICP monitoring could be appropriate. The factors to be considered when a nonsurgical decision is taken are: GCS score; hematoma width and volume; midline shift; basal cistern collapse; time elapsed since trauma and CT scan; IPC monitoring, pupillary and motor responses; use of opioids, sedatives and muscle relaxants; coagulation disorders and urgent availability of CT and neurosurgical team services.

35.3.6 Prognosis

Mortality related to subdural hematoma is between 42 and 90% according to different series. Younger patients (36-50 years) have better outcomes. The mortality rate in patients lucid at surgery is 6-10% but increases 4-6 fold in comatose patients. The mortality rate is twice as high when pupillary abnormalities are present as when not (75 vs. 35%). Timing is also an important factor for prognosis; Seelig reported 40% mortality for patients in coma operated within the first 4 hours versus 90% mortality for those operated 4 hours after trauma. There is no general consensus on whether hematoma size is a predictor of poor prognosis; however, its association with other intraparenchymal lesions seems to be related to the prognosis. Jamieson and Yelland compared the mortality rate in 3 patient subgroups: subdural hematoma without associated lesions (22%); subdural hematoma with increased ICP and temporal lobe contusions (>50%); and subdural hematoma with contusions (30%). Increased ICP during the pre- and postoperative period predicted poor prognosis.

35.4 Intra-axial Lesions

Intra-axial lesions refer to those located inside the brain. They are caused secondary to a direct blow to the skull area over the brain, thus injuring the small calibre vasculature, and are generally seen over the cortical and subcortical areas. They may evolve and grow in size over time.

35.5 Contusion and Cerebral Hemorrhage

Contusions are areas of brain damage with a variable degree of edema, ischemia, necrosis and bleeding. They may increase in volume with time, and coalesce to form an intracerebral hemorrhage. The edema that may be present from the beginning may also increase and generate mass effect. Intracerebral hemorrhage is a homogeneous collection of blood with well-differentiated margins and considerable diameter. Differentiating it from contusion is not usually easy.

Contusions are more frequent (89% of cases on autopsy) and are more often demonstrated on CT than intracerebral hemorrhage (20-40% vs. 15-20%, respectively). They are usually located on the frontal and temporal lobes. They tend more frequently to be multiple, whereas intracerebral hemorrhage is multiple in only 20% of cases.

Hypodense areas around contusions and intracerebral hemorrhage are related to low cerebral blood flow. Cytotoxic substances are released from these contused areas into the surrounding tissue and blood stream. The formation of free radicals, excitatory amino acids and the altered homeostasis of Ca and K in these areas further generate tissue injury. Some authors have argued that evacuation of these lesions may help to preserve more vulnerable cerebral areas.

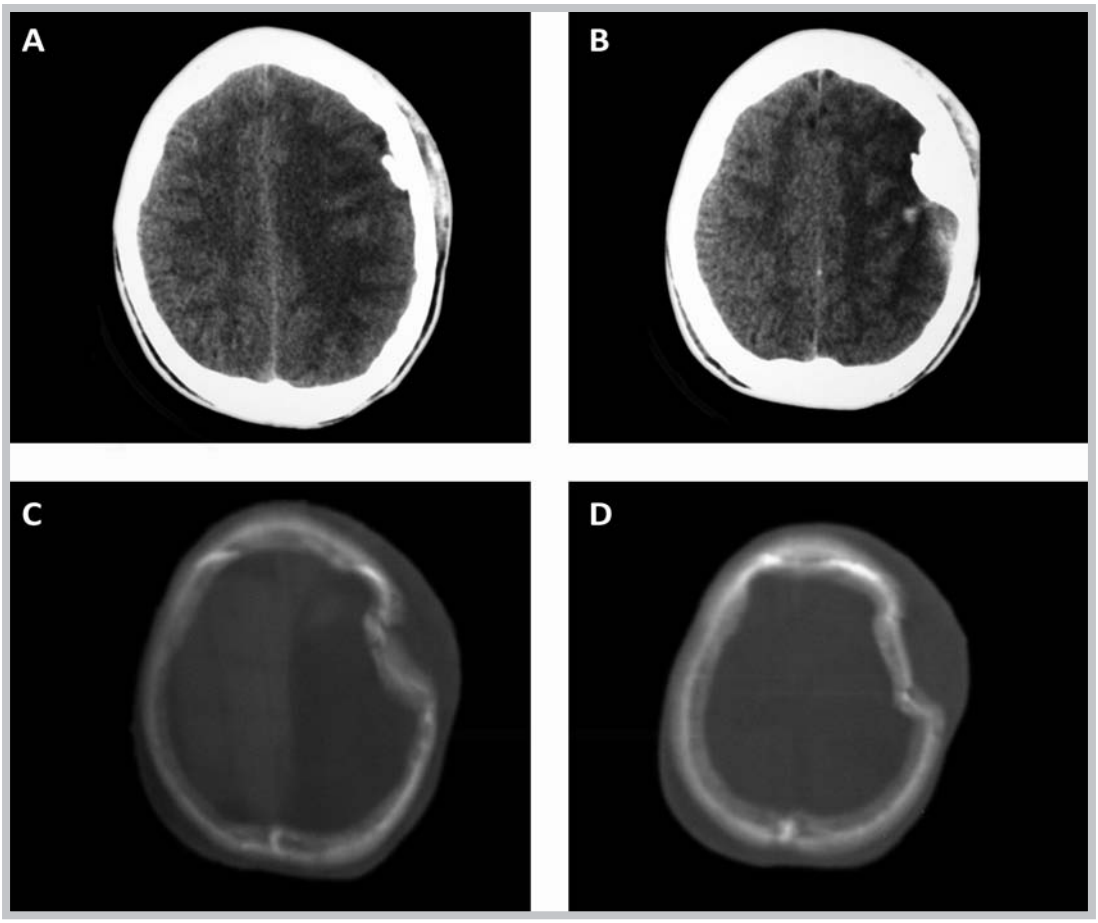

Figure 35.7. CT scan showing a left depressed skull fracture with an area of contusion and bone fragments over the brain (A). CT scan with bone window view showing the depressed skull fracture with a huge cephalo-hematoma (B).

35.5.1 Clinic Manifestations

Although contusions and intracerebral hemorrhage do not have a typical clinical presentation, more than 50% of patients present with a GCS score <8. Lesions located on eloquent areas will cause neurological deficits. Alteration of the level of consciousness may be due to big volumes and consequent ICP elevation or the association of diffuse bilateral lesions compromising the brainstem. The lesion may grow with time. Importantly, the definite volume will not necessarily show on the first CT scan, which is why CT scanning should be repeated every 8-12 hours, especially during first hours after trauma. Another dynamic component is edema which may evolve over the ensuing 7-10 days and cause delayed elevated ICP requiring prolonged ICP monitoring. A CT scan should be obtained 4-6 days after the trauma to determine evolution of the edema. Contusions and intracerebral hemorrhage on the temporal lobe may cause uncal herniation without increasing ICP. Surgical evacuation of lesions in this area with evidence of basal cistern collapse is advised to prevent this complication.

35.5.2 Diagnosis

The diagnosis is based on CT findings which show a pattern of multiple hyperdense spots <1 cm diameter surrounded by a circular hypodense area compatible with peripheral edema. Intracerebral hemorrhage is seen as hyperdense generally homogeneous lesions with a peripheral area of edema or ischemia that is better defined the day after the trauma (Figure 35.7).

35.5.3 Surgical Treatment

Contusions or intracerebral hemorrhage with mass effect and progressive neurological deterioration must be evacuated. Contusions over silent areas should be widely evacuated trying to resect all devitalized tissue, whereas the resection should be more modest in those located in eloquent areas. Small contusions not responsible for neurological

Indications for surgery	• Patients with parenchymal mass lesions and signs of progressive neurological deterioration referable to the lesion, medically refractory intracranial hypertension, or signs of mass effect on computed tomographic (CT) scan should be treated operatively • Patients with Glasgow Coma Scale (GCS) score of 6 to 8 with frontal or temporal contusions >20 cm^3 in volume with midline shift of at least 5 mm and/or cisternal compression on CT scan, and patients with any lesion >50 cm^3 in volume should be treated operatively • Patients with parenchymal mass lesions who do not show evidence for neurological compromise, have controlled intracranial pressure (ICP), and no significant signs of mass effect on CT scan may be managed non-operatively with intensive monitoring and serial imaging
Timing and type of surgery	• Craniotomy with evacuation of mass lesion is recommended for those patients with focal lesions and the surgical indications listed above, under Indications • Bifrontal decompressive craniectomy within 48 hours of injury is a treatment option for patients with diffuse, medically refractory posttraumatic cerebral edema and resultant intracranial hypertension • Decompressive procedures, including subtemporal decompression, temporal lobectomy, and hemispheric decompressive craniectomy, are treatment options for patients with refractory intracranial hypertension and diffuse parenchymal injury with clinical and radiographic evidence for impending transtentorial herniation

Table 35.3. **Guidelines for the surgical management of intraparenchymal lesions.**

deterioration, such as those located on the basal ganglia or white matter, should not be resected. Table 35.3 lists the recommendations for the management of these lesions [3].

35.6 Delayed Intracerebral Hematoma

These are hyperdense intracerebral lesions on the CT scan that were not present on first scan. The causes of these lesions are not clear; they usually occur in patients with coagulation disorders or those with hypoxia or hypotension. One theory relates their origin to the local loss of autoregulation. They may appear any time within the first 24 hours, 50% may appear after the 24 hours and very rarely after 7 days. They must be suspected whenever there is a sudden increase in ICP or neurological deterioration. In any of these circumstances a CT scan must be repeated even if the previous scan was normal.

35.7 Lesions of the Posterior Fossa

Lesions in of the posterior fosse account for 5% of post-traumatic lesions. Epidural hematoma is the most frequent and the etiology is similar to the lesions seen in the supratentorial compartment.

35.7.1 Clinical Manifestations and Diagnosis

One of the most important issues is that these lesions are located in a relatively small compartment near the brainstem and have different kinds of presentation. Diagnosis is based on CT findings and special care must be taken with regard to artifacts caused by the surrounding bone structures. We should look for asymmetries of structures and the fourth ventricle. For a better visualization, a special protocol for posterior fossa should be followed or a study with magnetic resonance imaging (MRI) obtained. The presence of hydrocephalus should prompt suspicion of a lesion of the posterior fossa.

35.7.2 Treatment

Intracerebral hemorrhage and/or contusions measuring 3 cm in diameter that show signs of progression should be evacuated, as should those in a deeper location. All ne-

Indications for surgery	• Patients with mass effect on computed tomographic (CT) scan *or* with neurological dysfunction *or* deterioration referable to the lesion should undergo operative intervention. Mass effect on CT scan is defined as distortion, dislocation, or obliteration of the fourth ventricle; compression or loss of visualization of the basal cisterns, or the presence of obstructive hydrocephalus • Patients with lesions and no significant mass effect on CT scan and without signs of neurological dysfunction may be managed by close observation and serial imaging
Timing	• In patients with indications for surgical intervention, evacuation should be performed as soon as possible because these patients can deteriorate rapidly, thus, worsening their prognosis
Timing and type of surgery	• Suboccipital craniectomy is the predominant method reported for evacuation of posterior fossa mass lesions, and is therefore recommended

Table 35.4. **Guidelines for the surgical management of posterior fossa mass lesions.**

crotic and contused tissue must be resected because it may generate edema or recurrence of blood accumulation and neurological deterioration. Hydrocephalus is resolved with a ventriculostomy and the CSF should be evacuated gradually in order to avoid ascending herniation of the posterior fossa contents. Since epidural hematoma in this area tends to expand and cross the midline and tentorium, all efforts must be made to identify and control the source of bleeding. Subdural hematoma should be evacuated, and contused tissue, if present, also resected to achieve adequate hemostasis. ICP monitoring has a limited value; pressure on the infratentorial space is poorly transmitted to the supratentorial space, and normal ICP does not ensure that the posterior fossa structures are out of danger [4]. Treatment guidelines are presented in Table 35.4.

35.8 Depressed Skull Fracture

Depressed skull fracture occurs when an object with a high level of kinetic energy hits against the skull and the energy is absorbed by the bone, causing deformation of the bone structure over the area of impact. Two groups of depressed skull fracture are distinguished: closed or simple when there is no continuity with superficial tissues (no skin laceration); and open or compound when there is laceration of the scalp adjacent to the fracture.

35.8.1 Diagnosis

X-ray in anteroposterior and lateral views may show the fracture; the Towne position may help to reveal fractures in the posterior fossa. CT scan with bone window view is the study of choice to detect even small depressed fractures and will help to evaluate the presence of associated lesions (Figure 35.7). Some linear anteroposterior fractures may be missed as they can be located in between CT slices in the axial plane. Coronal slices may help in such cases.

35.8.2 Treatment

Closed, linear cranial fractures are considered non-operative lesions unless associated with surgical intracranial masses. Compound depressed cranial fractures are depressed fractures with an overlying scalp laceration in continuity with the fracture site and galeal disruption, and have conventionally been treated with debridement and surgical elevation. Simple depressed cranial fractures that have no galeal disruption are traditionally managed with surgical elevation only if the extent of depression equals or exceeds the thickness of adjacent intact bone, or if there is an associated intracranial hematoma with mass effect that requires evacuation. The rationale for aggressive treatment of depressed skull fractures (DSF) stems from their association with infection and late epilepsy. Cosmetic deformity also plays a role in surgical decision making.

Compound depressed fractures are neurosurgical emergencies, and they should be solved in the first 24 hours, preferably the first 12 hours. The objectives of surgery are to remove foreign bodies and devitalized tissue, and to repair of tissue layers (dural, subcutaneous tissue, skin); bone fragments may be replaced if they are adequately disinfected and debrided. If surgery is done in the first 24 hours, without signs of infection and the dural can be closed in a watertight fashion, bone repositioning can be done safely and the risk of infection is the same as when we remove the bone fragments [5].

Indications for surgery	• Patients with open (compound) cranial fractures depressed greater than the thickness of the cranium should undergo operative intervention to prevent infection • Patients with open (compound) depressed cranial fractures may be treated non-operatively if there is no clinical or radiographic evidence of dural penetration, significant intracranial hematoma, depression >1 cm, frontal sinus involvement, gross cosmetic deformity, wound infection, pneumocephalus, or gross wound contamination • Non-operative management of closed (simple) depressed cranial fractures is a treatment option
Timing	• Early operation is recommended to reduce the incidence of infection
Timing and type of surgery	• Elevation and debridement are recommended as the surgical method of choice • Primary bone fragment replacement is a surgical option in the absence of wound infection at the time of surgery • All management strategies for open (compound) depressed fractures should include antibiotics

Table 35.5. **Guidelines for the surgical management of depressed cranial fracture.**

If the depressed fracture is located over the dural sinuses, bone removal is not recommended because of the risk of severe bleeding.
There is also some concern about delayed epilepsy related to DSF (incidence, 7.1-9.5%) and the duration of post-traumatic amnesia (<24 hours 5.4%, >24 hours 22%). Also, the presence of motor deficit, dural laceration and history of epilepsy may predispose to post-traumatic epilepsy. The incidence increases when these factors are combined. Table 35.5 summarizes the guidelines for the management of DSF.

35.9 Surgical Treatment of Increased ICP: Decompressive Craniectomy

In 1901 Kocher was the first surgeon to use decompressive craniectomy (DC) for the treatment of post-traumatic edema. In the ensuing controversy on the outcome after DC in these patients, the procedure was abandoned. We now know that elevated ICP in a setting of STBI is one of the most important independent predictors for mortality and morbidity. For patients who do not respond to first-line treatment for increased ICP, there are some second-line options proposed by the European Brain Injury Consortium (EBIC) [6] and the American Association of Neurological Surgeons (AANS) [7] that include barbiturate coma, controlled hyperventilation, hypothermia and DC. Although DC is currently a second-line treatment, some questions about the procedure remain unanswered: if DC changes the outcome of these patients, which group of patients are better candidates, which timing and the surgical technique are correct; issues that we will try to discuss below.

35.9.1 Indications

Presently, there is a lack of class I publications that support the routine use of DC for STBI. There is only one study in pediatric populations that favours the use of DC [8]. There is also a recent publication, the DECRA [9], that did not support the routine use of this procedure, but the study was later strongly criticized [10]. Rescue ICP (a randomized multicentre trial) is still ongoing and the results may perhaps answer questions about the usefulness of DC. Most publications are retrospective studies and only a few are pro-

spective non randomized in design. Most are class II; taken together the evidence shows that about 70% of patients who required DC will survive with a 51% of good outcome. These data are encouraging though they lack statistic evidence. Also, mortality is 30%, but prognosis is better if we compare with the data from the Traumatic Coma Data Bank (TCDB) in which patients had received only medical treatment.

The bulk of recent studies favour the use of DC [8,11-15]. There is no consensus about the timing of DC. One of the most important studies suggests that DC should be indicated in patients with brainstem signs secondary to increased ICP, CT findings compatible with diffuse encephalic lesion type III or increased ICP associated with neurological deterioration or the failure of medical treatment to keep ICP normal [12]. This large-scale study involved the largest population of patients to date but had some flaws related to the delay in the indications of DC and the inclusion of patients from the pre-CT scan era. A more recent publication suggests that DC is indicated when medical treatment fails to maintain normal ICP, with DC as an option of last resort. A very recent publication refers to DC as a preventive procedure even before adequate medical treatment is used; if the CT scan shows signs of poor prognosis or intraoperative findings (multiple con-

GCS score ≤8	
Marshall III-IV or non-evacuated lesion	
Adequate cerebral perfusion pressure (CPP)	• CPP ≥60 mmHg in adults • CPP ≥50 mmHg in infants
ICP >25 mmHg ≥5 minutes post-reanimation with medical treatment and within 48 hours of STBI	

Elevated ICP with no response to first level medical treatment	• Head and neck in neutral position
	• Head elevation 30°
	• Adequate sedation
	• Adequate analgesia
	• Muscular blockers if needed
	• Normothermia
	• Adequate oxygenation and ventilation
	  ▪ $SaPO_2$ ≥90%
	  ▪ PaO_2 ≥60 mmHg
	  ▪ $PaCO_2$ = 35-40 mmHg (normocapnia)
	• Na^+ ≥140mEq/l
	• Glucose = 80-150 mg%
	• Seizures or status epilepticus ruled out
	• Normal hemostasis
	• Hemoglobin ≥10g/l or hematocrit ≥30%

Increasing TIL (Therapeutic Index Level) in a few hours in order to obtain the same ICP	
Use of second and third level measures without achieving an ICP <20 mmHg	
Contraindication for the use of second and third level measures	• BAD IV: hemodynamic instability • Moderate/high hyperventilation: signs of ischemia as measured by PTO_2 or SjO_2/$DAVO_2$/EO_2 • Hypoperfusion pattern on Doppler ultrasonography
CT scan before DC	• To rule out the presence of new lesions not seen on previous images
Limited resources situation	• Unavailability of basic neurological monitoring

Table 35.6. **Indications for decompressive craniectomy.**

- Severe life-threatening extraneurological lesions
- Primary brainstem lesions
- Glasgow score 3/15 post-reanimation
- Age >60 years
- Bilateral unreactive mydriasis
- Massive cerebral infarction of dominant hemisphere
- Non-neurological causes of increased ICP (hyponatremia, hypovolemia, fever, hypercapnia, inadequate adaptation to ventilator, etc.)

Table 35.7. **Patients ineligible for decompressive craniectomy.**

tusions, generalized brain swelling), this suggests that the patient will have an increase in ICP [13,14,16,17]. It is well recognized that in young patients with slow progressive neurological deterioration early DC and adequate technique (extensive bone removal and dural plastic) may produce a good outcome.

The most commonly accepted criteria for the indication of DC are summarized in Table 35.6. They are based on initial CT scan and ICP management. The presence of borderline ICP increases with alpha or beta waves may help to decide whether to perform DC. Transcranial Doppler may also be useful in the decision-making process. Patients with worsening of the flow pattern and the presence of systolic peak have the worst outcome. This, together another factors, may help, especially if the indication for DC is unclear [9]. Also, it is very clear for some authors that patients with a GCS score <3, fixed dilated pupils, and signs of irreversible brainstem injury are not candidate for DC (Table 35.7).

35.9.2 Surgical Technique

There are two basic types of DC: hemicraniectomy and bicoronal. The election of the type of craniectomy will depend on the following criteria: CT findings; midline deviation; presence of multiple bilateral or unilateral contusions; and presence of symmetric collapse of basal cisterns (Table 35.8).

In hemicraniectomy (Figure 35.7) the incision is similar to that for trauma flaps, (big question mark) including the frontal, parietal and temporal bone, starting from the midline and finishing in front of the tragus. It is not necessary to expose the superior longitudinal sinus because of the risk of unnecessary bleeding and the space gain is not significant. Of great value is resection of all the temporal bone for adequate temporal lobe decompression as is the anterior two thirds of the parietal bone (Figure 35.8). As blood loss during craniectomy may be important, hemostasis is of great importance to avoid hypotension and secondary damage during the procedure. The dura is opened widely (Figure 35.8). If a contusion generates mass effect, it should be resected. A duroplasty is always recommended; autologous (galeal flap, temporal aponeurosis, facia lata aponeurosis) or heterologous (dural substitutes bovine, fibrillar, etc.) may be used in order to give adequate dural expansion. It is not necessary to close the dura in a watertight fashion. We pay particular attention to the galeal and skin closure to minimize the risk of CSF fistula.

In bicoronal craniectomy (Figure 35.9) as described by Polin et al. [18], the incision extends from ear to ear, trying to extend it as posterior as possible. We prefer to create two

Condition	Hemicraniectomy	Bicoronal
Midline shift	Yes	No
Unilateral multiple contusions	yes	No
Bilateral diffuse cerebral edema	No	Yes
Multiple bilateral contusions	No	yes

Table 35.8. **Guidelines to define type of decompressive craniectomy.**

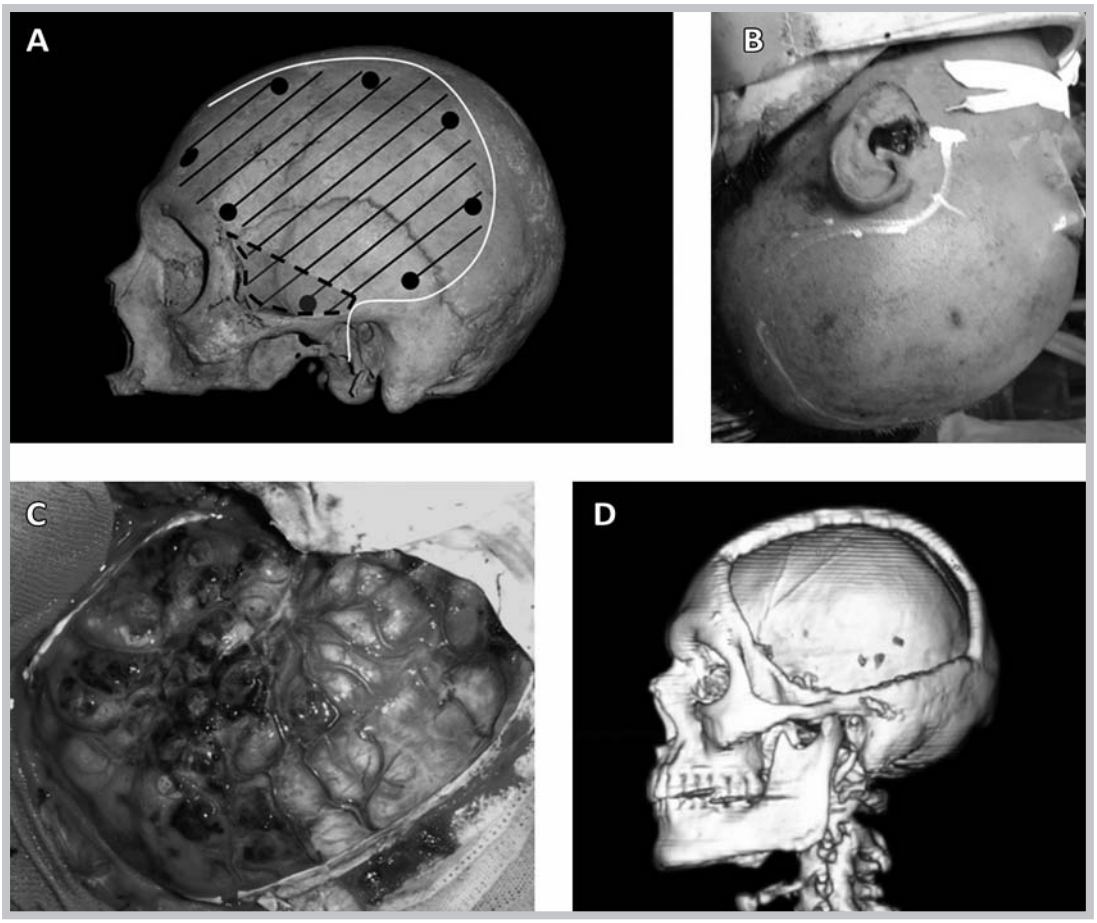

Figure 35.8. **Intraoperative image of a patient with STBI. Surgical position and skin incision prior to a left DC. The drawing shows the planned craniectomy for hemicraniectomy, bone of the fossa media to be removed (in grey) (A). Skin incision for DC (B). Intraoperative image showing swelling and multiple contusions over the brain (C). CT scan with 3D reconstruction of the area where the bone was removed (D).**

isolated bone flaps with an anterior-posterior bridge of bone over the midline 2-3 cm in width. As in hemicraniectomy, it is important to resect the temporal bone as basal as possible. Anteriorly, the frontal bone should be resected up to the supraorbital eminence while trying to avoid the frontal sinus because of the risk of CSF fistula through the sinus. The bone bridge over the superior sagittal sinus averts unnecessary blood loss and helps for a more easy craneoplasty surgery posteriorly. Some authors propose resection of this bone bridge and cutting of the falx at the base of insertion, but we believe this is unnecessary. With adequate bilateral exposure of the middle fossa, it is very important to avoid compression of the brainstem by the mesial aspect of the temporal lobe.

Intraoperative brain swelling it not commonly seen if the craniectomy is wide enough and timing is correct. The swelling may be also related to hyperperfusion phenomena, leading to intracerebral hematoma or cerebral infarction, especially if the surgery is delayed; therefore, we recommend performing the procedure as soon as possible.

The basic objective of DC is to resect an extensive portion of bone, especially in the temporal bone area, and to achieve a duroplasty without tension. The criteria for defining whether a bicoronal or hemicraniectomy should be performed (Table 35.8) depend on CT findings (midline shift, contusions, basal cisterns).

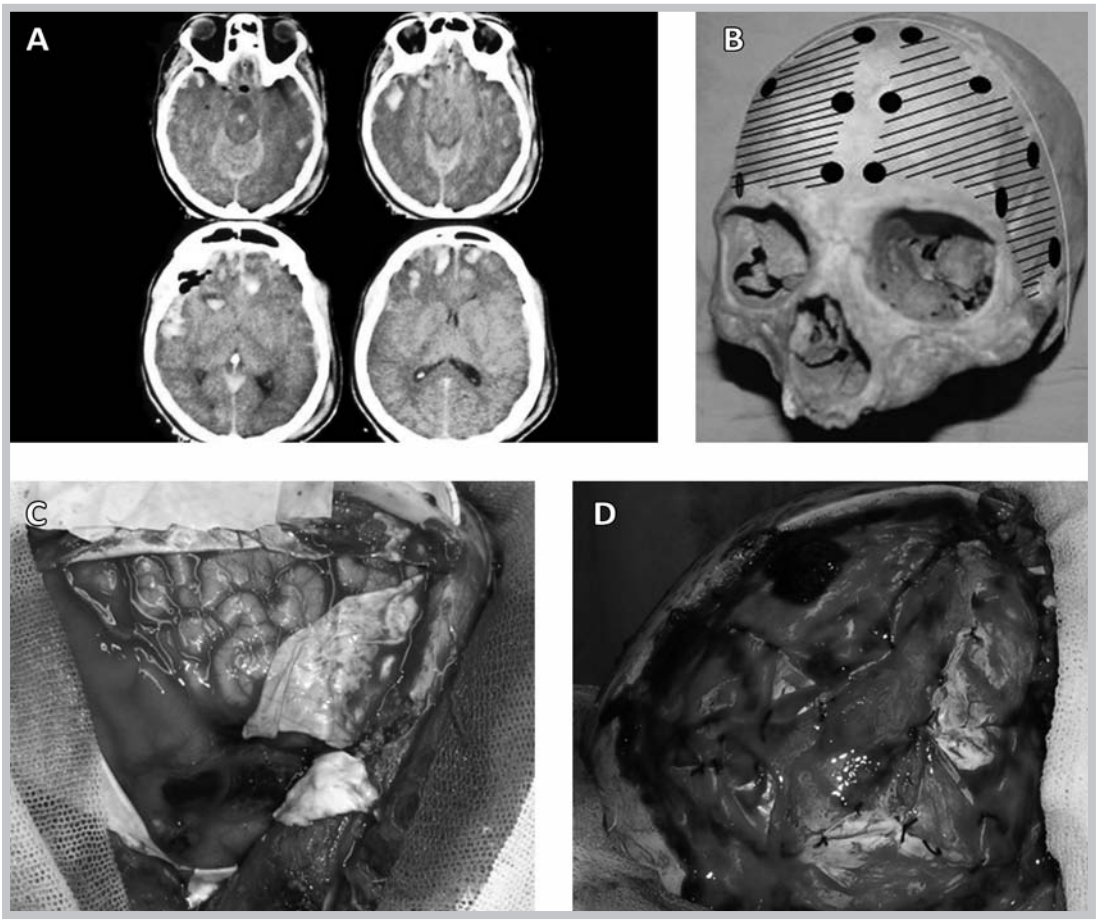

Figure 35.9. **CT scan of a patient with diffuse brain injury type III with multiple contusions; a bicoronal DC was performed (A). Surgical planning of the bicoronal DC; bone to be removed is marked with oblique lines (B). Intraoperative image showing the right hemisphere with frontal and temporal contusions, TSH and swelling (C). Photo showing a duroplasty with galea (D).**

The benefits of DC are improvement in cerebral perfusion as seen on SPECT (may be considered as hyperperfusion that could last up to 1 month with a peak during the first week), with right shift of the pressure-volume curve of ICP. Hyperperfusion phenomena could be deleterious if the DC is indicated too late. A reduction in ICP can be achieved (15-70%) with DC, but this is not always associated with a good outcome [12,17]. DC also improves cerebral oxygenation.

35.9.3 Complications

While DC can reduce ICP, certain physiological phenomena could give rise to possible complications, including altered CSF circulation, increased cerebral blood flow and cerebral metabolism (causing a hyperemic response), and loss of autoregulation mostly in the first 24 hours which generally resolves within 72 hours. Patients older than 60 years of age, with a history of anticoagulant therapy or a very low GCS score on admission are more prone to complications.

Immediate complications are an increase in the size of contusions or subdural hematomas, usually on the same side, and carry a poor prognosis if >20 cm^3 compared to the

initial lesions [19]. Another complication is cerebral herniation through the craniectomy (26% of cases), which may be caused by hyperemia during the first days and associated with the loss of autoregulation. If the craniectomy is small, we may see something known as cerebral fungus, which is extensive herniation of the brain with vascular cerebral alterations of the brain through the borders of the craniectomy which worsen the situation. Also, infections and CSF fistula may be seen in this period due to accidental opening of the frontal sinus, inadequate asepsis, or insufficient closure of the galeal and skin plane.

Other complications in the first 30 days include subdural hygromas caused by alterations in CSF dynamics that may lead to hydrocephalus (20-50% of cases), and may resolve spontaneously in several weeks or 2 months [20,21]. Paradoxal herniation is a sign of neurological deterioration with brainstem manifestations after a lumbar puncture in a decompressed patient and may occur days after the puncture; the mechanism is believed to be related to an increase in the negative pressure over the brain with the open skull. It is called paradoxical because the treatment is opposite to the management of a classic herniation; the patient should be positioned in the Trendelenburg position and hyperosmolar solution should be stopped. Closure of ventricular or spinal drainage or even cranioplasty are all alternatives for the management of this condition.

Hydrocephalus may appear after 1 month and is related to perturbations in CSF dynamics. Some authors advise resolving the cranial defect before beginning with surgical management of the hydrocephalus. Another complication seen in this period is the syndrome of the trephined characterised by headache, dizziness, irritability, memory disturbances and mood changes. Sometimes it can be associated with contralateral motor deficit. Theories to explain this condition include changes in atmospheric pressure [22], CSF dynamics [23,24], and disturbances in cerebral blood flow [25,26]; all of these symptoms resolve with cranioplasty. And if the bone flap was preserved on the subcutaneous plane of the abdomen with the idea of posterior reposition, 50% of partial reabsorption of the bone may occur if bone reposition is delayed.

DC may be considered a simple surgery if these details are kept in mind. Since the cases are usually emergency surgery, the surgeon should be fast while ensuring unnecessary blood loss and conditions of adequate asepsis.

35.9.4 Outcome

DC seems to offer a better outcome in patients with STBI with elevated ICP refractory to medical treatment [8,12,14,27]. There remain some questions about the procedure's real benefit in such patients, the timing, and if it is better than another second-line medical treatments. Comparative studies are needed to shed light on these issues.

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36 Severe Traumatic Brain Injury: Pathophysiology and Management Guided by Multi-modal Monitoring

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36.1 Introduction

Traumatic brain injury (TBI) is a major problem worldwide. It accounts for at least half of all trauma-related fatalities and incurs significant health care costs for treatment, rehabilitation and convalescent care of surviving patients. In the United States alone, costs are estimated at 60 billion dollars annually in both direct medical and indirect costs such as loss of productivity [1]. Modern trauma response teams, neurosurgical centres, and intensive care treatments have reduced mortality rates in severe head injury patients to 20-30%, according to a recent series [2]. Pre-hospital care, rapid radiographic diagnosis, early surgical intervention, and ultra-modern monitoring modalities are largely responsible for these reductions. Contemporary clinical series identifying deleterious markers, such as hypoxia, hypotension and hyperpyrexia have also contributed greatly. Despite these efficacious clinical advances, there is much room for improvement in all areas of TBI [3,4].

36.2 Clinical and Cellular Pathophysiology of Severe Traumatic Brain Injury

The cellular pathways and patho-mechanisms involved in TBI are extensive and complex. The detailed biochemistry, genetic regulations, and molecular occurrences are reviewed elsewhere and are beyond the scope of this chapter. We will provide an overview of the basic cellular and clinical pathophysiology, with a focus on the most relevant aspects for neuro-monitoring.

36.2.1 Cellular Pathophysiology in Traumatic Brain Injury

The cellular processes that continue to cause neuronal damage after TBI are traditionally classified as secondary brain injury. Primary brain injury results from the immediate mechanical disruption of brain tissue caused by the direct trauma itself. These secondary cellular events are thought to occur hours to days after the initial trauma, and they may continue for weeks or months [6]. It is these secondary mechanisms that dictate management and intervention by the treating physician, and they are closely related to pa-

tient outcome. Disruptions in calcium homeostasis ensuing from TBI have been shown to cause numerous cellular events [7].

The influx of intracellular calcium may occur through a number of mechanisms: membrane-associated channels or receptors (including excitatory amino acid receptors); and membrane disruption or trauma-induced depolarization altering the Na^+-K^+ exchange system. In both experimental and clinical TBI, a release of or an increase in excitatory amino acid concentrations, particularly glutamate and aspartate, occurs minutes after the initial injury and often lasts several weeks [8,9]. These excitatory amino acids may bind specific receptors in the brain, notably N-methyl-D-aspartate (NMDA) and AMPA/kainate receptors, which gate monovalent and divalent cations such as sodium and calcium. Once inside the cell, calcium is involved in various different processes, including phospholipase activation which leads to membrane disruption, production of free radicals which leads to DNA damage, up- or downregulation of the genes that control cell survival or apoptosis, and mitochondrial disruption, ultimately resulting in cellular demise.

Calcium influx activates phospholipases, specifically phospholipase A2 and phospholipase C, resulting in cell membrane disruption and the generation of free fatty acids. These free fatty acids, along with intracellular free radical species (e.g., nitric oxide, superoxide, and hydrogen peroxide), represent reactive species that can damage DNA and cell membranes and may affect cerebral blood flow, blood-brain barrier permeability, and cerebral edema [10].

Intact mitochondrial function is central to cellular energy metabolism and homeostasis of glutamate and glycerol, which are released when free fatty acids are liberated from triglycerides as part of membrane breakdown. They can now be measured in the living human brain: glutamate values after severe head injury are up to 100 times higher than normal and glycerol levels are 30-40 times normal values. Elevated intracytoplasmic and, consequently, intramitochondrial calcium, interrupt oxidative phosphorylation and the electron transport chain. Cell death due to disruption of the oxidative process, mitochondrial swelling, and failure of Na^+-K^+ ATPase are directly related events.

Genetic alterations, including upregulation of the so-called immediate early genes c-fos and c-jun, have been shown to occur in both experimental and clinical models [11,12]. These factors alter the expression of both pro-apoptotic and anti-apoptotic genes, but their significance is not fully understood. Apoptosis, or programmed cell death, is also likely under genetic regulatory control. The balance between anti-apoptotic factors, such as Bcl-2 and Bcl-xl and pro-apoptotic factors such as Bax and Bak, ultimately determine the fate of the cell [13-16]. If this ratio is tipped towards apoptosis, the family of cystein proteases (caspases) are called into action. Caspases 8 and 9, the so-called initiator caspases, directly influence caspase 3, the final executioner. Activated caspase 3 seeks out and targets multiple intracellular components, including cytoskeletal proteins, nucleic acid repair proteins, and DNA-ases [16].

Numerous cytokines, growth factors and inflammatory mediators have been implicated in TBI [17]. Disruption of the blood-brain barrier permits neutrophils, macrophages, and other inflammatory cells access to the central nervous system (CNS). These cells, along with various mediators (e.g., IL-1, IL-6, ICAM-1, TNF-α, nerve growth factor, FGF, among others) all play a potential role in cell demise or restoration. When the blood-brain barrier is disrupted, adhesion molecules recruit incoming leukocytes, resulting in the local release of reactive oxygen species (ROS), causing cellular damage and death, as well as the release of further pro-inflammatory cytokines and mediators.

Many of these mediators can now be measured in the injured human brain by means of microdialysis and the newly available 100 kDa MW cut-off membranes. Antagonizing or altering these separate but interrelated processes has been the focus of innovative TBI treatment. Calcium antagonists, NMDA receptor blockers, free-radical scavengers, gene

regulators, anti-inflammatories, anti-apoptotics, and temperature regulation, to name a few, are possible points of therapeutic intervention.

36.3 Clinical Pathophysiology

Five clinical variables have consistently been shown to correlate with poor patient outcome following TBI: hypoxemia; hypotension; reduced cerebral perfusion pressure; elevated temperature, and raised intracranial pressure [18,19]. These clinical occurrences are often termed secondary insults, as they aggravate initial and secondary injuries. Only age and initial Glasgow Coma Scale (GCS) score are more potent predictors of outcome. These clinical and cellular events ultimately lead to cerebral ischemia and neuronal cell death. It is through the identification, recognition, prevention and treatment of these secondary insults that we can prevent secondary brain injury and ultimately improve patient outcomes [3].

Treatment paradigms such as optimizing cerebral oxygenation and perfusion, maintaining normal intracranial pressure, and aggressive medical and surgical interventions constitute the standard of care today. Continued medical support of all other body systems should always continue simultaneously.

In order to understand the pathophysiology of severe brain trauma, a brief review of normal cerebral physiology is necessary. The human brain uses glucose almost exclusively as its energy source to produce adenosine triphosphate (ATP). The pathway through which glucose is utilized depends on the availability of oxygen, oxidative phosphorylation in most instances, and anaerobic glycolysis when oxygen is unavailable. Oxidative phosphorylation is much more efficient, producing a total of 38 molecules of ATP per molecule of glucose, as opposed to a mere two molecules of ATP and two molecules of lactate with anaerobic glycolysis. Two parameters are used when discussing cerebral metabolism: the cerebral metabolic rate of oxygen consumption ($CMRO_2$) and cerebral metabolic rate of glucose consumption (CMRG). Globally, normal resting values are 3.3 mg/100 g/min and 5.5 mg/100 g/min, respectively, with grey matter values being typically higher than white matter values [20,21].

Despite its relatively small percentage of total body weight (3%), the human brain utilizes an astounding 20% of cardiac output to maintain its high metabolic demand. Although neurons constitute about 50% of the cellular make-up of the human brain, they account for 90% of energy expenditure [22]. Glial cells, on the other hand, consume only 10%. Most of this energy expenditure goes into neuronal communication and synaptic transmission: 25% for biosynthesis and cellular transport, and 25% for maintenance of membrane ionic gradients [22]. Because the human cerebrum lacks the capacity to store glycogen, the brain relies on a constant flow of blood to carry oxygen and glucose to its cells. Maintenance of a constant blood flow under varying physiological states is termed autoregulation. Multi-modality clinical monitoring now allows continuous measurement of brain tissue oxygen tension ($PtiO_2$: Licox system) and the lactate/pyruvate ratio, a direct indication of oxidative phosphorylation (low L/P ratio <20), and of anaerobic glycolysis (L/P ratio >20). Clinical treatments can be directed at optimizing these parameters (see below).

36.4 Autoregulation

Cerebral autoregulation is the ability of the cerebral vasculature to compensate by constriction and dilation so as to maintain cerebral blood flow (CBF) constant over a

wide range of mean arterial pressures. Several mechanisms and theories have been advanced, most notably pressure autoregulation and metabolic autoregulation models. Pressure autoregulation is described by Poiseuille's equation:

$$Flow(Q) = k(\Delta P \times r^4)/(8 \times l \times v)$$

wherein blood flow is proportional to the pressure difference and vessel size, and inversely proportional to vessel length and blood viscosity. Changes in perfusion pressure will therefore result in changes in blood flow unless vessel size is altered: when blood pressure and perfusion pressure, in turn, decrease, the cerebral vasculature must dilate to maintain a constant flow. Similarly, when blood pressure and/or perfusion pressure increase, the vessels must constrict to maintain blood flow constant (Figure 36.1).
This phenomenon is generally seen under normal physiologic conditions across a blood pressure range of 50-150 mmHg; however, longstanding hypertension causes a "right shift" of the autoregulatory curve. Failure of pressure autoregulation typically occurs outside this blood pressure range, and there is strong evidence that it may become dysfunctional after TBI [23,24].
Metabolic autoregulation is represented by the Fick equation:

$$CMRO_2 = CBF \times AVO_2D$$

Because the cerebral metabolic rate, cerebral blood flow, and arteriovenous oxygen difference are all interconnected, the brain is able to precisely match local cerebral blood flow to local metabolic needs. The exact cellular mechanisms behind pressure and metabolic autoregulation are not completely understood, but there is evidence that the vascular endothelium has an integral role. Studies have shown that an intact vascular endothelium is essential for maintaining cerebrovascular hemostasis, largely through local metabolites and vasoactive substances such as H^+, CO_2, adenosine, K^+, calcium, nitric oxide, endothelin and thromboxane [25]. All these substances have all been proposed as possible mediators of cerebrovascular reactivity.
Cerebral blood flow may be accurately measured in the intensive care unit (ICU) using xenon gas, the ^{133}Xe method, in xenon-enhanced computed tomography (CT). Howev-

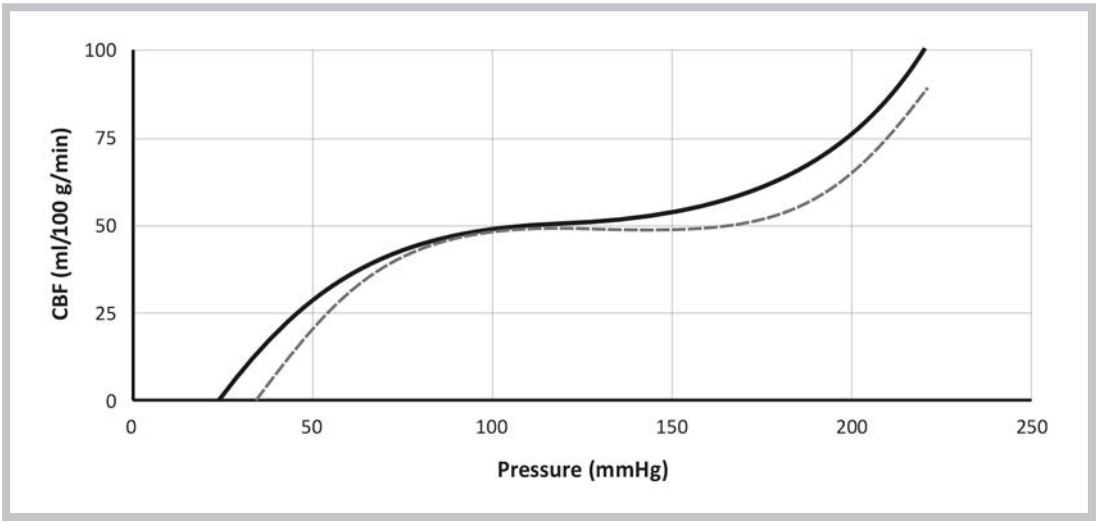

Figure 36.1. The cerebral blood flow (CBF)-pressure curve.

er, radiation exposure and costs limit the frequency of its use to 2-3 scans per patient. With the recent introduction of the Hemedex continuous CBF monitor based on a thermal diffusion method, both blood supply and metabolism can be measured in the ICU.

36.5 Secondary Brain Injury

Focal and global alterations in cerebral metabolism, cerebral blood flow, autoregulation, and intracranial pressure contribute to the development of secondary brain injury. The cerebral metabolic rate in head-injured patients is typically reduced, ATP generation is lower, and anaerobic glycolysis is critical under circumstances of severely reduced CBF or mitochondrial damage [26]. This results in increased lactate concentration and acidosis. Disturbances in autoregulation, or "dysautoregulation," a mismatch of cerebral blood flow and metabolism, and impaired CO_2 reactivity may occur together and have a harmful effect on the injured brain. These events, coupled with systemic perturbations, such as hypoxia and hypotension due to lung injury, airway obstruction or shock, can combine to wreak havoc on potentially salvageable neurons. Ischemic brain damage is very common after severe head injury, being demonstrated in up to 80% of autopsy subjects [27].

The brain's initial response to ischemia or declining blood flow is to extract escalating amounts of oxygen from the circulation. But when extraction reaches a maximum, further reductions in blood flow result in energy failure, mitochondrial and cell membrane disruption, cell swelling and cell death [28,29]. The ultimate determination of cell survivability versus cell death depends on a complex relationship between actual blood flow, duration and degree of ischemia, specific cell type, glucose concentration and temperature, among other factors. There seems to be a relatively constant value of blood flow associated with salvageable ischemic neurons and irreversible cell death: 18 cc/100 g/min and 8 cc/100 g/min, respectively [29].

Measuring cerebral perfusion pressure (CPP) is an indirect way to assess CBF in real time. Cerebral blood flow is related to intracranial pressure (ICP) and mean arterial pressure (MAP) by the equation:

$$CPP = MAP – ICP$$

Increased ICP is a common event contributing to secondary brain injury in severely injured patients, and it is often the main clinical concern that determines treatment.

36.6 Intracranial Pressure

The Monro-Kellie hypothesis states that the cranium is a rigid non-expandable box and that its contents consist of mainly three volumes: the brain (80%); cerebrospinal fluid (CSF) (10%); and blood (10%). In order for the pressure inside this rigid box to remain constant, the volumes of the contents must remain fairly stable. Any increase in volume of the original contents (hyperemia/edema) or owing to a mass-occupying lesion (hematoma) must be offset by a decrease in volume of one of the other components, otherwise the ICP will rise. The compensatory mechanism begins with the diversion of CSF and intracranial blood. Over 80% of severely head-injured patients have persistently elevated ICP [30]. In the healthy adult the ICP is 5-15 mmHg, and it is usually 0-10 mmHg

in children. Persistently elevated ICP has been associated with poor outcomes, and mortality is directly related to the degree and duration of elevated ICP [31,32].
As ICP rises and compensatory mechanisms reach their limit, CPP generally decreases, setting the stage for decreased blood flow, ischemia, and neuronal cell death. Much of the clinical care in the neuro-ICU is directed at preventing and managing increases in ICP by maintaining adequate perfusion pressures and aggressively avoiding ischemic situations brought about by hypoxia or hypotension. Other modalities include evacuation of intracranial mass lesions and limiting cerebral edema. Specifics on monitoring and treatment strategies for raised ICP will be discussed later in this chapter.

36.7 Intracranial Hypertension, Monitoring Modalities, and Treatment Strategies

36.7.1 Intracranial Hypertension

Elevated ICP is the leading cause of death in head-injury fatalities, and it is a major contributing factor to the secondary insult mechanism of brain injury. The capacity to accommodate up to 50 cc of new intracranial volume without a significant rise in ICP occurs by the displacement of venous blood into the general circulation and of CSF out of the cranial vault into the spinal subarachnoid space; however, these mechanisms are both age- and time-dependant. Since elderly people tend to have more cerebral atrophy, they may accommodate a larger amount of a slowly expanding volume. Younger individuals with an acute process, on the other hand, are much more likely to become rapidly symptomatic. All surgical lesions should be aggressively evacuated according to Brain Trauma Foundation surgical guidelines. Mass lesions will be discussed in the subsequent section.
Abnormal cerebral autoregulation, new hemorrhage, and cerebral edema are the major causes of delayed intracranial hypertension. Clinical trials have shown that head-injured patients with an ICP >20 mmHg, particularly when sustained or intractable to treatment, have a worse clinical outcome and are at high risk for the herniation syndrome [29-33]. There is also recent evidence that CPP <60-70 mmHg is associated with worsened parenchymal oxygenation, metabolism, and outcome [34]. Therefore, the goals of monitoring and treatment are to maintain adequate CPP, oxygenation, and metabolism, while limiting elevation in ICP, edema, and substrate perturbations.

Monitoring Techniques

Monitoring techniques in the head-injured patient can be loosely classified under three categories: pressure monitoring; blood-flow monitoring (Figure 36.2); and substrate monitoring (Figure 36.3). The choice between monitoring systems is becoming increasingly complex, and the capability to monitor multiple parameters such as oxygenation and substrate concentrations, as well as ICP is becoming increasingly common. As mentioned previ-

Figure 36.2. Cerebral blood flow monitoring device.

ously, brain ischemia, hypoxia, and cellular malfunction are common following TBI, and the reduction in blood flow and substrate delivery can occur within minutes, stressing the importance of early resuscitation and management of the intracranial environment.

Figure 36.3. Substrate monitoring.

Pressure Monitoring: Types and Indications

Lundberg introduced ventricular drainage as a management strategy for treating intracranial hypertension in the 1960s. However, the concept of ICP monitoring did not gain momentum until the mid-1980s with evidence-based literature describing the subarachnoid bolt. ICP monitoring technology has grown since its inception and current ICP monitoring options include subdural, epidural, parenchymal and intraventricular monitors. Today, most monitoring is limited to parenchymal and intraventricular monitoring because subdural and epidural monitors are inaccurate. Ventriculostomy is the gold standard for the evaluation of raised ICP. An intraventricular monitor allows for reliable diagnosis and the potential for therapeutic intervention through drainage of CSF for raised ICP. Intraventricular monitoring is a low-cost, highly accurate method; however, it carries a slightly higher post-insertion malfunction rate than parenchymal monitoring. Parenchymal monitors such as the fibre optic (Integra Neuroscience-Plainsboro, NJ) and transducer tipped devices, like the microstrain gauge (Codman-Raynham, MA.) are placed in the brain parenchyma but are generally more expensive and cannot be recalibrated once inserted [35-37].

The Brain Trauma Foundation Guidelines for the Management of Severe Head Injury recommend ICP monitoring in patients with a GCS score <9 and an abnormal CT scan (blood, edema, contusion) or a GCS score <9 with a normal CT scan, and two of the following three: 1) age >40; 2) systolic blood pressure (SBP) <90 mmHg; and 3) unilateral or bilateral motor posturing. With ICP and mean arterial blood pressure (MABP) measurements, cerebral perfusion pressure can then be determined to provide an indirect assessment of CBF. The CPP value necessary for preventing ischemia varies individually, depending largely on the integrity of autoregulation but generally lies between 50 and 70 mmHg [101,102].

36.7.2 Blood Flow Monitoring

Transcranial Doppler

Transcranial Doppler (TCD) is an inexpensive non-invasive tool that provides insight into cerebral hemodynamics, and it can alert the clinician to possible harmful events. TCD relies on an ultrasonic pulse signal that is transmitted through thin areas of the skull. Flow velocity through a vessel is determined, and flow volume may be calculated by multiplying the velocity by the cross-sectional area of the vessel. Since the amount of collateral flow and the actual vessel diameters are unknown, TCD cannot provide quantitative data on regional tissue perfusion. Changes in flow velocity can, however, provide relative data on changes in flow volume. Typically, flow velocities >200 cm/second indicate

severe vasospasm, vessel narrowing, and impending infarction. Hyperemia, a common occurrence in post-TBI, may also lead to elevated flow velocities. The so-called Lindegaard ratio or hemispheric index (middle cerebral artery [MCA]/extracranial internal carotid artery [ICA]) may help differentiate between the two situations, with normal values being <2 and critical values being >3 [38].

Xenon CT

Xenon CT is the most accurate non-invasive method for determining both regional and global cerebral blood flow. Xenon is a radiodense, inert and rapidly diffusible substance that allows precise quantitative measurement necessary for determining accurate blood flow values. Baseline plain CT scans are performed, followed by serial scans while the patient inhales 28-33% xenon. Complex mathematical models produce precise quantitative values, relying on Fick's principle which states the amount of a substance taken up by an organ equals the amount delivered minus the amount carried away by venous blood. Xenon CT is not devoid of technical pitfalls: patients must be free of cardiovascular disease, both functionally and structurally, in order to produce reliable results; and if portable CT is unavailable, moving the patient to the CT scanner multiple times may also become an issue. Two invasive methods for measuring continuous local CBF are now also available and have correlated well with xenon CT techniques: the thermal diffusion method (Hemedex) and the laser Doppler method. Both methods require open craniotomy or a twist-drill hole for placement, and both measure only small focal areas of brain tissue, which may or may not be representative of the global blood flow picture. Both are under evaluation in many centres.

Near-infrared Spectroscopy

Near-infrared spectroscopy (NIRS) technology has been developed as an emerging method for monitoring cerebral oxygenation, blood flow, and blood volume in both adults and children [39,43]. The technique involves the transmission of light from an emitting source through the brain to a sensor. Some studies suggest it can monitor cerebral oxygenation, blood flow, and blood volume in both adults and children [39-43]. NIRS has received technical criticism because, while transmission of the light source works well in neonates due to their semitransparent skull and scalp, monitoring in adults can be problematic due to dilution of the brain NIR signal by extracerebral tissues such as the skull bone marrow and scalp [44,45]. The emitter and detector are separated by specified distances on the scalp with the premise that a fixed amount of transmitted, reflected, and scattered light follows an elliptical path whose depth of penetration is proportional to the distance of separation between the emitter and the detector (Figure 36.2) [45]. Cerebral oximeter (Somanetics Inc, Troy, MI, Invos Cerebral Oximeter) is one such product used to estimate blood oxygen saturation in the brain. Optical transceiver pairs are placed on the scalp, and the attenuation of light signals at two wavelengths is used to estimate regional blood oxygen saturation. Its use in both operative procedures and ICU settings have been reported. Brawanski et al. demonstrated a correlation between intraparenchymal oxygen probes and NIRS probes in 9 patients following TBI, and Kirkpatrick et al. found that NIRS probes recorded changes in cerebral oxygenation that recovered once blood flow was restored during vessel cross-clamping in carotid endarterectomy [46]. The use of NIRS in conjunction with a bolus injection of indocyanine green (ICG) has been used to measure CBF. NIRS measurements may help to identify critical clinical parameters and guide treatment directions. As it is not sufficient as a stand-alone monitoring technique, these values should be considered in context with other monitoring methods.

Laser Doppler Flowmetry

Laser Doppler flowmetry (LDF) relies on an implanted subcortical fibre optic laser probe (diameter, 0.5-1 mm) that measures the shift of reflected laser light produced by the progression of red blood cells recorded in blood perfusion units (BPU.) Laser light from one fibre is scattered within the tissue and some is scattered back to the detector probe, which is another optical fibre that collects the backscattered light from the tissue and returns it to the monitor. The light returned to the monitor undergoes signal processing, wherein the emitted and returned signals are compared to extract the Doppler shift related to moving red blood cells. A BPU is a relative units scale determined using a carefully controlled motility standard comprising a suspension of latex spheres undergoing Brownian motion. The greatest benefit of LDF is that the data are presented in real time and variations in blood flow are detectable immediately. A major drawback is that the data are a qualitative and not a quantitative analysis. When used in conjunction with xenon CT, an absolute value can be determined, with xenon acting as a calibrator for the LDF [37,47].

Thermal Dilution Flow

Thermal dilution flow (TDF) methods (Hemedex, Codman, Cambridge, MA) are based upon the conductance of small amounts of heating between two small gold electrodes, one equipped with a sensitive thermocouple sensor. CBF is proportional to heat conductance, and the values are thus absolute. The probes are usually configured for placement in the deep white matter rather than the grey matter, with correspondingly much less CBF change (e.g., normal CBF in white matter is 22 ml/100 gm/min versus 80 ml/100 gm/min in the grey cortex). The sensors are usually placed via a “bolt” immobilizing system, but they can be placed at craniotomy (e.g., for aneurysm clipping). Clinical acceptance of either of these monitoring techniques has been slow thus far perhaps due to the reporting of relative values and the questionable reliability and validity of the commercial systems [27]. The development of non-invasive methods to assess both regional and global blood flow and oxygenation together are also being developed and may one day replace LDF and TDF.

36.7.3 Oxygen and Temperature

$SjvO_2$

Jugular venous oxygen saturation ($SjvO_2$) monitoring involves cannulation of the internal jugular vein and advancement of the catheter into the jugular bulb (about 13 cm) cephalically to the level of C1, confirmed with lateral and/or anteroposterior plain x-ray. Jugular venous oxygen saturation sampling was first utilized in the 1930s as a promising method to detect post-traumatic changes in global cerebral oxygenation, but its subsequent use has proved to be more difficult than originally envisioned [48]. The concept of $SjVO_2$ monitoring is based upon the fact that most (about 80%) of the cerebral venous blood drains into the internal jugular veins, so that jugular venous blood indicates brain events. The normal range of $SjvO_2$ is 50-75%, but typically lies between 50-60% in most patients. When CBF decreases, oxygen extraction increases to compensate it, and the cerebral metabolic rate does not change initially. If this relationship continues and decreases in CBF surpass this compensatory mechanism and the supply is unable to meet demand, the metabolic rate decreases and anaerobic metabolism takes over. $SjVO_2$ decreases <50% are associated with altered brain metabolism, and values <20% are associated with irreversible ischemic injury and poor outcome [49]. In head-injured pa-

tients, however, $SjvO_2$ measurements are widely variable, ranging from 34 to 96% in some series [50]. Measurements of $SjVO_2$ are obtained by draining blood from the internal jugular venous catheter. Widespread use of this monitoring method has been limited however, due to catheter migration, technical difficulties of insertion, poor positioning, calibration errors (e.g., light absorbance), and the difficulty in differentiating regional versus global brain oxygenation, leading to a reported 50% error rate [48,51-53]. Questions concerning the reliability, validity and new $PtiO_2$ technology (see below) have limited the use of $SjVO_2$ monitoring to a few centres.

$PtiO_2$/PbO_2

The Licox monitor is a direct means to measure brain oxygen and temperature. The probe measures 0.8 mm and is placed into brain tissue to determine local or regional oxygenation and neighbouring brain temperature depending upon the insertion site. The Licox (GMS-Integra, Kiel-Mielkendorf, Germany) system [54] is a small and easily inserted miniaturized Clark electrode with a polyethylene sheath (sampling area approximately 14 mm^2), and it has proved to be an accurate measurement of partial pressure of oxygen (Figure 36.4). Diffusion of oxygen from red blood cells to the extracellular space provides the substrate measurement, and the Licox system integrates both venous and arterial oxygen tension in the measured area [55]. Conformation of sensitivity can be accomplished by altering inspired FiO_2 to 100% following intracerebral placement, often referred to as an "oxygen challenge" [56]. When inserted near an area of injury or penumbra, the probe can detect localized hypoxia or evaluate global brain oxygenation. Normal brain tissue oxygenation (partial pressure of brain tissue oxygen [$PbtO_2$]) is 20-35 mmHg. Current Brain Trauma Foundation guidelines indicate a $PtiO_2$ of 15 mmHg. Values <10-14 mmHg should be considered a sign of tissue hypoxia [35,52] and values <5-10 mmHg indicate impending neuronal death and infarction.

In early trials, Robertson and Valadka et al. demonstrated that when pO_2 was maintained at normal values, it was a predictor of better outcomes in TBI patients. Bard et al. later showed some correlation with duration of low $PtiO_2$ and poor outcome. Van den Brink et al. looked at 101 patients with non-penetrating head injury and a GCS score ≤8 and found that the magnitude and length of time of low $PtiO_2$, as measured with the Licox system, was an independent predictor of unfavourable outcome and death. The authors noted that the device demonstrated little zero drift and that the values were reliable over the time course of monitoring [57].

Placement location remains a complicated issue to resolve. Studies have shown that direct placement of the catheter in contused brain provides inaccurate responses following increased FiO_2, suggesting that CBF may be inadequate to provide oxygen delivery in these contused areas [58]. Accordingly, some groups recommend placement in non-contused white matter of the frontal lobe in diffuse injury or on the affected side in a unilateral injury [54,58]. Although these measurements may help to identify critical clinical parameters and guide treatment directions, most authors agree that PO_2 monitoring is not sufficient as a stand-alone monitoring technique [55]. These values should be taken in context with other monitoring methods and

Figure 36.4. Licox system.

should help guide rather than dictate clinical action. The risk of infection or catheter-related hemorrhage is minimal. A randomized clinical trial of $PtiO_2$ versus non-$PtiO_2$ monitoring-guided therapy is currently underway in the United States (the "BOOST" study). The Licox probe also has an incorporated thermocouple allowing for brain temperature monitoring.

Hyperthermia in human and animal studies has proved to be another secondary insult resulting in poor outcomes [59]. Cerebral temperature typically differs from core temperature. Schwab et al. cite 1.5°C ± 0.3. A growing body of evidence in both animals and humans suggests that induction of mild hypothermia (32-35°C) early after injury may arrest or slow secondary brain damage mechanisms.

Microdialysis

The cerebral microenvironment changes rapidly after TBI. Excitatory amino acid release, calcium influx, pump and membrane failure, and lactate accumulation are just a few of the derangements. Many of these changes can be detected with the use of microdialysis in humans. Correlations between adverse clinical events (e.g., elevated ICP, hypotension or hypoxia) and increased dialysate concentration (lactate, potassium, excitatory amino acids [EAA]) or decreased levels (glucose) after head injury have also been reported [60-64]. Belli et al. noted that elevated lactate/pyruvate (LP) ratios and glycerol levels preceded malignant increases in ICP, suggesting that biochemical failure could be detected early [65] (Figure 36.6).

Such cerebral substrates can be collected utilizing a fine coaxial probe (diameter, 0.62 mm) with a dialysis membrane (typically 20 kDa MW cut-off) placed directly into the brain. The probe is slowly perfused with a sterile mock extracellular fluid (ECF) solution, allowing continuous sampling of the parenchymal extracellular environment across the dialysis membrane [66]. High-performance liquid chromatography (HPLC) techniques in small aliquots of dialysate fluid (60 µl) allow for the identification and measurement of various molecules, including glucose, lactate, potassium, pyruvate, nitric oxide, and glutamate [60,61,67].

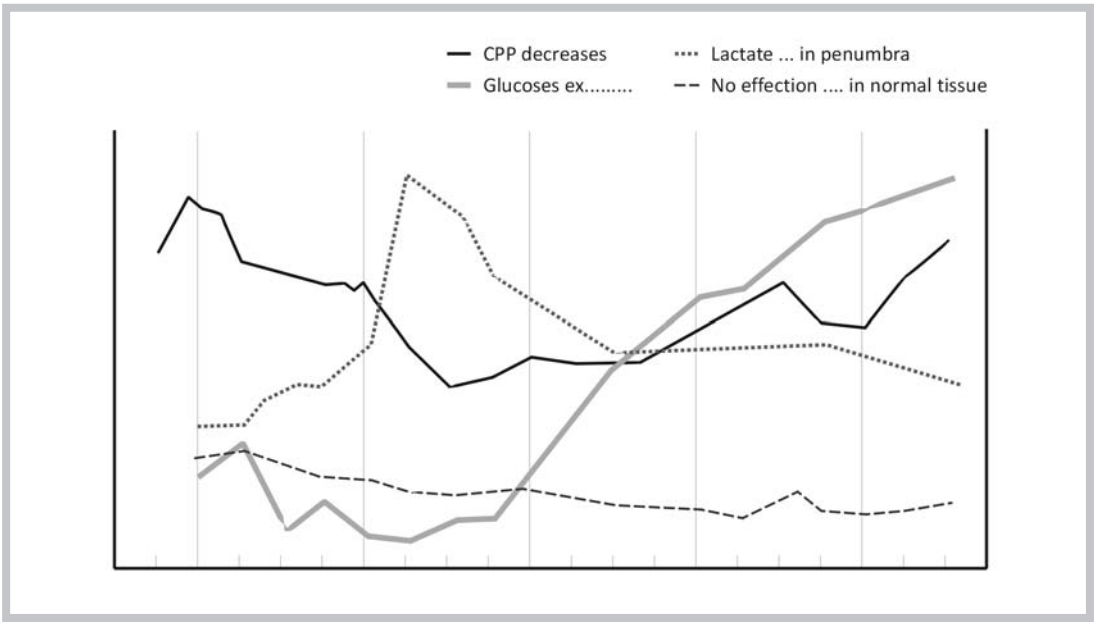

Figure 36.5. Effcects of lactate/pyruvate and glycerol levels on ICP.

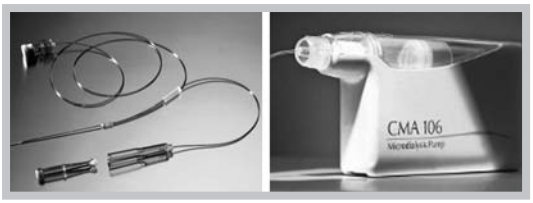

Figure 36.6. Microdyalisis system.

This tool was first utilized clinically in the 1980s by Meyerson et al. prior to lesioning for Parkinson's disease [68] (Figure 36.6). As with most monitoring systems, microdialysis may be combined with other modalities such as ICP and PO_2 probes [69]. Microdialysis has many limitations, however, one being that measurements are representative of relative concentrations of the extracellular molecules and so do not represent absolute concentrations, creating a problem when attempting to compare data between different machines and centres [70]. Other disadvantages are the lack of specificity of some results, sampling limitations of the microenvironment surrounding the catheter induced by cell edema, and changes in the ECF space [35,58,71,72], poor temporal resolution, and lengthy (1 hour) substrate analysis time. The use of microdialysis probes with a much higher molecular-weight cut-off (e.g., 100 kDa) allows protein fragments and small peptides such as cytokines (e.g., IL-1, IL-6, trophic factors, and amyloid precursor protein fragments) to be measured serially in the human brain following TBI and subarachnoid hemorrhage (SAH) [73]. Ongoing clinical investigations may address these drawbacks and eventually propel microdialysis into mainstream neurological ICU use.

36.7.4 Monitoring of Seizures and Spreading Depression: EEG/ECoG/CFM

Monitoring for epileptiform activity in the acute and subacute period post-TBI is an important adjunct to ICP, brain oximetry and CBF, as the incidence of subclincal/non-motor or partial seizures can be as high as 17-20% and chemical paralysis may mask overt motor seizures [35,74,75]. Electroencephalographic (EEG) data have also be used as an independent prognostic indicator and to institute therapeutic interventions before irreversible damage ensues [76,77]. The presence of epileptiform activity has also been linked to episodic increases in ICP and lactate/pyruvate ratios as measured by microdialysis [78]. Monitoring should continue until the ICP has normalized or cerebrovascular autoregulation has been re-established [78]. Additional benefits of obtaining EEG data post-TBI include testing the efficacy of new drugs without lengthy waiting to determine outcome measures. Vespa et al. studied 94 moderate to severe TBI patients and reported a 22% non-convulsive seizure rate. Classen et al. validated this study in 2004 and reported a 18% seizure rate in the same population.

Newer continuous EEG machines are smaller and portable, contain data reduction software, and real-time remote analysis, eliminating the need for a full-time technical assistant at the bedside [66]. The simplest form of EEG monitoring includes a non-invasive strip of 2-4 electrodes (e.g., Bispectral Index [BIS]) that analyzes the depth of sedation, reports on whether seizure activity is present, and can correlate with the GCS score [79]. A downside of this technique is that it cannot regionalize information. Larger units including 8-14 channel 10-12 electrode montages that are more regionally specific and can collect specific information such as alpha, delta, beta, and theta proportions of the raw EEG [76-78]. Several international studies are currently evaluating monitoring of cortical activity following decompressive craniectomy [80,81]. During the procedure, an electrocorticogram (ECoG) 6-electrode recording strip is placed on an area of the cortex near the parenchymal site of injury. Incorporated software provides data analysis and storage. The strip allows for bedside removal once the monitoring period is complete.

Cortical spreading depression (CSD), as previously described by Leao, refers to a wave of depressed cortical activity or amplitude that spreads slowly across the cerebral grey matter and can be diagnosed by the ECoG [82]. The depression is accompanied by a transient loss of ion homeostasis, changes in glucose and lactate, and an increase in CBF and oxygen followed by oligaemia. ECoG changes are similar to those recorded during peri-infarct depolarization (PID) which occur in the periphery of infarct regions [80,83-85]. PID and CSD differ from one another, however, in that PID contributes to irreversible ischemic damage, while it is unclear whether CSD can harbour long-term effects. It may precede certain events (e.g., seizures) and in some cases may even have a protective effect on the injured brain [81,86,87]. Differentiation between these two phenomena is critical.

CSD is not caused by one single mechanism. Animal studies suggest the influence of many different causative agents such as potassium and glutamate that flush out of the cells and into the ECF [88]. Although experimental work on this concept in animals spans 60 years, it has only recently been demonstrated that CSD post-TBI in humans is common, and it may even be more likely to occur in younger patients [80,89,90].

Fabricius et al. examined the incidence of co-occurrence of spreading depression and seizures following acute brain injury [81]: 54 patients were included in the study and each had a 6-electrode cranial strip placed below their craniotomy site; 19 of 54 patients exhibited cortical spreading depression, and in 8 of these 19 patients co-occurrence of seizures and CSD was documented. Three of these 19 patients had CSD that preceded a seizure, signifying the potential of CSD to trigger full seizures; however, this was not seen consistently. Only one of the seizures was observed clinically. More research into these two potentially co-occurring phenomena is necessary. Because CSD and PID events in animals can be attenuated with N-methyl-D-aspartic (NMDA) acid receptor blockade, monitoring these changes in humans may provide an important selection tool for those patients who could benefit from these therapies in the future [90].

36.7.5 Neuromonitoring-based Treatment Strategies

As mentioned earlier, the goals of monitoring and treatment are to maintain adequate cerebral perfusion, oxygenation, and metabolism, while limiting ICP elevation, desaturation, edema, and substrate perturbations. Specific values that may serve as a guide include maintenance of CPP between 60 and 70 mmHg, ICP <20 mmHg, $SjvO_2$ >50 mmHg, and local tissue oxygenation >15-20 mmHg. Traditionally, treatment of elevated ICP has proceeded in a step-wise fashion, beginning with a low-risk and high-benefit profile before progressing to high-risk therapy such as barbiturate coma. Elevation of the head of the bed to 30-45 degrees, maintenance of normotension, normothermia, and normocarbia, prevention of hypoxia, and sedation and analgesia remain the initial steps in the management of most head-injured patients. These are first-tier treatments in severe TBI. Progression to higher tier therapies should be initiated when there is a rise in ICP, and substrate deficiencies in multi-modality monitoring require some unique and specific interventions, as discussed below.

Osmotic Diuretics

Mannitol, currently the osmotic diuretic of choice, is initially given as a bolus of 0.25-1 gm/kg. It reduces ICP within 15 minutes, and its effects typically persist for 3-4 hours. The therapeutic effects of mannitol include initial improvement in red blood cell rheology, blood flow and oxygen delivery to the brain, as well as delayed osmotic water withdrawal from the brain into the circulating blood volume [91]. There is also weak evi-

dence that concomitant use of loop diuretics, such as furosemide, results in a greater and more sustained decrease in ICP when compared to mannitol use alone [92]. Clinical effects seem to peak when serum osmolarity is kept between 300 and 320 mOsm, and elevations beyond 320 mOsm can result in renal failure. Some authors advocate the use of hypertonic saline, but evidence does not support a superior effect in TBI.

CSF Drainage

The first step in managing a new rise in ICP is to rule out an evolving or delayed mass lesion by CT scan. Once this has occurred, and assuming a ventriculostomy is in place, drainage of 3-5 ml of CSF should be the initial therapeutic modality. In patients with intracranial hypertension, drainage of even a small amount of CSF may be very effective. An additional theoretical advantage of CSF drainage involves removal of potentially neurotoxic compounds from the CSF, such as glutamate, aspartate, and calcium. These compounds have been shown to be present after TBI, and facilitation of their removal may have a theoretical advantage.

Sedation and Neuromuscular Paralysis

An additional therapeutic option involves heavy sedation and/or neuromuscular paralysis. Agitation, anxiety, posturing, and resistance to mechanical ventilation can all contribute to elevations in ICP. Sedatives, such as midazolam or lorazapam, propofol coupled with narcotics such as morphine or fentanyl, and neuromuscular blocking agents such as vecuronium or rocuronium, are all commonly used agents. Specifics on dosing and benefit/side effect profiles are beyond the scope of this chapter. Routine neuromuscular paralysis of head-injured patients has been shown to increase pulmonary complications and prolong ICU stay however, and should therefore be reserved for those patients with persistent elevation in ICP [93].

Hyperventilation

Lundberg was the first to introduce hyperventilation as a form of treatment for intracranial hypertension in the 1950s, associating a significant decrease in ICP in patients with tumour or TBI when arterial PCO_2 was reduced from 40 to 25 mmHg [94]. Subsequent animal models confirmed that hyperventilation leads to cerebral vasoconstriction, decreased CBF and blood volume, and a reduction in ICP. Research has shown that CBF in the pericontusional area is indeed close to the ischemic/infarction threshold (<18 ml/gm/min) and that further reductions in blood flow may tip this balance towards brain ischemia. Routine hyperventilation to an arterial PCO_2 of 20-25 mmHg was shown to worsen outcome in a randomized controlled trial [95]. It is now recommended that PCO_2 be kept at or near 35 mmHg whenever possible. Aggressive hyperventilation should only be employed to treat acute changes and only for short periods of time; and $SjvO_2$ or $PTiO_2$ measurements should augment these treatments to ensure adequate oxygenation.

Decompressive Craniectomy

Although surgical indications will be addressed in subsequent chapters, decompressive craniectomy for treating refractory intracranial hypertension will be discussed briefly here. Decompressive surgical procedures remain controversial, but there is some evidence that they may reduce mortality rates. For example, Gower et al. reported a reduction in mortality from 80 to 40% in patients undergoing subtemporal decompression in the face of refractory intracranial hypertension. The “Guidelines for the Surgical Management of Traumatic Brain Injury” recommend the following: “Decompressive proce-

dures, including subtemporal decompression, temporal lobectomy, and hemispheric decompressive craniectomy, are treatment options for patients with refractory intracranial hypertension and diffuse parenchymal injury with clinical and radiographic evidence of impending herniation".

Two ongoing clinical trials, the Rescue-ICP (British Medical Research Council) and the DECRA (Australian Medical Research Council), should clarify the role of this treatment in the next few years.

Barbiturate Coma

Barbiturate use is considered the last line of treatment options for patients with refractory intracranial hypertension. Its use may be beneficial due to the action of different mechanisms, including free radical scavenging, lowering of cerebral metabolic rate, cerebral vasoconstriction in uninjured areas shunting blood to injured areas, calcium homeostasis, and lysosomal stabilization. Although routine use of barbiturates in unselected patients has not been shown to reduce morbidity or mortality after severe head injury, Eisenberg et al., in a randomized multicentre trial, showed a two-fold greater chance of controlling ICP in patients with refractory intracranial hypertension when barbiturate coma was induced [96].

Since barbiturates can cause profound hypotension, and neurologic exams cannot be performed during its use, patients with cardiovascular instability are not usually candidates. Pentobarbital is the most common agent, and systemic monitoring with Swan-Ganz catheters is recommended. Barbiturates can be useful in a select group of patients however, and those with sustained refractory intracranial hypertension likely have no other option.

Hypothermia

Studied and used intermittently for decades, hypothermia is attracting renewed interest. Therapeutic moderate hypothermia (32-35°C) has been shown to lower ICP and has been linked to improved outcome after TBI [97,98]. Hypothermia reduces CBF, metabolism, and inflammation, much akin to barbiturate use. At our institution, we treat most severe head injuries with 48-72 hours of moderate hypothermia, instituted as soon as possible after the injury.

36.8 Conclusions

Traumatic brain injury is common worldwide; treatment outcomes continue to improve through continued research and clinical advances. The trauma victim should be rapidly identified, stabilized and transferred to a trauma care facility where care should be smoothly transferred to an awaiting multidisciplinary team ready to combat all possible injuries. Rapid cardiovascular stabilization, radiographic diagnosis, and intervention should be the goal in every case. Treatment in the ICU should continue with the same vigilance and attention, as many outcomes continue to be determined by ICU management. Multi-modality neuro-monitoring continues to expand through information and randomized controlled trials, and new product developments and improvements. Most modalities on their own do not paint a clear portrait, but when combined the synergy of multi-modality monitoring has the potential for the sum to be greater than the parts. All of these products show great potential for application in appropriate contexts and interventions. Their wider acceptance may ultimately lead to better patient outcomes.

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37 Prognosis in Traumatic Brain Injury

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37.1 Introduction

37.1.1 Definition

Traumatic brain injury (TBI) is caused by a blow or jolt to the head or a penetrating head injury that disrupts normal brain function. TBI is also referred to as traumatic head injury which can involve any traumatic injury to the head, face or skull and may or may not be associated with a TBI.

37.1.2 Pathophysiology

Primary injury occurs immediately after the impact; this is followed by a secondary injury which, some authors believe, is responsible for part of the neurological damage observed in TBI. Edema formation, both vasogenic and cytotoxic, in a rigid structure such as the skull is followed by increased intracranial pressure (ICP) once the compensatory mechanisms are surpassed. The increased ICP reduces cerebral perfusion and the consequent ischemia generates further neurological damage.

37.1.3 Severity

TBI is a heterogeneous condition encompassing a wide range of manifestations from minor symptoms to profound coma. The Glasgow Coma Scale (GCS), the standard method for evaluating level of consciousness, comprises three different domains (motor, verbal and ocular). Adding the different components on the GCS, the total scores can range between 3 and 15 points (Table 37.1), wherein a GCS score ≤8 indicates severe TBI, a GCS score between 9 and 12 moderate TBI, and a GCS score ≥13 mild TBI.

	Score
Eye opening	
Spontaneous	4
To sound	3
To pain	2
None	1
Total eye score	1 to 4
Motor response	
Obeys commands	6
Localising	5
Normal flexion	4
Abnormal flexion	3
Extending	2
None	1
Total motor score	1 to 6
Verbal response	
Orientated	5
Confused speech	4
Words	3
Sounds	2
None	1
Total verbal score	1 to 5
Total GCS score	**3 to 15**

Table 37.1. Glasgow Coma Scale.

37.1.4 Mechanism

TBI can be classified as closed or penetrating. While closed TBI often results from road traffic accidents, penetrating TBI is more commonly the result of gunshot wounds. Some studies have shown that penetrating TBI is associated with a worse outcome. For example, Peek-Asa et al. studied 795 patients with moderate or severe TBI. After adjusting for GCS, age, gender, and presence of multiple trauma, the patients with penetrating injuries had an odds ratio of 6.6 (95% CI 3.9-11.1) for mortality compared to those with closed injuries.

37.1.5 Structural Damage

Structural damage can be assessed by neuroimaging (computed tomography – CT). It can be divided into diffuse axonal injury, focal contusions and intracranial bleeding. The latter can also be classified according to its location within the cranium. Epidural hematoma refers to collection of blood between the skull and the outer layer of the meninges (the dura mater) and is usually caused by a tear in the middle meningeal artery. Subdural hematoma refers to collection of blood between the dura mater and pia layers and has a typical crescent-shaped appearance on imaging scans. Subarachnoid hemorrhage is the accumulation of blood in the subarachnoid space and intraparenchymal hemorrhage occurs within the brain parenchyma.

37.1.6 Outcomes

In-hospital mortality and disability at 6 months are the most frequently used outcome measures in TBI research. According to the International Classification of Functioning, Disability and Health (ICF), disability can be defined under a biopsychosocial model that includes biological, individual and social perspectives on health. Disability includes: a) impairments (problems in body functions); b) activity limitations; and c) participation restrictions. Different scales have been developed for assessing disability after TBI. The most widely used in TBI research is the Glasgow Outcome Scale (GOS) devised more than 30 years ago. This scale reflects disability in terms of activity limitations and participation restriction rather than impairment. It encompasses five categories: death; vegetative state; severe disability; moderate disability; and good recovery. In randomised clinical trials (RCTs), it is generally dichotomized into favourable (moderate disability, good recovery) and unfavourable outcome (severe disability, vegetative state, death). The GOS assesses how well patients function in their daily social interactions and is generally completed 6 months after hospital discharge.

The fact that one of the main outcomes in clinical trials of TBI patients is measured at 6 months introduces a potential source of bias, as loss to follow-up is a common problem in this population. A 1998 survey of TBI trials found an average loss to follow-up of 19% at 6 months. Loss to follow-up reduces the study size, rendering effect estimates to less precise, and may introduce bias. Loss to follow-up appears to be particularly common in TBI trials, possibly because they mostly involve young males from disadvantaged social groups who are geographically highly mobile. At the moment there is no disability outcome measured at hospital discharge that can predict long-term disability. Such a measure could be potentially useful when dealing with loss to follow-up, for informing interim analysis, and could also be useful in clinical practice when communicating with patients and their families.

37.2 Prognosis

37.2.1 Definition

Prognosis, (from the Greek *pro* meaning before and *gnosis* meaning knowledge) is defined as "the result of looking forward". In the context of clinical epidemiology, prognosis can be defined as "the probable course and outcome of a health condition over time" or as "the future risk of adverse outcomes among people with existing disease".

Importance of Prognosis in Clinical Practice

Clinical practice involves three main activities: identifying disease (diagnosis); treating disease (therapy); and predicting disease course and outcome (prognosis). Although these three activities are interrelated, distinctions between them are made in clinical research. Prognosis-related research is considered to be the one most neglected.
Prognosis was historically one of the most important activities of medical practice. Up until the late 19th century, 10% of the content of medical textbooks was dedicated to prognosis; however, by 1970 this had decreased to almost zero. Predicting the future was traditionally the task of both priests and doctors, but with the advent of effective therapies the dominance of the clinical encounter shifted to diagnosis and therapy. Nonetheless, prognosis research has recently begun to attract increasing interest.[25]
Among the reasons for this resurgence, Christakis proposed:

- Interest in human terminal care and the decision of withdrawing or not life support from critical patients.
- Avoidance of futile treatment for reasons of justice or costs.
- Availability of new technologies (e.g., genetic testing and biomarkers).
- Increasing emphasis on patient autonomy.
- Increasing prevalence of chronic diseases.

37.2.2 Prognostic Models

Definition

Outcome prediction studies come under a variety of names: prognostic models; prediction models; risk scores; prognostic indices; clinical prediction rules; clinical prediction guides; and clinical decision rules. According to some authors, the term "clinical decision rules" applies only to those models that also provide a diagnostic or therapeutic recommendation. Throughout this chapter I will use the term "prognostic model" will be used and it can be defined as the "mathematical combination of two or more patient or disease characteristics to predict outcome".

Performance of Prognostic Models

The performance of prognostic models refers to how "accurate" a given model's predictions are in relation to observed data. According to Rothman, "accuracy in estimation implies that the parameter that is the object of measurement is estimated with little error". In the particular context of prognostic models, accuracy has two main components: calibration and discrimination.
Calibration refers to the agreement between predicted and observed probabilities. If, for example, according to the model, TBI patients with certain characteristics have a probability of mortality of 30%, it would be expected that 30 out of 100 patients with such characteristics would die if the model were perfectly calibrated. Calibration can be mea-

sured in different ways: graphically by plotting observed against predicted outcomes or with a statistical test such as the Hosmer-Lemeshow test. This test compares the observed number of people with events within risk groupings (e.g., deciles of risk) with the number predicted by the model. A small p value implies lack of fit.

Discrimination, on the other hand, is a measure of how well a given model separates those who develop the outcome from those who do not. It is generally measured with the area under the receiver operator curve (ROC) or the C statistic. A ROC is constructed by plotting pairs of true positive rate (sensitivity) and false positive rate (1-specificity) for several cut-off values of probability of the outcome. The area under the ROC can be interpreted as the probability that a randomly selected person with the outcome will have a higher predicted probability than a randomly selected person without the outcome. For example, if a model has an area under the ROC (or C statistic) of 0.7, this means that the model will estimate a higher probability of the outcome for subjects with the outcome 70 out of 100 times if we choose a random pair of subjects with and without the outcome.

The relative importance of calibration and discrimination will depend on the intended application of the prognostic model. For example, calibration of the model will be more relevant for counselling an individual patient, while discrimination could be more important for triage in a setting with limited resources.

In addition to the measures of discrimination and calibration, we might be interested in performance measures for specific thresholds when a clinically relevant cut-off is already established. The accuracy rate (or correct classification rate) is calculated as (true positive + true negative)/total and the complement that is the error rate (misclassification rate) that is defined as (false positive + false negative)/total. The problem with these measures is that equal weight is given to positive and negative results, whereas false negatives are generally more important than false positives. Furthermore, the accuracy rate will be high, by definition, for a frequent or infrequent outcome. For example, if the average mortality for a condition is 7%, the accuracy rate would be 93% if the model classifies all the patients as survivors.

More recently, new measures such as the net reclassification improvement (NRI) have been proposed. The NRI has four components: the proportion of individuals with events who move up or down a category and the proportion of individuals without events who move up or down a category. The NRI is obtained by combining the four components, but they should also be reported separately.

Finally there are also overall performance measures such as the R^2, which is the amount of explained variation in the outcome explained by the model, and the Brier score which is a measure of the difference between actual outcomes and prediction. These measures do not distinguish among the different performance components (calibration and discrimination), so they are not very useful.

Inaccuracy of Clinical Prediction

Given the lack of interest in prognosis, medical training in this area is weak. So it is not surprising that doctors feel poorly prepared and that they often disagree or are inaccurate in their predictions. Numerous studies have shown that physicians make errors when formulating a prognosis. In many of these studies the term accuracy is used in the more general epidemiological sense (measured with little error), and they do not necessarily use the standard specific measures of accuracy described above for evaluating prognostic models.

In a systematic review comparing physicians' clinical predictions of survival in terminally ill cancer patients with actual survival, the authors found eight studies (involving 1563

subjects) and reported that the median clinical prediction of survival was 42 days and the actual median survival was 29; overall, there was poor agreement (weighted kappa 0.36) between clinical prediction and actual survival.
In a cohort study involving 16 Dutch nursing homes and 515 terminally ill non cancer patients, the authors compared physicians' predictions with actual survival. The physicians were asked to predict death in the following periods: 1 week (0 to 7 days); 8 to 21 days; and between 22 and 42 days. The positive predictive value of physicians' predictions was high for those patients expected to die within 1 week (92%), but it much lower for patients who were expected to die within 8 to 21 days (16%) or within 22 to 42 days (13%).

37.3 Prognosis in Traumatic Brain Injury

37.3.1 Potential Role of Prognosis in TBI

Potential Role of Prognostic Models

Prognostic information could be potentially useful for decision making. Taking into account that most TBI cases occur in low and middle income countries, accurate prognostic information could be of paramount importance. The human brain is hard put to collect and summarize quantitative data for making predictions and even more so in emergency situations such as the treatment of TBI patients. Because common problems arising in emergency situations, e.g., stress, fatigue, poor communication, and interruption of thinking, are all exacerbated by the need to take rapid decisions, prognostic models could play a useful role in the management of TBI patients.
In the context of TBI, clinical prediction models instead of clinical decision models would be more appropriate because of the lack of evidence of effective interventions according to baseline risk. Nonetheless, clinical prediction models still have the potential to influence TBI management. As mentioned before, Murray et al. demonstrated that the introduction of computer-based outcome prediction altered TBI patient management. The potential impact of accurate prognostic information could be particularly important in low and middle income countries where resources are limited.
Furthermore, in such a critical setting, accurate and consistent prognostic information provided by a prognostic model may also be helpful for counselling patients and relatives. It has been shown that physicians change their own predictions when they need to communicate them to patients or relatives. Therefore, the use of prognostic models will not only result in more accurate predictions but will also increase the consistency when communicating with patients and their families.

Potential Role of Explanatory Prognosis Studies

The identification of prognostic variables in causal pathways could inform the design of RCTs of potential interventions. This is particularly important in the context of TBI research where evidence for effective interventions is lacking. There are two main pathophysiological mechanisms to be interfered after TBI. The first is related to the inflammatory response. Numerous trials have investigated inflammatory response (neuroprotection studies), but no evidence of a clinical effect has been found to date. The only trial large enough to detect a plausible clinical effect, the CRASH (Corticosteroid Randomisation After Significant Head Injury) trial, reported an increase in mortality. The second potential pathway of intervention is related to intracranial bleeding. Although there is some evidence that intracranial bleeding is associated with worse prognosis, its

relationship is not well characterized. Explanatory prognosis studies could shed light on this association, which would be useful to inform the design of future trials.

37.3.2 What is Already Known About Prognosis in TBI

Individual Prognostic Factors

The Brain Trauma Foundation conducted a systematic review of individual early indicators of prognosis in severe TBI. The authors evaluated each study in the systematic review according to criteria intended to establish study strength. These criteria included:

- Twenty-five or more patients in the series with complete follow-up.
- Outcomes measured – Glasgow Outcome Scale or Mortality – at 6 months or more.
- Data gathered prospectively, although retrospective examination from a database created for an ongoing cohort of patients could be used.
- Glasgow Coma Scale score measured within 24 hours.
- Appropriate statistics (e.g., multivariate analysis) used to include adjustment for prognostic variables.

According to these criteria, the evidence of prognosis was:

- Class I: Those papers containing all of the above characteristics.
- Class II: Those papers containing four of the five characteristics, including prospectively collected data.
- Class III: Those papers containing three or fewer of the above characteristics.

They also constructed 2 X 2 tables and evaluated the positive predictive value for mortality for each potential predictor.

The evidence reported for each of the most important predictors is described below.

Glasgow Coma Scale: Class I evidence of an increasing probability of poor outcome with a decreasing GCS in a continuous, stepwise manner. Since its introduction in 1974, the GCS has consistently shown a correlation with outcome: the lower the score, the worse the prognosis. Yet some controversies remain. For example, the type of relationship with outcome (linear or non linear) and the influence of timing of GCS measurement on its validity. It has been suggested that with more intensive pre-hospital management, which includes sedation and intubation, a valid GCS score is more difficult to obtain. Despite these concerns, the GCS score remains an important predictor in TBI. The motor component of the GCS has also been found to be associated with outcome.

Age: Class I evidence of an increasing probability of poor outcome with increasing age in a stepwise manner. It is well established that older age predicts poor outcome after TBI, which could be related to an increased risk of intracranial hematoma and a decreased capacity for repair of the brain with age. In addition, as in any other condition, it is possible that the worse prognosis associated with age is related to concomitant comorbidities. A meta-analysis evaluating the relationship between age and poor outcome in TBI patients reported that this relationship was better expressed as a linear and quadratic term and that the best fitting threshold was 40 years.

Blood pressure: A systolic blood pressure <90 mmHg was found to have a positive predictive value of 67% for poor outcome. Hypotension, defined as a systolic blood pressure <90 mmHg, is associated with a poor prognosis. Early hypotension appears to exacerbate the development of intracranial hypertension. A single episode of hypotension has been associated with a doubling in mortality.

Pupillary light reflex: Class I evidence of a positive predictive value of at least 70% for poor outcome was reported for bilaterally absent pupillary light reflex. Abnormalities of the pupillary light reflex are an indirect measure of herniation and brainstem injury.

Dilation and fixation of one pupil indicates herniation, while bilaterally dilated and fixed pupils reflect brainstem injury. It has been estimated that one fixed pupil is associated with a mortality of 54%, whereas patients with bilateral fixed pupils have twice the mortality (90%). Direct oculomotor trauma should be excluded when considering the prognostic information of pupil abnormalities.

CT Scan characteristics: Class I and Class II evidence of a positive predictive value of at least 70% for poor outcome was reported for abnormalities on the first CT scan, Traumatic Coma Data Bank (TCDB) CT classification, compressed or absent basal cisterns, and traumatic subarachnoid hemorrhage. Different CT classifications have been proposed as predictors of unfavourable outcome in TBI. The TCDB (or Marshall) classification (Table 37.2) is the most widely used and has been shown to be associated with increased mortality in the majority of studies but not in all.

The following individual CT characteristics have been shown to be associated with higher mortality: midline shift >5 mm, compression and obliteration of the basal cisterns.

Intracranial bleeding is divided into extracerebral (epidural, subdural and subarachnoid) and intracerebral or parenchymal. All types of intracranial bleeding are associated with a worse prognosis. Although some studies have shown an association between the size of intracranial bleeding and prognosis, the empirical evidence is limited, most studies having small sample sizes and restricted populations. The further subdivision between evacuated and non-evacuated hematomas proposed in the TCDB classification is criticized by some authors because, so they argue, it could be influenced by differences in patient management between centres. Recently, it has been proposed that combining individual CT predictors is preferable to using the TCDB classification for prognostic purposes.

Other predictors not included in the Brain Trauma Foundation Review are genes and biomarkers.

Genes. The presence of the apolipoprotein E4 (APOE4) allele has been associated with poor outcome after TBI. A recent systematic review identified 14 cohort studies involving 2527 subjects. Only seven studies (1868 subjects) presented dichotomous data on the GOS and could be included in the meta-analysis. The APOE4 allele was significantly associated with a poor outcome after TBI (relative risk [RR] = 1.36, 95% CI 1.04-1.78) However, the risk of bias was high in the majority of the studies, with only two having assessed outcome blinded to genotype and a follow-up larger than 80%.

Biomarkers. The protein S100B is a marker for brain damage and has been proposed as a marker for poor outcome after TBI. A review of 18 studies evaluating this association reported that patients with high levels of S100B may have a higher risk of disability. However, this systematic review had many limitations as it did not evaluate the risk of bias of the studies included nor did it address the probability of reporting bias.

Injury	Description
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift 0-5 mm and/or lesions; densities present; no high or mixed densities lesion >25 cc; may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0-5 mm; no high or mixed densities lesion >25 cc
Diffuse injury IV (shift)	Midline shift >5 mm; no high or mixed lesion >25 cc
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High or mixed lesion >25 cc not surgically evacuated

Table 37.2 **Marshal CT classification.**

the population to moderate and severe TBI. They found 31 studies and their conclusions were very similar to the those reported in this chapter. Most prognostic models included GCS, age and pupil reactivity, they were developed from small sample sizes, and they were rarely externally validated or presented in a practical way.

37.4 Prognostic Models

Since the publication of a prognostic model in TBI patients by Jennet et al. 30 years ago, many other prognostic models have been devised. Nevertheless, no model is universally accepted or widely used and a comprehensive review of all models is still lacking. A recent systematic review found that although studies on prognostic models for TBI are numerous, their quality is relatively poor. In addition, they are rarely validated on external populations or presented to physicians in a user-friendly way. Furthermore, few are developed using populations from low and middle income countries where most trauma events occur. It is noteworthy that only 2% of the models included patients from low-income countries, although 90% of trauma events occur in these countries. Although biologically prognostic factors should be the same worldwide, it is reasonable to consider that the baseline risk and the strength of the association could differ depending on the medical care received. This difference could affect the accuracy of the prognostic models in different settings.

GCS, age and pupil reactivity were the most common variables analyzed as predictors, whereas GOS and mortality were the most common outcomes investigated. Multiple logistic regression was the multivariable analysis most frequently used.

Several limitations in the quality of the models were found. The majority did not include a thorough discussion of the rationale for including predictor variables. Only a minority had a loss to follow-up of less than 10%. Potentially this is an important limitation as the loss to follow-up could be related to prognosis and could lead to bias. Furthermore, only four models handled the missing data by using statistical imputation. In the multivariable analysis, automatic procedures (stepwise) were quite common in logistic regression. There is no agreement on the appropriateness of this strategy. This is reflected by the conflicting recommendations for quality assessment in prognostic studies; while the use of stepwise was considered as good quality in one study, in another it was considered as a flaw. One of the limitations was that most studies did not explicitly consider the clinical criteria to enter the variables in the model beyond the automatic procedures. Interactions were hardly ever explored, although this is strongly recommended in multivariable analysis [2].2 Another common weakness was the lack of power of the models. Most were derived from small samples though it is well established that large samples are required for reliable selection of predictors. Only one third included at least 10 events per variable. It has been proposed that this is the minimum ratio of events to variables large enough to allow an adequate precision of the estimates.

It is also important to report how well the model works and to report performance measures. Remarkably, not all the studies reported a measure of discrimination and only a few reported a measure of calibration. Even when a discrimination measure was reported, less than half presented confidence intervals to provide readers with an estimation of its precision.

For a model to be generalizable to other populations, it is important to conduct an external validation. Only seven models (three reports) developed and validated a model, but in only two of them was the validation performed on patients from a different centre.

Finally, to be useful, the method to estimate prognosis should be clearly reported and, to be clinically practical, it should be user-friendly. Only half of the models clearly explained how to obtain the prognostic score, and only one tenth were reported in such a way that could be easily applicable in a clinical setting. None of the models evaluated the clinical credibility of the different presentations.

Two models developed by Hukkelhoven et al., one for mortality and the other for unfavourable outcome, were those which met most of the methodological and clinical criteria. A thorough discussion of the predictors was included, the missing data were handled appropriately, the assumptions of the model were tested, an external validation in two different populations was performed, and the discrimination and calibration measures were presented. The sample size was 2269 patients and 1542 patients for the validation. Furthermore, a simple score chart was developed to estimate the outcome probability. The predictors included in the final model were age, GCS motor score, pupil reactivity, hypoxia, hypotension, CT scan abnormalities, and the presence of traumatic subarachnoid hemorrhage. The discrimination of the model was >0.8 for both outcomes, however, the calibration was poor. The limitations were that the models included only patients from developed countries and were restricted to moderate and severe TBI cases.

37.5 CRASH Prognostic Models

Using variables that are available at the bedside, the CRASH investigators have developed prognostic models for predicting two clinically relevant outcomes in TBI patients. The models have good discrimination and good fit using internal validation. The models for high-income country (HIC) patients with moderate or severe TBI also showed acceptable discrimination when externally validated.

The basic model includes the variables: age; GCS; pupil reactivity; and major extracranial injury. The CT model includes the same variables as the basic model plus the CT scan findings: petechial hemorrhage, obliteration of the third ventricle, midline shift, subarachnoid hemorrhage, and non evacuated hematoma. After finding evidence for interaction between some of the predictors and the outcome, different models for HIC and low- and middle-income countries (LMIC) were developed. All the models are posted on the internet (Figure 37.1).

For selecting the variables those for which there was strong evidence of an association with the outcomes in both regions were selected, so that a common core of variables could be selected. The rationale for this strategy was that a common model for the different regions and outcomes would be simpler to use. In these models, the variable “hours since injury” was left out, because there was strong evidence of an association in the LMIC but not in the HIC.

On the other hand, for the variable “presence of major extracranial injury” there was strong evidence of an association with 6-month unfavourable outcome in

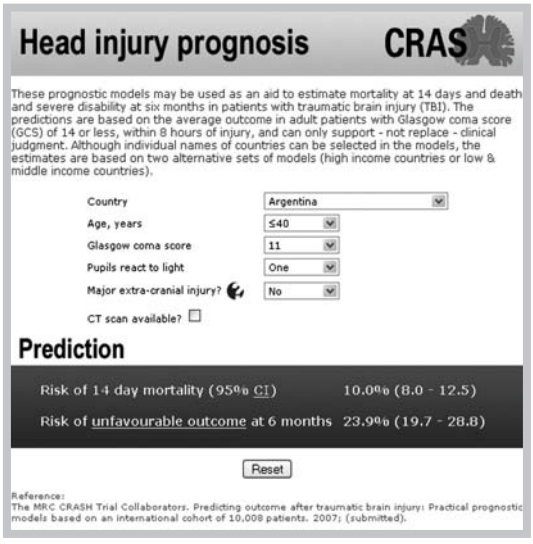

Figure 37.1. Screen shot of the CRASH model.

the two regions with both models, but there was weaker evidence for an association with mortality in the LMIC. In the basic model the odds ratio (OR) was 1.15 (95% CI 0.99-1.34) and the strength of this association weakened in the CT model (OR 1.08, 95% CI 0.91-1.28).Similarly, there was strong evidence for an association with the presence of petechial hemorrhages on the CT scan in the LMIC but it was weaker in the HIC, so this variable was kept in all the models.

37.6 Individual Predictors

37.6.1 Demographic and Clinical Predictors

Age

Increasing age was associated with worse outcomes, but this association was most apparent after 40 years of age. A similar threshold has been reported elsewhere. In their systematic review, Hukkelhoven et al. found the best fitting threshold for age was 39 years; however, they reported that the best way to analyse age was a linear and a quadratic term. However, it does not seem biologically plausible that the increased risk associated with age only starts after 40 years of age. However, it is unlikely that a different way of analysing this variable would have changed the main conclusions of the study. Whatever way is chosen to describe this variable, there is consistent evidence that a positive association exists between age and poor outcome. Plausible explanations for this relationship include extracranial comorbidities, changes in brain plasticity, or differences in clinical management associated with increasing age. Further research is needed to explore these mechanisms.

Glasgow Coma Scale

Total GCS score showed a clear inverse linear relationship with mortality. The finding that mortality was lower in patients with a GCS score of 3 than in those with a GCS of 4 may be due to GCS scores of sedated patients being reported as GCS 3. Previous studies have suggested that total GCS could have become less useful as a predictor in an era of early sedation and pre-hospital intubation. In this study, however, GCS still has an acceptable discriminative ability, particularly in the LMIC. When GCS was analyzed as a categorical variable (mild, moderate and severe), although it showed an acceptable discrimination, it was lower than the discrimination of GCS as a continuous variable.
In terms of discrimination, total GCS was superior to each of the individual components (motor, eye and verbal). Among the different GCS components, the motor item was the most discriminative. In a recent review of the predictive ability of GCS in TBI patients, the authors concluded that the motor component score has the same discriminative ability as the total GCS score. According to the findings of this study, however, total GCS is superior to the motor component in terms of discrimination.

Pupil Reactivity

In agreement with previous studies, the absence of pupil reactivity was a strong predictor of poor outcome. The effect estimate (odds ratio) for mortality was among the highest of all predictors. When measured with the Z score, however, it was only the third strongest predictor after age and GCS. This finding could be explained by random error, as the standard errors were larger due to the relatively low frequency of pupil abnormalities (6% with one pupil unreactive and 8% with both pupils unreactive).

Major Extracranial Injury

Patients with a major extracranial injury showed an increased risk of poor outcome. Other studies have shown an independent effect of extracranial injury. For example, Signorini et al. found that extracranial injuries as measured with the Injury Severity Score (ISS) were an independent predictor of mortality. Other studies have failed to report such an association. Nevertheless, it is well accepted that other variables which could be a consequence of presenting extracranial injuries, such as hypotension, are associated with poor outcome in TBI patients.

Hours Since Injury

Only patients from the LMIC who were randomised more than 1 hour after the injury had a higher risk of poor outcome than those randomised in the first hour. Although there is clinical consensus that TBI patients should receive rapid treatment after the injury, there is no empirical evidence demonstrating an association between time since injury and poor outcome. Furthermore, the CRASH trial cohort has limited information to evaluate this association, as only patients who were hospitalized within 8 hours of injury were included.

Cause of Injury

Cause of injury was not found to be an independent predictor of poor outcome. In a previous meta-analysis of 11 studies, the authors found that the cause "fall" was associated with increased mortality, but it did not remain as an independent predictor after adjustment for age. The only category found to be an independent predictor was "other", which was associated with a decreased risk in mortality when compared to the cause "road traffic accident" in the LMIC. Unfortunately, the "other" category includes a wide range of diverse causes, so it was not possible to disentangle the possible explanation for this finding.

Gender

There was no strong evidence for an association between gender and poor outcome. Although some studies have claimed a better outcome in female patients, a recent systematic review concluded that there is no evidence for a gender-related difference in outcome.

CT Scan Predictors

The majority of previous publications have used the CT Marshall classification to evaluate the predictive ability of CT findings; however, it has recently been shown analysis of an individual's CT predictors to be a better strategy. All abnormal CT findings, except for evacuated hematoma, were associated with poor outcome.

The CT category "obliteration of third ventricle or basal cisterns" was most strongly associated with poor outcome. This result is in keeping with the recent

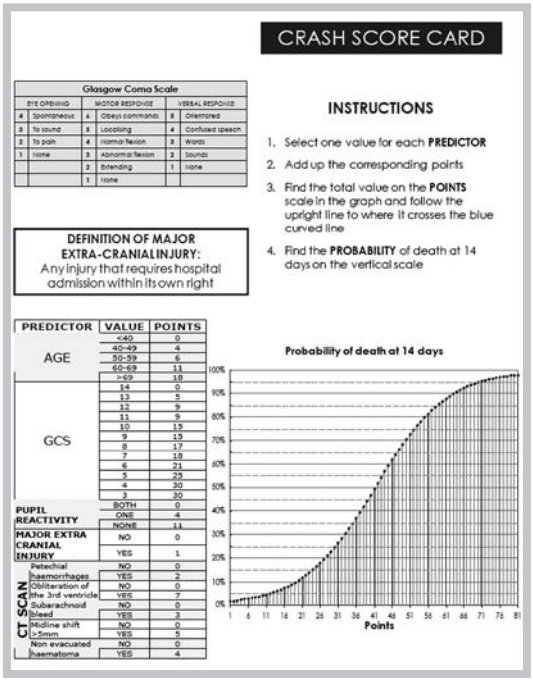

Figure 37.2. The CRASH score card.

findings that absence of basal cisterns is the strongest predictor of 6-month mortality. As previously reported, traumatic subarachnoid hemorrhage was found to be an independent predictor. The finding that a non-evacuated hematoma was associated with an increased risk of poor outcome is consistent with studies showing an increased risk of poor outcome with different types of intracranial hematoma. Unfortunately, the CRASH trial did not present enough data to explore this association in more detail (Figure 37.2).

37.6.2 Differences Between Patients From LMIC and HIC

Early Mortality

Patients from LMIC had a worse early outcome than those from HIC. Regional differences in TBI outcome between Europe and North America have been reported previously, but the difference in mortality between LMIC and HIC has not been explored.

The adjusted odds ratio for mortality at 14 days for LMIC patients versus HIC patients was 1.94 (95% CI 1.64-2.30). No conclusions about the causes for this difference can be drawn from the data presented in the CRASH trial. However, some findings could raise hypotheses to be tested in future studies. For example, LMIC patients arrived at the hospital later than HIC patients and a larger proportion had data on current GCS, a possible indicator that a smaller proportion of LMIC patients was intubated or sedated on hospital admission. These two findings indicate that treatment for LMIC patients is delayed longer. Furthermore, a lower proportion of LMIC patients underwent a CT scan, indicating that CT was not performed in some patients with potentially treatable lesions.

Unfavourable Outcome at Six Months

Another interesting finding was that although 14-day mortality was higher in patients from LMIC, there was no evidence for a difference in unfavourable outcome at 6 months. This could be because patients from HIC who did not die early had a higher frequency of disability or because disability at 6 months was measured with the GOS, the interpretation of which could vary between different settings.

Differences in the Strength of Association of Predictors

Another important finding was the difference observed in the strength of association between several important predictors and outcome. A recent study is the first study to report such differences according to whether patients are from HIC or LMIC.

Although GCS was a strong predictor of poor outcome in both regions, the authors have found that it had a higher discriminative ability in LMIC patients than in HIC patients. This might be due to differences in quality of care or because the low GCS scores reported for HIC patients reflected a greater use of sedation rather than TBI severity. In LMIC patients the GCS (measured as a continuous variable) had a C statistic similar to both the basic and the CT model, whereas the difference between the C statistic of the models and the GCS was larger in HIC patients.

The other variable that showed a different strength of associations according to the region was age. Increasing age was associated with a worse prognosis in HIC patients than in LMIC patients. This was because of the lower risks at younger ages in HIC, while HIC and LMIC patients have similar risks at older ages.

Some abnormal CT findings were stronger predictors in HIC compared to LMIC. This could be due to better technology and therefore more accurate CT diagnosis in HIC.

37.7 Comparison With Previous Studies

The systematic review reported above identified over 100 prognostic models for TBI patients, but methodological quality was considered adequate in only a few. Two of the more methodologically robust models showed similar findings to the CRASH models with good discrimination but worse calibration. They, too, included GCS, age, pupil reactivity and CT scan results as predictors but they did not include the presence of major extracranial injury, and none of them included patients from LMIC.

Subsequent to the publication of the CRASH prognostic models, the investigators from the IMPACT study, the database in which the CRASH prognostic models were validated, developed a series of prognostic models for TBI patients. The IMPACT dataset included 8509 patients with moderate and severe TBI from 11 studies conducted between 1984 and 1997 in HIC. They developed three types of models to predict mortality at 6 months, and unfavourable outcome at 6 months, as defined by the GCS. The three models developed were:

- A core model that included age, motor score component from GCS, and pupillary reactivity.
- An extended model that included the core model variables plus secondary insults (hypoxia and hypotension) and CT characteristics (Marshall CT classification, subarachnoid hemorrhage and epidural hematoma).
- A laboratory model that included the variables from the core and extended models, plus glucose and hemoglobin.

The core model was developed using the whole dataset (8509 patients), while the other two models used smaller samples as they were forced to restrict the sample to studies with the relevant variables.

The extended model was derived from 6999 patients and the laboratory model from 3554 patients. Because of missing values for some of the variables in the different studies, they used the method of chained equations to impute the missing data. A total of 5%, 13% and 8% of the values were imputed on the core model, the extended model and the laboratory model, respectively. For the internal validation, the area under the ROC was calculated with a cross-validation procedure, where each study was omitted in turn. The discriminatory ability of the models for predicting unfavourable outcome at 6 months in the internal validation ranged from 0.66 to 0.87, with the highest discrimination (0.87) reported for the extended model to predict mortality when evaluated in one of the observational studies.

The core and extended models were externally validated in 6681 patients with moderate or severe TBI from the CRASH trial. The area under the ROC for unfavourable outcome was 0.78 and 0.80 for the core and the extended model, respectively. The calibration was poor for all the models when assessed with the Hosmer-Lemeshow test ($p < 0.001$) and graphically. When they restricted their validation to patients from HIC, the discrimination did not change but the graphical display of the calibration for the extended model to predict 6-month mortality improved. The authors presented a simple score with an accompanying figure and also made the models available as a web-based calculator.

The models developed by the IMPACT study share some aspects with those derived from the CRASH trial. The variables included in the IMPACT core model and my included age, pupil reactivity and the GCS (although IMPACT models included the motor component, while CRASH trial included total GCS). Both CT models included subarachnoid hemorrhage as a predictor. A direct comparison of the strength of the association was not possible as the IMPACT study reported proportional odds logistical regression and

the effect measures are not comparable with the one derived from CRASH. Importantly for both studies, internal and external validation was performed. Finally, both studies attempted to make the models easily available to doctors worldwide with a web-based calculator and in a simple paper-based format. However, they presented some differences.

The models developed with data obtained from CRASH trial, were derived from patients from HIC and LMIC, while the IMPACT models were derived only from patients from HIC. Another difference is that the CRASH models were derived from a more recent period (1999-2004) than the IMPACT models (1984-1997). Also, the CRASH dataset had very few missing variables, while imputation methods were necessary to handle the extent of missing data for the IMPACT models. On the other hand, some of the IMPACT models included more variables which have also been shown to be strong predictors of poor outcome (i.e., hypotension, hypoxia, hemoglobin and glycemia). Finally, a common feature of the external validation for both studies was that the discrimination was acceptable, but the calibration was poor when assessed with the Hosmer-Lemeshow test.

37.8 Strengths and Weaknesses of This Study

Among the CRASH prognostic models strengths are the use of a well-described inception cohort of patients, prospective and standardised collection of data on prognostic factors, few missing data, very low loss to follow-up, and the use of a validated outcome measure at a fixed time following the injury. All of these factors provide reassurance about the internal validity of the models. The large sample size in relation to the number of prognostic variables examined is another particular strength.

With regard to its external validity, there are few prognostic models developed from LMIC patients. The models developed with CRASH dataset are the first with a large sample size and adequate methodology and included the complete spectrum of TBI patients ranging from mild to severe. The external validation confirmed the discriminatory ability of the models in patients from HIC and graphically showed good calibration for the CT model. Unlike most published prognostic models, my models. Finally, the data required to make predictions with the model are easily available to clinicians, and a web-based risk calculator was developed.

There are some limitations: the data from which the models were developed originate from a clinical trial and this could therefore limit its external validity. For example, the patients were recruited within 8 hours of injury and the accuracy of the models for patients evaluated beyond this time window cannot be estimated. Nevertheless, the CRASH trial was a pragmatic trial that did not require any additional tests and therefore included a sample of 'real-world' patients. Furthermore, not including other predictors such as hypotension and hypoxia. However, although these variables have been reported to be independent predictors, it has also been shown that they do not add much to the performance of prognostic models after most important predictors (age, GCS and pupil reactivity) are already entered into the model.

Another limitation was that the models validation came from HIC.

Furthermore, the variables "major extracranial injury" and "petechial hemorrhages" were excluded because they were not available in the IMPACT sample. However, neither of these variables were among the strongest predictors. The external validation showed good discriminatory ability, albeit somewhat lower than in the original data.

37.9 Implications

37.9.1 Implications for Patients in LMIC

Most of the burden of TBI is on LMIC countries where case fatality is high and resources are limited. Several predictors differed in their strength of association with outcome according to a country's income level, suggesting that it may be inappropriate to extrapolate from models based on HIC populations to poorer settings. Prognostic models developed with CRASH trial dataset, showed good discrimination and good calibration in this setting.
However, GCS used as a continuous variable demonstrated an acceptable ability to discriminate poor outcome in TBI patients from LMIC. When the discrimination was evaluated with categorical GCS, as is used in clinical practice (i.e., mild, moderate and severe), its discrimination was lower.
In terms of calibration, the models showed better agreement than total GCS between predicted probability and observed outcomes when analysed graphically, particularly for those patients with intermediate risk.

37.9.2 Implications for Patients in HIC

Basic and CT models showed good discrimination, and the latter showed the highest discrimination of all the models developed. The calibration of the models was good when evaluated with the Hosmer-Lemeshow test. Most importantly, the models kept an acceptable discriminative ability when externally evaluated, although the calibration, in particular for the basic model, was poorer.
Both models substantially increased the discriminatory ability of GCS. The CT model in particular showed very good calibration in the external validation in this setting.

37.9.3 Other Implications

These prognostic models have important implications in clinical decisions and can also inform research purposes, for instance, in the design and analysis of clinical trials, through prognostic stratification, or they can be used in clinical audits by allowing adjustment for case-mix.

37.10 Future Research

The differences between the prognostic models for LMIC and HIC patients are important. Although most of the burden of trauma occurs in LMIC, most research takes place in HIC. Very few prognostic models for TBI have been developed in LMIC. More research is therefore needed in the LMIC to obtain reliable data from these settings. An improved understanding of the differences between these regions might also clarify the mechanisms of predictors that are not immediately obvious when analysing a homogeneous population.
The models were developed and validated through a rigorous methodological process to ensure their internal validity. However, for prognostic models to be used, they need to be user friendly. Research into the different ways of presenting the models to physicians is needed to ensure that they are of practical use in the clinical setting.

As the CRASH models were developed using data from a clinical trial, further prospective validation in independent cohorts is needed to strengthen the generalizability of the models. The future challenge is to evaluate their impact on patient outcomes.

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38 Surgical Treatment of Spinal Cord Injury

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38.1 Introduction

Trauma-induced spinal cord injury (SCI) and the deficits in sensory and motor function associated with it constitute one of the most devastating of critical illnesses. The ensuing disability and impairment deeply undermine self-esteem and productivity, placing an enormous socioeconomic burden on the individual, the family and the community as a whole. The estimated incidence of traumatic SCI resulting in quadriplegia is 30-40 cases or 100,000 inhabitants per year, with 6000 new cases annually in Brazil, one new case per day in the State of Parana alone, and one person every week in the city of Curitiba. It predominantly affects young males (80%); the average age of patients in most published studies is around 25 years. The cervical spine is the most vulnerable segment, accounting for 50% of cases. The other 50% refer to the thoracic (29%), lumbar (15%) and sacral (4%) segments. The most frequent causes are motor vehicle accidents (approx. 60%), falls, including diving in shallow water (20%), urban violence (15%), sports (4%), and work-related accidents (1%). Only 5% of spinal injuries occur in children. In children less than 9 years of age, 67% of spinal injuries involve the upper cervical spine (occiput-C2). Unlike head trauma in adults, the mortality rate is higher in children, and the leading cause of death is related to injuries other than the spinal lesions. Early identification of traumatic SCI at the accident site is essential for optimizing the recovery of these patients. The identification of patients at risk is the first step in the pre-hospital care of SCI. Risk groups are:

- All victims of serious accidents.
- Trauma patients with loss of consciousness.
- Trauma patients with minor complaints about the spine (lower back or neck pain or muscle contracture) or the spinal cord (partial loss of sensation or numbness, weakness, paralysis).
- Signs suggestive of SCI: abdominal breathing, priapism.

Some 20% of all patients with SCI have a second serious spinal injury at another level not always accompanied by the primary SCI. Such patients often have other concurrent injuries either directly associated with SCI, including arterial dissection (carotid and/or spinal artery), or not related to thoracic trauma and/or abdominal pain.

Although the nature of SCI, its causes and consequences have been known since antiquity, and despite considerable advances in its treatment, the main obstacle that has remained since Hippocratic times is that the damaged neurons do not heal. Hence, the focus of therapy is injury prevention and rehabilitation.

In 1927 Cushing published a series of cases of cervical spinal trauma seen in soldiers during the First World War, reporting 80% mortality in the first 4 weeks, mainly due to respiratory tract infections or decubitus sores. These figures have changed considerably

since then. In a series published by this author of 230 patients treated for cervical subaxial fractures (C3-C8) over a 5-year period (1996 to 2000), the survival rate was 94%. That many survive with severe neurological sequelae argues for the creation of specialized rehabilitation centres, as has been done in some areas of the country.

The main advances in recent years have derived from a better understanding of the pathophysiological mechanisms underlying the genesis of SCI. Two types of injury are involved in determining neurological injury of the spinal cord: primary and secondary injury. Primary injury (passive) results from the kinetic forces to the spinal cord during the accident, causing loss of normal nerve impulse transmission and acute paralysis. The primary injury is composed of morphological, metabolic and electrolyte alterations. Morphological changes include: petechiae, hemorrhages, axonal swelling, rupture of the myelin sheath, ischemic endothelial injury, and hemorrhagic necrosis. The metabolic changes are mainly characterized by altered glucose utilization, with an increase in glucose consumption in the first hour after injury, anaerobic glycolysis due to the decreasing oxygen content in the tissues, the subsequent reduction in ATPase activity of the enzyme, and interference with the cell's energy production. This cascade of events leads to abnormalities in calcium, sodium and potassium electrolyte levels due to the abnormal flow of electrolytes into the cells and the release of metabolites and lysozymes.

Secondary injury, mediated by active cellular and molecular processes, occurs over the hours and days after the accident. It involves the activation of an inflammatory cascade, where post-traumatic ischemia leads to changes in calcium metabolism, formation of edema and free radicals, release of excitatory amino acids and endogenous opioids. This mechanism results in oxidation, lipolysis and cell death, and represents the main therapeutic window in spinal trauma.

38.2 Terminology

38.2.1 Standards for Neurological and Functional Classification of SCI

In response to disparate SCI classification schemes which hindered the interpretation of results and comparison across patient series and different types of treatment, the American Spinal Injury Association (ASIA) called together an interdisciplinary commission (in-

Point	Description	Explanation
A	Complete	No sensory or motor function preserved, including absence of anesthesia and anal contractions and anesthesia in segments S4-S5
B	Sensory incomplete	Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-5 or deep anal pressure) and no motor function is preserved more than 3 levels below the motor level on either side of the body.
C	Motor incomplete	Motor function is preserved below the neurological level and more than half of key muscle functions below the single neurological level of injury have a muscle grade <3 (grades 0-2)
D	Motor incomplete	Motor function is preserved below the neurological level and at least half of key muscle functions below the neurological level of injury have a muscle grade ≥3
E	Normal	If sensation and motor function as tested with the International Standards for Neurological Classification are graded as normal in all segments, and the patient had prior deficits

Table 38.1. ASIA (American Spinal Injury Association) Impairment Scale (modified from Frankel).

cluding experts from neurosurgery, orthopedics, physical rehabilitation medicine, physiotherapy and epidemiology) to unify the standards for SCI evaluation and to allow accurate communication between different health services. In 1992 the committee published its own classification system: the International Standards for Neurological and Functional Classification of SCI (ISNCSCI 3rd revised edition).
Through a systematic examination of specific dermatomes and myotomes, as described below, one can determine the segment affected by SCI. This test allows the definition of several indicators of neurological damage, for example: Neurological Level, Sensory and Motor Speed (right and left sides), Sensitivity Index (pain and sensitivity to light touch), Motor Index, and Zone of Partial Preservation.
The protocol developed by ASIA also introduced the ASIA Impairment Scale (AIS) (which replaces the modified Frankel classification) and the recommended Measure of Functional Independence (FIM), a new approach to assess the impact of SCI on activities of daily living and functions and to assess a patient's capacity and progress in rehabilitation (Table 38.1).

38.2.2 Sensitivity Examination

This exam involves testing the sensitivity of specific points (key points) in 28 dermatomes on the left and right sides of the body. In each of these key sensory points pain sensitivity (using a pin prick) and sensitivity to light touch (light touch with cotton) are examined. The perception of pain and sensitivity to light touch at each of the key points is scored on a scale of 0 to 2:

- 0: Absent.
- 1: Altered (or partial perception altered, including hyperesthesia).
- 2: Normal.
- NT: Not testable.

When one examines the perception of pain, the patient's inability to distinguish between blunt sensation (pin head) and the tip should be scored as 0 (absent). Table 38.2 shows the location of the key sensory points.

Point	Description
C2	Occipital protuberance
C3	Supraclavicular fossa
C4	Upper border of the acromion – clavicular joint
C5	Lateral border of the antecubital fossa
C6	Thumb
C7	Middle finger
C8	Little finger
T1	Medial (ulnar) from the anticubital fossa
T2	Apex of the axilla
T3	Third intercostal space (IC)*
T4	Fourth IC space (nipples)*
T5	Fifth IC space (between T4 and T6)*
T6	Sixth IC space (at the level of the xiphoid process)*
T7	Seventh IC space (half way between T6 and T8)*
T8	Eighth IC space (half way betweenT6 and T10)*
T9	Ninth IC space (half way between T8 and T10)*
T10	Tenth IC space (navel)*
T11	Eleventh IC space (half way between T10 and T12)*
T12	Midpoint of the inguinal ligament*
L1	Half the distance between T12 and L2
L2	Middle third of anterior thigh
L3	Internal femoral condoyle
L4	Internal malleolus
L5	Dorsum of the foot at the level of the third metatarsophalangeal joint
S1	Outer edge of the calcaneus
S2	Midline of the popliteal fossa
S3	Ischial tuberosity
S4-S5	Perianal area (evaluated as a single level)

Table 38.2. Key sensory points.
* Indicates that the point is in the middle clavicular line

Assessment of postural sensation and perception of pressure or pain is considered optional for in-depth evaluation of SCI. If examined, it is recommended to classify them using the same sensitivity scale (absent, altered, normal). When examining an extremity, the index finger and the first toe on each side of the body should be tested.
Besides these key sensory points, during the digital rectal exam, you should try to assess the deep anal pressure, which will be used along with the perianal sensitivity score (S4-S5) for determining whether the injury is complete or incomplete.

38.2.3 Motor Examination

This exam tests 10 specific muscles (key muscles) on both sides of the body graded on a 6-point scale (Table 38.3). Table 38.4 lists the key muscles to be examined.
In addition to the examination of these muscles, the external anal sphincter should be examined for contraction around the finger of the examiner and the voluntary anal contraction classified as present or not (yes or no on the form). The latter information is used exclusively to determine if the injury is complete or incomplete.
As an option, other muscles should be examined to assess motor function in SCI; however, the results are not used to determine the motor index, motor level, or complete injury. It is suggested that the following muscles be examined: diaphragm, deltoid, and crural biceps. Muscle strength is scored as absent, weak or normal.

Point	Description	
0	Without contraction (total paralysis)	
1	Visible or palpable muscle contraction without movement	
2	Active movement without gravity	
3	Active movement against gravity	
4	Active movement against gravity	• 4- light resistance • 4 moderate resistance • 4+ high resistance
5	Normal active movement against gravity and sufficient resistance to be considered normal if inhibiting factors (i.e., pain, disuse) are not present	
NT	Not testable	

Table 38.3. The 6-point scale.

38.2.4 Sensitivity Index and Sensitivity Level

The sensory scores (0, 1 or 2) noted on the grid generate four values: pin prick right and left sides and light touch right and left sides, with a maximum score of 56 for each side. Adding the pin prick and light touch scores for both sides of the body yields the total pin prick and light touch score (maximum 112 each). The sensory index is a numerical way to document altered sensory function, allowing for comparison and analysis of the patient's evolution over the following days.
The sensory level on each side of the body is defined as the most caudal dermatome where the sensory score is normal (score=2) for both pin prick and light touch. The zone of partial preservation (ZPP) is defined as the region on each side of the body where sensory function (not absent) is present but not normal (score=1).

	Muscle
C5	Elbow flexors (biceps)
C6	Wrist extensors (extensor carpi radialis brevis and longus)
C7	Elbow extensors (triceps)
C8	Finger flexors (distal phalanx of middle finger)
T1	Finger abductor (little finger)
L2	Hip flexors (ileopsoas)
L3	Knee extensors (quadriceps)
L4	Ankle dorsiflexors (tibialis anterior)
L5	Long toe extensors (extensor hallucis longus)
S1	Ankle plantar flexors (triceps surae)

Table 38.4. Muscles to be examined.

38.2.5 Motor Index and Motor Level

The test grades motor function of the right and left sides of the body. The total scores are obtained by summing the scores of the different muscle groups (0-5) on each side of the body. The motor index provides a means to document motor function numerically.
Determination of the motor level differs from that used to define the sensory level. This is due to the fact that most muscles are innervated by a single peripheral nerve formed by nerve roots from more than one nerve segment (usually two segments). So the selection of a muscle or a muscle group, or a key muscle in this case, to represent a single spinal segment is a simplification, which is the idea that subsidies in any muscle, the innervation by one segment and the absence of innervation by another segment will result in a weakened muscle. Briefly, a muscle with function graded 3 at least is considered to have intact innervation from the proximal segments. To determine the motor level, the proximal key muscle should have a grade of 4 or 5, since this muscle has two intact segments that innervate it. For example, if there is no response of the key muscles of C7 and C6 has a grade of 3, then the motor level of the body that was examined is C6, and C5 for the muscle to do so, will have a grade of at least 4.
The examiner will determine if the muscle with a grade 4 is completely innervated. This is necessary because in some patients several factors could inhibit maximum effort during the clinical examination at certain stages after injury. Examples include pain, patient position, hypertonicity and disuse. A grade 4 should not be considered normal if the examiner finds that none of these factors inhibiting pain is present and the patient is doing his utmost and still has only grade 4.
In conclusion, the motor level (the lowest motor segment with normal function, which can differ for the two sides of the body) is defined as the lowest key muscle that has at least grade 3, if the muscles in the segment above this level are classified as normal (grade 4 or 5).

Type of Injury

Complete Injury

There is no preservation of motor or sensory function below the neurological level of injury, including lack of voluntary anal contraction and sensation of the anal and perianal region. The ASIA classification emphasizes the importance of examining perineal sensation and anal contraction in the diagnosis of complete injury, because they are the most sacral fibres in relation to the internal somatotopic organization of the tracts and the most protected from injury. About 3% of patients with complete injury at initial examination will recover some function within 24 hours. The persistence of complete injury over 24 hours indicates that the probability of recovery of distal function is practically nil.

Incomplete Injury

Any residual sensory or motor function below the injury must be included in the concept of distal protection:

- Preservation of sensation (including sense of position) or movement in the lower limbs (including isolated voluntary finger flexion(s) of the foot).
- “Sacral preservation” preserved perianal sensitivity (sensitivity in the union of perianal skin and mucosa, as well as deep anal sensitivity) and counter-voluntary external anal sphincter on digital examination.
- For the characterization of incomplete injury, the contraction is voluntary and not an anal reflex. An injury should not be considered incomplete if there are preservation, isolation, and sacral reflexes (e.g., bulbocavernous). Priapism is a sign often associated with complete injuries.

Types of incomplete injury are:

- Brown-Séquard syndrome (ipsilateral proprioceptive and motor and sensory loss of contralateral pain and temperature).
- Central cord syndrome (occurs almost exclusively in the cervical region, with preservation of sacral sensitivity and greater weakness in the lower than the upper region).
- Previous marrow syndrome (produces a loss of motor function and sensitivity to pain and temperature, while preserving proprioception).

The term "**spinal shock**" has been used to characterize two different situations which occur simultaneously in SCI:

- Hypotension (shock) is observed in patients with SCI (arterial blood pressure is usually around 80 mmHg), which is caused by multiple factors:
- Loss of muscle tone due to paralysis of skeletal muscles below the level of injury resulting in venous plethora and therefore relative hypovolemia.
- Interruption of the sympathetic with: loss of vascular tone (vasoconstriction) below the level of injury; parasympathomimetic neurotransmitter inhibition without bradycardia.
- Blood loss, injuries associated with true hypovolemia.
- Transient loss of all spinal reflexes below the level of injury accompanied by paralysis lasting a variable period of time (approximately 2 weeks to several months); its resolution is manifested by spasticity below the level the lesion.

38.3 Initial Treatment

Patients with SCI are admitted to the intensive care unit (ICU) for two reasons: hemodynamic or respiratory instability due to trauma associated with spinal cord injuries or severe injury. One should take into account that the therapeutic options in traumatic SCI are based on the potential for reversal of pathophysiological changes that occur after trauma and that determine the irreversibility of the injury or its aggravation. These changes include: ischemia, hypoxia and lipid peroxidation, and will dictate the most important initial care.

38.4 Spine Immobilization

The spine should be immobilized before removing the patient from the accident site and maintained during transport to prevent active or passive movement of the spinal column. Patients with traumatic spinal cord injury admitted to the ICU, especially if unconscious, must remain immobilized and retained on the transport stretcher with containment systems, such as sandbags and supports or hard paste (Philadelphia type), until fixation and fracture stabilization.

38.4.1 Cervical Traction

Cervical traction serves to reduce displacement fractures, restore spine alignment, and immobilize it to prevent subsequent damage. The three most commonly used devices for this purpose are: the pin type (blunt pins requiring skin incision and pre-drilling of the skull), Gardner-Wells pins (more practical and often used), and fixing rings (mainly used with a halo vest).

For placement of the pins of Gardner-Wells tongs, the patient is positioned on a stretcher to facilitate access to the cranial region, the temporal region of the head is shaved, an antiseptic (PVP-iodine) is applied to the skin, and a local anesthetic infiltrated (lidocaine with epinephrine or xylocaine with epinephrine 1:200,000). The insertion point is located in the temporal crest, immediately above the insertion of the temporalis muscle, 3-4 cm above the pinna. The head is pulled into a neutral position in line with the spinal column. An insertion point 2 cm posterior will achieve flexion (facet block) and a point 2 cm above will achieve extension. The skin may or may not be incised at the site; however, it is useful to mark the spot where the insertion is performed in order to place the device in symmetrical traction. Both pins should be pushed simultaneously to the limit while feeling bone resistance. The pins should be checked 24 hours later and retightened to prevent them from loosening. If the intention is to maintain traction and there is no need to correct subluxation, traction should be applied initially with weights of 2.5 kg to higher segments (up to C4) and 5 kg for the lower segment at a maximum of 10% body weight in adults. To reduce blocked facets, the rule is:

$$\text{Weight (kg)} = 1.5 \times \text{Number of the affected segment}$$

You can increase the weight (2 kg each time) every 15 minutes, with radiographic control (X-ray in profile), up to 25% of body weight. Relaxation of spinal muscles can be achieved with diazepam 50-10 mg IV, taking care not to sedate or cause respiratory failure. Once achieved, the reduction is maintained at a weight of 2.5 to 5 kg.
The patient should be kept under daily radiographic control or repeated after each move or transport.
The main steps to be taken are:

- Check for neurological deterioration after reduction due to extrusion of disc herniation with spinal cord compression (if neurological worsening is observed, magnetic resonance imaging scan should be obtained).
- Do not hold in traction fractures involving the occipito-C1 segment or hanged fractures (hangman or traumatic spondylolisthesis of the axis).
- Do not pull the pin in children <3 years of age.
- Avoid penetration of the skull: set too low (in the temporal squama) in osteoporotic bone or excessive pressure.

38.5 Maintenance of Blood Pressure

Blood pressure should be monitored closely and mild hypertension induced to ensure adequate spinal cord blood flow in the first hours after trauma. Fluid replacement is a crucial point in initial therapy and the infusion of an appropriate combination of crystalloids and colloids will depend on the presence of associated lesions and urine output. One must be careful, however, to avoid overhydration, which can lead to overloading of the right heart chambers and pulmonary edema.
Because there is traumatic sympathectomy, and the predominant tone of the parasympathetic autonomic nervous system, as an adjunct in the treatment of refractory hypotension, dopamine (2-5 μg/kg/min) is recommended provided there are no other contraindications, mainly due to injuries to other organs. Phenylephrine should be avoided because it has a positive inotropic action and because of the possible effect of increased vagal tone, leading to intense bradycardia. Atropine (0.5 mg) can be used to aid in the treatment of bradycardia.

The use of pneumatic or medical antishock trousers (MAST) can be useful to stabilize the lumbar spine and compensate for the loss of vascular tone in the lower limbs, preventing venous retention.

38.6 Maintenance of Oxygenation

In SCI patients, paralysis of the intercostal muscles (neck injury) and even the diaphragm (lesions above C4) will determine situations of inadequate ventilation.
Hypoxia in the injured spinal cord regions will contribute to worsen the pathophysiological cascade known to occur after trauma; therefore, it is extremely important to maintain adequate oxygenation by closely monitoring changes in blood gases, if possible with appropriate probes and registers. Arterial blood gases should be obtained at regular intervals. Clinical signs of agitation, restlessness and disorientation signal insufficient oxygen and should be observed closely.
To maintain adequate oxygen supply (fraction of inspired oxygen [FiO_2] and ventilation), one can resort to:

- A nasal breathing tube
- Intubation. If intubation is indicated in the presence of cervical SCI, it must be done without moving the spinal column (without producing extension) by means of blind nasotracheal or flexible fiberscope intubation. Tracheotomy may sometimes be necessary.

Although a multicenter, randomized, double-blind trial (NASCAR II) compared three groups (methylprednisolone (n=162), naloxone (n=154) and placebo (n=171); however, some design flaws can be observed and are grounds for criticism:

- There were no pre-established anatomical limits.
- Patient selection did not require a minimum motor impairment for inclusion.
- Patients were randomized to treatment within 12 hours yet the study concluded that 8 hours was the “cut-off time”.
- Medical treatment (monitoring, blood pressure, respiratory care, deep venous thrombosis prophylaxis, nutritional support and early rehabilitation) was not taken into consideration among the different centres.
- Surgical treatment was not specified in terms of protocol treatments for the same types of injury.
- It was not reported whether the modest clinical improvement observed affected the measure of independence function.
- There were potential statistical errors of interpretation: it was not clear which statistical methods were used and why when comparing the groups, there was simplification of subgroups, incomplete presentation of odds ratios and post hoc analysis; ultimately, findings were graded as evidence class.

The prognosis worsens if treatment is started 8 hours after injury.
Duration of the maintenance infusion initiated within 3 hours of trauma must be maintained for 8 hours. If started between 3 and 8 hours after injury, there may be a greater benefit with infusion at the same dosage for 47 hours, with a slightly higher risk of infection and pneumonia (NASCIS III).

38.6.1 Monsialoganglioside GM1

There is growing evidence that substances like monsialoganglioside GM1 (SYGEN®) may affect neuronal survival by exerting an action like that of neurotrophic factors. As ob-

served in vitro and in vivo, its mechanism of action rests is similar to that of neurotrophic factors, with a direct anti-apoptotic action on tyrosine kinase receptors (TrK), preventing DNA fragmentation. In a study published by Geisler in the United States, involving about 800 patients, the use of GM1 was compared versus placebo. The results were favourable, with improved sensory and motor function observed in the GM1 treated group.
Dosage:

- Initial dose: 300 mg as loading dose (IM or IV).
- Maintenance dose: 100 mg/day for 30 days (IM or IV).

The drug should not be administered concomitantly with methylprednisolone because its effect does not appear to show synergism of action but competitiveness instead.

38.6.2 Other drugs

Tirilazad (a drug with action similar to methylprednisolone but without most of the side effects), naloxone, calcium channel blockers, antioxidants and free radical blockers, neurotrophic factors, are among the drugs being investigated for the pharmacological treatment of SCI; however, no evidence of their effectiveness has been forthcoming.

38.7 General Care of SCI Patients

38.7.1 Nasogastric Tubes

Nasogastric tubes are especially useful for suction, to prevent vomiting and aspiration, and to decompress the abdomen if distended, which can interfere with breathing. Ileus is common in the acute stage and may last several days. Unless there are contraindications, nutrition should be initiated early.

38.7.2 Bladder Catheterization

In the acute stage, exacerbated by the degree of hypotension, there is a significant reduction in the captive volume of urine produced, up to complete anuria, which can last from 3 to 12 hours. In the acute phase, the bladder is unable to empty by reflex (so-called areflexic bladder). This occurs even in cervical lesions, and can progress to spastic bladder. Placement of a urinary catheter (Folley catheter) is useful at this stage, especially for tight control of urine output, which will serve to guide fluid restoration and prevent bladder distension due to urinary retention.
Placement of an indwelling catheter, however, to keep the bladder sphincter open, predisposes in the long term to atrophy with a higher probability of urinary incontinence. As it is necessary to keep the bladder in a regime of low pressure, preventing vesicoureteral reflux and hydronephrosis, limiting the likelihood of infection and preventing incontinence, intermittent bladder catheterization should be instituted as soon as the patient's general condition is stabilized (usually within 24 hours), then replacing the indwelling catheter.

38.7.3 Thermal Regulation

Vasomotor paralysis produces a state of poikilothermia (loss of temperature control). One must be careful to avoid situations of hypothermia in cold weather, keeping the pa-

tient warm with blankets or thermal quilts, as well as situations of hyperthermia, which can be particularly harmful in acute SCI. Spraying water on the skin of the limbs and trunk or applying cold compresses are useful and practical measures to promote heat exchange on hot days.

38.7.4 Skin Care

Prevention of decubitus sores should be initiated starting from the time of admission of the SCI patient to the ICU. Care should be taken to avoid prolonged periods on long on hard surfaces (transport boards, X-ray or CT table), the bed kept dry with sheets stretched at all times, and the skin kept hydrated. Whenever possible, the patient should be mobilized, even as a block, at least every 2 hours. In patients with major instabilities, guards with special air or water mattresses or supports with gel or water bags at the points of greatest pressure should be placed (ankles, heels and sacral region, elbows and shoulder blades). The recognition of areas of hyperemia or catastrophic skin changes should initiate more aggressive therapeutic measures, including massage with moisturizing oils and creams, while preventing direct contact between body areas and hard surfaces.

38.8 Laboratory Evaluations

38.8.1 Radiological Evaluation

The proper treatment of spine fractures relies on accurate radiological examination. Several techniques available, including: plain radiographs of the spine, dynamic studies in flexion/extension, computed tomography (CT), myelography and CT myelography, and magnetic resonance imaging (MRI). Each o has its advantages and their combined use will allow visualization and assessment of bone structures, ligaments, the compromising stability, spinal cord, and soft tissues.
It is generally agreed that bone structures are more visible on plain radiographs and that CT and MRI allow better visualization of the spinal cord and soft tissues.

X-ray

The Advanced Trauma Life Support (ATLS) instruction manual recommends that a profile radiograph of the cervical spine be obtained in all patients with multiple trauma. Additional views such as anteroposterior (AP) and transoral may be necessary, especially in patients with neck pain or muscle spasm revealed by palpation of the vertebral tissues, those with a supraclavicular injury, or those with high-speed, high-impact injuries, such as ejection from a moving vehicle.
X-ray of the thoracic and lumbar spine should be obtained in all trauma patients who: 1) have been thrown out of a moving vehicle or fallen from height >3 m; 2) complain of chest or lumbar pain; 3) are unconscious; 4) are unable to refer back or chest pain or have altered mental status examination that prevents a correct evaluation of the back; 5) present with injury sustained from an unknown mechanism of trauma, or other lesions that suggest SCI.
The correct interpretation of cervical spine X-rays depends on adequate visualization of the cervicothoracic junction. For the radiograph to be declared as satisfactory, there is no need to see at least the upper plateau of T1. Failing that, this view should be repeat-

ed with a lateral view of the caudal traction arms. If you still cannot view the cervicothoracic junction, radiographs should be obtained in the swimmer position (incidence of Fletcher). If it is not displayed, and the patient is neurologically intact, the patient remains in a collar and seeks a planar tomography (single) (polytomogram) in a non-emergency or if there is a neurologic deficit, a CT scan of the spine at levels not seen properly should be performed. In this case, reconstruction or three-dimensional sagittal reconstruction can be useful for assessing the alignment.

The cervical spine radiograph is evaluated in a sequence of steps:

- **Evaluation of alignment**. Observe four lines superimposed over the radiograph and define their outline. The first line (marginally above), the smoother, less curved than the others, the convexity above, is formed by a line joining the front edge of the vertebral body. Two similar lines tangential to the posterior edge of the body and the base of the spinous processes (and subsequent marginal spinolaminar lines). These two lines enclose the spinal canal. The last line is traced following the union of the tips of the spinous processes.
- **Evaluation of the odontoid process**. Measure the distance between the posterior arch of C1 and the odontoid process. In children this distance can be up to 5 mm, while the adult it should not exceed 2 mm.
- **Swelling or bruising of the soft parts**. The space between the front edge of the upper cervical vertebrae and the pharyngeal air column has at most two thirds the thickness of the body of the second cervical vertebra. Below the C3-C4 level the prevertebral soft tissue should not exceed the anteroposterior diameter of the vertebral body. Sometimes the observation of these changes, even in the absence of obvious fracture or dislocation, serves as an indicator for a more thorough investigation with CT or MRI.
- **Intervertebral spaces and vertebral bodies**. Intervertebral distances may be altered in cervical degenerative disc disease, usually, with accompanying osteophytes. The evaluation of the regularity of the contour of the vertebral bodies may show fractures with displacement of fragments. A characteristic feature is the displacement of a small fragment of the plateau above the lower vertebra, which is accompanied by a sagittal fracture of the body and displacement of fragments into the canal, known as the tear drop fracture.
- **Interspinous distances**. Abnormal opening or spacing of a pair of spinous processes reveals a ligament rupture. AP projection should be obtained to analyze the interspinous distance. If it is 1.5 times greater than that of both adjacent levels, this indicates posterior ligament rupture. AP projection will display alignment of the spinous processes in the midline, which is altered with lateralization of one, when there is unilateral blockade of the facets.
- **Dynamic imaging studies**. It is possible to observe situations of pure ligamentous injury with trauma, involving posterior ligament complex rupture without fracture. Flexion-extension can help detect these lesions, aiming to find hidden instability. If head bending is limited due to muscle spasm of the spine, a hard paste (Philadelphia) should be applied and the radiographs in flexion/extension repeated within a week or two. It is recommended that this study be performed by a radiologist or under the supervision of a neurosurgeon. The patient must be conscious and cooperative (to avoid dynamic study in traumatic brain injury patients, or under the influence of drugs or alcohol). You should not notice any dislocation >3.5 mm in the previous X-rays, in which case the instability is already defined. Patients must be neurologically intact. If there is neurologic deficit, other type of imaging study, for example, MRI, should be done. The patient should be placed in a chair and instructed to flex the neck slowly and stop when he beings to feel pain. X-ray series are ob-

tained at intervals of 5-10 degree increments in flexion or extension, and if normal, the patient should be encouraged to go ahead. This is repeated until a diagnosis of instability is made, or the patient cannot flex due to pain or limited mobility. The study of flexion/extension may show mild subluxation in all cervical spaces but always with displacement

38.8.2 Computed Tomography

Computed tomography (CT) has proven extremely useful in assessing spinal trauma. The level to be studied can be determined by the abnormalities found on the radiograph or the simple level of neurological deficit, identified clinically, if the chest X-rays are normal or inconclusive. This happens most often with thoracolumbar than with neck fractures. CT allows perfect delineation of the vertebral bodies and determining the integrity of the spinal canal. It should be made thin sections (1.5 to 3 mm), the levels of suspicion, and sagittal or three-dimensional reconstruction techniques can be useful for assessing alignment of the vertebral bodies. CT is not a screening test for spinal trauma. Determination of an inadequate level to be examined, by either inappropriate radiographs or incorrect clinical assessment, can cause injuries to go unnoticed. Although highly accurate in demonstrating blocking facets and retropulsion of fragments into the canal, sometimes subluxations cannot be revealed.

38.8.3 Magnetic Resonance Imaging

Until the introduction of MRI, no radiological method was able to directly visualize the traumatized spinal cord. MRI can show precisely ligament injuries and damage to the spinal canal by bone fragments, herniated disc, epidural hematoma or subluxation. However, it is the direct visualization of the spinal cord, al-

Figure 38.1. Plain radiograph showing cervical spine fracture and dislocation of C5-C6 with bilateral locking of facets.

Figure 38.2. Dynamic radiograph showing cervical spine in flexion with subluxation of C4-C5.

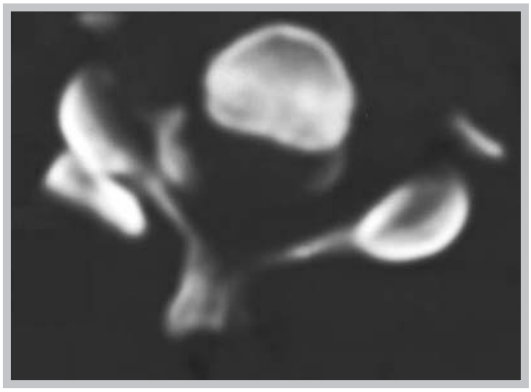

Figure 38.3. Axial tomography of the spinal column showing unilateral facet lock on the left.

lowing the diagnosis of spinal cord transection, contusion, edema, or ischemia hematomyelia that makes MRI superior to all other methods. MRI should be performed in situations of incomplete injury, alignment with normal or no apparent bone lesion, to exclude cord compression by soft tissue such as disc herniation or hematoma. It is also indicated in situations of deterioration, with worsening of the deficit or new deficit, or when the fracture level differs from the level of the deficit observed.

The disadvantages of MRI are that it is not always possible to perform in acutely traumatized patients, it is unavailable in many emergency rooms, and it is not impossible to perform in patients under respiratory or cardiovascular support. Access to manoeuvre the patient can be extremely difficult and MRI takes longer to perform than CT. MRI in a patient wearing a cervical collar is not always possible or will produce images of poorer quality. Patients in traction and wearing metal devices are also ineligible for MRI.

Figures 38.1-38.6 show some examples of laboratory findings.

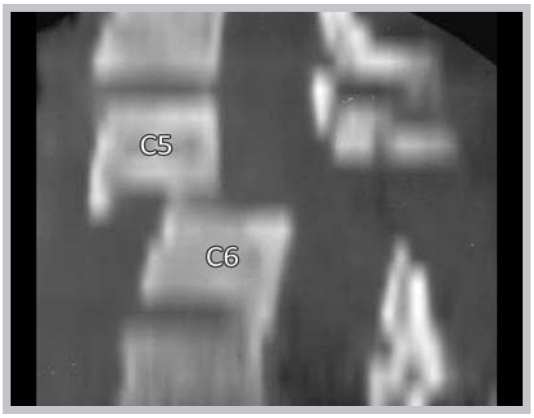

Figure 38.4. **Computed tomography sagittal reconstruction of a spinal column fracture with dislocation of C5-C6, canal stenosis and rupture of the posterior ligaments.**

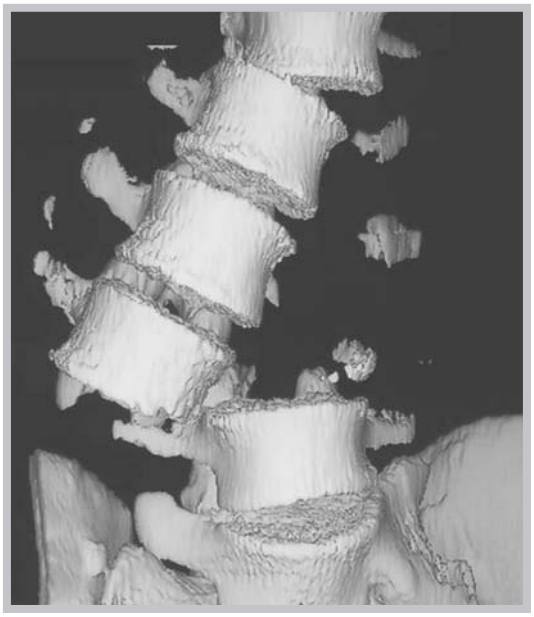

Figure 38.5. **Computed tomography 3D reconstruction of the spinal column with a fracture and loss of articular segment L2-L4.**

38.9 Surgical Treatment

The aim of surgical treatment of spine fractures is to decompress the spinal cord and protect it, restore stability, and promote neurological recovery. In many cases, however, stability can be achieved with the use of external orthoses (vests, halo traction, etc.).

Some types of fractures are inherently unstable and require surgery with internal fixation. In such circumstances, opinions differ about what should be done (anterior, posterior, type of instrumentation) and when it should be done (immediate surgery, early or late).

The only universally accepted indication for immediate surgery is progressive neurological deterioration in a patient with spinal canal stenosis due to bone fragments, disc, or hematoma, or an irreducible dislocation. Also, spinal cord compression in a patient with incomplete neurological injury is allowed in some centres as a criterion for immediate decompression.

Figure 38.6. **MRI of the cervical spine (T2). Postoperative C5 corpectomy. Note the signal change in the vertebral bodies corresponding to the implant material (screws and plate) and the signal change in the spinal injury showing hemorrhagic contusion and perilesional edema.**

There are several published studies showing increased morbidity and neurological deterioration after early surgery for traumatic SCI. In contrast, more recently, several authors recommended early surgical intervention, especially in the anterior cervical spine, to allow early mobilization of the patient and reduce complications. In fact, the SCI patient is susceptible to various systemic and neurological complications despite treatment, including pneumonia, decubitus ulcer, thrombophlebitis and pulmonary embolism. It seems obvious that keeping the patient immobilized in bed will not help to avoid this type of complication. Wilberger in 1991 showed a significant reduction (by half) of such complications with early surgery without increasing neurological morbidity. One can also argue that decompression of the spinal cord in the acute phase, by reducing the degree of ischemia, can reduce the effect of the secondary pathophysiological cascade that occurs after trauma. In a recent study, a reanalysis of NASCAR II, there was no statistically significant benefit from early or late surgery in relation to the degree of recovery. There was a trend toward better recovery in patients operated on in the first 25 hours or after 100 hours as compared to the intermediate surgery group.

Currently, it is accepted that if surgery is needed for the treatment of a broken column, assuming that the patient is clinically stable, there is no significant increase in risk associated with early intervention and reduction of downtime can be considerably conducive to patient recovery.

38.10 Functional Independence Measure (FIM)

To fully describe the impact of SCI on the individual and to monitor and evaluate the progress associated with treatment, assessment of activities of daily living is performed. The Functional Independence Measure (FIM) is a tool to assess the degree of function; it is widely used in the United States and is gaining acceptance internationally.

FIM focuses on six areas of functioning: self-care, sphincter control, mobility, locomotion, communication and psychosocial interaction. For each area two or more activities/elements are evaluated for a total of 18 items. For example, self-care is composed of six activities: eating, grooming, bathing, dressing the upper body, dressing the lower body, and personal hygiene (Figure 38.7).

Each of the 18 items is evaluated in terms of independence of function on a 7-point scale (Table 38.5).

- 7: Complete Independence. Fully independent.

- 6: Modified Independence. Requiring the use of a device but no physical help.
- 5: Supervision. Requiring only standby assistance or verbal prompting or help with set-up.
- 4: Minimal Assistance. Requiring incidental hands-on help only (subject performs >75% of the task.
- 3: Moderate Assistance. Subject still performs 50-75% of the task.
- 2: Maximal Assistance. Subject provides less than half of the effort (25 to 50%).
- 1: Total Assistance. Subject contributes <25% of the effort or is unable to do the task.

Thus, the total FIM score (the sum of all activities) estimates the degree of disability in terms of safety, dependency on others and devices needed. The profile of scores by area are specific aspects of daily life that are most affected by SCI.

When assessing SCI patients with the FIM, it should be taken into account that the tool was originally developed for evaluating the disabled in general and that it covers broad areas of activities affected by disability. Although we have explored the reliability and validity of the FIM, its validity as an instrument to accurately measure the degree of function across the population with SCI has yet to be demonstrated empirically. For example, it is unclear whether the self-care items are sufficiently sensitive to assess changes in function observed during the rehabilitation of quadriplegics. In addition, we found the items investigating areas of communication and social life less reliable than other areas of evaluation.

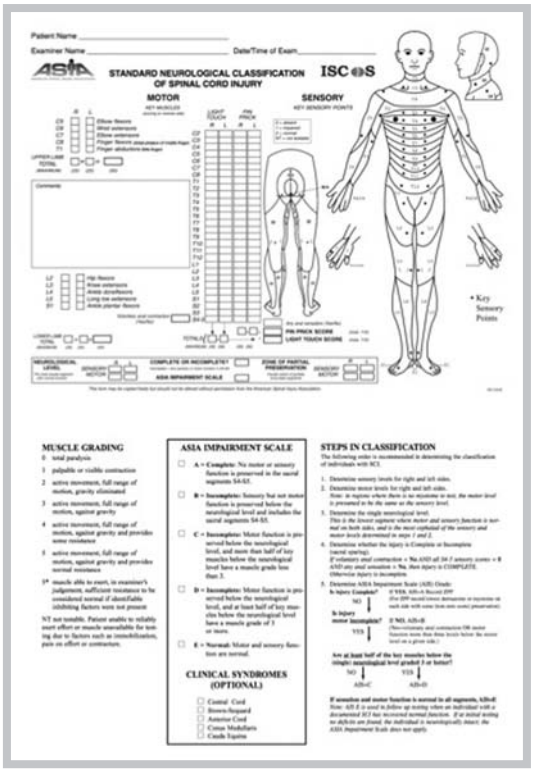

Figure 38.7. FIM form.

Despite these difficulties, we recommend the use of FIM as it is relatively easy to use, reflects major functional aspects in SCI, and the parameters for its use were carefully constructed.

Points	Item	Assistance
7	Total independence (timely, safely)	Not needed
6	Modified independence (extra time, devices)	
	Modified dependence	Needed
5	Supervision (coaxing, cuing, prompting)	
4	Minimal assistance (performs 75% or more of task)	
3	Moderate assistance (performs 50-74% of task)	
	Complete dependence	
2	Maximal assistance (performs 25-49% of task)	
1	Total assistance (performs <25% of task)	

Table 38.5. The Functional Independence Measure (FIM) scale.

Personal care	Admission	Release	Date
A. Eating			
B. Grooming			
C. Bathing			
D. Dressing upper body			
E. Dressing lower body			
F. Toileting			
Sphincter control			
G. Bladder control			
H. Bowel management			
Mobility transfer			
I. Bed, chair, wheelchair			
J. Toilet			
K. Tub or shower			
Locomotion			
L. Walking, wheelchair			
M. Stairs			
Communication			
N. Comprehension (audio/visual)			
O. Expression – verbal, non-verbal			
Psychosocial adjustment and cognition			
P. Social interaction			
Q. Problem solving			
R. Memory			
TOTAL			

Table 38.6. Functional Independence Measure chart.

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39 Acute Spinal Cord Injury: Pathophysiology and Intensive Care Management

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39.1 Introduction

In this chapter, we lay the scientific foundation for managing acute spinal cord injury by discussing the definitions of primary and secondary spinal cord injury (SCI). Understanding these concepts is important to implementing effective strategies aimed at reducing long-term neurological deficits. Afterwards, we review the important distinction between spinal and neurogenic shock and outline management strategies for patients suffering from diminished autonomic function. We describe the various spinal cord syndromes that will help clinicians correlate neurological findings to specific areas of pathology in the spinal cord. Lastly, we will cover specific patient management practices and clinical concepts essential to the care of patients during the acute stages of SCI and for optimizing neurological outcome.

39.2 Pathophysiology of Spinal Cord Injury

Acute SCI can be considered in terms of the primary injury, usually as a result of trauma or assault, and the biological mechanisms subsequent to this event, termed secondary injury. It is of critical importance to be aware of these secondary mechanisms because most of the intensive care and surgical strategies performed immediately after the injury aim to limit this damage in the attempt to improve the chances of functional neurological recovery.

Primary SCI refers to the damage inflicted on the neural elements as a result of an acute traumatic event. This can take the form of shear forces disrupting white mater tracts or hemodynamic compromise from blood vessel disruption. This damage occurs at the time of the injury and is, to date, irreversible. Secondary SCI is a se-

Primary mechanisms of injury	• Initial injury to the spinal cord; occurs at the time of trauma • Severing of axons • Cellular death
Secondary mechanisms of injury	A complex cascade of events that invariably follows primary injury: • Hypotension and hypoxia often cause or exacerbate these events • Ischemia • Vasospasm • Delayed axonal loss and apoptosis (programmed cell death) • Ion-mediated cell damage • Excitotoxicity • Neuroinflammation • Mitochondrial dysfunction • Oxidative cell damage

Table 39.1. **Primary and secondary mechanisms of spinal cord injury.**

quence of hemodynamic and biochemical events that occur in response to the initial injury. While a detailed review of these mechanisms is beyond the scope of this chapter, we will highlight a few of the essential mechanisms to offer an introductory understanding. Secondary injury can take the form of systemic hypotension or hypoxia resulting in focal ischemia around the area of injury. Another form of secondary injury occurs at the cellular level and can take the form of ion-mediated cellular damage, excitotoxicity, apoptosis, oxidative cell damage, mitochondrial dysfunction, neuroinflamation or vasospasm. Each of these secondary mechanisms can theoretically be mitigated with various medical or surgical strategies. Such strategies will be outlined in the second and third part of this chapter. A summary of primary and secondary mechanisms of SCI are summarized in Table 39.1.

In managing a patient with a SCI the treating team must adhere to Advanced Trauma Life-support (ATLS) Guidelines. The neurological examination should be done following stabilization of the airway, breathing, circulation and management of any other immediately life-threatening situation. Following this, a neurological examination should be carried out with the following two concepts in mind: spinal shock and neurogenic shock.

39.2.1 Spinal Shock

Spinal shock refers to depressed spinal reflexes caudal to the injury site following SCI. This is an important concept to understand as the initial neurological examination may not be an accurate reflection of disrupted neuronal circuits, including those that control motor and sensory pathways. Normally, these reflex pathways receive continuous input from the brain. When this tonic input is disrupted, the normal reflex pattern is disrupted and can vary from areflexic through to hyperreflexic depending on the time since the original injury.

Ditunno recently proposed a four-phase model to explain the clinical observations that occur caudal to the site of injury [1]. Briefly, these phases are as follows: Phase 1 (from the time of the injury to approximately 24 hours later) is characterized by hypo- or areflexia, which ensues from disrupted descending modulation. Phase 2 (between 24 and 72 hours following injury) is characterized by gradual return of the reflex. This is thought to result from neurotransmitter receptor up-regulation or denervation supersensitivity. Phase 3 (1-4 weeks following injury) is clinically characterized by hyperreflexia, which is the result of axon-supported synapse growth. Phase 4 (1-12 months after injury) is also characterized by hyperreflexia and results from cell-body-supported axon growth. The important point to gain from this discussion is that descending modulation can be suspended in the phase immediately following SCI. Clinically, this translates into the potential for a misleading representation of deficits if spinal reflexes are absent following injury. It is therefore recommended that patients not only be examined on presentation to the treating physician but also at the 72-hour mark following injury.

39.2.2 Neurogenic Shock

Neurogenic shock is a potentially life-threatening condition and must be managed as such. Without a clear understanding of this condition, inappropriate management of a trauma patient, who often suffers concomitant hemodynamic instability, could be fatal. Neurogenic shock is defined as a disruption of the sympathetic nervous system with preserved parasympathetic activity. This typically occurs in patients suffering a severe SCI at the level of T6 or higher. A comprehensive, open-access review was recently published in 2008 [2] and the reader is referred to this for a detailed understanding. The sa-

lient clinical aspects are reviewed here. Disruption of the sympathetic division of the autonomic nervous system has three effects on the cardiovascular system: coronary blood flow, cardiac contractility and heart rate [3]. With preserved parasympathetic activity this translates clinically into bradycardia (and possibly other cardiac arrhythmias) in a setting of profound hypotension [4]. A prudent clinician must look for these characteristics in combination, as many trauma patients are hypotensive as a result of blood loss or intravascular hypovolemia but will mount an appropriate tachycardia response.

The treatment of neurogenic shock is therefore quite difficult. While it is theoretically possible to distinguish between hypovolemic and neurogenic shock, this is not so clinically. In fact, acute trauma patients sustaining a high cervical SCI may suffer from both conditions. It has therefore been recommended by the Consortium for Spinal Cord Medicine to rule out other causes of shock before assuming a diagnosis of neurogenic shock [5]. The practical treatment of these patients rests on initially restoring intravascular volume and if symptoms of neurogenic shock persist, vasopressors (such as dopamine) should be used. The goal of treatment in the first week after sustaining a SCI is to maintain a mean arterial blood pressure of 85 mmHg [6,7].

39.2.3 Spinal Cord Syndromes

A detailed and consistent neurological exam is essential to the management of the patient with acute SCI. We recommend the use of the American Spinal Injury Association and International Spinal Cord Injury Society (ASIA-ISCoS) scale for characterizing the severity of injury [8]. In brief, an ASIA A grade refers to a complete injury with no sensory or motor function present from the level of injury to the sacrum. An ASIA B grade is assigned to a patient with some preserved sensation but no motor function from the level of injury to the sacrum. ASIA C and D grades are differentiated by the absence or presence of grade 3 power (full motion against gravity), respectively. ASIA E is reserved for acute SCI patients who are neurologically intact. A form illustrating how the neurological examination is recorded according to the ASIA-ISCoS standards can be obtained for free from the ASIA website (http://www.asia-spinalinjury.org).

Neurological examination of the patient should be performed immediately following the injury and ideally within 72 hours, especially if spinal shock is suspected. One should be aware of the terminology used to describe deficits and different SCI syndromes. Paresis refers to weakness or partial paralysis. For example, hemiparesis describes weakness on one side of the body. In contrast, both paralysis and the suffix plegia refer to no movement. For example, hemiplegia refers to no movement on one side of the body. Keeping these terms in mind, we turn our attention to spinal cord syndromes that occur when a select region of the spinal cord is damaged, resulting in a predictable pattern of neurological deficit. These syndromes are outlined in Table 39.1 and expanded on in the paragraphs that follow.

Transverse spinal cord lesions disrupt all motor and sensory pathways at and below the level of the lesion. There is a sensory level that corresponds to the level of the lesion. Common causes of this syndrome include trauma or more rarely spinal cord tumours.

Hemi-section of the spinal cord, commonly referred to as the Brown-Sequard syndrome, is characterized by damage to one half of the spinal cord and all motor and sensory pathways at that level and neurological deficits at and below that level. This results in ipsilateral upper-motor neuron weakness and ipsilateral loss of vibration and position sense at and below the level of lesion. There is contralateral loss of pain and temperature sensation below the level of the lesion. There may also be ipsilateral loss of pain and temperature at the level of the lesion for one or two spinal segments if the lesion has damaged

posterior horn cells before the fibres have crossed to the other side. Common causes of this type of injury include penetrating trauma or a tumour compressing only one side of the spinal cord.

Central cord syndrome is commonly caused by a traumatic spinal cord contusion, post-traumatic syringomyelia or a medullary spinal tumour. This lesion tends to affect pathways that are in the immediate vicinity of the central portion of the spinal cord and the symptoms differ depending on the size of the lesion. Small lesions affect the spinothalamic fibres that cross in the ventral commissure and cause bilateral regions of suspended sensory loss to pain and temperature. If the lesion is larger, anterior horn cells, corticospinal tracts and posterior columns may be affected. Loss of these pathways respectively results in lower-motor neuron deficits at the level of the lesion, upper-motor neuron signs below the level of the lesion, and loss of vibration and position sense below the level of the lesion. In addition to suspended pain and temperature loss with small lesions, larger lesions can result in complete loss of pain and temperature below the level of the lesion if the anterolateral pathways are compressed from a medial aspect. Given the spinal cord laminations, sacral sparring is observed.

Posterior cord syndrome involves bilateral loss of vibration and position sense below the level of the lesion as a result of disruption of the posterior columns. If the lesion is large enough, one may observe upper-motor neuron signs below the level of the lesion indicating involvement of the lateral corticospinal tracts. Common causes include trauma or a posterior located tumour. In addition, vitamin B12 deficiency or tertiary syphilis can cause isolated involvement of the posterior columns.

Anterior cord syndrome results in loss of pain and temperature sensation below the level of the lesion (spinothalamic pathways), lower-motor neuron signs at the level of the lesion (anterior horn cell damage) and upper-motor neuron signs below the level of the lesion (lateral corticospinal tracts). In addition, urinary incontinence is common because of the ventral location of the descending pathways controlling sphincter function. Common causes of this syndrome include trauma and anterior spinal artery infarct.

39.3 Acute Management of the Patient With Spinal Cord Injury

The ATLS guidelines emphasize the need to establish and stabilize airway, breathing and circulation in trauma patients. These important steps in resuscitation precede neurological examination or imaging of the neuraxis. Spinal precautions should be implemented throughout resuscitation, with special care to avoid manipulation of the cervical spine during intubation. Major life-threatening thoracic, abdominal or extremity injuries may be masked by SCI. Continuous cycling through primary and secondary trauma surveys should minimize the risk of missing such injuries or changes in neurological function.

39.3.1 Hemodynamic Support and Oxygenation

Serial neurological examination is paramount to detecting any deterioration in function quickly and preventing permanent deficit. Accurate neurological examination may not be possible in a patient who is sedated or under general anesthetic. Furthermore, the pharmacological agents administered may produce hypotension and small vessel vasoconstriction, which can induce further ischemic damage to the injured spinal cord. The period of induction during administration of a general anesthetic may be a period of rel-

ative hypoperfusion secondary to hypotension. Under these circumstances, all members of the health care team must be vigilant in maintaining the hemodynamic parameters outlined in the next paragraph.

As stated in the first part of this chapter, a mean arterial blood pressure of 85 mmHg should be maintained during the first week following SCI [6,7]. Vale et al. employed arterial lines and Swan-Ganz central catheters to monitor patient hemodynamics. Volume resuscitation with crystalloid and blood products were initially used to maintain a mean arterial blood pressure of 85 mmHg. If required, a dopamine (2.5-5 μg/kg/min) infusion was started to meet this target. Mean arterial pressure was further supplemented with levophed (0.01-0.2 μg/kg/min) when needed. When administering vasopressors to the patient with SCI, it is important to avoid agents that would produce vasoconstriction of the small vessels supplying the spinal cord. Aggressive management of mean arterial pressure and oxygenation are one the most important aspects of acute care in the patient with SCI. Similarly, intraoperative blood loss should be closely monitored. Vale et al. administered blood products to keep hematocrit >32%. We often administer blood products early, as opposed to waiting for hemoglobin/hematocrit to reach critical levels [7].

39.3.2 Neuroprotection

Inducing regional or systemic hypothermia for acute SCI aims to minimize secondary injury by lowering enzymatic activity and energy requirements of the injured spinal cord. Many of the studies examining the impact of hypothermia on acute SCI reported the experience in small groups of patients with heterogeneous clinical characteristics. The results were further confounded by the administration of multiple neuroprotective measures simultaneously. Kwon et al. [9] reviewed the relevant literature in 2008 and concluded that there is no compelling evidence that hypothermia (systemic or regional) improves neurological outcome in acute SCI. Furthermore, systemic hypothermia carries an increased risk of bacteremia/infection, coagulopathy, raised intracranial pressure and cardiac arrhythmia. While a randomized control trial to examine the utility of hypothermia in SCI is under development, we do not recommend inducing hypothermia for neuroprotection in acute SCI.

The administration of pharmacological agents to mitigate the effects of primary and secondary mechanisms of acute SCI remains controversial. Methylprednisolone, GM-1 ganglioside, thyrotropin-releasing hormone, nimodipine and gacyclidine have been tested in prospective randomized control trials of acute SCI in humans [10,11]. Only methylprednisolone and GM-1 ganglioside have shown modest benefits in neurological outcome [10]. For the purposes of this text, we will focus on the protocol for administering methylprednisolone in acute SCI.

The National Acute Spinal Cord Injury study (NASCIS I) randomized SCI patients into two cohorts; a 100 mg loading dose of methylprednisolone followed by 25 mg every 6 hours for 10 days in one group, and a 1000 mg loading dose of methylprednisolone followed by 250 mg every 6 hours for 10 days in a second group [12]. There were no differences in neurological outcome between the two groups at 1 year after injury [12]. NASCIS II investigated a 30 mg/kg bolus of methylprednisolone over 1 hour followed by 5.4 mg/kg/h over the following 23 hours and included a placebo group and naloxone administration group [13]. The results from the overall group showed no significant differences in neurological outcome at 6 months, though subgroup analysis demonstrated improved motor and sensory outcomes in the patients receiving methyprednisolone within 8 hours of injury [13]. NASCIS III examined outcomes in acute SCI patients receiv-

ing 30 mg/kg bolus of methypredniosolone followed by 5.4 mg/kg/h for either 23 hours or 47 hours [14]. Patients could be randomized into a third group receiving tirilazad mesylate [14]. The patients treated with methylprednisolone for 48 hours had better neurological outcomes in comparison to the other treatment groups if therapy was initiated within 3-8 hours of injury [14]. The 48-hour regimen was associated with an increased risk of sepsis and pneumonia [14]. Bracken reviewed five studies (including NASCIS I, II and III) investigating methyprednisolone in acute SCI and concluded that high-dose therapy was safe and modestly effective in improving neurological outcome [15].

There is still considerable debate as to whether or not high-dose methylprednisolone should be administered in the context of acute SCI. This has led to variability in the decision to administer methylprednisolone and specific protocols [16]. The senior author of this chapter has published his protocol for administering methylprednisolone following acute SCI based on the timing of administration [10]. Patients with acute non-penetrating SCI should receive methyprednisolone as per the NASCIS II protocol if started less than 3 hours after injury. If started between 3 and 8 hours after injury, then the NASCIS III 48-hour protocol should be applied. If therapy cannot be administered within 8 hours of injury, or there is a penetrating SCI, then methylprednisolone should not be administered for neuroprotection. The decision to administer methyprednisolone must account for medical comorbidities. For example, the risks of administration may outweigh the benefits in a patient with diabetes mellitus and a complete thoracic SCI injury. Blood glucose levels must be carefully monitored during the course of methylprednisolone therapy, and hyperglycemia aggressively managed with an insulin infusion.

39.3.3 Surgical Management of Acute Spinal Cord Injury

Prior to discussing the surgical management of SCI, it is necessary to outline appropriate imaging used to identify the extent and type of bony and soft tissue injuries. Selecting the anatomic spinal area to be imaged depends on the neurological examination. A quadraplegic patient requires imaging of cervical spine (skull base to top of T1), while a paraplegic patient with a thoracic sensory level requires a radiograph of the entire thoracic spine. While plain radiographs may be an appropriate first step, computed tomography (CT) scan is essential for characterizing bony pathology, while magnetic resonance imaging (MRI) is used to identify soft tissue injury, including injury to the spinal cord. The clinician should be aware that a significant proportion of SCI patients have more than one anatomic level of spinal injury, which may or may not be contiguous. Appropriate imaging is essential to planning further surgical management.

Closed reduction aims to relieve compression of the spinal cord by restoring normal bony alignment. The technique involves applying traction force to the skull through rigid fixation with Gardner-Wells tongs or Halo, and reducing a cervical dislocation. Increasing weight is added over time while neurological status and radiographic monitoring of the cervical fracture dislocation are assessed between traction increments. Traction may be an appropriate first step in a conscious patient who can undergo reliable serial neurological assessment, especially in the setting of bilateral locked facets [17]. This technique does not address compression secondary to hematoma or soft tissues. It may be impossible to obtain and/or maintain bony reduction with this technique. Surgical decompression and reduction offer the advantage of addressing all compressive etiologies immediately and providing the opportunity for internal fixation. Attempts at closed reduction should not delay definitive surgical decompression, open reduction and internal fixation of the spine. Evolving evidence suggests that early decompression may enhance recovery after cervical SCI and has acceptable safety, though this remains somewhat controversial. The

guidelines for the management of acute cervical spine injuries published in 2002 include early open or closed reduction of cervical fractures as a management option for SCI [18]. However, in actual practice, there appears to be considerable heterogeneity in the timing of surgery for acute SCI [19]. This variability in surgical timing may be due, in part, to a lack of a clear definition of "early surgery" or other factors, including logistical issues such as delays in medical transfers and the availability of key imaging or surgical resources.

Recent systematic reviews of the literature suggest that there is a biological basis for surgical decompression of the spinal cord within 24 hours of injury [10,19-21]. Preliminary results from the Surgical Treatment of Acute Spinal Cord Injuries Trial (STASCIS) indicate that decompression within 24 hours of injury may actually improve outcome in patients with isolated SCI [22]. Early decompression (within 24 hours) should be considered as part of the therapeutic management of any patient with SCI, particularly those with cervical SCI. Very early decompression (within 12 hours) should be considered for a patient with an incomplete cervical SCI (with the possible exception of the central cord syndrome). An international survey [23] indicates that the majority of spine surgeons prefer to decompress the acutely injured spinal cord within 24 hours. The majority of spine surgeons prefer to decompress the cervical spine for patients with complete or incomplete cervical spinal cord injury within 24 hours.

39.3.4 Pressure Ulcers

Preventing pressure ulcers is a life-long concern in SCI patients. The risk of developing a pressure ulcer is stable over the first 10 years after injury, with a reported prevalence of 11.5% within the first year of injury and 14.3% within 10 years of injury [24]. Preventing pressure ulcer following acute SCI may initially be overshadowed by issues of transportation, resuscitation, decompression and stabilization.

A recent systematic review of the literature identified a number of possible risk factors for the development of pressure ulcer in the acute SCI period (defined as prior to admission to a rehabilitation facility) [25]. Mobility level, activity level, lung disease, decreased mental status and nutritional status were identified as risk factors for the development of pressure ulcer, though the evidence was considered insufficient based on conflicting evidence between studies included in the review [25]. Low blood pressure was considered a possible risk factor with moderate evidence, as were transport time to hospital and time on a spine board [25]. Length of stay in hospital, tracheostomy and vertebral osteomyelitis were reported as possible risk factors with insufficient evidence[25]. Based on these results, both patient factors and medical management factors seem to play a role in the development of pressure ulcer.

There are no recognized guidelines for pressure ulcer prophylaxis in the acute phase of SCI. We would recommend removing the patient from the spine board upon arrival to hospital and optimizing oxygenation, hemodynamics and nutrition. These measures are supported by other authors [26]. A high level of clinical suspicion and vigilance, with frequent inspection of anatomical pressure points are required to provide adequate protection and early detection of pressure ulcer.

Results of a recent multicenter, international, prospective cohort study (STASCIS) indicate that not only is early surgery safe and feasible but results in better neurological outcomes at 6-months follow up relative to SCI patients who undergo surgical decompression beyond 24 hours. This trial defined early surgery as <24 hours and the mean time to surgery of the early group was 14.2 +/- 5.4 hrs. Late surgery was defined as occurring beyond 24 hours and in this study had a mean time 48.3 hr [27].

39.3.5 Venous Thromboembolism

Venous thromboembolism (VTE) is common in the SCI population. A recent review indicated that clinically symptomatic deep venous thrombosis (DVT) and pulmonary embolism (PE) occur in 12 to 64% of SCI patients not treated with thromboprophylaxis, while asymptomatic VTE may be more common [28]. The Guidelines for Management of Acute Cervical Spinal Injuries recommend prophylactic VTE treatment for patients with severe motor deficits [18]. In 2004, guidelines for the prevention of VTE recommended starting all acute SCI patients on thromboprophylaxis once primary hemostasis is evident [29]. Low-molecular-weight heparin was recommended over single therapy with unfractionated heparin, compression stockings or an inferior vena cava filter [29]. A combination of these latter modalities was recommended in instances where there was a contraindication to low-molecular-weight heparin during acute phase SCI [29]. The recommendations included in both sets of guidelines were based on strong clinical evidence in the scientific literature [18,29].

There are currently no recommendations for a particular low-molecular-weight heparin. Most guidelines are based on studies employing enoxaparin for VTE prophylaxis [18,29,30]. A retrospective study comparing the rate of VTE in SCI patients on prophylactic dalteparin or enoxaparin reported clinically symptomatic DVT or PE in 1.6% of the enoxaparin group and 9.7% in the dalteparin group [30]. The difference was not statistically significant due to insufficient power [30]. The balance of evidence favours the use of enoxaparin (40 mg subcutaneous once daily) for VTE prophylaxis in the acute SCI population.

39.3.6 Nutritional Support

The early period of acute SCI is characterized by disturbed metabolic activity and increased nitrogen excretion [26,31]. While the benefits of enteral nutrition in critically ill patients are accepted, there is little information supporting early feeding in acute SCI. A pilot, randomized control trial demonstrated no differences in septic complications between patients fed within 72 hours of SCI and those fed after 120 hours of the injury [31]. Only 17 patients were included in the analysis, making it difficult to draw any conclusions from the results. A retrospective review of 27 SCI patients started on enteral feeds a median of 2 days after injury reported no major complications in the group, though two patients had feeds interrupted due to high gastric aspirates [32]. Early enteral feeding should be considered in the acute SCI population, with consideration of their hypercatabolic state, with enough nutritional support to accommodate 1.5 times the normal basal metabolic rate.

39.4 Conclusion

Understanding the pathophysiology of SCI is essential to optimizing patient management. Maintaining a mean arterial pressure ≥85 mmHg, appropriate administration of methylprednisolone, and early surgical decompression are essential to optimizing the neurological outcome. Recognition of the common medical issues encountered by SCI patients (thromboembolism, pressure ulcer, altered nutritional requirements) and their avoidance are essential to improving overall outcome. We recommend that the reader be familiar with the following key references.

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Section 6.
Cerebrovascular Diseases

40 Stroke Units: Organization, Past, Present and Future

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40.1 Objective

The creation of stroke units has been a milestone in the management of cerebrovascular diseases. Paving the way was the change from a nihilistic attitude, which precluded stroke patients from care and left them to face the natural evolution of stroke, to one of responsive action undertaken as a first level emergency. In this chapter we give a brief historical overview of the development of the stroke unit and the organizational aspects that have been shown to be essential for its effectiveness.

40.2 Historical Overview

In the 1970s the first stroke units were designed as intensive care units, with monitoring of vital functions and the use of aggressive treatments. Admitted to such units were patients with severe stroke, major neurological deficits, and poorer general status. Although the results were variable and fewer complications were reported, the stroke units did not convincingly demonstrate they could effectively reduce mortality.

Subsequently, the concept of stroke units evolved into non-intensive acute care units characterized by systematization of patient care, with trained staff, admission criteria, systematic diagnostic and therapeutic procedures, attention to acute management and early functional and social rehabilitation, and effective multidisciplinary collaboration.

Several randomized trials have demonstrated stroke unit effectiveness in terms of mortality, functional recovery and chronic institutionalization rates (Table 40.1).

Intensive Care Stroke Units		
Kennedy et al. 1970	Prospective Randomized	No differences in mortality Reduction in complications rates
Drake et al. 1973	Retrospective Non randomized	No differences in mortality Reduction in complications rates Trend toward reduction in long-stay hospitalization
Pitner and Cornelius 1976	Prospective	Not effective with respect to mortality
Norris and Hachinski 1976	Prospective Non randomized	Not effective with respect to mortality

Non-intensive Care Stroke Units		
Strand et al. 1985, 1986	Prospective Randomized	Decrease in length of stay Reduction in long-stay hospitalization
Indredavik et al. 1991, 1997, 1999	Prospective Randomized	Reduction in mortality Decrease in length of stay Better functional outcomes Reduction in long-stay hospitalization 5-10 years follow-up: persistent benefit in terms of mortality and functional outcome
Stroke Teams		
Wood-Dauphinee et al. 1984	Randomized vs. general wards	Non significant efficacy
Webb et al. 1995	Prospective Historical controls	Decrease in length of stay Reduction in complications rates (↓ urinary infections)
Dey et al. 2005	Prospective Randomized	Premature interruption of the study No significant differences in mortality at 6 weeks or at 12 months
Van der Walt et al. 2005	Retrospective Historical controls	Reduction in severe complications rates Decrease in length of stay Increase in percentage of patients functionally independent at discharge
Stroke Units vs. General/Neurological Wards		
Jorgensen et al. 1995	Prospective Community-based	Reduction of in-hospital, 6-month and 12-month case-fatality Decrease in length of stay Reduction in long-stay hospitalization
Ronning and Guldvog 1998	Quasi-randomized Controlled	Reduction in 10-day, 1-year and 18-month mortality
Jorgensen et al. 1999	Prospective Community-based	Reduction in relative risk of death at 5 years
Stegmayr et al. 1999	Transversal Multicenter	Reduction in mortality Increase in discharge to home Reduction in long-stay hospitalization
Glader et al. 2001	Prospective Cohorts	Reduction of daily activities dependence Lower mortality at 2 years of follow-up
Krespi et al. 2003	Retrospective Historical controls	Reduction in mortality Decrease in length of stay
Cabral et al. 2003	Prospective Randomized	Non-significant trend toward reduction in mortality
Stavem et al. 2005	Case-control	20% reduction in mortality at day 30 after adjustment for age, gender and stroke subtype
Candelise et al. 2007	Retrospective Multicenter	Reduction in mortality or dependence rates
Zhu et al. 2009	Retrospective Historical controls	Reduction in mortality Decrease in length of stay
Stroke Units vs. Stroke Teams		
Kalra et al. 2000 Evans et al. 2001	Randomized 3 groups • Stroke Unit • Stroke Team • Home	Stroke Unit group: Reduction in mortality at 3, 6 and 12 months Better functional outcomes at 3, 6 and 12 months Reduction in complications

Díez Tejedor et al. 2001 Fuentes et al. 2006	Prospective Historical controls	Better functional outcome at discharge Decrease in length of stay Reduction in complications Reduction in long-stay hospitalization Decrease in health costs Consistent long-term benefits after operation.
Cadilhac e Ibrahim 2004	Prospective Simple blind	Higher rates of adherence to key processes of stroke unit care compared with other care models
Non-monitored Stroke Units vs. Critical-care Monitored Stroke Units		
Sulter et al. 2003	Pilot study Randomized	Reduction in mortality in the monitored stroke units
Cavallini et al. 2003	Prospective Non randomized	Better functional outcome in monitored stroke unit

Table 40.1. **Selected studies comparing different stroke care models.**

Furthermore, several meta-analyses have confirmed the effectiveness of stroke units in reducing early mortality and at 1 year after stroke, with a reduced risk of death and of death or long hospitalization, as well as a non-significant trend for reduced death or dependency. It has been demonstrated that all stroke patients, regardless of age, severity or etiological subtype, benefit from stroke unit care.

Although stroke unit care is considered a care measure with evidence level grade I based on randomized trials and meta-analyses, there is currently no widespread implementation of such care, unlike what has happened to coronary care units. Various studies and surveys on stroke unit population coverage showed disparate figures, with about 10% of stroke patients admitted to a stroke unit in France or Italy and 60-70% in Scandinavian countries. This contrasts with the epidemiological, social and health impact of reduction in stroke mortality and the higher percentage of patients who are able to return home after hospital discharge, as the number of stroke units in a given country rises. In fact, stroke unit care is the only organization proved to reduce stroke-related death and it is also the only intervention that has been shown to be associated with lower rates of functional dependence on long-term follow-up. And unlike other treatments for cerebral infarction such as intravenous thrombolysis, stroke care may be applicable to most patients.

For these reasons, international health organizations such as the World Health Organization, the World Stroke Organization and the European Stroke Organization have supported recommendations to implement stroke units.

40.3 Current Concept of the Stroke Unit

Over time and following the publication of several studies, the term “stroke unit” has been used to describe different care models based on different organizational aspects such as timing of admission from the onset of symptoms (acute stroke unit, <7 days vs. non-acute stroke unit, >7 days); or the specific objectives of a stroke unit: acute care, rehabilitation, and mixed when acute care and rehabilitation are combined.

At present there is some variability in the departments where a stroke unit can be set up (neurology, geriatrics, internal medicine, and rehabilitation). Stroke units attached to neurology and internal medicine wards seem to focus more on the specific acute care of stroke, whilst those operating within geriatrics or rehabilitation departments

are more oriented to physical rehabilitation. Within and across countries experience in stroke management may reside in different hospital departments (general medicine, geriatrics), mainly due to the provisions of local health policy and the availability or development of medical specialties; however, it is generally recommended that a stroke unit be attached to a neurology department. A stroke unit may consist of a multidisciplinary structure coordinated by a neurologist specialized in cerebrovascular diseases, specially trained medical personnel, and dedicated beds for stroke patients.

This heterogeneity of concepts and designs has generated confusion as well as the difficulty of comparing studies. It is therefore essential to distinguish the stroke unit from other systems of stroke care. A stroke unit may be defined as a geographic area where acute stroke patients arriving from emergency services, outpatient clinics or from other hospitals are admitted and from which, once stabilized, they can be transferred to the neurology and rehabilitation wards of the hospital, home or another hospital. Thus, acute stroke unit care includes critical non-intensive measures during the acute stroke phase. Following stabilization, the patient is then transferred to a neurology ward for general neurological diagnostic and therapeutic evaluation before being discharged home or transferred to a rehabilitation ward or a geriatric unit. As this concept of acute

Infrastructure	Personnel	Services	Other
Minimum			
Dedicated beds for stroke patients	Multidisciplinary Team Stroke-expert neurologist Trained nurses Rehabilitation physician and physiotherapists Speech and occupational therapists	Non-invasive monitoring: • EKG • Oxygen saturation • Blood pressure Body temperature Neuroimaging 24/7 (at least CT) Extracranial doppler sonography	Written protocols for stroke diagnosis, management and prevention Early mobilization and rehabilitation Continuous medical education in stroke management Professional education programs for health personnel Education programs for patients, relatives and caregivers
Recommended			
Stroke outpatient clinic		Transcranial doppler sonography Extracranial dupplex sonography Availability of echocardiographic studies: TTE, TEE Neuroimaging: MRI Vascular neuroimaging: angio-CT, magnetic resonance angiography, transfemoral cerebral angiography	Stroke pathways Stroke database

Table 40.2. **Minimum and recommended requirements for a stroke unit according to current international recommendations.**

CT = computed tomography
EKG = electrocardiogram
MRI = magnetic resonance imaging
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography

stroke unit care is the one most widely accepted today as a paradigm for the stroke unit, this is the model to which we will refer in the rest of this chapter.
The medical specialty considered as embodying "stroke expertise" varies from country to country, depending on health policy and the various systems of medical specialization; nonetheless, the stroke care delivered by medical specialists in neurology has been shown to be superior over other specialties. Therefore, it is now recommended that a stroke unit be attached to a neurology department. Without any prejudice to its multidisciplinary nature, stroke care should be coordinated by a neurologist expert in stroke management and provided by specially trained staff. The activity of the stroke unit must be operative around the clock, with the physical presence of a neurologist on call. It is important to state admission criteria and to develop explicit diagnostic and treatment protocols, as well as coordinated work programs with other specialties such as cardiology, neuroradiology, neurosurgery, vascular surgery, rehabilitation and geriatrics. It is also recommended that the stroke unit be equipped with facilities for non-invasive multi-parameter monitoring (EKG, oximetry, blood pressure and temperature) and with an ultrasound laboratory for studying cerebral circulation (at least transcranial Doppler and continuous Doppler for cervical arteries) (Table 40.2).
Numbering among the factors associated with stroke unit benefits is the reduction in hospital-related complications and a greater adherence to care protocols for general care, diagnostic procedures and documentation.

40.4 Evolution and Development of Stroke Units

Although the effectiveness of the stroke unit is amply demonstrated, further organizational measures have been proposed to increase their benefits: non-invasive continuous monitoring and implementation of clinical pathways.

40.4.1 Stroke Unit With a Non-invasive Continuous Monitoring Facility

Early rehabilitation has long been considered as the most important component of stroke unit care and a determinant of its effectiveness. But since Indredavik noted the influence of general care, particularly in relation to blood pressure control and early treatment of hyperthermia, the importance of maintaining homeostasis has become increasingly evident, as it has also been associated with short-term outcome and fewer complications. These beneficial effects were shown in a stroke unit where assessment of vital signs was performed four times daily and non-invasively. Several recent studies have underscored the importance of continuous monitoring of these parameters; and their involvement in the prognosis of patients demonstrated lower mortality at 3 months and 1 year and a better prognosis at discharge. This benefit was probably due to prompt detection of complications (cardiac events, fever, hypertension, hypotension and hypoxia) in the monitored patients, and therefore the ability to act quickly on them. At present, the provision of continuous monitoring is essential for a new stroke unit.

40.4.2 Clinical Stroke Pathways

Several approaches to the implementation of clinical pathways in stroke care, mainly in rehabilitation, have been described, but the impact such pathways can have on the

acute phase of stroke remains to be elucidated. What has been pointed out is an increase in diagnostic procedure performance and a reduced risk of urinary tract infections or rate of hospital readmission. However, we still lack enough scientific evidence about its benefits in stroke outcomes, as indicated by two Cochrane reviews, because of methodological limitations (non-randomized design of most studies). Only one study with historical controls has analyzed the impact of the introduction of a clinical pathway in an acute stroke unit, showing higher quality in the diagnostic process and reduction in urinary tract infection rates as an in-hospital complication. In addition, clinical pathways specifying the different daily diagnostic and therapeutic measures that should be applied to stroke patients would ensure continued quality of care. On the other hand, such pathways could avoid reducing the provision of services on weekends and holidays, as several studies have shown, concluding that patients admitted to a stroke unit on a weekend or during holiday periods had higher mortality and worse functional recovery. This fact has been attributed to the reduction of clinical staff, with a lower intensity of multidisciplinary treatment and delays in the rehabilitation process. It is therefore necessary to ensure continued care in the stroke unit that includes not only an appropriate ratio of nurses but also the proper implementation of diagnostic, physiotherapeutic and rehabilitation processes on weekends and holidays.

40.5 Future: Stroke Networks and Stroke Centers

Unquestionably, the creation of stroke units has been a milestone in stroke care, yet we must recognize that they cannot act in isolation. There is an increasing need for the coordination of stroke care networks to ensure the best care for the entire population, as it would be impossible to establish high-level stroke units operating diagnostic and therapeutic services in all hospitals. Therefore, many scientific societies and governments are developing stroke care plans for the coordinated organization of available resources to create networks of care for stroke patients. The objectives of these systems go beyond the medical care of acute stroke patients to include aspects of population health education in primary and secondary prevention, develop stroke warning systems for the rapid response of emergency services, specialized stroke treatments, rehabilitation and advocacy for the quality of life of these patients.
Thus, from an organizational point of view, we can consider three levels of stroke care.

40.5.1 Stroke Centers

In addition to having a stroke unit, they also ensure the provision of complex diagnostic or therapeutic procedures for selected patients. The minimum facilities for these centers include:

- Infrastructure:
  - Stroke Unit.
  - Intensive Care Unit.
  - Emergency Department.
  - Stroke Database.
- Personnel:
  - Neurologist physically present in the hospital every day and 7 days a week.
  - Interventional neuroradiologist 24/7.
  - Stroke Medical Coordinator.
  - Stroke-trained neurologists.

- Stroke-trained nurses.
- Rehabilitation physician and physiotherapists.
- Stroke-expert neurosurgeons.
- Vascular surgeons with experience in carotid surgery.
- Diagnostic radiologists expert in stroke diagnosis.
- Intensivists.
- Social workers.

- Diagnostic procedures:
  - Extracranial and transcranial doppler sonography.
  - Extracranial and transcranial duplex sonography.
  - Brain diagnostic imaging: CT and MRI.
  - Vascular neuroimaging: angio-CT, magnetic resonance angiography, transfemoral cerebral angiography.
  - Functional neuroimaging.
  - Echocardiography.
- Invasive treatments:
  - Revasculazation procedures: carotid surgery, angioplasty and stenting.

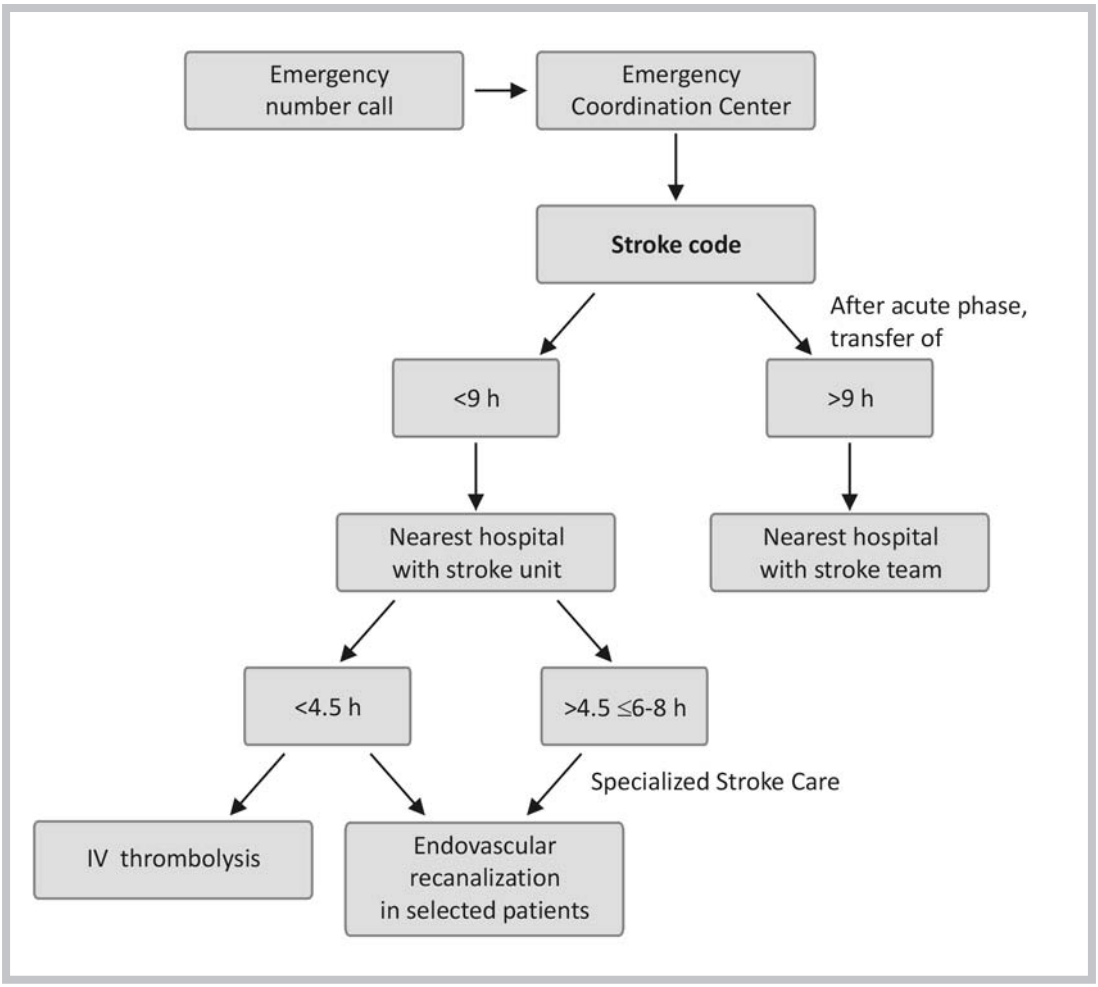

Figure 40.1. **Stroke Code of The Madrid Stroke Network. Activation and distribution of stroke patients by the emergency coordination center.**

- Endovascular procedures: aneurysm and intracranial vascular malformations, intraarterial reperfusion and recanalization.
- Neurosurgical procedures: hemicraniectomy, surgical evacuation of brain hemorrhage, external drainage for hydrocephalus, surgical excition of aneurysms and intracranial vascular malformations.
- Cardiovascular surgery.

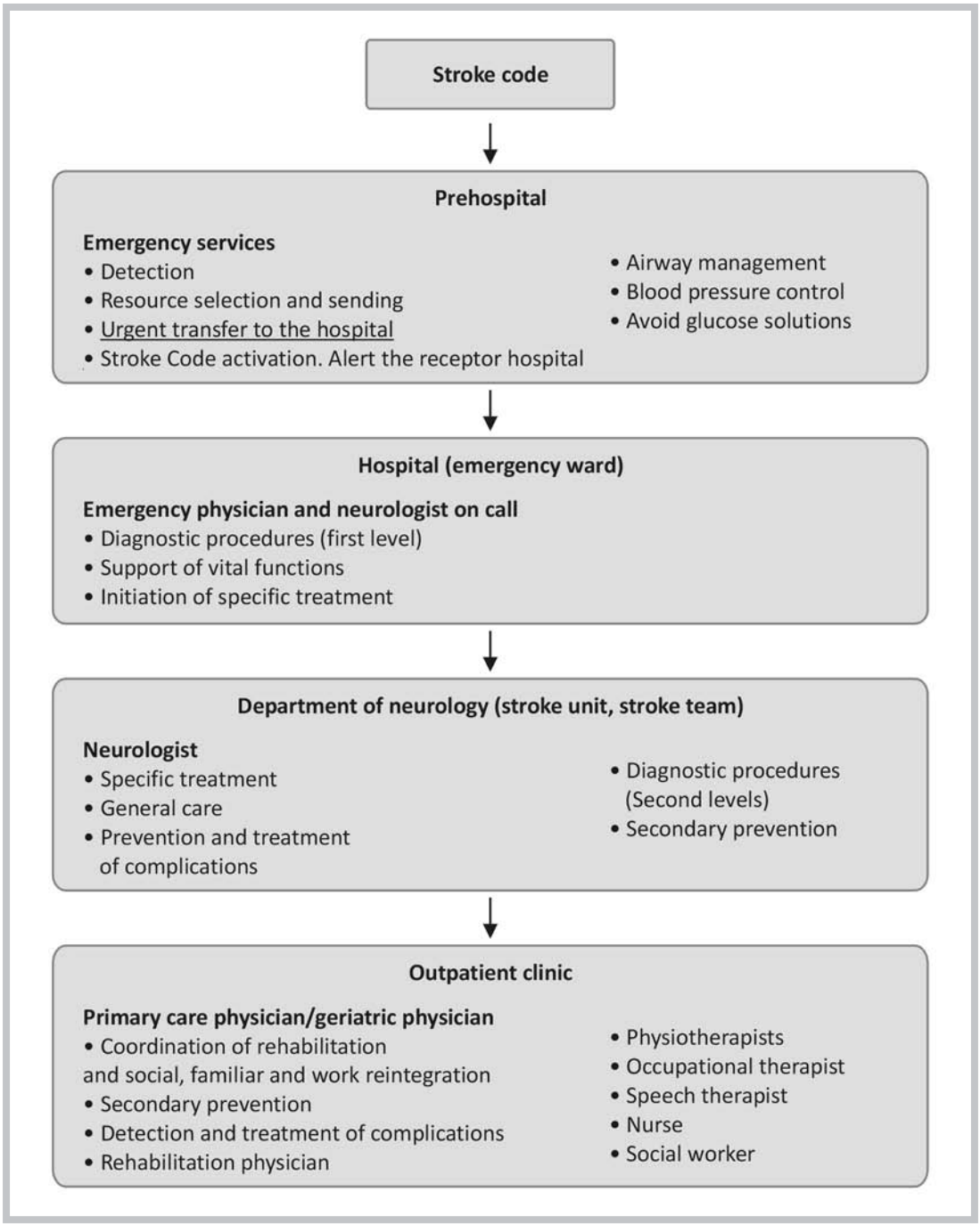

Figure 40.2. **Integration of extra-and intra-hospital stroke code in a stroke care network. Priorities and tasks.**

- Programs:
  - Established networks with extra- and intra-hospital stroke codes (Figures 40.1 and 40.2).
  - Multidisciplinary work plans with participation of different specialists involved in stroke management: vascular surgeons, neurosurgeons, cardiologists, rehabilitation physicians, neuroradiologists.
  - Diagnostic and therapeutic protocols.
  - Education and research programs.

40.5.2 Stroke Unit Hospitals

They are provided by a stroke unit with all the diagnostic and therapeutic procedures needed for acute stroke care, with a neurologist physically present in the hospital every day and 7 days a week. Recommended organizational elements are:

- Infrastructure:
  - Stroke Unit.
  - Intensive Care Unit.
  - Emergency Department.
  - Stroke Database.
- Personnel:
  - Stroke Medical Coordinator.
  - Neurologist physically present in the hospital every day and 7 days a week.
  - Stroke-trained nurses.
  - Physiotherapists.
- Diagnostic procedures:
  - Brain CT scan 24/7.
  - Emergency laboratory 24/7.
  - Extracranial and transcranial sonography.
  - Non-invasive multiparametric monitoring.
- Programs:
  - Established networks with extra- and intra-hospital stroke codes.
  - Multidisciplinary work plans with participation of different specialists involved in stroke management: vascular surgeons, neurosurgeons, cardiologists, rehabilitation physicians, neuroradiologists.
  - Diagnostic and therapeutic protocols.

40.5.3 Stroke Team Hospitals

In those hospitals where a stroke unit is not possible, mainly because of the scarce number of acute stroke patients admitted, stroke care is provided by stroke teams, defined as multidisciplinary teams specialized in stroke management. As they are not large enough, these hospitals do not generally have a neurologist physically present 24/7 nor the facilities for specific treatments like intravenous thrombolysis during the acute stroke phase. When necessary, patients are transferred to a hospital with a stroke unit or to a stroke center in order to complete the treatment. To ensure fluidity of patient referral systems and to allow early administration of drugs within a narrow therapeutic window, it is essential to develop inter-hospital coordination systems included in the stroke networks. These hospitals will have:

- Infrastructure:
  - Emergency Department.

- Personnel:
  - Stroke Team directed by a stroke-expert neurologist.
  - Physiotherapists.
- Diagnostic procedures:
  - Brain CT scan 24/7.
- Programs:
  - Stroke care protocols.
  - Inter-hospital referral protocols.

Finally, we wish to underscore the need to regularly assess the performance of patient care in the stroke unit to verify that the benefit is maintained over time. For this task indicators are being developed in relation to diagnostic and therapeutic procedures applied, including evaluation of time to treatment.

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41 Regional Stroke Systems of Care and the Role of Telemedicine in Supporting Acute Stroke Care: Case Study of the US system

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41.1 Introduction

Stroke affects 15 million people worldwide each year, leaving 5 million disabled, and 5 million dead [1]. Intravenous thrombolytic therapy (tissue plasminogen activator, t-PA) has been shown to reduce disability after ischemic stroke, if administered within a 3 hour time window [2] and this has been replicated safely in community practice registries in the US and Europe [3,4]. More recently it has been shown to be beneficial in selected patients in a 3-4.5 hour time window [5,6]. While it has redefined acute ischemic stroke care, it has been demonstrated again and again that there are barriers that limit the optimal availability of this therapy. Such barriers are multifold and range from ineffective candidate identification to loss of opportunities for drug administration (summarized in Table 41.1).

The delivery of intravenous t-PA encompasses more than simply the reconstitution and administration of a drug for a well-defined indication. Whether a patient gets t-PA and how rapidly is influenced not only by where the patient is when symptoms occur, but also by where the patient is brought to medical attention. Whereas coronary artery ischemia is heralded by characteristic chest pain and other associated "positive" symptoms, ischemic stroke is marked by the sudden loss of function, often with the inability to recognize the situation or obtain help. Patients experiencing acute ischemic stroke symp-

Community education	Pre-hospital period	Emergency Department
• Stroke symptom recognition • Availability of t-PA and awareness of the limited time window	• Negative or loss of symptoms associated with brain infarction • Isolation at time of symptom onset • Knowledge to activate Emergency Medical Services • First contact to a primary care site or non-stroke center • Stroke recognition by call-takers • Lack of an established Emergency Medical Services/Ambulance Triage System	• Workflow processes within emergency departments (emergent imaging, laboratory evaluations) • Lack of bedside neurology or stroke expertise within time window

Table 41.1. Barriers to intravenous t-PA administration [7,8].

toms are dependent upon their companions and passersby for recognition and activation of Emergency Medical Services.

The indication for t-PA is moderate to severe ischemic stroke patients identified and treated within 4.5 hours of onset, with a thoughtfully considered exclusion of several relative and absolute contraindications. Thrombolytic administration in a well-selected group carries with it a 6% risk of symptomatic brain hemorrhage; this risk is presumably higher in poorly selected candidates. In the hyperacute setting, the risk of drug administration despite relative contraindications must be weighed against the risk of disability after an untreated moderate to severe ischemic stroke. This medical decision-making process often occurs in the context of a medicolegal environment which, at least in the US, has found in favor of plaintiffs most often in the setting of failure to provide IV t-PA rather than in the setting of symptomatic hemorrhage after tPA [9].

Access to needed stroke expertise (ideally, but not necessarily, at the bedside) is integral to the timely and appropriate administration of t-PA. Ultimately, whether a patient in that moment has access to such expertise is determined largely by geography, economic circumstance, and the existence of an established and functional stroke system of care delivery. It can have profound impacts on outcomes (Figure 41.1). The universal availability of stroke neurologists in the US is limited by a shortage of trained specialists and varying desirability of practice environments.

To ensure equitable access to acute stroke care within a region, pre-hospital and hospital organizations must work together to pre-specify a communication and transfer plan for any patient arriving at any given location. Hospitals with available stroke physicians and specialized resources for endovascular therapy should accept responsibility for collaborating with other facilities within their region to promote access to advanced acute stroke care [10].

In most regions, such informal relationships exist, in the form of consults via plain old telephone service (POTS). Over a simple telephone connection, advice is given "blind-

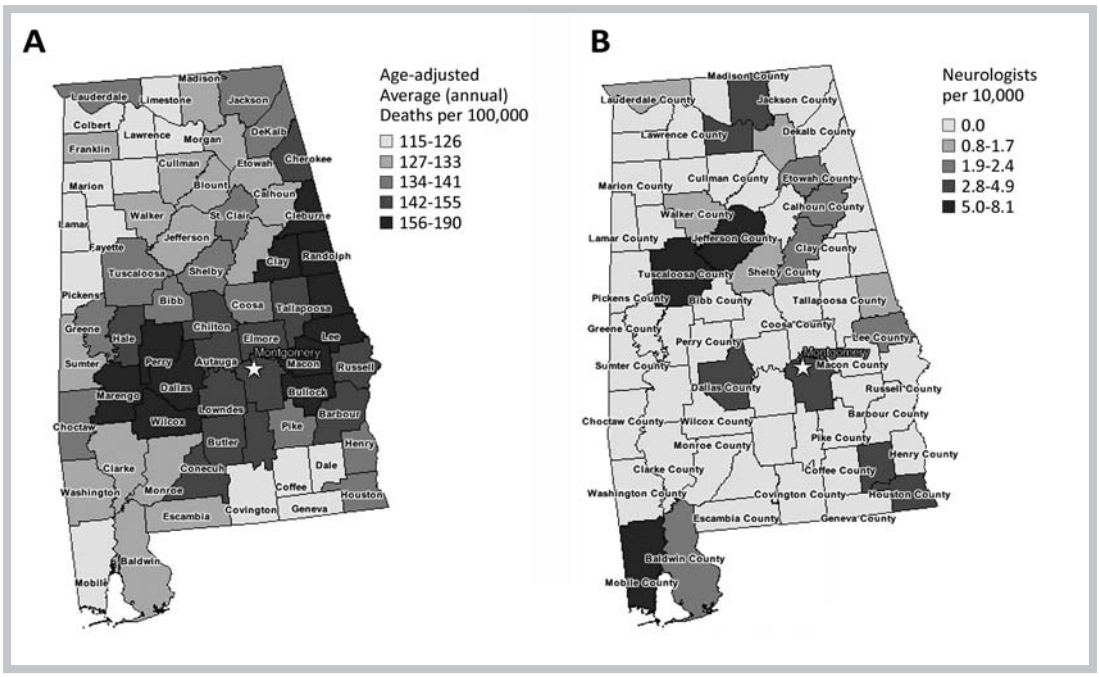

Figure 41.1. **Stroke death rates in relation to availability of neurologists in Alabama. From CDC Heart Disease and Stroke Maps. A. Stroke death rates, total population aged 35+, 1991-1998. B. Neurologists.**

ly" without the ability to evaluate a patient's neurologic exam or CT scan, interview multiple family members, and based on the description of a local physician with variable stroke experience. While there are advantages to a telephone stroke system because of its relative safety [11] and wide availability, a direct comparison study suggested that telemedicine is associated with reduced mortality after stroke and required less correction of initial impressions [12]. In cases where the available information does not foster confidence, a transfer might be initiated without administration of t-PA with the hope that the patient can be evaluated in person at the receiving hospital. In such cases, eligible patients may miss the time window for administration while in transit.

Stroke outcomes in a region can be improved by developing a system of care around an infrastructure that addresses the needs of the stroke patient through all phases of their care. This involves the entire time-treatment spectrum from prevention to rehabilitation. The components of an ideal stroke system have been defined elsewhere[10] and are summarized in Table 41.2.

- Primordial and primary prevention
- Community education
- Notification and response of emergency medical services
- Acute stroke treatment
- Subacute stroke treatment and secondary prevention
- Rehabilitation
- Continuous quality improvement activities within each domain and across the system itself

Table 41.2. **Components of an ideal stroke system (adapted from the American Stroke Association's Recommendations [10].**

- Telemedic Pilot Project of an Integrative Stroke Care in Eastern Bavaria (TEMPiS) (Bavaria, Germany)
- Partners Telestroke Center (Massachusetts, USA)
- Southwestern Ontario Telemedicine Network (Ontario, Canada)
- Remote Evaluation in Acute Ischemic Stroke (REACH) (Georgia, USA)
- Michigan Stroke Network (Michigan, USA)
- Colorado Neurological Institute/Swedish Medical Center Telestroke Network (CO-DOC) (Colorado, USA)

Table 41.3. **Examples of some successful telestroke programs employing different models of care delivery pre- and post-thrombolysis decision-making.**

Telemedicine can be a tool within a stroke system that offers safe and effective universal access to acute stroke care [11,13,14] (Table 41.3.). In addition to telemedicine-supervised t-PA administration for neurologically underserved areas, it can allow the retention of appropriate patients while referring high-risk and interventional cases to a comprehensive stroke center. When transferred patients are first consulted via telemedicine, the receiving doctors (and patients) are at a distinct advantage of having already been introduced and may pick up the course in mid-treatment rather than initiating new assessments upon arrival at the comprehensive stroke center. Telestroke can increase use of tPA at spoke sites and decrease time to tPA administration [14,15].

In addition to clinical care, there are educational benefits of an established relationship and audiovisual connection between hospital organizations within a stroke system. Continuing medical education around stroke care can easily be accomplished on a scheduled basis. Ongoing site training and quality assurance meetings can also be accomplished via audiovisual connection, overcoming geographic and time barriers.

41.2 Conclusions

Achieving excellence in ischemic stroke care across a geographic region begins with the collaboration of key stakeholders and institutions to develop the necessary infrastruc-

ture for a system of care delivery. The entire spectrum of a stroke patient's care, from prevention to rehabilitation, can be positively affected by the establishment of stroke systems. Telemedicine is a tool for a stroke system that can enhance the equitable distribution of stroke education and access to urgent neurologic expertise.

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42 Acute Ischemic Stroke: General Approach

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42.1 Introduction

Ischemic stroke includes several entities that have in common the disruption of cerebral blood flow resulting in transient or permanent dysfunction of one or more regions of the cerebral or cerebellar parenchyma. Ischemic stroke has multiple etiologies and its pathophysiology varies accordingly. It is a very heterogeneous disease; therefore, knowledge of its triggering mechanisms will aid in interpreting the manifestations of stroke correctly and to properly plan therapy and secondary prevention.

Disorders of cerebral circulation are the third leading cause of death in the developed countries and the leading cause of long-term disability. While there are little official data, the incidence of stroke in Argentina is estimated to be between 110 and 285 cases per 100,000 individuals, with more than 500,000 people living with the sequelae of stroke.

Much of the permanent and irreversible brain damage occurs in the early hours after the event: this explains why ischemic stroke is a “true medical emergency” requiring high levels of suspicion, skill, determination and timely response by medical staff. The term “brain attack” was created to draw a parallel with heart attack, thus reaffirming the severity of the event and the urgency with which these patients should be treated. Recent U.S. surveys reveal that most people are unable to recognize stroke symptoms when they occur. Educational programs targeting the population are needed, since only through prompt recognition of symptoms can effective treatments be initiated.

42.2 Pathophysiology of Ischemic Stroke

42.2.1 Brain Metabolism

The brain weighs about 1200 to 1500 grams, accounts for only 2% of body weight, but receives 15% of total cardiac output and utilizes 20% of the oxygen and 25% of the glucose consumed by the body. The high energy requirement of the brain, without available oxygen or glucose reservoirs, makes the availability of energy substrates critical in ensuring the normal functioning of brain tissue.

Normally, the brain’s energy demand is met almost exclusively by the metabolic oxidation of glucose. The oxygen consumption of an adult human brain is around 170 mmol/g/min, whereas glucose consumption is near to 30 mmol per minute per gram of tissue, with a oxygen/glucose consumption ratio of 6:1.

Cerebral blood flow (CBF) is normally 50 to 60 ml per 100 grams of tissue per minute. The brain extracts 33% and 10% of the total available oxygen and glucose, respectively. 60% of the energy produced is used to maintain transmembrane ion gradients, and the

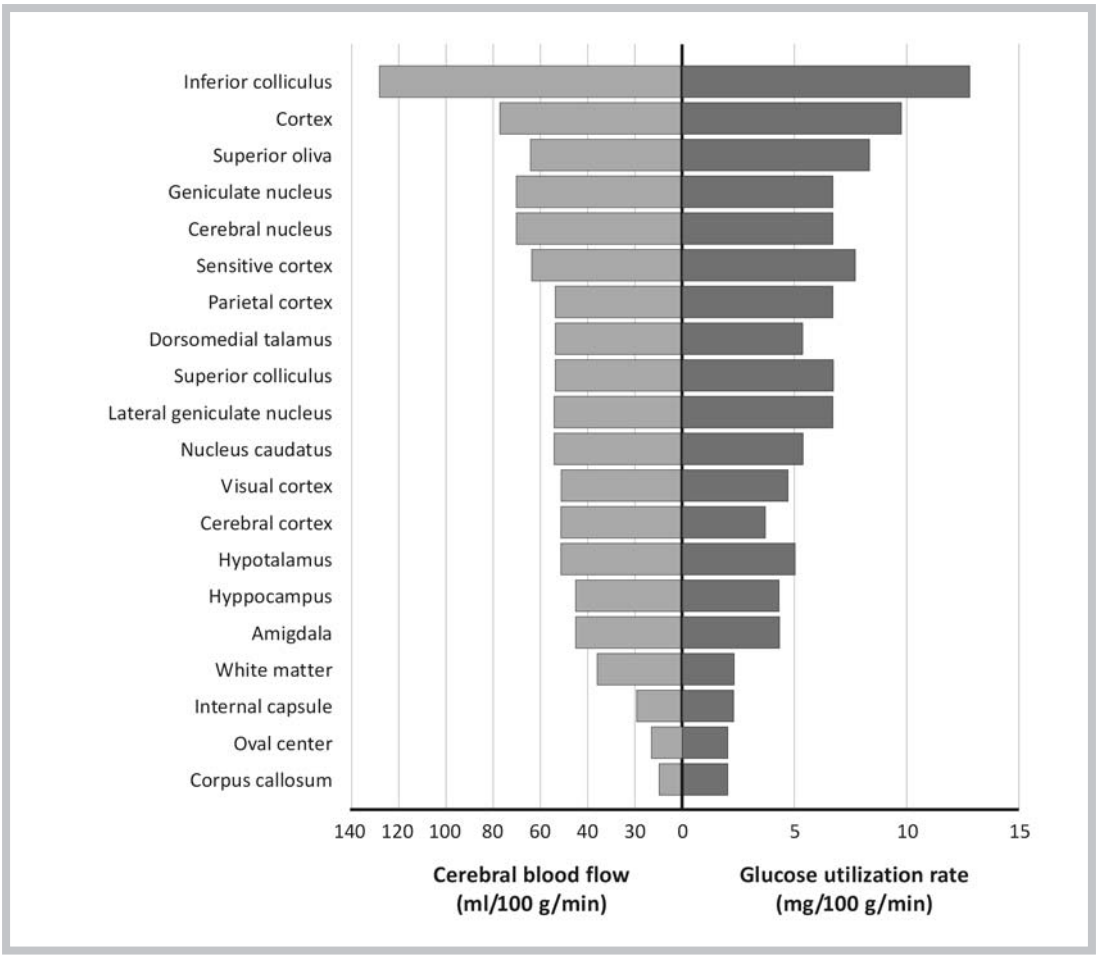

Figure 42.1. **Differences in cerebral blood flow and glucose utilization rate according to anatomic region.**

remaining 40% is used for synthesis, release and reuptake of neurotransmitters and the replacement of cell structures. Both oxygen and glucose consumption, as well as CBF, vary according to the different needs and functions of each anatomic region (Figure 42.1). The gray matter requires a greater availability of energy substrates than the white matter due to the presence of cell bodies and high synaptic activity.

42.2.2 Determinants of Cerebral Blood Flow and Cerebral Autoregulation

The major determinants of CBF are:

- Cerebral perfusion pressure (CPP).
- Vessel diameter expressed as cerebral vascular resistance (CVR).
- Blood viscosity.

$$CFF = CPP/CVR$$

CPP is defined as the difference between mean arterial pressure (pressure at the beginning of the circuit [MAP]) and cerebral venous pressure (pressure at the end of the cir-

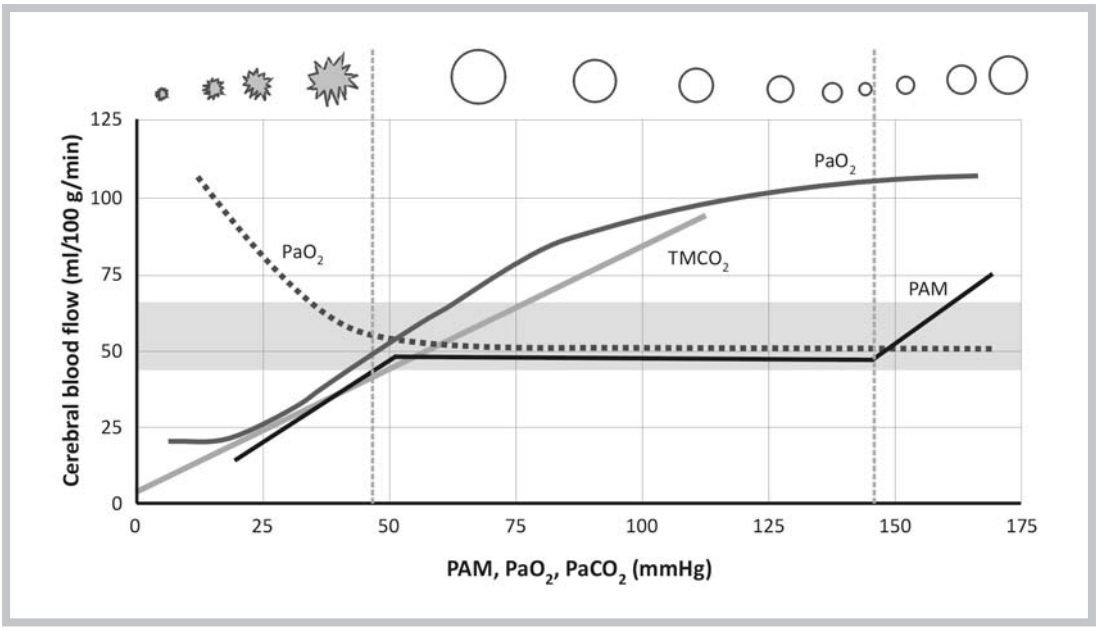

Figure 42.2. **Cerebral autoregulation.**

cuit [CVP]). However, from a practical point of view, the latter is very difficult to measure and is fairly accurately reflected by intracranial pressure (ICP), thus:

$$CPP = MAP - ICP$$

Cerebral vascular resistance is determined by the ability of the cerebral blood vessels to contract or expand in different situations or in response to stimuli. This property of the cerebral vasculature, which allows it to maintain CBF constant despite variation in CPP, is called cerebral autoregulation (Figure 42.2).

Normally, CBF is maintained relatively constant between 50 and 150 mmHg of mean arterial pressure. Outside these limits, CBF passively follows arterial pressure, which means that the vasculature will collapse at MAP <50 mmHg, with a consequent decrease in CBF. At the other extreme, MAP >150 mmHg overloads vasoconstrictive capacity, leading to vasodilation with a consequent increase in CBF.

Cerebral oxygen consumption is another determinant of CBF. As metabolic demands rise, CBF increases directly and proportionally to meet them.

42.3 The Ischemic Penumbra Area

42.3.1 Definition

After an acute ischemic attack, at least two areas in the brain parenchyma can be observed: a central one, the “core”, with established and irreparable structural damage, and therefore necrotic, and a larger peripheral around the core with the potential to recover lost functions, known as the “penumbra”. The penumbra is a region of brain tissue with functional damage at risk of being affected irreversibly but still potentially viable, so that the damage may be reversed with appropriate therapeutic measures.

42.3.2 Concentric Four-compartment Ischemia Model

Hypoperfused brain parenchyma, depending on the magnitude and duration of ischemia, can be compartmentalized into (Figure 42.3): a center or core (4) which represents the irreversibly damaged or infarcted tissue. Surrounding the core with variable extension it is the penumbra area (3) at serious risk of definitive stroke. Between the unaffected area (1) and the ischemic penumbra there is a zone of "benign oligemia" (2) which usually survives the attack, even without early reperfusion, depending primarily on the "time" factor.

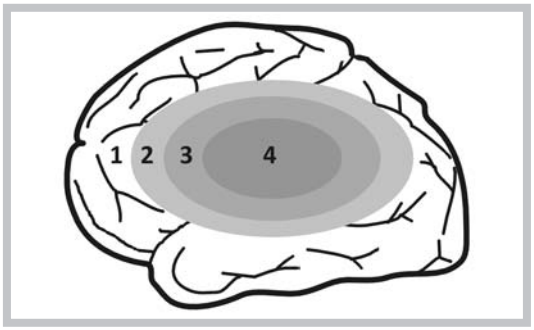

Figure 42.3. **Four-compartment brain ischemia model.**
1 = unaffected area
2 = benign oligemia
3 = penumbra area
4 = ischemic core

42.3.3 Relationship Between Cerebral Blood Flow and Penumbra Area

By definition, the penumbra is an ischemic region with decreased CBF. Experimental and clinical studies have demonstrated two critical thresholds during focal cerebral ischemia. When CBF drops below 20 ml/100 g/min, the neurons lose their spontaneous or induced ability to conduct electrical impulses: this is the "threshold of electrical failure" characterized by alterations on the electroencephalogram (EEG) and in evoked potentials. Typical EEG findings in this phase are the slow pathologic activity (theta and delta waves), with the concomitant disappearance of physiological alpha and beta rhythms.
When CBF reaches 10 ml/100 g/min, the cells are unable to maintain transmembrane ion gradients: this is the "threshold of ionic failure", which produces ionic collapse, causing a massive influx of calcium into the cell, triggering cascades of different nature and complexity that interact with a single purpose – neuronal death.

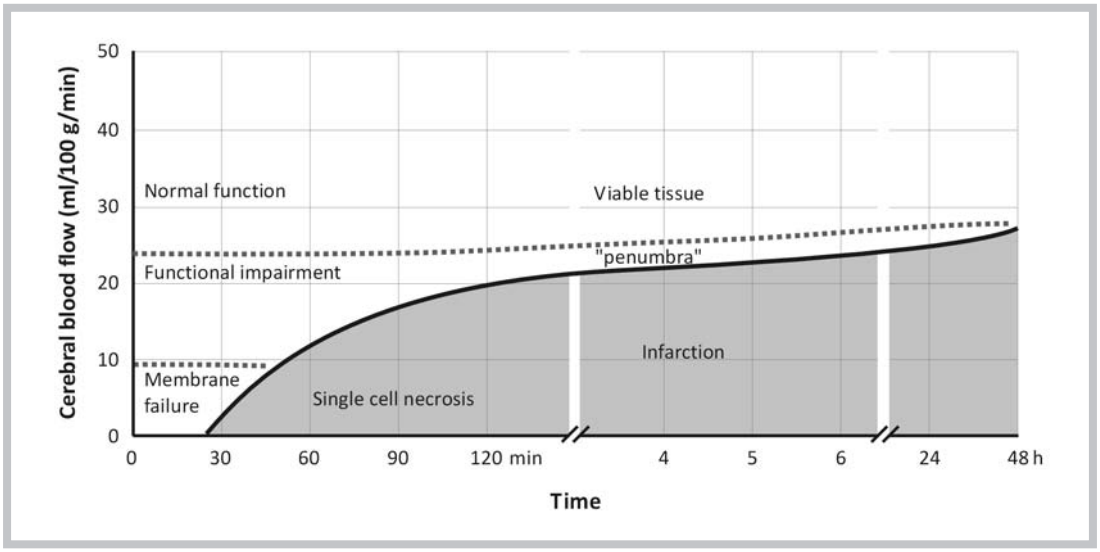

Figure 42.4. **Schematic relationship between CBF and ischemia/infarction. CBF below the threshold and with the "time" since the event causes cell death and infarction.**

Hence, it is very important to keep in mind that the value of CBF determining the "point of no return" depends on the time elapsed since the beginning of ischemic insult.
Although the penumbra develops consequent to an ischemic event, positron emission tomography (PET) and magnetic resonance imaging (MRI) studies have shown that during the acute phase the CBF may be decreased, normal or increased, depending on the immediate reperfusion of the ischemic but not the necrotic tissue. And although reperfusion occurs relatively quickly, it is not always beneficial nor does it guarantee functional recovery of the affected area.
From a metabolic point of view, the penumbra is characterized by increased cerebral oxygen extraction and a decreased rate of oxygen utilization. In this way, areas with a metabolic rate <1.7 ml/100 g/min almost invariably progress towards infarction, whereas those areas which maintain an oxygen utilization rate >2.5 ml/100 g/min remain unchanged. Intermediate values are associated with an indistinct evolution towards necrosis or full recovery.

42.3.4 The Concept of Therapeutic Window

"Time is brain" is the American sentence created to raise public awareness, and to awaken health providers involved in the chain of care of these patients, to the fact that every hour of ischemia and tissue injury that elapses increases the degree and the extent of irreversible neuronal damage. An average of 6 hours is considered as the period during which threatened or at risk cells can be kept viable by restoring blood flow or initiating therapeutic measures to prevent the spread of the penumbra towards infarction. This period is called "therapeutic window".

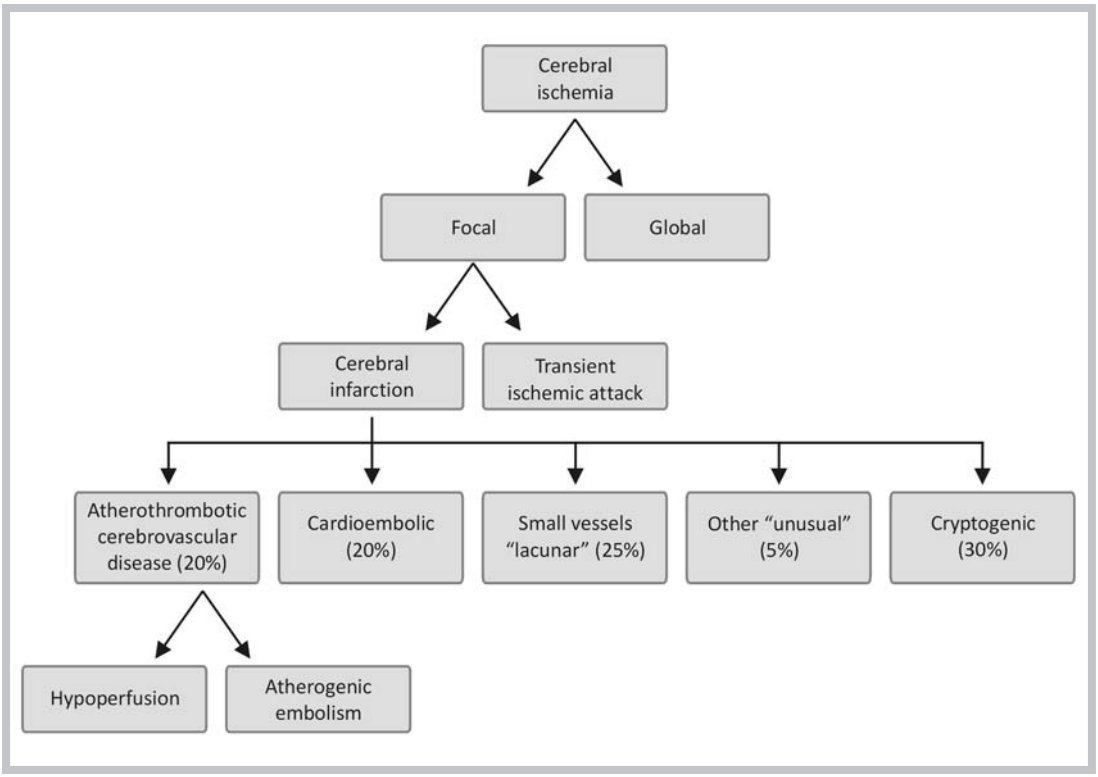

Figure 42.5. **Classification of ischemic stroke according to the triggering mechanism.**

42.3.5 Classification and Diagnostic Criteria of Ischemic Stroke

Grouped under the term "cerebral ischemia" are those entities that share qualitative or quantitative abnormalities in blood supply to the brain. Two main groups are distinguished: a) focal when ischemia affects only one region of the brain parenchyma, and b) global when ischemia affects the whole brain. Focal cerebral ischemia is further subdivided into: a) transient ischemic attack (TIA); and b) stroke.

42.4 Transient Ischemic Attack (TIA)

In light of current knowledge, primarily supported by advances in neuroimaging techniques, TIA is defined as a "brief episode of neurologic dysfunction caused by cerebral or retinal ischemia with signs and/or symptoms lasting no more than 60 minutes and without evidence of infarction on neuroimaging." Recent guidelines suggest eliminating the time factor from the definition. There is a trend towards considering TIA as a benign entity: nothing could be more wrong. It is a serious entity which carries the risk of death or severe disability, and it should never be underestimated. Nonetheless, TIA provides a unique opportunity to start early treatment and prevent progression to stroke. It is estimated that after a first episode of TIA, 10 to 20% of patients will have an infarction in the next 90 days (half in the subsequent 24-48 hours), so that: t**he development of signs and/or symptoms of cerebral ischemia is a medical emergency.**

The causes of TIA are the same as those for stroke (atrial fibrillation, carotid disease, etc.). They will be discussed in detail below, along with measures to prevent future attacks. The diagnosis of TIA, because problematic, requires high index of suspicion and common sense. The clinical history is important; but as it is sometimes impossible to collect data from a patient with altered speech or consciousness during the event, the neurologic examination may identify or clarify the existing deficits.

The clinical features of a TIA depend on the origin and the vascular territory affected. Often, carotid TIAs present with unilateral ocular symptoms such as transient monocular blindness or "amaurosis fugax"or sensory-motor deficits contralateral to the lesion, whereas vertebrobasilar TIAs are generally less localized and last shorter. Isolated unilateral sensory or motor deficits affecting at least two body regions (face, arm or leg) can guide us towards the diagnosis of lacunar TIA.

Since metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hypoxemia, etc.) can obscure the clinical features, laboratory measurements should include: complete blood count (CBC), glycemia, uremia, creatinine, coagulation studies, C-reactive protein and blood gases according to the situation. In addition, routine studies should include chest radiograph, electrocardiogram (ECG), Holter monitoring if occasionally necessary to detect paroxysmal arrhythmias and an echocardiogram is mandatory to determine not only cardiac function but also the possibility of cardioembolic sources detection. In this context, and where feasible, a transesophageal echocardiography is preferable, as because it is more sensitive and specific, especially when checking the aortic arch, the mitral valve or the presence of a patent foramen ovale. It is essential to obtain computed tomography (CT) or MRI studies for diagnosis, as they will rule out or confirm other causes of neurologic dysfunction such as: brain tumor, subdural hematoma, bleeding, or others. Also important is examination and study of the carotid arteries with either Doppler ultrasound or MR angiography, which have a sensitivity of 83 and 86%, respectively, to detect stenosis >70%. Digital angiography is used only to confirm the findings and for selecting the surgical technique and tactics to employ.

42.4.1 Risk Assessment

TIA must be properly evaluated not only to define the most appropriate treatment but also to refer the patient to the most appropriate facility and to prevent recurrence and/or occurrence of stroke or cerebral infarction. Rating scales such as the California or ABCD score have been developed and independently validated. A recently modified version of these scores, called ABCD2, has shown better predictive power of stroke within 7 days of the event. The scale is composed of clinical variables (Table 42.1): the risk is considered high when the score is >4 points.

These scores do not incorporate the findings of neuroimaging which by themselves have a high predictive value. For instance, the presence of new infarction increases from 2 to 15 times the possibility of a short-term stroke, whereas blood vessel occlusion demonstrated by MR angiography raises that possibility fourfold.

Variable		Score
Age >60 years		1
Arterial pressure >140/90 mmHg		1
Symptoms: speech disturbance	Without focal weakness	1
	With focal weakness	2
Duration of symptoms	10 to 59 minutes	1
	>60 minutes	2
Diabetes		1

Table 42.1. ABCD2 score.

42.4.2 Treatment

Antiplatelet Drugs

Aspirin reduces the relative risk (average 22%) of cerebrovascular accidents and long-term cardiovascular events after a first episode of stroke or TIA. Aspirin also prevents recurrence and improves functional outcomes. The optimal dose has not been determined; however, while the beneficial effect of the drug is indifferent for doses from 75 to 1300 mg a day, low doses between 200 and 325 mg are preferred due to the lower probability of side effects.

In patients allergic to aspirin or in whom TIA recurs under treatment with the drug, some authors suggest the use of clopidogrel 75 mg daily. A recent study suggested that combining clopidogrel with aspirin or vice versa doesn't enhance the benefit in relation to aspirin or clopidogrel alone in reducing the rate of cerebral and myocardial infarction or cardiovascular death. The ESPS II European study showed that the association of dipyridamole and aspirin slightly improves aspirin's effectiveness.

Anticoagulants

While the use of anticoagulants has not been tested in TIA, the wide experience gained in ischemic stroke suggests that in patients with atrial fibrillation, anticoagulation therapy reduces the risk of recurrence. In patients without atrial fibrillation, the use of anticoagulants afford no greater benefit than with aspirin. A meta-analysis of 21 placebo-controlled trials of several anticoagulants in patients with cerebrovascular ischemic stroke failed to show benefits.

Statins

Recent studies support the use of statins based on their pharmacological effects independent of inhibition of HMG-CoA reductase and thus their effects on cholesterol or atheromatous plaque. They can reduce endothelin levels, prevent the degradation of

oxidized LDL by nitric oxide synthase, with an indirect vasodilator effect; they can inhibit cell proliferation and have other properties such as anti-inflammatory action, inhibition of thrombogenesis, and platelet aggregation and atherosclerotic plaque stabilization.
Several recent, properly designed large-scale studies with long follow-ups have demonstrated that statin use (specifically pravastatin, lovastatin and simvastatin) significantly reduces morbidity and mortality due to vascular events, including strokes and TIAs.

Carotid Endarterectomy

This topic will be discussed in more detail in another chapter. TIA secondary to carotid stenosis >70% clearly benefits from this therapeutic modality.

Control and Prevention of Risk Factors

All measures to reduce or eliminate the risk factors for brain or cardiovascular diseases are also effective in preventing the recurrence of TIA or its evolution towards stroke. Statins reduce the relative risk by 29%, even in the absence of dyslipidemia, while antihypertensive drugs lower the relative risk by 25-30%.
In diabetic patients the strict control of glycemia is a priority. Weight control, exercise, smoking cessation and moderate alcohol consumption are other voluntary preventive measures that should not be overlooked.

42.5 Atherosclerotic Carotid Disease

Carotid stenosis is an entity that clearly predisposes to TIA or stroke. An estimated 20% of ischemic cerebrovascular accidents are caused by atherosclerotic plaques in the initial portion of the internal carotid artery. Involved in its pathogenesis are many factors: mechanical forces that damage the endothelium, triggering reflexes and the release of inflammatory mediators, expression of adhesion molecules, and secretion of growth and chemotactic factors that induce the proliferation of smooth muscle cells and macrophages in the vessel wall. Other mechanisms included are: synthesis of a connective tissue matrix incorporating cholesterol, platelets, fibrin and lipoproteins, thus forming atherosclerotic plaques.
The clinical picture and Its signs and symptoms are similar to those described for TIA.
Assessment must be completed with high-resolution Doppler ultrasound, MR angiography, transcranial Doppler with the study of cerebral vasoreactivity and detection of emboli.

42.5.1 Therapeutic Approach

The therapeutic approach to patients with carotid atherosclerosis should be directed towards achieving the following goals:

- Stabilize and halt the progression of atherosclerotic plaque by modifying or removing the above risk factors, together with the use of statins, angiotensin-converting enzyme inhibitors and aspirin.
- Eliminate or reduce the stenosis by carotid endarterectomy or angioplasty with stent implantation.

Endarterectomy in Symptomatic Carotid Stenosis

The use of this technique for symptomatic stenosis ≥70% is strongly supported by three studies: NASCET, the American Veterans cooperative study, and the European ECST.

The NASCET showed that, after 2 years, the rate of ischemic stroke ipsilateral to the affected carotid territory was 26% in the medically treated group versus 9% in the surgical group: this amounts to a relative risk reduction of 65% and an absolute reduction of 17%. For patients with stenosis <50%, the three trials unanimously agreed on the lack of efficacy of surgery.
In moderate stenosis (50-69%), surgery does not provide a significant benefit according to the ECST. For this same group, the NASCET showed that the rate of fatal and nonfatal ischemic accidents was 22.2% in the group under medical treatment versus 15.7% in individuals undergoing endarterectomy, with an absolute risk reduction of 6.5%.
Factors associated with better outcomes were: gender (being male), age >75 years, more severe stenosis, stroke with hemispheric symptoms in the last 3 months, intracranial stenosis, the absence of microvascular ischemia (leukoaraiosis or small hypodense images in the periventricular white matter), and presence of collateral vessels.

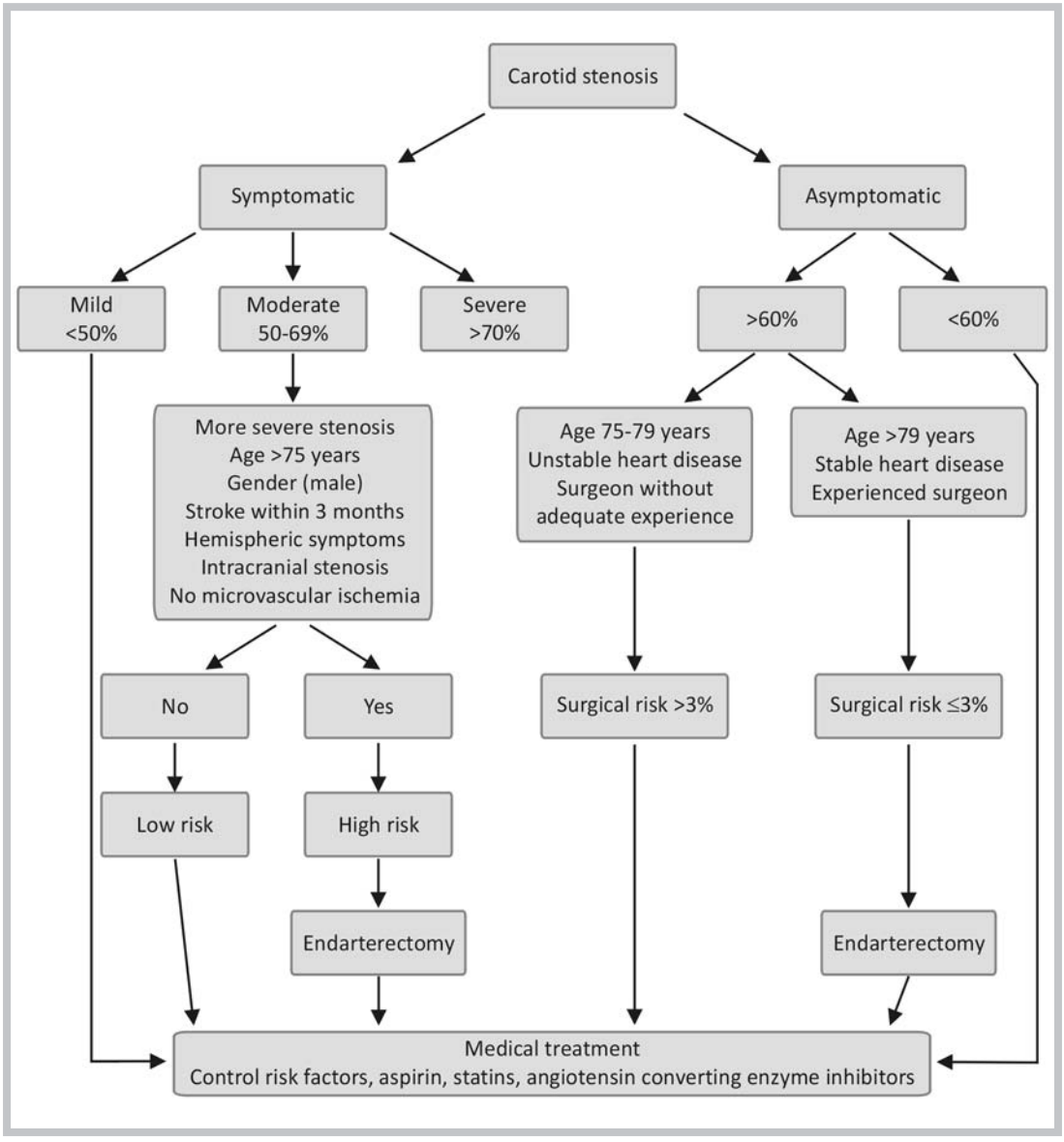

Figure 42.6. **Systematic management of patients with carotid stenosis.**

An additional aspect to consider in global assessment is the presence of ulcerated or complicated plaques, a finding that often aids in the selection of intervention.
When outlining the strategy to follow, the presence of co-morbidities and surgeon's experience should not be omitted.

Role of Endarterectomy in Asymptomatic Carotid Stenosis

Patients with significant carotid lesions (>60%) and no symptoms were evaluated in a multicentre US-Canadian study (ACAS) involving 1661 subjects followed for a 5-year period. The rate of cerebral ischemic event and/or death was 5.1% among the operated patients and 11% for the medical treatment group (absolute risk reduction of 6%).
The key to success in this group of patients resided in the excellent results obtained by the surgical teams involved. Surgery-related morbidity and mortality was about 1.4%. Based on these data, if the perioperative complication rate exceeds 3%, the potential benefits of surgery are nullified.

Endarterectomy Versus Endovascular Treatment

The effectiveness of endarterectomy has been widely demonstrated in large-scale studies throughout the world but the studies lack validation in those individuals considered at high surgical risk. In such patients, endovascular treatment is an attractive alternative. As endovascular techniques and prosthetic material were being developed, as well as neuroprotection measures, postoperative care studies (characterized by a heterogeneity of the patients enrolled as well as the techniques used) comparing both treatment modalities were performed. Some studies viewed surgical endarterectomy as the gold standard, while others found that endovascular treatment had the same or better results than surgery. An evidence-based medicine analysis by the Cochrane group of five trials involving a total of 1269 patients concluded that to date there is no reason to change current recommendations to perform endarterectomy. Moreover, the use of endovascular techniques should be limited to clinical trials to date.

42.6 Cerebral Infarction

When cerebral circulation is suddenly interrupted and causes tissue necrosis, we speak of cerebral infarction. Several subtypes are distinguished; therefore, the following aspects should be considered in the evaluation of stroke patients:
According to the underlying pathophysiological mechanisms, different entities are recognized:

- **Atherothrombotic infarction.** Large (>1.5 cm in diameter) usually compromising the cortical, subcortical, carotid or vertebrobasilar territory. Diagnosis requires the presence of risk factors and previous generalized vascular compromise (peripheral arterial disease, ischemic heart disease, previous TIA, etc.) or vascular compromise demonstrated on further imaging studies such as Doppler, angiography, etc. Cardioembolic source should be excluded.
- **Cardioembolic infarction.** Usually cortical, moderate to large in size, with acute onset. Maximum neurological deficit from the beginning. TIA in several territories supports the diagnosis. Embolic sources (echocardiogram) and lack of atherothrombosis in large arteries must be demonstrated.
- **Lacunar or small vessel infarction.** Deep brain injury or small injury in the brainstem (<1.5 cm in diameter). Arterial hypertension and diabetes support the diagnosis. Microatheromatosis and lipohyalinosis are characteristics in anatomopathology.

- **Infarction of undetermined etiology or "cryptogenic".** Features similar to atherothrombotic, two or more etiologies can coexist. Diagnosis is made by exclusion after checking the most common causes of infarction.
- **Infarction of unusual cause.** Variable size, without predilection for any vascular territory. It usually develops in individuals without classcrisk factors for cerebrovascular disease. It may be the beginning of a disease or occur during its course, e.g., vasculitis associated with connective tissue diseases (systemic lupus erythematosus, etc.), infections (endocarditis, pneumococcal meningitis, etc.), cancer, etc. Other causes: traumatic arterial dissection, complicated migraine, etc.

According to evolutionary profile:

- **Formed or established infarction.** When clinical manifestations occur from the beginning without worsening or improvement. An infarction can be considered established in a carotid territory if the neurological deficit remains changed after 24 hours, while the time period is extended to 72 hours for infarctions involving the vertebrobasilar territory.
- **Progressive or evolving infarction.** Worsening of the initial clinical features with either deepening of the deficit or the occurrence of new symptoms or both.
- **Infarction with trend toward improvement.** Follows a regressive course;usually recovery rate is near to 80% within 3 weeks.

According to the compromised vascular territory, we propose the draft of the classification of stroke in the community of Oxfordshire:

- Total Anterior Circulation Infarction (TACI). The following criteria must be met:
  - Cortical dysfunction or dysfunction of higher brain functions such as aphasia, acalculia or visuospatial impairment.
  - Motor and/or sensory disorders in at least two of the following areas: face, upper limbs, lower limbs.
  - Homonymous hemianopsia.
- Partial Anterior Circulation Infarction (PACI). When some of the following criteria are present:
  - Cortical dysfunction or dysfunction of higher brain functions.
  - Two TACI criteria.
  - Motor and/or sensory deficit narrower than the LACI (e.g., deficit in only one limb).
- Lacunar Infarction (LACI). This subtype doesn't affect higher brain functions or cause hemianopsia. One or more of the following signs or symptoms may be present:
  - Pure motor syndrome affecting at least two of the three body parts (face, arm, and leg).
  - Pure sensory syndrome affecting two of the three body parts.
  - Sensory-motor syndrome compromising two of the three body parts.
  - Ipsilateral ataxic hemiparesis.
  - Clumsy hand.
  - Focal and acute abnormal movements.
- Posterior Circulation Infarction (POCI). Diagnosed when one of the following events is present:
  - Ipsilateral involvement of cranial nerves with contralateral motor and/or sensory deficit.
  - Bilateral motor and/or sensory deficit.
  - Oculomotor pathology.
  - Cerebellar dysfunction.
  - Isolated homonymous hemianopia.

42.6.1 Role of Neuroimaging in Ischemic Stroke

Imaging is essential in the initial evaluation of stroke victims. It is virtually impossible to differentiate ischemia from bleeding based purely on clinical medicine. CT without contrast material is the initial method of choice for diagnosis of a patient with acute neurological deficit, since it is available in most emergency units, can be performed quickly, and is the best method for identifying acute hemorrhage. It can also be performed in critically ill patients and patients under multiple monitoring devices or mechanical ventilation. Diagnosis of ischemic stroke is more difficult in the first 12 hours. Characteristics of the infarction in CT scan are a decrease in attenuation of parenchyma or hypodensity of about 10 to 30 HU, however, it may not be visible for until 24 hours after stroke onset. Only 5% of cerebral infarctions remain isodense during their evolution.

It is essential to investigate for the "early signs of infarction" visible in the first 6 hours in 85% of patients with ischemia of the middle cerebral artery. These signs can appear isolated or coexist with others. They are:

- Spontaneously hyperdense sylvian artery (Figure 42.8).
- Blurring of the boundaries of the lenticular nucleus (Figure 42.9).

Figure 42.7. Structured sylvian infarction.

Figure 42.8. Sign: hyperdensity of the middle cerebral or sylvian artery.

Figure 42.9. Blurring of the boundaries of the lenticular nucleus.

Figure 42.10. Effacement of the insular ribbon.

- Insular effacement (Figure 42.10).

Cerebral edema manifested by effacement of sulci, ventricular distortion, deviation of the midline, and blurring of the boundary between the gray and white matter (Figure 42.11).

Valuable when present, these signs are not often seen in the initial study and their absence does not necessarily rule out ischemic infarction. They allow for the selection of patients eligible for thrombolytic therapy.

Magnetic resonance imaging is very useful in the evaluation of acute stroke. T1 and T2 sequences identify acute ischemia in an earlier stage compared with CT. The development of new techniques such as diffusion (diffusion-weighted imaging) and perfusion seem to be more sensitive and specific in the early hours.

The evaluation of images obtained by the diffusion imaging technique helps the clinician to identify 98% of infarctions in the early hours and is very effective in differentiating new ischemic strokes from existing ones. The combination of both techniques (diffusion and perfusion) may provide prognostic information to differentiate ischemic brain tissue from tissue with irreversible damage.

The comparative disadvantages of MRI versus CT are that MRI takes longer to perform, is not always available in all hospitals, is susceptible to patient motion artifacts, and is contraindicated in patients with pacemakers, intracranial surgical clips and very obese patients.

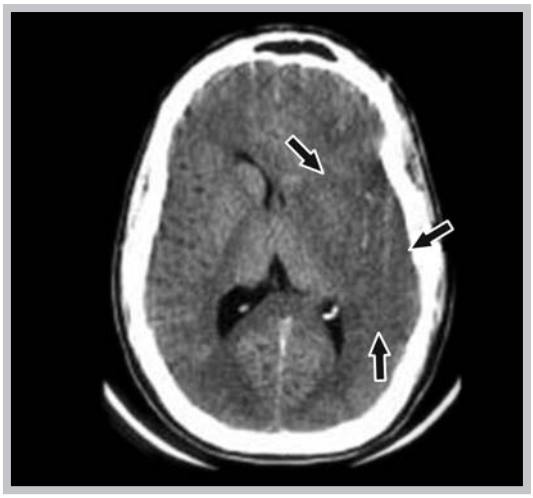

Figure 42.11. Early signs of cerebral edema (effacement of cortical sulci, ventricular distortion, absence of differentiation between the gray and white matter, midline deviation).

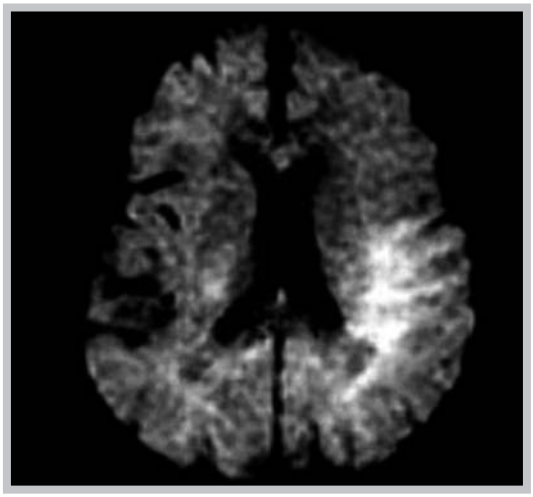

Figure 42.12. MR scan obtained with diffusion-weighted imaging.

42.6.2 Clinical Assessment Scales

Assessment scales are useful tools to reliably and objectively quantify the severity of stroke, its evolution, the final result, and when evaluating the benefit of a therapeutic measure.

Neurological scales allow us to detect deterioration or improvement in basic neurological functions; they must be applied systematically on admission and at set intervals at follow-up. The best one for the evaluation of patients in stupor or coma is the Glasgow Coma Scale (GCS), which was initially designed for assessing traumatic brain injury (TBI) and not for stroke. Among the neurological scales specific for stroke, the most widespread in Latin America is the scale devised by the US National Institutes of Health (NIH Stroke Scale). Other neurological assessment scales for stroke are the Scandinavian or Canadian neurological scales (www.strokeassociation.org).

42.6.3 Acute Phase Treatment

The best therapeutic results are unquestionably obtained with early recognition and diagnosis of the situation. The "nihilistic" concept must be set aside to make way for a strategy to shorten times, as aptly summarized with the concept "Time is brain." Furthermore, efforts should focus on educating the general population and health professionals in the early identification of stroke symptoms to minimize the time of arrival at a specialized centre where these patients can be treated.
Cerebral resuscitation, together with clinical assessment and initial treatment, should begin without delay, as the final results largely depend on the speed with which this true medical emergency is approached.

42.6.4 Prehospital Phase

Depending on infrastructure facilities and human resources available, the initial steps should be directed to the diagnosis of the situation. Clinical examination is essential, because the patient is often unable to communicate, minimizes symptoms or reports them as simple and unspecific malaise. In the United States, abbreviated neurological assessment scales, such as the Cincinnati or Los Angeles scales, have been developed for use by paramedics assisting patients in the prehospital phase. Paramedics with basic training have demonstrated a sensitivity of about 62% in the detection of stroke, which increases to 90% on average when they have received trained in using a rating scale.
In Argentina, as in many other Latin American countries, prehospital emergency services have a doctor on board, providing a unique opportunity to achieve the established objectives.
The next step – perhaps the most important – is to establish the "time zero or time of onset of symptoms." If the patient is "awake" with symptoms of stroke, time zero is when the patient was seen "normal" for the last time.
During transfer, support is the same as in any medical emergency. The ABC rules are followed, i.e. ensuring airway patency and ventilation, monitoring cardiovascular and neurological status, as well as checking blood glucose levels if possible.
Stroke patients may have an altered state of consciousness and reduced cough and deglutition reflexes: the risk of aspiration and airway obstruction due to relaxation of the laryngopharyngeal muscles makes them particularly predisposed to the development of such secondary insults such as hypoxemia or hypercapnia.
Oxygen should be administered when arterial oxygen saturation monitoring is not available or when <92%.

42.6.5 Evaluation in the Emergency Room

Upon arrival at the hospital, monitoring of vital signs and ABC measures will continue. In the meantime, preferably two venous accesses will be placed, samples taken for blood tests, and chest radiograph and an electrocardiogram should be obtained. The latter can identify acute myocardial infarction or arrhythmias predisposing to stroke, such as atrial fibrillation. Beginning infusion of isotonic fluids (normal saline); and if present, hypoglycemia will be quickly treated, oxygen administration will continue and the stroke team recluted. Neurological status is will be assessed with a scale such as NIH Stroke scale. A CT scan will be obtained after clinical stabilization. Every effort should be made to ensure that all the above measures, including analysis of the images, take no longer than

45 minutes. The management of arterial hypertension, controversial and debated, is considered in detail below. Here, we mention only the formal contraindication to the use of vasodilators such as sublingual nifedipine as an abrupt drop in pressure levels may increase the extent of infarction. If CT detects no bleeding, ischemic stroke is diagnosed, and if the patient is in the window period, i.e., within 3 hours since the onset of symptoms, thrombolytic therapy should be considered.

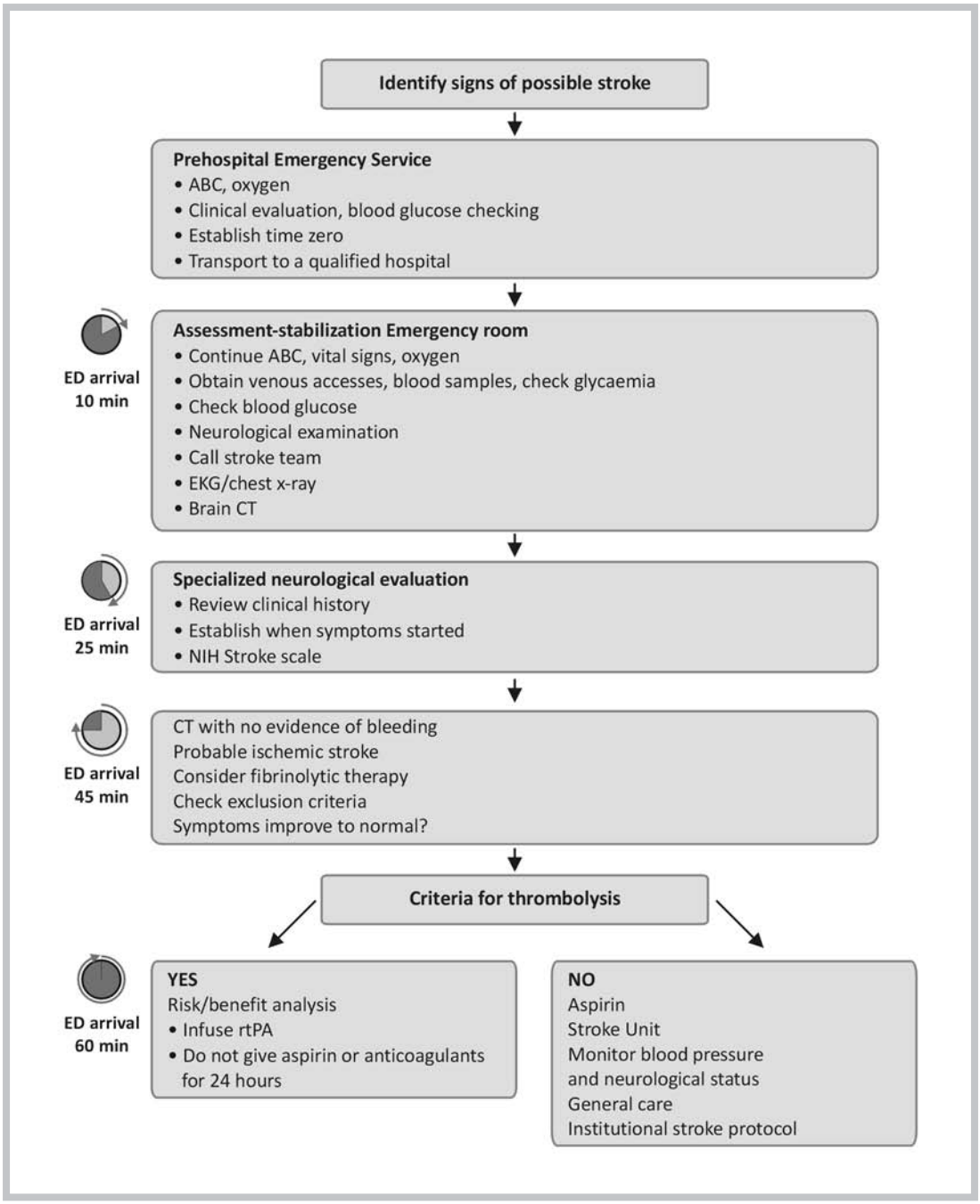

Figure 42.13. **Algorithm for the management of patients with suspected stroke.**
rtPA = recombinant tissue plasminogen activator

42.6.6 Stroke Units or Neurointensive Care Unit

Stroke units were first developed in North America in the 1960s in the wake of the success of coronary care units. Basically, a stroke unit is a section of a hospital where stroke patients are treated by a multidisciplinary team with a special expertise in stroke, including physicians, nurses, physiotherapists, occupational therapists, speech therapists and social workers.

Recent studies show an 18% relative decrease in mortality, a 3% absolute reduction in mortality and in the need for home care. Additional benefits were obtained with a 6% increase in the number of surviving patients able to perform activities of daily living.

Minimum requirements	Additional tests (performed according to physician's opinion)
• 24-hour availability of CT • Multidisciplinary team composed of internists/ intensivists, trained nurses, physiotherapists, speech therapists, rehabilitation experts, occupational therapists • Guidelines and protocols • Echocardiography, neck vessel Doppler • ECG, Holter monitoring • Biochemical laboratory tests (coagulation test) • ECG monitoring, blood pressure, blood oxygen saturation, temperature and blood glucose levels	• MRI/MR angiography • Diffusion-perfusion MRI • CT angiography • Digital subtraction angiography • Transesophageal echocardiogram • Transcranial Doppler • Diagnostic and interventional neuroradiological consultation • Neurosurgical consultation

Table 42.2. Essential requirements for the management of stroke patients.

- CT
- ECG/chest x-ray
- Blood chemistry: blood count, platelet count, international normalized ratio (INR), kaolin partial thromboplastin time (KPTT), prothrombin time and concentration, serum electrolytes, glucose, C-reactive protein (CRP), erythrocyte sedimentation rate, cardiac enzymes, blood gases, urea, creatinine, liver profile, complete urine
- Pulse oximetry
- Lumbar puncture in selected cases
- Carotid and transcranial Doppler
- ECG
- Transthoracic and transesophageal echocardiography
- Electroencephalogram
- MR angiography
- Cerebral angiography

Table 42.3. Supplementary examinations in an acute stroke emergency.

- Postictal paralysis (Todd's paralysis)
- Migraine
- Tumours
- Abscess, herpes encephalitis, meningococcal meningitis, other infections
- Chronic subdural hematoma
- Metabolic disorders (hyponatremia, hypoglycemia, hyper-hypocalcemia, etc.)
- Cerebral venous thrombosis
- Demyelinating diseases (multiple sclerosis, etc.)
- Hysteria, conversion disorder crisis

Table 42.4. Situations that can be mistaken for ischemic stroke and should be ruled out.

42.6.7 Management in the Critical Care Unit

General Treatment

The basic support measures are determined by the adequate support of vital functions, monitoring of neurological status, cardiorespiratory function, and early detection and correction of all situations that could potentially exacerbate or perpetuate the initial damage.

Airway management is essential as these patients constitute a high-risk population. Airway obstruction, aspiration of gastric contents, pulmonary edema and its consequences (hypoxemia and/or hypercapnia) are deleterious situations in the context of brain injury. These alterations are the end product of a number of disorders including: decreased level of consciousness, loss of cough and/or swallowing reflex, laryngopharyngeal muscle relaxation, etc. If a patient is able to maintain an "adequate ventilatory drive", the administration of supplemental oxygen via nasal tube, masks, continuous positive airway pressure (CPAP) or pressure support are recommended. Normoxemia (PaO_2 >90 mmHg, arterial oxygen saturation >95%) and normocapnia ($PaCO_2$ = 35-40 mmHg) are the objectives to be achieved. Based on clinical judgement, the decision whether to initiate endotracheal intubation should be made as quickly as possible, since delayed implementation exacerbates pre-existing injuries and increases morbidity and mortality as a result of secondary damage caused by hypoxemia, hypercapnia or aspiration of gastric contents.

With regard to mechanical ventilation indication, we adopt an aggressive policy and we indicate in the following situations:

- GCS ≤8 points.
- Neurological deterioration.
- Intracranial hypertension.
- Respiratory failure.
- Abnormal ventilatory patterns.
- Inability to achieve normocapnia and normoxemia, in spite of supplemental oxygen, bronchodilators, intensive kinesiotherapy, etc.

Another cornerstone of treatment is the achievement of cardiocirculatory stability. Arterial hypotension should be avoided at all costs because it is one of the secondary factors causing increased progression of injury. Since most of these patients are hypovolemic, volume expansion with isotonic fluids becomes a priority.

Controversy surrounds the type of solutions to infuse and the colloids versus crystalloids debate continues. Nevertheless, we recommend the use of isotonic solutions (saline 0.9% or slightly hypertonic 3.5%), with the goal of obtaining central venous pressures of about 10 to 12 cm of water. Under no circumstances (except in hypoglycemia) should hypotonic solutions such as dextrose or Ringer's lactate be prescribed as they induce and/or worsen cerebral edema, promote the synthesis of neurotoxic agents such as glutamate, cause local tissue acidosis: when combined, all these factors increase intracranial pressure.

The association of brain and cardiovascular disease is very common because they share the same risk factors, so the presence of arrhythmias is not surprising.

EKG in the acute phase may show ST segment changes, or T wave, which simulate an acute myocardial infarction, including an increase in cardiac enzymes. Arrhythmias are rarely life-threatening. Atrial fibrillation with high ventricular response or ventricular arrhythmias require immediate and aggressive treatment. Not to be forgotten in the search of etiology, the detection and correction of electrolyte disturbances, mainly of magnesium and potassium. Heart failure, acute myocardial infarction or sudden death can complicate the clinical course.

Achieving a physiological balance between organ systems becomes a priority when resuscitating the brain. Maintenance of homeostasis of the interior milieu, particularly with regard to metabolism and the compartmental distribution of water and sodium, is of vital importance. Inevitably, disturbances in sodium and water balance alter the osmolarity: such changes, in turn, result in profound changes in all cells of the CNS. In hyperosmolar states, water leakage from the cell interior occurs, resulting in dehydration of the cell itself. Conversely, in hyposmolar states there is a net gain of water with consequent cellular edema. The incidence of hyponatremia in neurocritical patients is about 10%, but more important is that it contributes to increased mortality according to the associated disease: the reported increases range from 7 to 60%.

Hypernatremia, less frequent (1%), is an epiphenomenon reflecting the severity of brain insult. The etiologies of both disorders are multifactorial and have been discussed elsewhere in this book; however, it's important remember here the ordered and systematic search for causes, because therapies can be diametrically opposed.

Elevated blood glucose levels, a product of metabolic alterations, response to stress, etc., are common in critical illnesses, including those of neurological origin. Current evidence demonstrates that hyperglycemia has deleterious effects in several acute brain diseases, including ischemic stroke, contributing to worsening of outcome in both diabetic and non-diabetic patients.

Hyperglycemia exerts its harmful effects through multiple mechanisms, including impaired blood-brain barrier permeability, production of oxygen free radicals, local tissue acidosis, stimulation of inflammation and the release of excitatory amino acids, etc.

Tight control of blood glucose, at least in theory, is associated with multiple benefits, including elimination of osmotic diuresis, maintenance of neutrophil and macrophage function, decreased production of oxygen free radicals, stimulation of nitric oxide production, etc.

Furthermore, insulin has both anti-inflammatory and neuroprotective effects, allowing us to hypothesize benefits while adopting aggressive treatments of elevated blood glucose levels in the acute phase of stroke.

However, studies investigating this issue in neurocritical patients have not yet been designed or carried out. We don't even know the glycemic cohort suitable for initiating treatment. American and European guidelines only recommend starting treatment at greatly increased levels, i.e., >180 mg/dl or >300 mg/dl, respectively. Both are too high if we consider the available evidence, i.e., that lower levels of about 153 mg/dl are associated with poor outcome at 3 months, and that values >140 mg/dl reduce the efficacy of thrombolytic therapy.

In our unit, we monitor blood glucose levels at frequent intervals, i.e., initially every 2 hours, correcting values >150 mg/dl with regular intravenous insulin. We will later (in another chapter of this book) analyze this aspect in greater detail.

Hyperthermia should be treated urgently and aggressively, as it has noticeable deleterious effects on neurons and the blood-brain barrier by triggering inflammation, stimulating the production of oxygen free radicals, increasing the levels of excitatory amino acids, increasing the cerebral metabolic demand of oxygen: taken together, all these variables contribute to the establishment of the initial damage and the extension of the ischemic area. Moreover, the presence of fever exerts negative effects on the subsequent evolution of these patients, but it is unclear which methodology should be used for its correction. As a general rule, we will take all necessary measures, either pharmacological (paracetamol, ibuprofen) or physical (cold baths, thermal blankets), in order to maintain a core body temperature <37.5°C.

Furthermore, swallowing and digestive disorders should not be underestimated in this patient population. Intestinal paralysis (ileus) and gastroparesis are common. Num-

bering among the pathophysiologic mechanisms involved are an altered reflex action caused by brain damage, the interaction of inflammatory mediators such as cytokines or commonly used drugs such as morphine, fentanyl, phenytoin, norepinephrine, etc. Moreover, a typical practice in intensive care units throughout the world is the prophylaxis of gastric ulcers or stress-related hemorrhagic gastritis with the use of proton pump inhibitors, like omeprazole, or H2 receptor antagonists, like ranitidine: but both raise intestinal pH, thus favouring the growth of bacteria, mainly Gram-negative bacilli.

In addition, if we consider that the lower esophageal sphincter (whose main function is to prevent the reflux of gastric contents) does not work properly, it comes as no surprise that the risk of continuous pulmonary microaspiration is very high: this explains one of the most important reasons for the genesis or development of pneumonia associated with mechanical ventilation.

Therefore, we add to the therapeutic regimen gastrokinetics like metoclopramide or cinitapride, along with simple measures as maintaining the patients in a semi-recumbent position. The hypercatabolic state and swallowing disorders in these patients require that they be fed early, i.e., within the first 24 hours, preferably via the enteral route using nasojejunal tube.

These seemingly obvious measures should not be overlooked. Their importance is sometimes underestimated, or worse, not taken into due account: the care of the eyes, skin and mucous membranes, and, above all, the gingival mucosa and oral cavity, which must undergo periodic washing with chlorhexidine or other similarly effective mouthwashes. Patient position should be regularly changed to prevent the development of pressure ulcers, and deep vein thrombosis prophylaxis instituted with elastic bandages, pneumatic sequential compression sleeves or the use of low-molecular-weight heparins.

Finally, some words with regard to the management of arterial hypertension, 80% of ischemic stroke patients in the acute phase have blood pressure values above the threshold considered normal by the current definition (>140 mmHg systolic and/or >90 mmHg diastolic). It is also true that in most cases the blood pressure will spontaneously decrease with time.

The debate over whether or not to treat arterial hypertension continues. TSome supporting treatment are based on the fact that very high blood pressure values may cause direct endothelial damage or would exacerbate or trigger cerebral edema, increase the likelihood of hemorrhagic transformation of infarction, especially in patients undergoing revascularization by drug therapy with tissue plasminogen activator, and cause direct endothelial damage.

Those claiming otherwise argue that a loss of cerebral autoregulation occurs in the acute phase of ischemic stroke, so that CBF becomes “pressure dependent”: lowering blood pressure would therefore decrease CBF, thus exacerbating the already compromised situation of the penumbra area. Recent clinical studies have indicated that the extent of decline in arterial pressure in the first 24 hours post-stroke is independently associated with neurological deterioration, increased infarct size and poor outcome 3 months after the event.

There are certain situations accompanying stroke where arterial hypertension should be inevitably and immediately treated:

- Aortic dissection.
- Acute myocardial infarction.
- Acute pulmonary edema.
- Hypertensive encephalopathy.
- Hypertensive nephropathy with malignant course.

Table 42.5 lists the current American and European recommendations for the management of arterial hypertension in the acute phase of ischemic stroke.

Arterial pressure (mmHg)	ASA	EUSI
SAP ≤220 or DAP ≤120	Do not treat	Do not treat
SAP >220 or 140 <DAP <120	• Labetalol • Nicardipine	• Labetalol • Nicardipine • Urapidil • Captopril • Clonidine • Hydralazine
DAP >140	Sodium nitroprusside	Sodium nitroprusside- nitroglycerin

Table 42.5. **Management of blood pressure in the acute phase of ischemic stroke. Current guidelines suggested by the American Stroke Association (ASA) and the European Stroke Initiative (EUSI).**
DAP = diastolic arterial pressure
SAP = systolic arterial pressure

Patients selected for thrombolysis have had a greater risk of hemorrhagic complications, so that the target to obtain in arterial pressure values are lower than those mentioned above, i.e., about 185/105 mmHg.

42.6.8 Specific Therapy

Thrombolytic Agents

Fortunately, the last decade was marked by a noticeable change of attitude toward the treatment of ischemic stroke. Like a phoenix rising from the shadows dominated by nihilism, active intervention lit up the dark horizon.

As we said previously, neurons begin to die almost immediately when deprived of oxygen for even a few minutes. Around this area of irreversible brain damage so called "core'', there is a hypoperfusion area which receives blood flow and sufficient oxygen to maintain cell viability. Time is fundamental to preserve the "stunned brain". This area so called "penumbra'' is threatened but potentially salvageable with prompt and appropriate therapy.

The recombinant tissue plasminogen activator (rtPA) when administered intravenously has proved effective in restoring blood flow to ischemic myocardium. By analogy, the principle of recanalization of obstructed vessel with thrombolytic agents was applied to ischemic stroke.

In 1995, the American National Institute of Neurological Disorders and Stroke (NINDS) published the results of a randomized, placebo-controlled study in which rtPA was administered to ischemic stroke patients within 3 hours from the onset of symptoms. The study involved 625 patients and showed no significant differences in terms of mortality: however, at 3-month follow-up there was an 11% absolute increase in the number of patients who had completely recovered or with minimal consequences. The dose used was 0.9 mg/kg body weight at a maximum dose not exceeding 90 mg; 10% of the total dose was administered as a bolus, the remaining as continuous infusion for 1 hour. CT without evidence of bleeding was an indispensable requirement, and inclusion and exclusion criteria for the study were properly specified. To date, they are used in the protocols of thrombolysis in almost all centres around the world, including ours (Table 42.6) with minor modifications mainly concerning neuroimaging.

Two European studies (ECASS I-II) did not replicate the results of the NINDS; however, the ECASS I used a higher dose of rtPA (1.1 mg/kg), and both trials tested a more wide therapeutic window lasting up to 6 hours. Another difference in the methodology of

these studies in reference to the NINDS was that the presence of major signs of early infarction was a reason in CT scan for excluding patients.

A first meta-analysis of the three cited studies (NINDS, ECASS I-II) showed a 45% reduction in the probability of unfavourable results if we use the dose and therapeutic window recommended by the NINDS.

Recently, the results of six studies (total of 2775 patients) on the time of beginning of rtPA infusion were released. In brief, the shorter the time interval between the onset of stroke and thrombolysis, the greater probability of better results, strengthening the concept of "Time lost, brain lost."

Always keep in mind that after rtPA infusion, "antiplatelet agents or anticoagulants should not be administered in the following 24 hours." During the infusion period, frequently and obsessively monitoring of arterial pressures levels should be guaranteed and, as noted above, do not allow pressures to rise higher than 180/105 mmHg of systolic and diastolic respectively.

If there is neurological deterioration, the presence of brain hemorrhage should always be suspected, the infusion of rtPA should be immediately stopped, coagulation parameters checked, a CT scan urgently obtained, a neurosurgeon alerted, and hemotherapy with cryoprecipitates, fresh plasma, and platelets ordered..

Based on the results of ECASS-III, it has recently been recommended to widen the therapeutic window for fibrinolytic infusion to 4.5 hours from symptom onset. This trial, designed and carried out in Europe, compared versus placebo the efficacy of rtPA infusion versus placebo at doses used in the NINDS study in the period of 3 to 4.5 hours from the onset of symptoms.

Inclusion criteria for fibrinolysis in ischemic stroke	• Age >18 years • Clinical diagnosis of stroke with NIH Stroke scale score >4 and <25 • Onset of symptoms within 4.5 hours • CT without evidence of hemorrhage

Exclusion criteria for fibrinolysis in ischemic stroke	• Medical history
	  · Stroke or head trauma in the previous 3 months
	  · History of intracranial hemorrhage may increase the risk of bleeding
	  · Surgery or major trauma in the previous 2 weeks
	  · Gastrointestinal bleeding or hematuria in the previous 3 weeks
	  · Arterial punctures in the previous week
	  · Pregnancy or breastfeeding
	• Clinical findings
	  · Rapidly improving neurological symptoms
	  · Seizures at admission
	  · Clinical picture with suspected subarachnoid hemorrhage despite negative CT
	  · SBP >185 mmHg or DBP >110 mmHg despite treatment
	  · Acute myocardial infarction
	  · Pericarditis
	• Diagnostic imaging
	  · CT evidence of hemorrhage
	  · CT hypodensity or effacement of the sulci in more than one third (33%) in the territory of the middle cerebral artery
	• Laboratory
	  · Glycemia >400 mg/dl or <50 mg/dl
	  · Platelet count <100,000/mm^3
	  · Patients taking anticoagulants with increased INR
	  · Patients receiving heparin for 48 h with prolonged KPTT

Table 42.6. **Criteria for the use of rtPA in ischemic stroke patients in the neurointensive care units at the Pasteur Sanatorium, Catamarca, Argentina.**

In this study, were excluded patients older than 80 years, those who were treated with oral anticoagulants, or with severe stroke as defined by a NIH Stroke scale score >25 or individuals with a prior history of diabetes and stroke. Moreover, the inclusion and exclusion criteria were similar to the NINDS. The symptomatic hemorrhage rate varied according to the definition used, but was consistent with previous trials, being higher in the group treated with fibrinolytics. The mortality of the groups was similar, but the patients treated with rtPA had a better functional outcome (52.4 vs. 45.2%, OR 1.34, 95% CI 1.02-1.76; RR 1.16; p 0.04) after 90 days from the event.

Intra-arterial thrombolysis is a promising option, as evidenced by a series of cases which must be validated in the future. In theory, this technique would offer some advantages compared to intravenous therapy, including more effective recanalization rates, widening of the therapeutic window (all by direct infusion into the thrombus), as well as the possibility of reducing the adverse effects of the drug, etc. Prourokinase and rtPA are agents used in the trials. Disadvantages include the need for a specialized neuroradiologist and team available 24 hours 7 days a week. To date, its use is restricted to clinical research.

Antiplatelet Agents. Anticoagulation

Aspirin. It's the only drug tested on a large scale for the treatment of ischemic stroke in acute phase. Two studies, international (IST) and Chinese (CAST) trials, have concluded that aspirin started within 48 hours from stroke reduces the immediate risk of recurrence or death in hospital, as well as the risk of death or functional dependence 6 months later. The daily doses were 160 and 300 mg for the CAST and IST, respectively. In addition, the two studies showed a good safety profile for the drug. It should not be administered within 24 hours after thrombolysis.

Anticoagulation. Different heparins and regimens have been used and all have failed to show any positive effect in the acute stage of stroke; therefore, it is not recommended for routine use. However, there are situations where it may be beneficial:

- Presence of cardioembolic stroke at high risk of recurrence; for example: atrial fibrillation, artificial heart valves, acute myocardial infarction with mural or intracavitary thrombi, left atrial thrombosis.
- C and S protein deficiency.
- Antiphospholipid syndrome.
- Carotid and/or vertebral dissection.
- Cerebral venous thrombosis.
- Intra-extracranial symptomatic stenosis: before surgery.
- In crescendo TIA or stroke-in-progression.

Statins. The last decade was characterized by experimental and clinical studies which demonstrated in different ways the benefits of treatment with inhibitors of hydroxymethyl-glutaryl CoA reductase, independently of their effects on serum cholesterol levels, since, paradoxically, hypercholesterolemia is not a validated risk factor for ischemic stroke. Moreover, hypocholesterolemia is considered a predisposing factor for the development of spontaneous intracerebral hemorrhage, and not ischemic stroke. Statins have potential benefits, including:

- Protection of the vascular endothelium.
- Increased nitric oxide synthesis.
- Anti-inflammatory.
- Immunomodulation.
- Stimulation and regulation of progenitor cells.
- Neuro- and synaptoplastic effect.
- Stabilization of atherosclerotic plaques.

- Increase of cerebral blood flow.

From a clinical point of view, statins:

- Decrease the incidence of brain and cardiovascular events.
- Improve the functional outcome after ischemic stroke.
- Reduce mortality.
- Withdrawal of therapy has a rebound effect on the cerebral and coronary vasculature, with devastating effects.

It is our current practice to use of simvastatin or atorvastatin 40 mg daily for 1 week and then continue with 20 mg/day for the first 3 months after an ischemic cerebrovascular event.

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TIA, Antiplatelet Agents, Anticoagulation, Statins

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43 Ischemic Penumbra: Role of Neuroimaging in Treatment Decision

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43.1 Introduction

Thrombolysis with alteplase is the only medication approved for acute ischemic stroke. Alteplase has shown to be effective if given within 3 hours after symptoms onset. However, due to the narrow time window, less than 5% of patients with this condition receive this drug. To be able to treat a greater number of patients it would be crucial to extend this time window.

There are different approaches aimed at increasing the traditional 3 hour time window. There are studies analyzing the efficacy of alteplase in eligible patients who present with acute ischemic stroke in either the 3-4.5 hours (in the third European Cooperative Acute Stroke Study; ECASS III), or the 3-6 hours (in the third International Stroke Trial; IST-3) time windows. The recently published positive result of ECASS III has extended the time window to 4.5 hours, although there might be some delay in establishing this in standard clinical practice. The second approach is to select patients that are more likely to respond to the thrombolytic treatment. The main target for this selection is based on the ischemic penumbra concept.

This chapter aims at describing what ischemic penumbra is, how we can assess penumbra in clinical practice, what evidence we have for using penumbra as a tool for treatment decision, and what the future of penumbra in stroke treatment is.

43.2 Definition of Ischemic Penumbra

After the occlusion of a major cerebral vessel the brain tissue of the corresponding vascular territory suffers from focal ischemia. This will lead to ischemic injury, which magnitude and localization will depend on the extent, severity, and duration of the perfusion deficit. Experimental studies employing middle cerebral artery occlusion have established that local cerebral blood flow (CBF) values below 0.10-0.12 ml/g/min lasting 2 hours or longer are associated with consistent infarction, whereas higher flows avert irreversible injury.

While the blood vessel is still occluded, there will be different zones in the ischemic region if the CBF values are taken into account (Figure 43.1). In the ischemic core, due to the low CBF values, injury is irreversible. This area is surrounded by brain tissue that is functionally affected but still viable if adequately reperfused: the ischemic penum-

bra. However, not all the hypoperfused tissue surrounding the ischemic core can be called ischemic penumbra. There is an area in the periphery of the ischemic penumbra where there are low CBF values, the fate of which will not depend on recanalization. This area that will not be recruited into the ischemic core is called "area of benign oligaemia".

Therefore, ischemic penumbra is the potentially salvageable cerebral ischemic tissue that is present around the ischemic core. This concept arose by clinical observations of fluctuating neurological deficits that suggested different perfusion thresholds for loss of neuronal function and cell death. After the description of these thresholds in experimental models of ischemia, penumbra was defined as the portion of the ischemic zone with reduced cerebral blood flow, absent electrical activity, but preserved ion homeostasis and transmembrane electrical potentials. However, in clinical practice it is more relevant to define ischemic penumbra as the portion of the ischemic tissue that is still potentially viable.

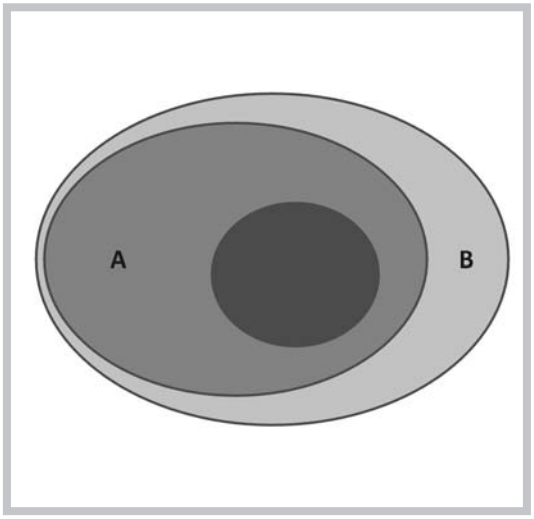

Figure 43.1. **Schematic representation of the ischemic tissue after a major vessel occlusion. In black there is represented the ischemic core, irreversibly damaged. The ischemic penumbra is represented by the "A" area. This is the tissue that can be salvaged after the use of thrombolytic therapy. Surrounding the ischemic penumbra, there is the benign oligaemia area ("B" area), which will survive regardless there is reperfusion or not.**

Penumbral tissue is an abnormal tissue with physiological and biochemical characteristics of cellular dysfunction but not cellular death, caused by hypoperfusion. This tissue has to be in the same vascular territory as the infarct core. The main relevance of this tissue is that it can either survive or progress to necrosis, and its salvage is associated with better clinical outcome. Thus, ischemic penumbra can be defined as the ischemic tissue which function is impaired and it is at risk of infarction. The clinical relevance is, therefore, that this tissue can potentially be salvaged if there is reperfusion. If reperfusion is not achieved this tissue at risk will be recruited into the infarct core.

The tissue surrounding the infarct core remains viable, but severely compromised because of metabolic, hemodynamic, and neurochemical alterations characteristic of the ischemic environment. In this region, endogenous protective mechanisms (i.e., local expression of survival factors) and residual collateral blood flow are only able to delay the otherwise inevitable cell death process leading to infarct growth. In normal brain an increase in local glucose metabolism is closely coupled to a reactive increase in local CBF to match the metabolic demands. The dissociation between metabolism and flow is pronounced in focal cerebral ischemia. Maintenance or focal increases in glucose utilization have been observed in brain regions adjacent to the ischemic core. Therefore, the uncoupling of metabolism and flow is an important pathogenetic mechanism that affects the critical energy balance in the penumbra.

Lastly, the ischemic penumbra is a dynamic tissue structure of limited viability surrounding a focus of dense cerebral ischemia. The flow thresholds for electrical and membrane failure are not constant but increase in a time-dependent manner. Therefore, with time increases the viability of the penumbra will decrease and more tissue will be recruited in the core.

43.3 Neuroimaging Tools to Assess Ischemic Penumbra

Just a conventional cranial computed tomography (CT) is enough to select stroke patients to receive alteplase in the 3 hour time window (or 4.5 hours if we take into account the results of ECASS III). However, many authors defend the use of more sophisticated technology to improve the selection of patients and the avoidance of hemorrhagic complications, but there is not enough evidence to recommend further neuroimaging assessment in the approved time window.

While conventional CT can detect hemorrhage and the ischemic core, the new neuroimaging tools are able to characterize the ischemic penumbra by assessing brain perfusion and metabolism. This information can help us to extend the therapeutic window, to exclude patients that do not require thrombolysis because they do not have penumbra, to detect patients who more probably will be harmed by treatment or are unlikely to respond (for example in the malignant pattern in which a very large diffusion weighted image on MR is matched by a similarly sized perfusion image), or to select patients that have not responded to intravenous alteplase to rescue intra-arterial thrombolysis.

There are many neuroimaging tools that have shown efficacy in penumbra assessment. However, there is lack of consensus on the appropriated method to measure penumbra.

43.3.1 Positron Emission Tomography

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three-dimensional image of functional processes. It is based on the detection of pairs of gamma rays emitted by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Multitracer PET using the ligands $H_2{}^{15}O$ and $^{15}O_2$ has been used to quantitatively measure cerebral blood flow (CBF), cerebral metabolism of oxygen ($CMRO_2$) and cerebral oxygen extraction fraction (OEF). The quantitative measurement of CBF, $CMRO_2$, OEF and cerebral blood volume (CBV) allows the assessment of perfusion and energy metabolism. Thus, in ischemic stroke is possible to detect the four tissue subtypes: core, penumbra, oligaemia and unaffected tissue, as well as the thresholds that reliably and efficiently separate them.

^{11}C-flumazenil is a PET radioligand that binds to the benzodiazepine site on the neuronal [gamma]-aminobutyric acid receptor and has been applied with $^{15}O_2$ tracers in acute stroke patients. This ligand it is able to distinguish ischemic core from penumbral tissue early after acute stroke. ^{11}C-flumazenil binding below 3.4-times the mean of contralateral white matter predicts irreversible tissue damage, and a CBF of 14.1 ml/100 g per minute is the penumbral threshold.

Another marker, ^{18}F-fluoromisonidazole, provides a direct image of the penumbra, but not of the ischemic core. Studies with ^{18}F-fluoromisonidazole have shown that penumbra may last for long periods in some patients, and that penumbral salvage is time-independent, with at least 50% tissue survival even beyond 12 h.

PET is considered the gold standard to study ischemic penumbra, because it provides quantitative mapping of many physiological parameters. However, its utilization is not practical in clinical studies, because of it complexity, cost, and its limited availability.

43.3.2 Magnetic Resonance Imaging

The ischemic penumbra can be evaluated with magnetic resonance imaging (MRI), using diffusion-weighted (DWI) and perfusion-weighted (PWI) sequences. Currently, DWI

and PWI MRI studies are the most widely used clinical imaging modalities to detect the presence of penumbra.

DWI measures alterations in the diffusion of water molecules. The degree of free diffusion of water molecules can be quantified with the apparent diffusion coefficient (ADC). The changes detected with DWI are due to metabolic failure leading to disruption of ion homeostasis and cytotoxic edema. The DWI image visualizes acute ischemic lesions within minutes, and identifies acute infarcts within 6 hours after onset with high sensitivity and specificity. The hyperintense lesions represent the irreversible damaged brain tissue, so the altered region detected with DWI is a reasonable representation of the infarct core.

PWI detects the signal loss of flow that occurs during the dynamic tracking with the use of gadolinium, an intravenous paramagnetic contrast agent. With this technique it is possible to delineate ischemic areas as an abnormal perfusion area, which is commonly defined by time domain parameters on dynamic contrast-enhanced imaging, including mean transit time (MTT), time to peak (TTP), or T_{max}. MTT is the time between arterial inflow and venous outflow. TTP represents the time from the beginning of gadolinium injection to the maximum enhancement within an intracerebral region of interest. T_{max} is the time to peak of the residue function, indicating bolus delay between the site of selection of the arterial input function and the tissue. Therefore, T_{max} represents bolus arrival time, without the confounding effects of bolus administration.

The mismatch between a PWI lesion and a DWI lesion is the MRI signature of the ischemic penumbra. The PWI-DWI mismatch region is defined as the difference in volume of tissue between the smaller diffusion lesion and the larger perfusion lesion. The mismatch provides an estimation of the extent of penumbra and can be used to monitor infarct growth over time. Ischemic penumbra is defined when there is at least a 20% discrepancy between the two volumes. It is observed in over 50% of middle cerebral artery territory stroke patients when studied up to 6 hours after the symptoms onset of stroke, and it may persist up to 24 hours. In the absence of reperfusion the DWI lesion typically expands into the PWI volume. This expansion is not only dependent on time, as it might be influenced by blood glucose concentrations, temperature, hematocrit, systemic hypoxia, and age.

However, using MRI in the acute stroke setting has some disadvantages. The time taken to acquire the data is longer than in conventional CT. Moreover, the procedure is not applicable in some patients because of claustrophobia or the presence of pacemakers or metal objects. There is also a small risk of nephrogenic systemic fibrosis in patients with severe renal impairment who receive gadolinium, but the use of contrast agents could be avoided in the future by the use of new techniques such as arterial spin labelling. Another limiting factor is the need for automated, online image analysis.

Although it has shown to be a good tool to assess acute ischemic stroke patients, there are some uncertainties regarding MRI to assess penumbral tissue. In animal models of ischemia and some clinical studies, it is possible to observe a very early reversibility of the DWI lesions. Therefore, the acute DWI lesion may not only represent tissue destined for infarct, but also severely ischemic tissue that may still be saved from necrosis. Even severely reduced ADC values, very early after stroke, are reversible in some patients. Also, DWI lesions can reappear after an initial disappearance following treatment. This is probably due to inflammatory tissue injury, delayed mitochondrial dysfunction, and apoptosis. Moreover, there can be false negatives of DWI in patients with ischemia in the posterior circulation.

On the other hand, PWI can detect areas of hypoperfusion that are not really penumbral tissue, but benign oligaemia. Thus, PWI techniques may overestimate the amount of tissue that is critically hypoperfused. This is important in penumbra assessment, as these

areas of benign oligaemia will survive regardless of reperfusion. It is possible to reduce the volume of benign oligaemia, and therefore to improve the precision of PWI for estimating the volume of penumbral tissue in acute stroke patients and improve the accuracy of early prediction of final infarct volume, by using a threshold to exclude areas with minimal delay in contrast arrival times. The use of a strict T_{max} threshold (>4 or >6 seconds) might reduce the percentage of patients considered to have a mismatch, but identifying mismatch patients who are more likely to have salvageable tissue. TTP maps are easiest to generate and to interpret visually. However, MTT or TTP can be increased even in areas without hypoperfusion if the perfusion pressure is reduced, as happens in autoregulation.

There are alternative methods to improve the definition of mismatch, such as a larger mismatch ratio than the typically selected 1.2. The original concept of PWI-DWI mismatch introduced an arbitrary ratio of 20%, but there is no evidence to support it. This volume ratio is very conservative and the increases are more modest because of the cubed root relation of radius with volume.

Despite these uncertainties, MRI remains the most practical tool for identifying tissue at risk of infarction in the early phase of acute ischemic stroke. Moreover, there are new MRI techniques than can help to avoid the uncertainties in infarct core and penumbra assessment. Arterial spin labelling, a non-invasive perfusion MRI technique, uses electromagnetically labelled arterial blood water to measure CBF. A quantitative estimate of the OEF can be obtained using MRI with the results in good agreement with values reported in the PET literature. By combining MRI-measured OEF and CBF via quantitative perfusion studies it might be possible to obtain a measure of the $CMRO_2$ using MRI in acute stroke patients.

43.3.3 CT Perfusion

Conventional cranial CT is the most important imaging technique for acute stroke because of its easy availability and accessibility. It is helpful to discard intracranial hemorrhage and to detect the appearance and extent of early infarct signs. However, it gives little information about the presence and extension of ischemic penumbra. Although hypodensity on CT within the first 6 h may represent irreversibly infarcted tissue, tissue at further risk of damage cannot be clearly distinguished with conventional CT.

However, the combination of CT perfusion and CT angiography allows the evaluation of ischemic penumbra. The baseline CT perfusion should have 3 components: unenhanced CT, vertex-to-arch CT angiography (CTA), and dynamic first-pass CT perfusion.

CT perfusion involves the dynamic acquisition of sequential CT slices during the administration of contrast material and an analysis of time-concentration curves for each pixel. Brain tissue flow can be described by several parameters including CBF, CBV, and MTT. CBV is the total volume of flowing blood in a given volume in the brain, with units of millilitres of blood per 100 g of brain tissue. CBF is the volume of blood moving through a given volume of brain per unit time, with units of millilitres of blood per 100 grams of brain tissue per minute. MTT is the average transit time of blood through a given brain region, measured in seconds. In CT perfusion, the ischemic core is defined as the CBV lesion volume, i.e. the equivalent to the DWI lesion in MRI. The mismatch between the MTT or CBF lesion and the CBV lesion represents the ischemic penumbra.

Ischemic penumbra is defined by a CBF below 34% of the non affected hemisphere, with a CBV above 2.5 ml/100 g, and a MTT of be more than 145% of the contralateral side. The infarcted tissue is defined by a CBV below 2.5 ml/100 g.

The general principles underlying the computation of perfusion parameters such as CBV, CBF, and MTT are the same for both MR imaging and CT. The most important advantage of CT perfusion is the linear relationship between contrast concentration and attenuation in CT, which facilitates quantitative measurement of CBF and CBV. The main disadvantage of CT perfusion is the relative limited coverage, as most machines are only able to cover 4 brain slices, so the volumetric assessment of the core and penumbra might be incomplete. Nevertheless, newer CT equipment is able to cover the whole brain with a single bolus injection, similar to PWI-MRI.
The advantages of this technique are their wider availability, as it can be performed in any centre that has spiral CT. Also, the assessment is quicker than with MRI, and there are no concerns about claustrophobia, pacemakers, or metallic objects. Studies can immediately follow plain CT and be completed within about 5 minutes. However, the risk of contrast-induced nephropathy is more important than with MRI.

43.4 Clinical Relevance of Ischemic Penumbra: Using Penumbra as a Proof-of-concept

The aims of thrombolytic therapy are the recanalization of the occluded artery and salvage of the ischemic penumbra. Imaging penumbra might allow selection of patients for thrombolysis beyond 3 hours. Two phase II trials of thrombolysis with alteplase – the DEFUSE and the EPITHET trials – incorporated penumbral imaging and are worthy of further discussion.
The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) trial was a prospective, open label, non randomized, multicenter trial aimed at confirming eligibility for intravenous thrombolysis with alteplase within 3 to 6 hours after onset. It included 74 patients, who received open-label alteplase and were analyzed using MRI and MRA within 3-6 hours of stroke onset and at 24 hours. The main hypothesis was that prespecified MRI profiles could be used to identify patients who have a robust clinical response to reperfusion when treated with alteplase 3-6 hours after stroke onset. The presence of mismatch was assessed if the PWI lesion was more than 20% larger than the DWI lesion. This study showed that it is safe to use MRI to define mismatch, and that thrombolytic treatment is effective in patients with mismatch. However, patients were not selected on the basis of MRI findings. In DEFUSE, early reperfusion in patients with a mismatch was associated with favourable outcome. These results were better after the exclusion of patients with malignant mismatch (i.e., a baseline DWI ≥100 ml, and/or PWI ≥100 ml with a T_{max} ≥8 seconds). This positive effect of alteplase was not observed in patients without mismatch.
The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was a phase II trial aimed at analyzing the effect of intravenous alteplase on ischemic lesion growth, reperfusion, and clinical outcome in patients with ischemic penumbra 3 to 6 hours after stroke onset. It was a randomized, double-blinded, placebo-controlled, multinational trial. Patients were treated with either alteplase or placebo, and were imaged with MRI before treatment and repeated at day 3-5. Mismatch was defined as a PWI/DWI volume >1.2 ml, and PWI-DWI volume ≥10 ml, and hypoperfusion volumes were defined using a T_{max} delay of 2 seconds or more. MRI was not used to select patients, but to determine the effect of alteplase on lesion growth, reperfusion, and clinical outcomes. The primary endpoint was a greater attenuation of infarct growth in patients with an imaging mismatch who received alteplase than in those who received placebo. The study enrolled 101 patients, 52 allocated to alteplase and 49 allocated to placebo. The prevalence of

mismatch was 86%, and arterial occlusion on MRA was seen in 62% of patients. The geometric mean growth of the ischemic lesion was about two-thirds in the alteplase group compared to the placebo group, although this difference was non significant. The incidence of reperfusion was significantly higher in patients with mismatch who received alteplase. Recanalization was associated with lower infarct growth and good neurological outcome in patients with mismatch. Although EPITHET was not powered to test differences in clinical outcomes, there was a better functional recovery at 3 months in the treatment group. The primary outcome measure of this study was negative, but other measures supported the hypothesis of attenuated infarct growth with alteplase beyond 3 hours.

Both studies provide strong biological support for the relation between infarct growth, reperfusion, and clinical outcome in the 3-6 hours time window after onset of stroke. However, these trials had some limitations. The analysis of the imaging data might have led to an underestimation of the true mismatch volumes, and neither study was powered to test the mismatch hypothesis.

There are other studies testing demosteplase, another thrombolytic agent which has some theoretical advantages over alteplase. In the DIAS trial there was a dose-response effect on reperfusion rates seen on PWI with greatest benefits with either 90 μg/kg or 125 μg/kg desmoteplase in the 3-9 hour time window. These results were replicated in the US Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trial. With this encouraging data, the phase III DIAS-2 study, the largest penumbral selection trial with 186 patients, was undertaken. The primary outcome measure was clinical recovery at 3 moths. Good outcome was similar in the placebo and in the 90 μg/kg desmoteplase groups. However, patients who received 125 μg/kg desmoteplase had lower recovery and higher mortality. Most deaths in the latter group were non-neurological and occurred late in the trial, and were more likely due to chance.

There are other trials in acute ischemic stroke that have used the principle of penumbral selection (GAIN MRI substudy, Citicoline study, Normobaric oxygen study, COOL AID hypothermia). These are phase II trials that have tested the hypothesis that improving reperfusion or recanalization is safe, feasible, and might provide infarct growth attenuation on imaging. For example, in the GAIN trial, patients treated with gavestinel showed attenuation on infarct growth on DWI.

43.5 Future Analysis of Ischemic Penumbra

The DEFUSE and EPITHET studies have provided biological support for the therapeutic responsiveness of patients with mismatch. However, there is still no evidence that these patients would have better clinical outcomes when given alteplase. Therefore, new studies are needed to provide proof that mismatch tissue is a viable therapeutic target in human beings. Using larger sample sizes, such as combining the DEFUSE and EPITHET databases, could provide further indirect evidence.

The evidence given in the EPITHET study has encourage the investigators to plan a phase III trial (the EXTEND trial) which will randomize patients with mismatch detected by MRI to receive alteplase or placebo in the 4.5-9 hour time window.

Also, an ongoing trial, Magnetic Resonance and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) is assessing the benefits of reperfusion interventions, comparing patients with and without penumbral mismatch.

Other stroke groups are conducting observational studies assessing penumbra with CT perfusion to select patients. A conventional CT is used before starting treatment with al-

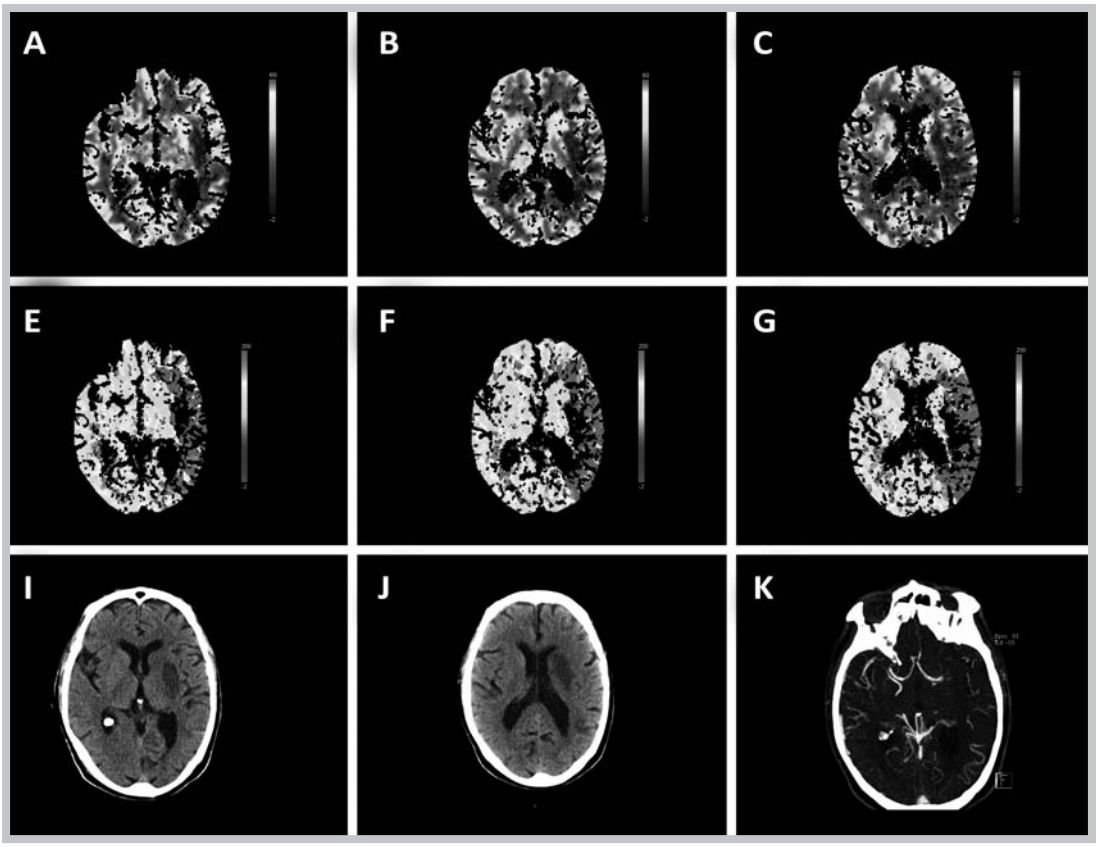

Figure 43.2. **Perfusion CT in acute stroke performed after intravenous treatment with alteplase. A-D: The CBV maps showed a moderate area of volume alteration in the deep territory of the left middle cerebral artery (MCA). E-H: The TTP maps disclosed a larger area of hypoperfusion that includes most of the left MCA territory. K-L: Angio-CT detects and occlusion of the left MCA in the M1 segment. This patient received rescue treatment with intra-arterial alteplase, and the conventional CT performed 3 days after stroke onset showed a moderate infarction in the deep territory of the MCA, closely resembling the initial CBV lesion. Thus, this case illustrates how neuroimaging assesses ischemic penumbra, and how thrombolytic treatment can limit lesion growth.**

teplase, and after treatment a CT perfusion is performed to detect patients with a large mismatch or a persistent arterial occlusion. After that, selected patients receive rescue intra-arterial thrombolysis.

To conclude, we have robust data which suggests that it is possible to extend the therapeutic window of thrombolysis using the mismatch (i.e. the ischemic penumbra) as a proof of concept. However, more evidence is needed to use it in routine clinical practice. This information will become available in the next years, once the ongoing phase III trials are published.

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44 Thrombolysis in Acute Ischemic Stroke

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44.1 Introduction

In order to optimize outcomes, the management of the acute stroke patient must be an organized, concerted effort. The focus of treatment in the acute setting is to stabilize the patient and restore blood flow to the brain. There are multiple steps which must be addressed before successful treatment can begin in a timely fashion. This chapter will briefly discuss the pathophysiology and goals of treatment and will highlight the critical steps necessary in rapid evaluation and management of the acute stroke patient.

44.2 Pathophysiology

Ischemic stroke causes death of brain tissue due to interruption of blood flow to a region of the brain, most commonly due to occlusion of a cerebral or cervical artery. Thus, the primary goal of therapy is to open the artery and re-establish blood flow as quickly as possible. The ischemic "core" is the area of brain destined to die. The core is surrounded by an area at risk of death, the ischemic "penumbra". In the penumbra, there is blood flow within the thresholds necessary to preserve function; however, this flow is tenuous [1]. The penumbra remains salvageable if blood flow is re-established in a timely fashion. However, as time passes, the ischemic core expands to include the penumbra and decreases the amount of viable tissue. It has been estimated that every minute that passes without treatment, a patient loses about 2 million neurons [2].

44.3 Pre-hospital Care

The care of the acute ischemic stroke patient begins with recognition of signs and symptoms of stroke by the patient and/or family members. Since future therapies are likely to have similar time constraints, increasing the number of patients eligible for AIS (acute ischemic stroke) treatment is paramount. The use of emergency medical services (EMS) transport can significantly decrease the time to emergency evaluation and treatment [3-6]. EMS use is strongly associated with decreased time to initial physician examination, initial computed tomography (CT) imaging, and neurological evaluation [6-9]. In addition, family members are most often responsible for initiating calls to EMS for AIS [10] thus increasing stroke symptom awareness in this group may increase the number of patients who arrive at the emergency department within the treatment window. It is also worthwhile for EMS to consider transporting a witness with the patient or at least a cell phone number of someone who can verify the history. Based on this information, a plan

for acute stroke treatment must include coordination of pre-hospital care. It is also necessary to consider whether EMS should bypass hospitals which do not have resources to treat stroke in favor of the closest facility that can initiate acute stroke treatment [11]. The American Heart Association and the American Stroke Association have described the "Stroke Chain of Survival" which links the actions by patients, family, and healthcare providers to maximize outcomes [12]:

- Rapid recognition and reaction to stroke warning signs.
- Rapid EMS dispatch.
- Rapid EMS system transport and hospital pre-notification.
- Rapid diagnosis and treatment in the hospital.

44.4 Emergency Evaluation and Diagnosis of Acute Ischemic Stroke

While this section is organized by different components of the initial evaluation, in reality these assessments should happen concurrently and as rapidly as possible.

44.4.1 History

Once the diagnosis of stroke is suspected, time of onset of symptoms should be established. If the patient wakes from sleep or is "found" with symptoms, then **time of onset is the last time the patient was observed to be normal**. Determination of symptom onset time is critical for establishing eligibility for acute therapies. Often, inaccurate times are initially provided at the scene but with further probing and additional information from witnesses, time of onset becomes more accurate. Useful questioning walks the patient or witness through their routine for that particular day in order to accurately establish the time the patient developed symptoms or when EMS was activated [13]. Atherosclerotic risk factors and other co-morbidities should be assessed as well as medications.

44.4.2 Physical Examination

The physical exam can provide important clues to stroke etiology and possible contraindications for thrombolysis, especially in an aphasic patient, e.g.:

- **Head and neck**: Signs of trauma, carotid bruits, jugular venous distension.
- **Cardiac**: Rate and rhythm, murmurs.
- **Skin**: Recent surgical scars or hematoma, trauma, livedo reticularis or other findings which might suggest recent procedures, hepatic dysfunction, or coagulopathy.

Stabilization of the patient is a priority. Airway, breathing and circulation (ABCs) should all be supported. Intubation may be necessary if the patient cannot protect his/her airway. In this case, your neurologic assessments become limited. While you are preparing to intubate the patient, take a moment to be sure simple measures such as positioning or suctioning do not improve the situation.

44.4.3 Neurological Examination

Initial stroke severity is an important predictor of outcome. The NIH Stroke Scale (NIHSS) provides a rapid, reliable, and reproducible assessment of stroke severity and can be followed over time to monitor for recovery or neurologic worsening [14,15]. It can be obtained electronically at http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf (Table 44.1).

	Stroke Scale Items		Score
1a	Level of consciousness (0-3) 0 = Alert; keenly responsive 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped) 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic		___
1b	LOC questions (0-2) 0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly		___
1c	LOC commands (0-2) 0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly		___
2	Best gaze (0-2) 0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver		___
3	Visual (0-3) 0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness)		___
4	Facial palsy (0-3) 0 = Normal symmetrical movements 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (total or near-total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)		___
5 & 6	Motor arm and leg 0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls 4 = No movement UN = Amputation or joint fusion, explain: _____	5a Motor left arm (0-4 or UN) 5b Motor right arm (0-4 or UN) 6a Motor left leg (0-4 or UN) 6b Motor right leg (0-4 or UN)	___ ___ ___ ___
7	Limb ataxia (0-2 or UN) 0 = Absent 1 = Present in one limb 2 = Present in two limbs UN = Amputation or joint fusion, explain: _____		___
8	Sensory (0-2) 0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg		___

9	Best language (0-3) 0 = No aphasia; normal 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response 3 = Mute, global aphasia; no usable speech or auditory comprehension	___
10	Dysarthria (0-2 or UN) 0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric UN = Intubated or other physical barrier, explain:_____	___
11	Extinction and inattention (formerly Neglect) (0-2) 0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space	___
	Total score	

Table 44.1. NIH stroke scale. Adapted from http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf

Diagnostic Tests

There are some diagnostic studies that should be performed routinely on all patients in whom ischemic stroke is suspected. These tests can help to identify other conditions which may influence treatment options.

- **Non-contrast head CT or MRI**: Excludes intracranial hemorrhage.
- **Laboratory evaluation**: Blood glucose, electrolytes, complete blood cell count with platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, and renal function.
- **Cardiovascular studies**: Cardiac enzymes, 12-lead ECG, cardiac monitoring.

Additional tests may be performed as indicated by the patient's history, exam, or comorbidities:

- Liver function studies.
- Toxicology.
- Pregnancy test.
- Chest X-ray.
- Lumbar puncture (recall, if the patient has an emergent LP, thrombolysis would no longer be considered a treatment option).

The NIH has published recommended time frame goals in which each important aspect of evaluation should occur (Figure 44.1) [16].

Each institution will have its own strengths and weaknesses. When reviewing these goal time frames, it is important to take a critical view of treatment paradigms and find ways to improve our systems. When goals have been met, it then becomes important to sustain these efforts with regular assessments. Equally as important is ensuring protocol

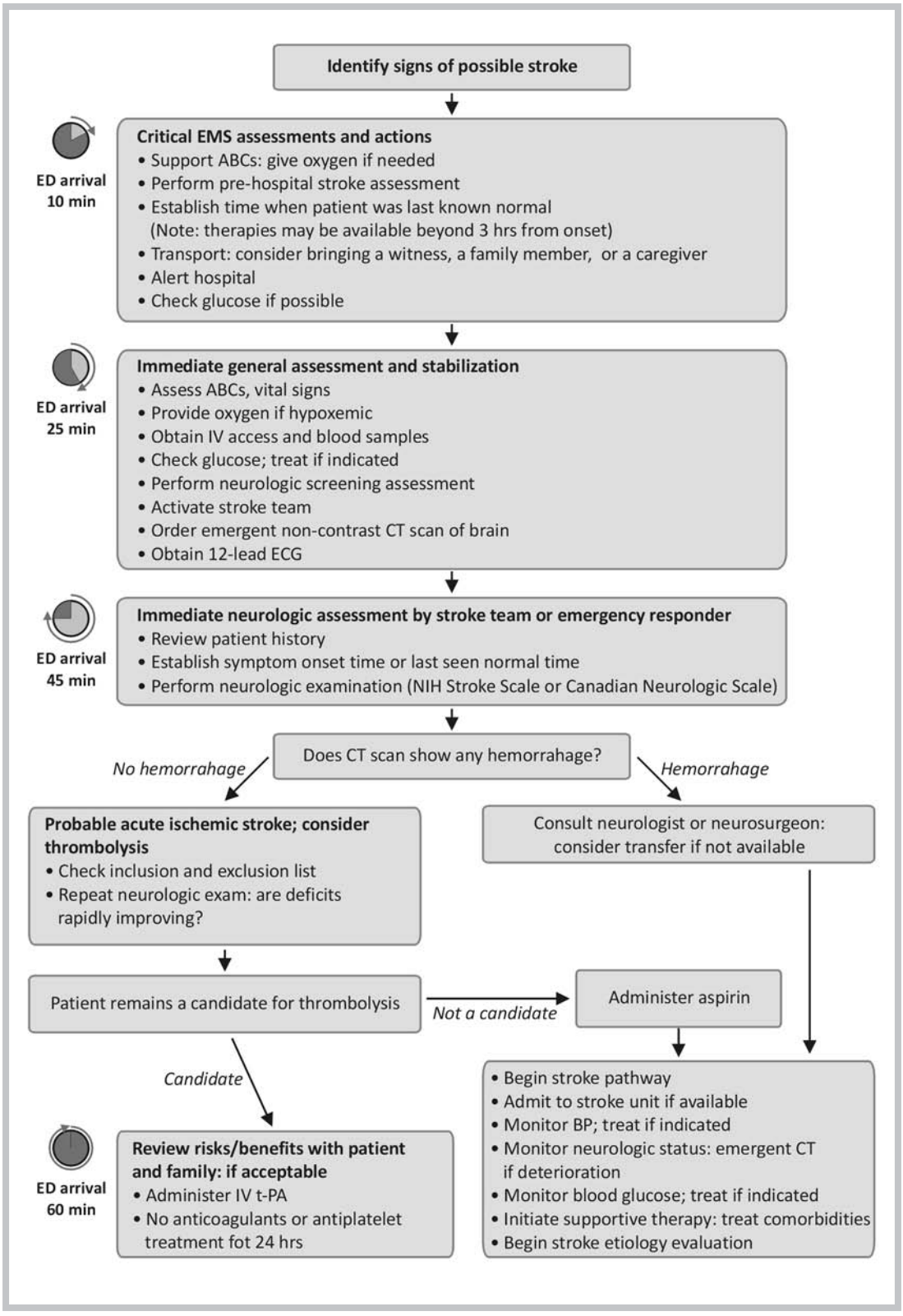

Figure 44.1. **Goals for the management of patients with suspected stroke. Adapted from [12].**

compliance since protocol adherence has been demonstrated to lower the risk of hemorrhagic complications [17]:

- A physician should evaluate a stroke patient within 10 minutes of arrival at the ED doors.
- A physician with expertise in the management of stroke should be available or notified within 15 minutes of patient arrival. Depending on the protocol established, this may be accomplished by activating a stroke team.
- A CT scan of the head should begin within 25 minutes of arrival. The CT interpretation should be obtained within 45 minutes of arrival. This gives adequate time to perform the scan, process the images, and interpret the results.
- For ischemic stroke, treatment should be initiated within 60 minutes.
- The time from patient arrival at the ED to placement in a monitored bed should not exceed 3 hours.

44.5 General Medical Care

44.5.1 ABCs

As mentioned previously, the acute stroke patient must be managed as any other acutely ill patient with attention to stabilization of airway, breathing and circulation (ABCs). All patients must have continuous cardiac and oxygenation monitoring. Pneumonia is a common complication of stroke and steps to reduce the risk of aspiration should be taken. In general, most patients receive supplemental oxygen via nasal cannula with a goal pulse oximetry ≥92% [12].

44.5.2 Hyperglycemia

Hyperglycemia in the acute setting of stroke has been associated with worsened outcome [18] and we tend to be aggressive with treatment. The ideal range for glucose levels in the acute setting of stroke has yet to be determined. Thus, at this time, the goal should be to maintain glucose in a normal range.

44.5.3 Hyperthermia

Fever in the acute setting of stroke has been associated with an increase in mortality [19] and worsened outcome [20]. It has been estimated that for an increase of 1 °C, the risk of poor outcome doubles [19]. Thus, sources of fever should be treated and antipyretic treatments should be employed to lower the temperature of febrile patients to the normal range. Hypothermia as a treatment for stroke appears promising and is currently under investigation.

44.5.4 Hypertension

Management of hypertension in the acute setting of stroke remains controversial. There is evidence to suggest that lowering BP rapidly from very high values may be detrimental by reducing penumbral blood flow, which may increase infarct volume and result in worse outcome [21,22]. However, theoretical reasons for lowering blood pressure in-

clude decreasing the risk of developing edema, hemorrhagic transformation, and neurologic deterioration [11].

Treatment of hypertension in the acute setting of stroke differs depending on whether the patient is a thrombolytic candidate:

- Patient is **not** a thrombolytic candidate: Current recommendations are to withhold antihypertensive agents unless BP >220/120 mmHg [11].
- Patient **is** a thrombolytic candidate: BP should **not** be >185/110 mmHg at the time of and during treatment with IV rt-PA in order to decrease the likelihood of hemorrhagic transformation. Medications listed in the most recent treatment guidelines to control BP include [11]:
  - Labetalol 10-20 mg, may repeat x 1; or
  - Nicardipine infusion starting at 5 mg/hr and titration of 2.5mg/hr at 5-15 minute intervals to a maximum of 15 mg/hr; or
  - Nitropaste 1-2 inches.
- If blood pressure cannot be maintained within the specified range with the above treatments, then rt-PA should not be administered.

When antihypertensive treatment is indicated, the patient should be under close monitoring. Some patients may have a hemodynamic component to their stroke mechanism and lowering BP too aggressively could cause neurologic deterioration.

There is a U-shaped relationship between mortality and admission blood pressure [23]. While definitive evidence for optimal blood pressure parameters during the acute setting of stroke is lacking, current practice is to avoid excessively high or low blood pressure, especially when associated with neurologic deterioration. A reasonable goal would be to reduce blood pressure by 15-25% over the first 24 hours [11].

After the first 24 hrs, it is reasonable to initiate oral antihypertensive agents for gentle blood pressure control. It is preferable to know the status of the blood vessels before being too aggressive with blood pressure management. For example, if a patient has carotid stenosis, one might consider starting with a low dose of a short acting agent to avoid dropping the blood pressure too quickly for a prolonged amount of time.

44.6 Treatment Considerations

It is generally accepted that the more rapidly flow is re-established to the ischemic tissue, the more complete recovery will be. Thus, the goal of treatment is restoration of blood flow to the ischemic area. If flow cannot be re-established through the affected vessel, then the goal of treatment is to maximize collateral flow and minimize the risk of developing secondary complications (e.g. cerebral edema, infection, deep venous thrombosis). Currently, the most effective proven way to re-establish blood flow within the first three hours of stroke is IV rt-PA. With the recent publication of ECASS-III*:* Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke [29], guidelines in Canada and Europe have been amended to recommend the use of IV rt-PA up to 4.5 hours in patients with acute ischemic stroke who meet the treatment criteria. However, as of now, guidelines in the US have not yet changed and the use of IV rt-PA after 3 hours remains an off-label use of the drug. Unfortunately, many patients will not present within the time frame to receive this medication. For this reason, aggressive supportive care after the stroke remains equally as important in maximizing outcome.

When a patient presents within the first 3 hours after symptom onset, he/she must be considered for thrombolysis. Once the initial assessment and diagnostic studies have been completed, the emergency responder should discuss the possibility of thrombol-

ysis with the patient and family, if able. This gives the family and patient some time to process the emergent situation and the treatment possibilities **before** a definitive decision has been made.

If you know you have significant delays with any particular step in the treatment pathway, start fixing it now. If it takes an hour for your laboratory to report an INR, start identifying the problem and the appropriate people to help fix it. If you cannot get a head CT within the recommended time frame (25 minutes), start figuring out ways to decrease your time; the problem could be transport or it could be that stroke patients don't have the appropriate priority in the radiology system. It is critically important to involve administration in helping you to minimize the time to treatment. Even if the patient is not eligible for IV rt-PA, rapid assessment and management is the best treatment for all patients.

IV rt-PA remains the only FDA approved treatment in the US for acute ischemic stroke within the 3 hour window. There have been 6 large multicenter, randomized, placebo-controlled trials (RCT) to test the benefit of rt-PA for AIS [24-28,29]. The studies differ slightly in terms of time to treatment, dose of medication, exclusion criteria, and definition of symptomatic ICH. However, the primary and secondary outcomes evaluated were similar, as were safety data, allowing interpretation as individual studies as well as facilitating evaluation via pooled analysis. In a pooled analysis [30], all 2775 patients who had been randomly allocated to rt-PA or placebo were included. In this analysis, the odds of a favorable outcome at 3 months increased as the time to treatment with rt-PA decreased ($p = 0.005$). These findings strongly confirm that rapid treatment with rt-PA is associated with better outcomes at 3 months. Outside the 3-hour window, the benefit of rt-PA is small in an unselected group. As such, the sample size necessary to demonstrate a positive effect in this time window is quite large. Recently, a large, randomized trial of the use of IV rt-PA in the 3-4.5 hr window was published and demonstrated the efficacy of IV rt-PA in acute ischemic stroke [29]. ECASS III confirms the findings reported in the pooled analysis which suggested that the benefit of IV rt-PA extended beyond the 3 hour window. However, because the treatment effect decreases with time, a larger number of patients must be treated to demonstrate this beneficial effect. The number needed to treat (NNT) to prevent 1 additional patient from death or disability is 11 for all rt-PA doses and times [31]. When only patients treated with 0.9 mg/kg in under 3 hours are considered, the NNT ranges from 3-7 [2,31]. Despite this data, IV rt-PA remains underutilized. With the recent findings in ECASS III, it is necessary to underscore the importance of rapid assessment and treatment. Expanding the treatment window to 4.5 hrs means that more patients will be eligible for treatment, NOT that we have more time to treat those patients who present within the 3 hr window. The likelihood of a good outcome is closely linked with time to treatment and so the goal door-to-needle time remains ≤60 minutes.

A re-analysis of the NINDS rt-PA trial found that while increasing age, stroke severity, a history of diabetes, and pre-existing disability were all associated with a decreased likelihood of having a favorable clinical outcome at 3 months, there was no evidence that any of these variables modified the rt-PA treatment effect to a significant degree [32]. In fact, among patients who qualify for therapy according to the NINDS study inclusion and exclusion criteria, no sub-group can be identified based on demographic, historical, or physical exam variables that benefits less or more from IV rt-PA when administered within 3 hours of symptom onset [33]. What is clear, however, is that the risk of hemorrhage increases when the NINDS protocol is not followed [17].

In order to reduce the risk of complications with rt-PA, there should be a clear treatment protocol. It is helpful to review the inclusion and exclusion criteria with the patient/family as well as with another treating physician or nurse to make sure that all the important

	Yes	No
Inclusion criteria: A NO answer to any of the criteria below excludes the patient from thrombolysis		
• Age 18 or older		
• Time last seen normal well established to be less than 180 minutes before treatment would begin		
• Clinical diagnosis of ischemic stroke causing a potentially disabling neurological deficit defined as: impairment of language, gait, motor function, cognition, gaze, and/or vision; or neglect		
• CT scan rules out hemorrhage		
Absolute contraindications: A YES answer to criteria below excludes the patient from thrombolysis		
• Intracranial hemorrhage on pretreatment neuroimaging		
• Patient has a clinical presentation that suggests subarachnoid hemorrhage, even if the initial CT scan is normal		
• Recent (within 3 months) intracranial or intraspinal surgery, serious head trauma, or previous stroke		
• History of intracranial hemorrhage		
• Uncontrolled hypertension at time of treatment (e.g. >185 mmHg systolic or >110 mmHg diastolic) on repeated measurements.		
• Intracranial neoplasm, arteriovenous malformation, or aneurysm		
• Known bleeding diathesis* including but not limited to: ▪ Current use of oral anticoagulants (e.g., warfarin sodium) or an International Normalized Ratio (INR) >1.7 or a prothrombin time (PT) >15 seconds ▪ Administration of heparin within 48 hours preceding the onset of stroke and have an elevated activated partial thromboplastin time (aPTT) at presentation ▪ Platelet count <100,000/mm^3		
• Active internal bleeding		
Relative contraindications: A YES answer to criteria below warrants a careful consideration of the risks and benefits of thrombolytic therapy. In some cases, it may be reasonable to proceed with thrombolysis, despite a relative contraindication		
• Patient has: ▪ Only minor stroke symptoms ▪ Major symptoms which are rapidly improving by the time treatment would begin		
• Patient has had major surgery in the previous 14 days		
• Patient is lactating or known or suspected to be pregnant		
• Patient has history of GI or urinary tract hemorrhage in previous 21 days		
• Patient has had arterial puncture at a non-compressible site or a lumbar puncture or any spinal epidural injection in the previous 7 days		
• Patient has a history of MI in the previous 3 months		
• Patient has clinical presentation consistent with post MI pericarditis		
• Active bleeding or acute trauma (fracture) on exam		
• Abnormal glucose level (<50 mg/dl)		
• Patient had a seizure at onset of stroke and lacks clinical evidence of ischemic stroke		
• CT shows evidence of new hypodensity greater than 1/3 of MCA territory		
• Patient is menstruating or has dysfunctional uterine bleeding		

Table 44.2. **Checklist for administration of thrombolytic therapy for acute ischemic stroke.**
* In patients without recent use of oral anticoagulants or heparin, treatment with rt-PA can be initiated before availability of coagulation study results but should be discontinued if the INR is >1.7 or the partial thromboplastin time is elevated by local laboratory standards.

details of the medical history have been captured and verified. Things are (hopefully) happening very quickly in the ED and it's easy to get distracted. Adherence to protocol will ensure every patient gets treated quickly and safely. A sample check-list of exclusion criteria is included in Table 44.2, adapted from the alteplase package insert.

44.6.1 Treatment With IV rt-PA

Note: only rt-PA has been approved for treatment of acute ischemic stroke. Other drugs that are used for acute myocardial infarction may not be used for stroke. These include reteplase, tenecteplase, and streptokinase. Make sure to double check the name of the drug since some hospitals do not carry rt-PA [13].

The serious adverse effects of rt-PA are mainly hemorrhagic complications. For this reason, absolute contraindications to the use of IV rt-PA include:

- Evidence of ICH on pretreatment evaluation.
- Suspicion of subarachnoid hemorrhage on pretreatment evaluation.
- Recent (within 3 months) intracranial or intraspinal surgery, serious head trauma, AIS in the past 3 months.
- History of intracranial hemorrhage.
- Active internal bleeding, intracranial neoplasm, arteriovenous malformation, or aneurysm.

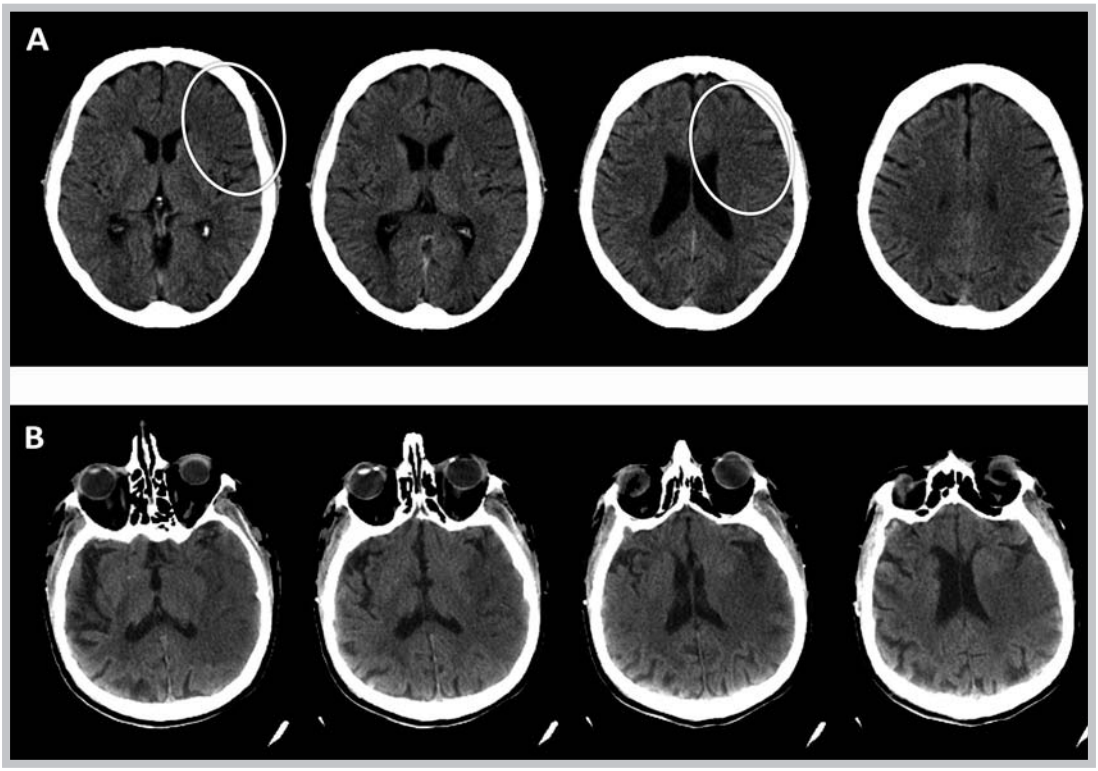

Figure 44.2. **CT findings in acute ischemic stroke. (A). Early ischemic changes which do not exclude the use of thrombolysis: circles demonstrate loss of the gray-white junction and mild sulcal effacement. Neither of these signs on CT precludes the use of thrombolysis. (B). Ischemic changes which do exclude the patient from thrombolysis: this figure demonstrates a clear hypodensity that is well-demarcated and is >1/3 of the left MCA distribution. This extent of change is typically not seen within 3 hours of symptom onset.**

- Known bleeding diathesis including current use of oral anticoagulants with an INR >1.7 or PT >15 seconds, administration of heparin within 48 hours preceding onset of stroke and an elevated aPTT at presentation, platelet count <100,000/mm^3.

Relative contraindications include:

- Uncontrolled hypertension at time of treatment (e.g., >185 mmHg systolic or >110 mmHg diastolic).
- Seizure at the onset of stroke.
- CT shows evidence of new hypodensity greater than 1/3 of MCA territory (Figure 44.2).

Points to keep mind:

- All invasive procedures that are necessary should be performed prior to administration of rt-PA (e.g. Foley, NGT, intubation, IVs, etc.) to minimize the risk of bleeding complications. However, treatment should not be delayed for these procedures unless they are required to stabilize the patient. It is ideal to have 2 large bore IVs in place for rt-PA treated patients.
- The use of aspirin or clopidogrel does not exclude the patient from thrombolysis.
- Early ischemic changes on CT do not exclude the patient from thrombolysis (Figure 44.2).

At times, it can be difficult to differentiate between acute stroke and conditions which mimic stroke, e.g. Todd's paralysis, complicated migraine, conversion disorder, etc. Recent data on misdiagnosis of stroke suggest that when patients with these conditions are treated with thrombolytics, hemorrhagic complication is not frequent [11,34].

Patients with seizure as presentation of stroke were not included in rt-PA trials. Thus, seizure at presentation should be considered only as a relative contraindication.

There is no lower or upper limit on NIHSS that qualifies (or disqualifies) a patient for treatment with thrombolysis. Rather, the treatment decision should be based upon whether the patient has a debilitating deficit which warrants treatment. For example, an NIHSS of 2 for a homonymous hemianopsia in a 50 year-old truck driver is a disabling deficit and warrants treatment despite the low score. Similarly, a high NIHSS also should not exclude the patient from thrombolysis. While we know that stroke severity is associated with increasing rate of ICH [35], this group of patients, overall, still stands to benefit from thrombolysis.

Procedure [13]:

- Dose:
  - Infuse 0.9 mg/kg (maximum dose 90 mg).
  - 10% of the dose given as IV bolus over 1 minute.
  - Remaining 90% infused over 60 minutes.
  - In order to help avoid dosing errors, utilize tools that automatically calculate dose when weight is known instead of relying on manual calculation; verify dose and weight with nurse or other emergency responder; some treating clinicians opt to "waste" the rt-PA that will not be used in order to avoid a possible overdose if the infusion pump does not work as expected.
- Post-rt-PA orders:
  - Admit the patient to an intensive care or stroke unit for monitoring.
  - Perform neurological assessments every 15 minutes during the infusion and every 30 minutes thereafter for the next 6 hours, then hourly until 24 hours after treatment.
  - Monitor blood pressure every 15 minutes for the first 2 hours and subsequently every 30 minutes for the next 6 hours, then hourly until 24 hours after treatment.
  - If necessary invasive monitoring is not able to be placed prior to rt-PA administration, delay placement of nasogastric tubes, indwelling bladder catheters, or

intra-arterial pressure catheters until 30-60 minutes after the rt-PA infusion has been completed.

- Patients should NOT receive aspirin, Aggrenox, clopidogrel, ticlopidine, warfarin, heparin or any other antithrombotic or anticoagulant for 24 hrs after receiving rt-PA.
- If the patient develops severe headache, acute hypertension, nausea, or vomiting, discontinue the infusion (if rt-PA is being administered) and obtain emergency CT scan.
- Obtain a follow-up CT scan or MRI at 24 h before starting anticoagulants or antiplatelet agents.

44.6.2 Anticoagulants and Antiplatelet Agents

Acute Anticoagulation

Data from recent trials do not support the routine use of urgent anticoagulation as treatment for acute stroke. Urgent anticoagulation with unfractionated heparin or low molecular weight heparins has been associated with an increased risk of bleeding complications, symptomatic hemorrhagic transformation of the ischemic stroke, and has not been shown to improve outcomes. Currently, the use of anticoagulation should be restricted to special cases such as cerebral venous thrombosis and possibly extracranial arterial dissection.

Acute Antiplatelet Agents

If a patient is not eligible for IV rt-PA, then aspirin 325 mg should be administered [11]. Aspirin should not be considered instead of IV rt-PA if the patient meets thrombolytic criteria. Aspirin is the only oral antiplatelet agent that has been studied in the acute setting of stroke. The International Stroke Trial [36] and the Chinese Acute Stroke Trial [37] demonstrate a small, but significant reduction in death and disability when aspirin is administered within 48 hrs of stroke. Other oral and IV antiplatelet agents have not been definitively studied in the acute setting of stroke and cannot be recommended instead of or in addition to aspirin in the acute setting for routine care.

While clopidogrel has been proven safe and effective in acute coronary syndromes, this has not been prospectively tested in the setting of acute ischemic stroke. Plavix is currently being evaluated within 12 hours of TIA or minor stroke in the Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) Trial [38]. A phase III trial studying the glycoprotein IIb/IIIa receptor inhibitor, abciximab, within 5 hrs of symptom onset was halted due to safety concerns [39]. Thus, at this time no other antiplatelet agent can be recommended in the acute setting of stroke.

44.6.3 Complications of Thrombolysis

Hemorrhage

The risk of symptomatic intracranial hemorrhage (ICH) is increased with the use of IV rt-PA and ranges between 1.7 to 6.4% depending upon how symptomatic ICH is defined [24,40-42]. In a multicenter retrospective and prospective investigation of individual data from 1205 patients treated in routine clinical practice with rt-PA within 3 hours of symptom onset, patients who developed ICH often had diabetes mellitus, atrial fibrillation, or other cardiac disease. Higher levels of serum glucose, lower platelet counts, increasing age, and stroke severity were associated with increasing rate of ICH [35]. While

these factors may be associated with ICH, their presence or absence does not necessarily reflect which patients may or may not benefit from treatment with rt-PA. Thus, these factors should not be used to guide treatment, but rather for individualized counseling of patients and their families as well as to provide insight into the pathophysiology of rt-PA related ICH for future studies.

rt-PA related ICH [13]:

- Stop rt-PA infusion if still running.
- Goal fibrinogen level >100 mg/dl with cryoprecipitate.
- Type and cross.
- Check fibrinogen level immediately and every 6 hours.
- Give 10-20 units of cryoprecipitate before level returns (1 unit raises fibrinogen by 5-10 mg/dl. Assume there is no fibrinogen and adjust dose when level is back).
- Repeat cryoprecipitate if needed.
- May use fresh frozen plasma (FFP) in case of no cryoprecipitate (1 unit of cryoprecipitate is made from 1 bag of FFP).
- May give platelet concentrate if low.

Angioedema

In one report, angioedema occurred in 5.1% of patients treated with IV rt-PA and was associated with the use of angiotensin-converting enzyme inhibitors and signs on initial CT of ischemia in the insular and frontal cortex [41]. Most of the cases were mild, but severe reactions do occur and can progress rapidly, necessitating close observation of patients who receive thrombolytics, both for neurologic changes and angioedema.

44.6.4 Intra-arterial Thrombolysis and Endovascular Therapy

With the publication of ECASS III, it is clear that the benefit of IV rt-PA extends beyond 3 hrs in an unselected population. Thus, whereas previously, patients presenting outside the 3 hr window might have been considered primarily as candidates for IAT, these patients are now candidates for IV thrombolysis, which, in many facilities can be initiated much sooner than IAT. Given the time involved in preparing for IAT, whenever possible, all eligible patients should receive IV rt-PA and IAT should not be considered instead of IV rt-PA in eligible patients. This ensures that thrombolytic therapy has been initiated as quickly as possible, even while still considering additional therapeutic options. There is a small amount of data which demonstrate that full dose rt-PA may be just as safe as a lower dose [41,43]. This combined treatment approach should take place at experienced centers and **ideally within the framework of a randomized, controlled trial**.

A majority of the patients who present with an NIHSS ≥10 will have a large vessel occlusion [44,45]. IV rt-PA is still the best treatment option for these patients who are eligible, however the recanalization rates of IV rt-PA alone warrant consideration of additional 'rescue' therapy in carefully selected patients.

New mechanical retrieval devices for embolectomy are promising in achieving recanalization. However, they have not been demonstrated in a randomized controlled fashion, to improve outcomes. Based on the available literature, consider IAT in the following situations where large vessel occlusion is suspected.

≤6 hrs after symptom onset:

- In patients with an NIHSS ≥10 or with a disabling deficit in whom a large vessel occlusion has been identified on TCD, CTA, MRA regardless of whether or not IV rt-PA has

been administered. Keep in mind, all patients who are eligible for IV rt-PA should receive it while considering IAT.

- In patients who are not eligible for IV rt-PA, endovascular therapy is a reasonable consideration (e.g. recent surgery, INR >1.7), with or without IA thrombolytics, though in these patients, IA thrombolytic should not be considered a "safer" alternative to IV rt-PA.

As with IV rt-PA, the "window" for treatment with IAT is difficult to define and is certainly different in select patient populations. Assigning the same arbitrary time restrictions to IAT is counter-intuitive to our clinical reasoning and ignores the clinical experience we have gained over the last decade since PROACT as well as the technological advances in neuroimaging. We have made significant progress in achieving recanalization with endovascular techniques and demonstrating "tissue at risk" vs. irreversibly damaged tissue with new imaging modalities. However, we have still not demonstrated the best way to interpret this information, nor the best way to apply this information to clinical decision making. Again, these treatments ideally should occur within the framework of a randomized, controlled trial. That said, it would also be reasonable to consider IAT in patients 6-8 hrs after symptom onset in the scenarios listed below. With rare exception, these cases have more advanced imaging than the routine head CT prior to proceeding with treatment.

6-8 hrs of symptom onset:

- Basilar artery occlusion: the natural history of this disease carries such a poor prognosis that our own treatment window extends to 24 hrs.
- Patients with large artery occlusion in whom advanced neuroimaging demonstrates a significant amount of "salvageable" tissue and only limited or no irreversible damage.

44.6.5 Acute Medical Complications

Patients with acute ischemic stroke are at an increased risk of developing medical complications. These include:

- Infections: aspiration pneumonia, urinary tract infection. It is important to maintain aggressive pulmonary toilet and to screen all patients for dysphagia. In addition, all invasive monitoring should be discontinued as soon as is deemed safe from a medical standpoint.
- DVT: unless there is a contraindication (e.g. IV rt-PA within the last 24 hrs) all ischemic stroke patients should be started on DVT prophylaxis as soon as possible. Typically, a dose of enoxaparin 40 mg SC [46] is started as soon as possible. The dose should be adjusted for decreased renal function.
- Sundowning, confusion, agitation: patients with stroke tend to be older and can become disoriented in an unfamiliar setting. Frequently these patients try to get out of bed and are at risk of falling; they pull out feeding tubes and IVs. Supportive measures such as allowing the family to stay with the patient, familiar objects or pictures can be very helpful in keeping the patients calm. In general, try to avoid the use of sedating medications. However, if absolutely necessary, low doses of antipsychotic agents can be helpful. Keep in mind that older patients with AIS may be sensitive to the side effects and it may be prudent to administer an initial dose lower than one would use in the outpatient setting, e.g. haldol PO or IV 0.5-1 mg; risperdone 1 mg PO, quetiapine 25 mg PO. There is data to suggest that newer antipsychotic agents increase mortality in patients with dementia with prolonged treatment [47], so these medications should be used with caution.

44.6.6 Acute Neurological Complications

With neurologic worsening, the same principles apply in terms of stabilizing the airway and circulation. Early neurologic deterioration in the first few days tends to be related to a neurologic reason compared with deterioration in the subacute setting which is usually due to systemic reasons [48].

Stroke Enlargement

Stroke enlargement can occur when there is clot progression, an arterial stenosis which worsens or progresses to occlusion, or when there is re-occlusion after recanalization [13,48]. Ideally, one prefers to treat the acute vascular abnormality **before** the neurologic deterioration occurs rather than treating after the fact. The key is emergent neurovascular imaging to detect larger artery stenosis/occlusion by TCD, CT angiography (CTA), or MR angiography (MRA). Patients with mild deficits who have abnormal vascular imaging tend to be at risk of deterioration. The finding of a small diffusion weighted lesion on MRI and relatively minor neurological deficit in the setting of large artery occlusion indicates a high risk of progression. In such patients, one might consider early intervention such as IV thrombolysis despite the low NIHSS score, intra-arterial therapy, carotid endarterectomy, or carotid stenting.

Drop in Perfusion Pressure

Simple things such as dehydration, a drop in blood pressure, and body positioning can affect neurologic status. All patients should receive IV fluids with normal saline (avoid hypotonic or saline with D5). In addition, if tolerated, the ideal position is to have the head of bed flat. This horizontal position has been shown to improve cerebral perfusion pressure [49] and in some cases has been associated with neurologic improvement [50].

Recurrent Stroke

Recurrent stroke due to an embolic event can occur in the same region or can be in a different location. TCD can be useful to detect microemboli.

Cerebral Edema and Mass Effect

Patients with large proximal occlusion (terminal ICA, MCA) are at high risk of neurologic deterioration due to a large area of injured tissue developing edema and subsequent mass effect. In younger patients, this process can be rapid, developing with the first 12-24 hrs, and is heralded by increasing lethargy followed by focal signs of herniation. Recent randomized controlled trials demonstrate that urgent hemicraniectomy is not only life-saving but is also associated with improved outcome [51-53]. Of note, the patients in these trials were younger, <60 years, and so were likely better able to recover from the trauma of surgery and stroke severity and were taken for early surgical treatment. Younger patients with this type of “malignant” syndrome should be considered for early surgical treatment.

Hemorrhagic Transformation

Symptomatic hemorrhagic transformation (HT) occurs more frequently in patients who receive IV thrombolysis, ranging from 2-6.4% depending upon how ‘symptomatic’ is defined. The risk factors associated with HT are discussed elsewhere.

Seizure

Seizure is more common in cortical ischemic stroke. The reported frequency of seizures during the first days of stroke ranges from 2% to 23% [54,55] but is probably on the lower end of the range. Seizures are more likely to occur within 24 hours of stroke and are usually partial, with or without secondary generalization. Status epilepticus is uncommon [13]. Seizure prophylaxis is not recommended, however treatment of acute seizures with continued therapy to prevent further seizures is recommended.

44.6.7 Evaluation of Stroke Etiology

Once the acute treatment phase is complete, the goal of the diagnostic evaluation is to determine stroke etiology in order to guide secondary prevention treatment. The "routine" stroke evaluation consists of laboratory studies, a limited cardiac evaluation and neurovascular imaging. Most patients should undergo the following studies:

- Laboratory evaluation: Chemistry, CBC, PT/PTT, fasting lipids, hemoglobin A1C.
- Cardiac studies: 12-lead ECG, transthoracic or transesophageal echocardiogram with a bubble study; if a bubble study demonstrates a right-to-left shunt, in the appropriate patient, it would be reasonable to consider an evaluation for DVT (paradoxical embolus).
- Neurovascular imaging: MRI is desirable. CT is a great screening tool for the emergency setting, but MRI provides a wealth of information that can help with determining stroke etiology. Vascular screening in the form of TCD, MRA, CTA or carotid ultrasound. If screening studies are abnormal, it may be necessary to proceed to conventional cerebral angiogram. In patients in whom the etiology is unclear, it is preferable to include the great vessels as well as the extracranial carotids and intracranial vasculature.

When patients are younger or have few or no vascular risk factors, additional evaluation should be tailored to the individual patient and can include:

- Laboratory evaluation for hypercoagulable state.
- Laboratory evaluation for systemic vasculitis.
- Lumbar puncture for CNS vasculitis (primary or secondary); don't forget infectious causes of CNS vasculitis (syphilis, VZV, HSV, etc.).
- Diagnostic cerebral angiogram.

44.7 Additional Considerations

Once the acute plan of care for treatment has been completed and the neurologic status is stable, it is important to begin treatments that will improve the patient's chances for improved outcome and avoid the medical complications of stroke. These plans should include:

- Rapid mobilization of the patient with occupational, physical and speech therapy as soon as possible to assist with a long-term plan for rehabilitation and a safe nutritional plan (i.e. can the patient tolerate an oral diet or will he require placement of a feeding tube).
- Education of the patient and family of stroke risk factors, prevention, and the importance of activating emergency services should this happen again; counseling about the patients residual deficits and what to expect in the next few days to weeks.
- Secondary stroke prevention treatment targeted toward the patient's risk factors.

44.8 Conclusions

In summary, acute ischemic stroke is a neurologic emergency which requires a rapid, multidisciplinary approach in order to achieve the best possible outcomes. Acute stroke treatment begins with the recognition of stroke and activation of emergency medical services. Once the patient is in the emergency department, stabilization of the patient and restoration of blood flow are priorities. All patients should be considered for thrombolysis. If the patient meets inclusion criteria, IV rt-PA should be administered as quickly as possible with a goal door-to-needle time ≤60 minutes. Intra-arterial therapies (IAT) are an option when large vessel occlusion is suspected but should not be considered instead of IV rt-PA in otherwise eligible patients. IAT should take place at experienced centers. When patients are not eligible for thrombolysis, aspirin should be administered. The importance of aggressive medical management to avoid the complications of stroke cannot be over-emphasized. Diagnostic evaluation for stroke etiology can help tailor secondary prevention treatment to the individual patient's risk factors.

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45 Acute Management of Ischemic Vertebrobasilar Stroke

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45.1 Introduction

Updated guidelines on the immediate or early management of ischemic stroke and transient ischemic attacks (TIAs) are available. These guidelines do not specifically address the management of ischemic vertebrobasilar stroke. In the beginning of this chapter, the clinical scenario of acute basilar artery occlusion is illustrated by a case. This chapter will briefly outline the vascular anatomy, pathophysiology, presentation, imaging findings, and prognosis of ischemic vertebrobasilar stroke. Early recanalization is the treatment goal. The emphasis is on the recent advances in intravenous (IV) and intra-arterial (IA) thrombolysis, angioplasty and stenting, and mechanical thrombectomy.

The vertebrobasilar arterial system constitutes the posterior circulation. Ischemic vertebrobasilar stroke accounts for about 20% of ischemic stroke. Compared to strokes in the anterior circulation, ischemic vertebrobasilar stroke is generally more severe and has higher fatality rates of up to 90%. Prior to the catastrophic presentation of severe ischemic vertebrobasilar stroke, most patients have experienced milder symptoms for days to weeks. Recent advances in chemical thrombolysis and mechanical thrombectomy provide some hope for better outcomes. These have also aroused interest in management protocols aimed at early detection and/or staged escalation therapy for ischemic vertebrobasilar stroke.

45.2 Case Report

A 69-year-old woman is known to have diabetes mellitus, a past history of carcinoma of vulva treated with chemotherapy and radiotherapy in 2006, and a more remote history of modified radical mastectomy for carcinoma of the right breast. There was no history of any prior neurologic symptoms. She presented with sudden collapse at 18:30. Assessment at the emergency room showed a raised blood pressure of 202/96 mmHg and a low Glasgow Coma Scale (GCS) score of 4. Her right pupil was dilated with sluggish response to light. She was intubated at the emergency room. Urgent computed tomography (CT) of the head revealed normal findings at 18:58. Urgent magnetic resonance imaging (MRI) and angiography (MRA) of the brain revealed acute basilar artery occlusion with no restriction defect on diffusion-weighted imaging (DWI) at 20:13 (Figure 45.1).

Neurological examination at 21:30 showed absent Doll's eye sign, spastic tetraplegia with no active limb power and bilateral upgoing plantar responses. Her National Institutes of Health Stroke Scale (NIHSS) score was 40. Urgent cerebral digital subtraction angiography (DSA) confirmed the presence of acute basilar artery occlusion (Fig-

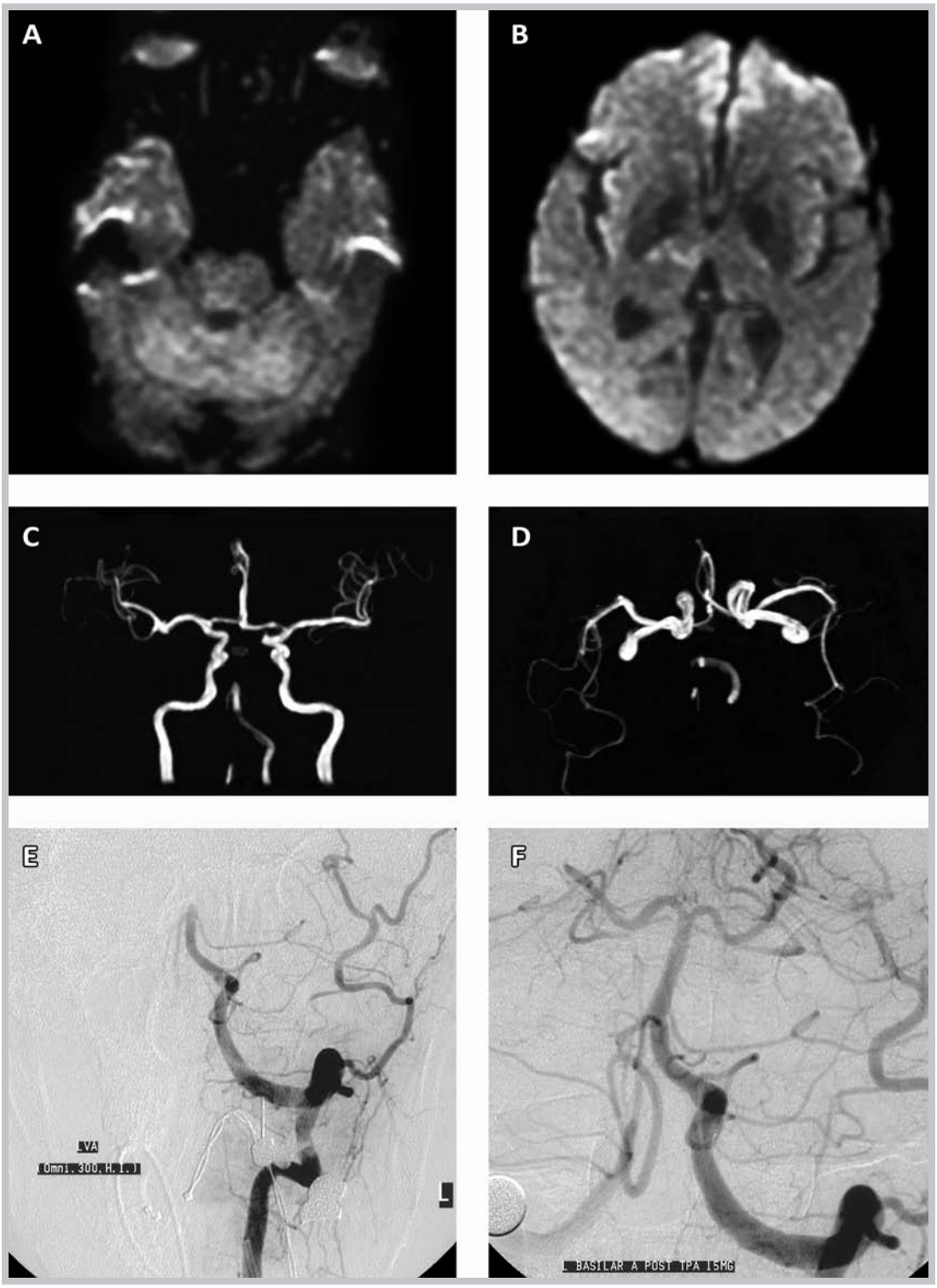

Figure 45.1. **Urgent MRI revealed no restriction defect on DWI (A, B) but urgent MRA revealed acute basilar artery occlusion (C, D). Urgent DSA confirmed the presence of acute basilar artery occlusion with no visualisation of the right vertebral artery, the PICA on both sides, the AICA on both sides and the basilar perforators. The basilar artery was recanalized using mechanical thrombectomy plus IA rtPA (F).**

ure 45.1). In addition, the right vertebral artery, the posterior inferior cerebellar artery (PICA) on both sides, the anterior inferior cerebellar artery (AICA) on both sides, and the basilar perforators were not visualized on DSA. Mechanical thrombectomy was attempted using a 3-mm alligator retrieval device, and IA infusion of 15 mg of recombinant tissue plasminogen activator (rtPA) was commenced at 23:00 (about 4.5 hours after onset).

The basilar artery was successfully recanalized about 8 hours after onset (at around 02:30 on the next day) (Figure 45.1).

Unfortunately, she developed severe shock from lower gastrointestinal bleeding, hematuria and sepsis, and inotropic agents at high doses were required to maintain her blood pressure. The bleedings were due to post-irradiation colitis and cystitis. Repeat CT of the head 2 days later revealed an extensive pontine infarction with multiple bilateral infarctions in the cerebellum, occipital lobes and thalami (Figure 45.2).

Repeat MRA of the brain and neck showed that all major extra- and intracranial arteries were patent. She remained in a locked-in state. Despite maximal supportive care, she developed recurrent episodes of septic shock, lower gastrointestinal bleeding, and hematuria. Finally, she died of irreversible shock about 4 months after her ischemic vertebrobasilar stroke.

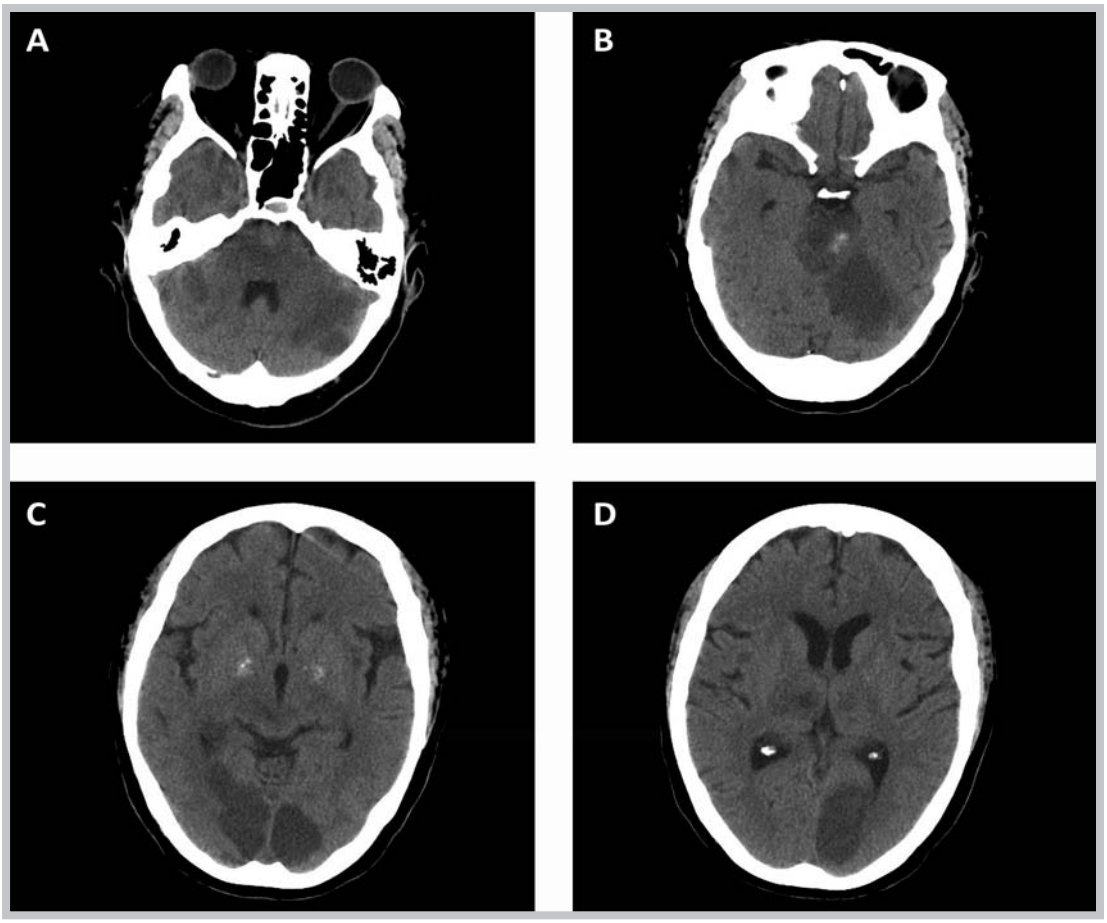

Figure 45.2. **Repeat CT of the head 2 days after presentation revealed an extensive pontine infarction (A, B) with multiple bilateral infarctions in the cerebellum (A, B), occipital lobes (C, D) and thalami (D). A hyperdense area over the left side of the pons (B) might represent hemorrhagic transformation.**

45.3 Vascular Anatomy

The vertebral artery, a branch of the subclavian artery, passes through the transverse foramina from C5 or C6 to C2 and arches around C1 to enter the foramen magnum. Its PICA supplies blood to the posterior and inferior part of the cerebellum, the inferior vermis and the lateral part of the medulla. At the pontomedullary junction, the left and right vertebral arteries combine to form the basilar artery. The AICA, superior cerebellar artery (SCA) and three groups of penetrating pontine arteries are branches of the basilar artery before its termination into two posterior cerebral arteries (PCAs) at the upper pons. The AICA supplies the anterior and inferior part of the cerebellum and mid-pons. The SCA lies close to the PCA and supplies the superior part of the cerebellum and the upper pons. The three groups of penetrating arteries supply the pons. The PCA supplies the medial and inferolateral parts of the temporal lobe and the medial and lateral parts of the occipital lobe. The thalamogeniculate and thalamoperforating branches of the PCA supply the lateral part of the thalamus, the lentiform nucleus and the midbrain. Following acute basilar artery occlusion, it is not surprising to find multiple and bilateral infarctions over the pons, cerebellar hemispheres and occipital lobes.

45.4 Pathophysiology

Similar to ischemic strokes in the anterior circulation, atherothrombosis, cardioembolism, artery-to-artery embolism and small vessel disease are the major mechanisms of ischemic vertebrobasilar stroke. Atherosclerotic steno-occlusive disease of the vertebral artery is commonly encountered at either its origin extracranially or its distal part intracranially. Common sites of atherosclerotic steno-occlusive disease of the basilar artery are seen around the AICA and the basilar artery tip. Cardiogenic and artery-to-artery emboli to the posterior circulation are less common than the anterior circulation; emboli typically lodge in the distal part of the vertebral artery or the basilar artery or at a site proximal to a pre-existing stenosis. Rare causes of ischemic vertebrobasilar stroke include fibromuscular dysplasia, temporal arteritis, migraine, dissection, and dolichoectasia. Apart from diabetes mellitus, no cause of acute basilar artery occlusion was identified in the index case.

Neurons place a high metabolic demand on energy in the form of adenosine triphosphate (ATP) to maintain their transmembrane ionic gradients, electrical activities, synaptic transmission, macromolecular synthesis, efficient intracellular transport, and cytoskeletal integrity. ATP is derived from the oxidative metabolism of glucose under normal circumstances; anaerobic glycolysis generates only one-sixteenth the amount of ATP from oxidative metabolism and also leads to lactic acidosis. During focal ischemia, reduction in cerebral blood flow is severe at the centre (ischemic core) and milder in the surrounding peripheral zone (ischemic penumbra). Rapid reversal of ischemia (reperfusion) within a treatment time window is an effective treatment of ischemic stroke.

45.5 Presentation

The clinical presentation of ischemic vertebrobasilar stroke is highly variable, ranging from TIAs or minor stroke to rapidly progressive brainstem dysfunction or coma at onset. Important determining factors are the etiology, location of occlusion, and severity

of ischemia. Typical symptoms include headache, dizziness, vertigo, diplopia, confusion, coma, dysarthria, unilateral or bilateral weakness, unilateral or bilateral numbness, and/or homonymous visual field loss or total blindness. Neurological examination may reveal pupillary abnormalities, abnormal ocular movements, ataxia, facial palsy, hemiplegia or quadriplegia, bilateral extensor plantar responses, homonymous hemianopia or total cortical blindness, and/or depressed GCS score. The index case presented with severe symptoms due to acute basilar artery occlusion. Despite immediate diagnosis and early recanalization, she fell into a locked-in syndrome or state. This dreadful consequence is due to severe destruction of the basis pontis. In the majority of patients, preceding warning symptoms of vertebrobasilar ischemia occur over an interval of 2 days to several weeks, but these were absent in the index case.

45.6 Diagnostic Imaging

The index case illustrates the usefulness of neuroimaging in confirming the diagnosis of ischemic vertebrobasilar stroke. Urgent brain CT effectively excludes intracerebral hemorrhage, subarachnoid hemorrhage and many mimics of stroke. MRI with DWI is very useful in detecting early or hyperacute infarction in the vertebrobasilar territory, and CT angiography, MRA or DSA is required to confirm acute vertebrobasilar occlusion.

45.7 Prognosis of Acute Basilar Artery Occlusion

Acute basilar artery occlusion carries a high mortality rate of 80 to 90% when untreated or upon treatment failure. The most critical factors for natural prognosis are the degree of ischemia and the site of occlusion. Incomplete occlusion with good collateral supply is associated with better outcome. A proximal occlusion is worse than a distal occlusion. A high NIHSS score >20, quadriplegia or coma at presentation predicts a poor outcome. In contrast, a better prognosis is associated with a low NIHSS score at baseline, shorter length of occlusion, younger age, embolic occlusion, and absence of brainstem infarction. Thus, the index case was expected to have a high mortality from the beginning. Timely and successful recanalization could have improved her prognosis. Unfortunately, the potential benefits of early recanalization were nullified by the severe shock plus the use of vasoconstrictive inotropic agents at high doses. There is no evidence that anticoagulation and other supportive treatments would improve the outcome. The spontaneous recanalization rate within a clinically meaningful time window is estimated to be 20% or less.

45.8 Development

Depending on the etiology and severity of ischemic vertebrobasilar stroke, the natural prognosis of ischemic vertebrobasilar stroke is highly variable, and some patients may respond better to a specific treatment than others. Numerous case series are available in the literature, but there are no randomized controlled trials to identify a superior treatment strategy. The general consensus on treatment targets of acute severe vertebrobasilar occlusion is rapid recanalization by IV thrombolysis, IA thrombolysis, angiographic stenting, and/or mechanical thrombectomy. A prospective, observational, mul-

ticentre, international registry of consecutive patients presenting with a symptomatic and radiologically confirmed BA occlusion was set up in November 2002: the Basilar Artery International Cooperation Study (BASICS) registry. With a target number of 500 patients, the BASICS registry will address the relationship between functional outcome and clinical presentation, duration of symptoms, early changes on brain CT, location of occlusion, type of treatment, recanalization, as well as stroke etiology. It will also document the most common complications of three treatment options, i.e., antithrombotic treatment alone, IV thrombolysis, and IA therapy. Furthermore, the registry will report on some outcome parameters at 1-year follow-up. As of December 2006, the data of 400 patients from 12 countries were collected; 61% of patients had a NIHSS score ≥20, 55% were treated with IA therapy, 29% were treated with antithrombotics alone, 6% were treated with IV thrombolysis, and 10% received no acute treatment. The overall mortality was 45%, and 29% had a good outcome.

45.8.1 Intravenous Thrombolysis

IV thrombolysis using rtPA is the standard treatment of ischemic stroke presenting within 3 hours and up to 4.5 hours of onset. The dose is 0.9 mg/kg body weight (maximum 90 mg), with 10% given as a bolus followed by a 60-min infusion. All exclusion criteria should be absent. The blood pressure should be kept <185/100 mmHg prior to and during the first 24 hours of thrombolysis. The increased risk of symptomatic hemorrhagic transformation is associated with a history of diabetes, elevated blood glucose, severe stroke, advanced age, longer delay of treatment, use of aspirin, history of congestive heart failure, and protocol violations. Randomized controlled trials of IV thrombolysis using rtPA did not specifically include or exclude patients with ischemic vertebrobasilar stroke. In a recent systematic analysis comparing IV and IA thrombolysis as therapy for acute basilar artery occlusion, Lindsberg and Mattle reported that 76 of 420 (18%) patients were given IV thrombolysis. The recanalization rate was 53%, the survival rate was 50%, and 22% had good outcomes. Most centres allow for a treatment time window of 6 to 12 hours in patients with severe neurological deficits due to acute basilar artery occlusion and up to several days in patients with a progressive stroke of lesser severity. Studies are ongoing to evaluate the benefits of IV thrombolysis within 24 hours of ischemic vertebrobasilar stroke, as well as the potential of newer IV thrombolytic agents.

45.8.2 Intra-arterial Thrombolysis

The intra-arterial approach has been advocated because the thrombolytic agent can be locally delivered to the thrombus at a high concentration. Multiple case series support the notion that IA thrombolysis achieves a better recanalization rate in large artery thrombosis. Nevertheless, data on the clinical efficacy of IA thrombolysis are lacking from randomized trials. The only randomized study on IA thrombolysis for acute stroke is the Prolyse in Acute Cerebral Thromboembolism (PROACT) II study which included acute stroke due to proximal middle cerebral artery occlusion within 6 hours of onset. Successful recanalization was associated with good outcomes and survival. IA thrombolysis can be achieved using rtPA or prourokinase (Prolyse®). Clinical use of the latter has not been approved by regulatory agencies. IA thrombolysis has become a standard treatment for acute large artery thrombosis in many comprehensive stroke centres. The treatment time window of IA thrombolysis is 6 hours. Compelling but unproven reasons for IA thrombolysis include severe neurological deficits, presentation between 3 and 6 hours after onset, recent history of major surgical procedures, and occlusion of major

extra- or intracranial arteries. Lindsberg and Mattle compared IV and IA thrombolysis as therapy for acute basilar artery occlusion and reported that 344 of 420 (82%) patients were given IA thrombolysis. The recanalization rate was 65%, the survival rate was 45%, and 24% had good outcomes. A higher mortality rate despite a better recanalization rate after IA thrombolysis can be due to the selection of more severe patients and/or a greater delay in IA thrombolysis when compared to IV thrombolysis. Macleod and colleagues randomized 16 patients with confirmed vertebrobasilar occlusion within 24 hours of onset to either IA urokinase or conservative management; good outcomes were seen in 4 of 8 (50%) patients in the IA arm and in 1 of 8 (13%) patients in the control arm. Unfortunately, the trial was prematurely terminated because of slow recruitment and withdrawal of the sponsor.

45.8.3 Transluminal Angioplasty and Stenting

Re-occlusion may occur after successful thrombolysis, especially at the site of atherosclerotic stenosis. When symptoms are due to residual atherosclerotic stenosis and/or re-occlusion at an atherosclerotic plaque, transluminal angioplasty with or without stenting may be considered. Gomez and colleagues reported their experience in 12 patients with symptomatic basilar artery stenosis. The mean stenosis was reduced from 84 to 44%; at 6 weeks, 8 patients had good outcomes, 2 had arterial dissection and 2 had thromboembolism. In a retrospective study, Imai and colleagues reported their experience on primary transluminal angioplasty and stenting in 28 patients with occlusive lesion of the intracranial vertebrobasilar artery within 7 days of onset. Of 16 patients with total occlusion, 81% had a baseline NIHSS score >20, 81% had technical success, and 19% had a good outcome. Of 12 patients with high-grade stenosis, 8% had a baseline NIHSS >20, 92% had technical success, and 75% had a good outcome. In the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS), an international multicentre trial, 16 patients with symptomatic vertebral artery stenosis were randomized to receive endovascular angioplasty and stenting or best medical treatment alone. Endovascular intervention was successful in all 8 patients, but 2 had TIAs during the procedure. During a mean follow-up of 4.7 years, there was no recurrence in vertebral artery stroke in either group. Nevertheless, 3 patients in each group died of myocardial infarction or anterior circulation stroke, and 1 endovascular patient had a non-fatal anterior circulation stroke.

45.8.4 Endovascular Mechanical Thrombectomy

The Mechanical Embolus Removal in Cerebral Embolism (MERCI) trial evaluated a device which can mechanically remove an occlusive thrombus from an intracranial artery within 8 hours of onset of stroke. A recanalization rate of 48% was reported in 141 patients. In a pooled analysis of the MERCI and Multi-MERCI trials, recanalization was achieved in 21 of 27 (78%) patients with acute vertebral artery occlusion. Good outcomes were seen in 41%, and the mortality rate was 44%. Good outcomes were associated with successful recanalization. In the Multi-MERCI trial, patients with persistent large artery occlusion despite IV thrombolysis were recruited.

Another mechanical device, named the Penumbra System, was evaluated in a prospective, single-arm study within 8 hours of onset of stroke due to intracranial artery occlusion. Altogether, 21 arteries of 20 patients were successfully recanalized, the mortality rate was 45%, and good outcomes were seen in 45% of patients. The U.S. Food and Drug Administration has approved the clinical use of both the MERCI Device and the Penumbra System.

45.8.5 Combined Therapy

Combined Local Fibrinolysis and Intravenous Abciximab in Acute Vertebrobasilar Stroke Treatment (FAST) is a multicentre study designed to evaluate the potential benefit of combining IA rtPA at half dose and IV Abciximab (bolus followed by 12-hour infusion) in 47 patients with acute vertebrobasilar occlusion. Percutaneous transluminal angioplasty and stenting was performed in case of severe residual stenosis. Eligible patients had preserved brainstem reflexes. Recanalization was achieved in 72%, a good outcome was seen in 34%, and the mortality rate was 38%. The FAST cohort has demonstrated the feasibility of the combination therapy to improve recanalization and clinical outcome within a mean treatment time window of 6 hours from onset.

45.8.6 Staged Escalation Therapy

Pfefferkorn and colleagues proposed their staged escalation therapy in acute basilar artery occlusion. All eligible patients with acute basilar artery occlusion were given standard IV thrombolysis within 6 hours of onset in a community hospital. Upon transfer to a comprehensive stroke centre, brain CT and CT angiography were repeated. When there was persistent basilar artery occlusion, endovascular mechanical thrombectomy was performed to achieve recanalization. This approach is similar to that of the Multi-MERCI trial. Of 16 patients, 15 achieved recanalization, 7 required mechanical thrombectomy, 4 were dead at 3 months, and 7 had a good outcome.

45.8.7 Subsequent Management

Management in a stroke centre or an acute stroke unit is highly desirable. In addition to supportive care and rehabilitation, secondary prevention should be achieved by effective control of vascular risk factors, use of a statin, use of antiplatelet agents in atherothrombotic strokes, and use of anticoagulation in cardioembolic strokes. Intracranial large artery stenosis, including basilar artery stenosis, carries a higher risk of recurrent stroke. Warfarin treatment cannot be recommended because of its association with a higher rate of myocardial infarction, sudden death and hemorrhage. Instead, transluminal angioplasty with or without stenting may be considered.

45.9 **Key Concepts**

Ischemic vertebrobasilar strokes are less common but generally more severe than anterior circulation strokes. Angiographically documented acute vertebrobasilar occlusion is a clinical catastrophe with a mortality rate approaching 90% despite standard medical therapy including anticoagulation. Prompt detection and early recanalization may alter the outcome. Recanalization can be achieved by IV or IA thrombolysis and/or mechanical thrombectomy. An effective protocol to identify acute vertebrobasilar occlusion is crucial. Combination therapy and staged escalation therapy are feasible. As new and newer modalities of therapy become available, randomized studies are required to prove the effectiveness of these treatment options. In addition, studies on outcome predictors and appropriate selection of newer therapeutic modalities are needed.

45.10 Acknowledgments and Funding

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46 Stroke in Young Patients

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46.1 Introduction

Population studies highlight that stroke is the third leading cause of death and the leading cause of disability in developed countries. Incidence and prevalence of this condition increase exponentially with age. Young patient have different characteristics from the adults and therefore deserve an independent analysis. From the public health point of view, stroke in young patients carries a great challenge not only for individuals but for society as a whole. The disability acquiered early in life means a significant loss of years of productivity of the patient, resulting in a significant economic burden for the entire population.

In this chapter we review the epidemiology, more frequent etiologies and prognosis of ischemic stroke in young patients. Cerebral venous pathology and bleeding, as well as therapeutic alternatives in patients with stroke are treated in their respective chapters.

46.2 Epidemiology

46.2.1 Incidence

The Northern Manhattan Stroke Study (NOMASS) is a prospective population study designed to determine incidence, risk factors and prognosis of stroke in a multiethnic urban population.The inclusion criteria for this study included: 1) individuals over 20 years of age; 2) diagnosis of first stroke; and 3) at least 3 months of residence in the area of northern Manhattan. Patients with transient ischemic attacks were not included. The main racial group in this cohort is African-American of Caribbean origin. In a period of 4 years, 924 cases of stroke were detected. Of these, 74 were individuals between 20 and 44 years of age with an estimated age-specific annual incidence of stroke of 23 per 100,000 inhabitants. In patients older than 45 years, 80% of cases were cerebral ischemia, 15% parenchymal hemorrhages, and only 5% SAH. In the subgroup of individuals with cerebral ischemia, the distribution by stroke subtype in young patients and adults is shown in Figure 46.1. The results indicate that the mechanisms of ischemic stroke vary with age. Cardioembolic stroke is observed more frequently in adults; in comparison, younger patients have a higher rate of cryptogenic stroke. This suggests that the causes of ischemia in young patients are more heterogeneous and that the evaluation of this group should differ significantly from that of adult patients with typical cardiovascular risk factors.

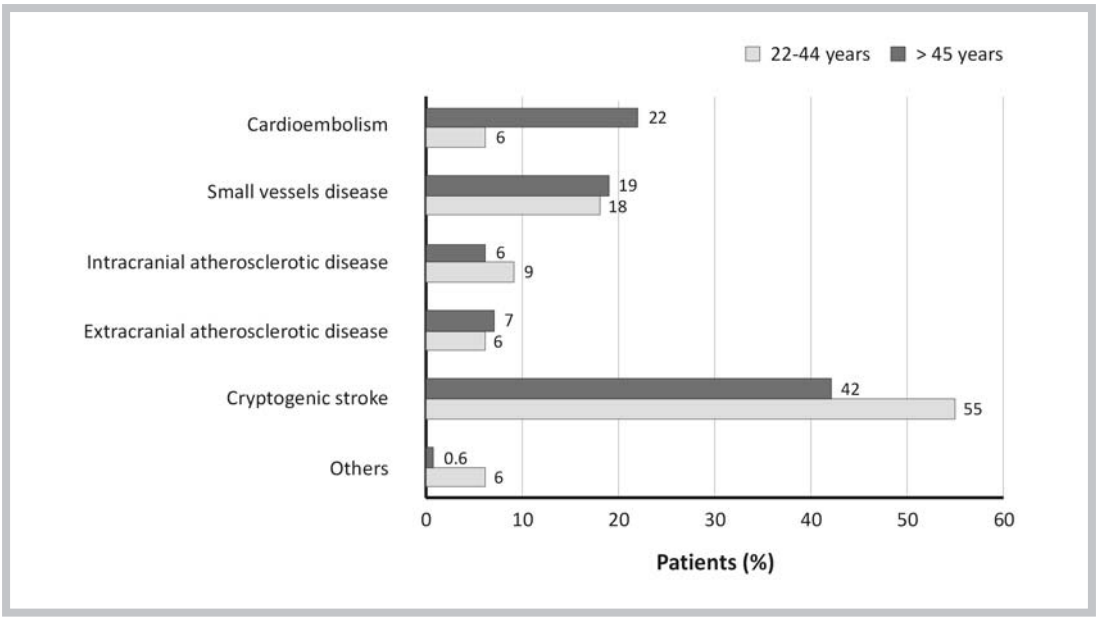

Figure 46.1. **Subtype mechanism of ischemia in patients between 20 and 44 (white bar) and more than 45 years (black bar) of age at first stroke in the Northern Manhattan Stroke Study [Jacobs, 2002].**

The NOMASS study, like other epidemiological studies, shows that the incidence, prevalence and consequences of stroke differ across different racial or ethnical groups. In younger patients, the relative risk of stroke in Hispanic or African-Americans is about 2.5 times higher than in white Caucasians. Even more significant are the racial differences observed in the Greater Cincinnati/Northern Kentucky Stroke Study which involved 3136 patients with first stroke. The sample analyzed a biracial metropolitan population

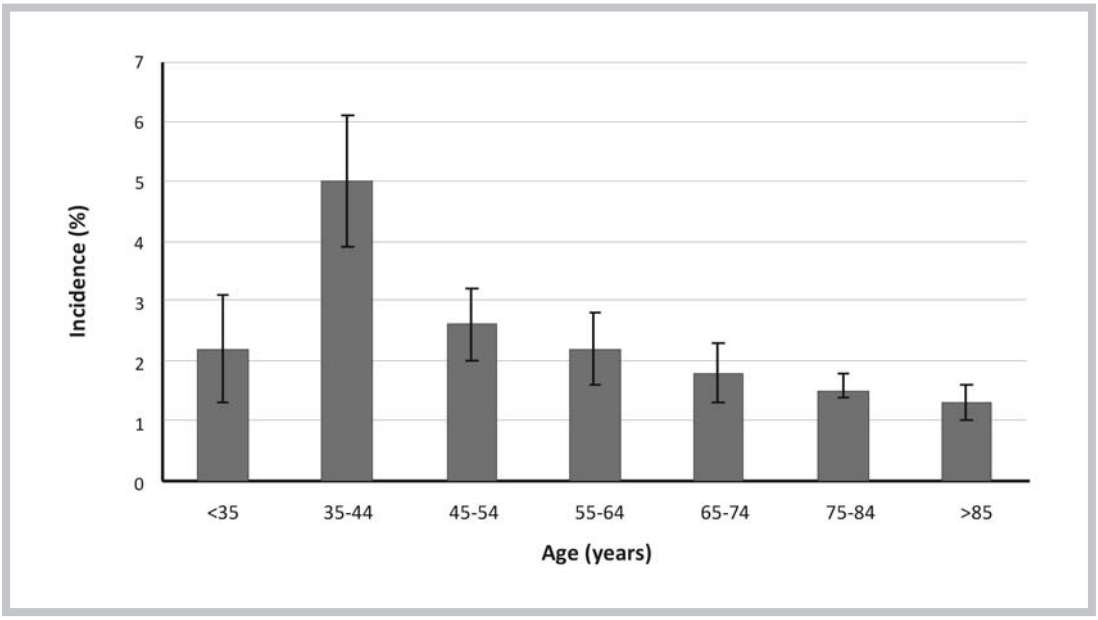

Figure 46.2. **Relative incidence of first stroke by age in African-Americans as compared to whites in the Northern Manhattan Stroke Study [Jacobs, 2002].**

composed mostly of white Caucasians (~70%) and African-Americans (29%). Compared to Caucasians, the relative risk of first stroke in African-Americans was 2.2 for those under 35 years of age, 5.0 for those aged 35-44 years, and 2.6 for those aged 45-54 years. These racial differences were attenuated at older ages (Figure 46.2).

Although the causes of these differences have not been determined, epidemiological studies suggest differences in vascular risk factors. Population studies show an increased prevalence and suboptimal control of cardiovascular risk factors (hypertension, diabetes, and obesity) in populations with low socioeconomic status and a higher prevalence of smoking in middle-high socioeconomic levels.

46.2.2 Prevalence

In 2005, the "Behavioral Risk Factor Surveillance System" (BRFSS) survey was performed in the United States. The study used randomly generated telephone numbers for questioning the civilian outpatient population over 18 years of age. Subjects had to answer the question "Have you ever been told by a doctor or other health professional that you had a stroke?". Of a total of around 356,000 individuals, approximately 2.6% responded affirmatively. On the basis of the data obtained from this survey, it has been estimated that the prevalence of cerebrovascular disease is 0.8% in individuals aged 18-44 years, 2.7% for those between 45 and 64 years, and 8.1% in those over 65 years.

Many strokes are asymptomatic or unrecognized. This suggests that the prevalence of this disease is in the general population underestimated. The NOMASS study illustrates this concept. In this trial, 892 subjects aged 55 years and older who were never diagnosed with stroke were assessed by magnetic resonance imaging (MRI) of the brain. The overall prevalence of subclinical brain infarction was 17.7%. Due to the design of this study, no data are available for patients younger than 55 years. However, the prevalence of subclinical ischemic stroke in relatively young individuals (55-65 years) was 9.5%; this rate is higher than that expected on the basis of the information obtained in the BRFSS survey. Similar to what was observed with incidence, the prevalence of ischemic stroke in relatively young African-Americans (55-65 years) was significantly higher (28.9%) than that observed in Caucasians (4.1%). These results confirm that the prevalence of stroke in the general population, even in relatively young patients, is greater than estimated.

46.2.3 Risk Factors

Cerebral ischemia in adult patients is close linked to traditional cardiovascular risk factors like hypertension, hypercholesterolemia, diabetes, obesity, and smoking. The presence, severity and suboptimal control of these co-morbidities increase the risk of small-vessel atherosclerotic disease, large-vessel occlusive disease, cardiomyopathy, valvulopathy, and cardiac conduction disorders. A worrying observation is the exponential increase observed in the last two decades in the prevalence of vascular risk factors related to eating habits, sedentary lifestyle, obesity and diabetes. Population studies conducted in the United States indicate that these conditions affect mostly African-Americans and Hispanics.

Cardiovascular risk factors are the pathophysiological basis for the vast majority of strokes in adults. In young patients suffering from cerebral ischemia, the prevalence of cardiovascular risk factors is significantly higher than in the general youth population. As in adult patients, the severity of these risk factors is directly related to the risk of developing cerebral ischemia. For example, data obtained in the Stroke Prevention in Young Women Study show that the risk of stroke in young women between 15 and 49 years of

age increases with the number of cigarettes smoked per day (odds ratio [OR] = 2.2 for 1 to 10 cigarettes/day, 2.5 for 11 to 20 cigarettes/day, 4.3 for 21 to 39 cigarettes/day, and 9.1 for 40 or more cigarettes/day).

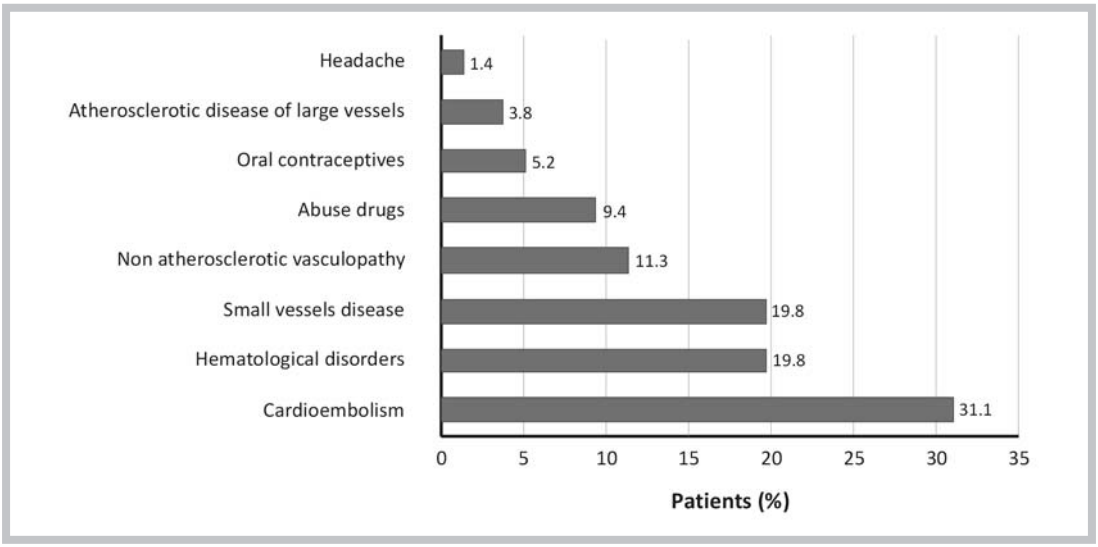

Figure 46.3. **Causes of ischemic stroke in young patients (15-44 years) in the Baltimore-Washington Cooperative Young Stroke Study [Kittner, 1998].**

Area	Age	n	Subtype (%)				
			ASVD	ALVD	CE	OC	C
South America							
Brazil	14-40	106	12.5	8.5	28.3	34.9	16.0
North America							
Canada	14-45	356	8	6	14	28	44
USA-NOMASS**	20-44	74	18	15	6	6	55
USA-BWCYSS	15-44	428	10	2	15	23	32
Mexico	<40	300	3*		24	40	32
Asia							
Taiwan**	15-45	241	22.4	7.9	19.5	24.5	25.7
Korea	15-44	149	17.4	20.8	18.1	26.8	16.8
Europe							
Spain	15-45	272	5	19.5	17.5	22	36***
Italy	15-44	333	33.1*		23.7	8.1	35.1
Sweden	18-44	107	4.7	12.1	32.7	29.9	20.3
Switzerland	15-44	202	2.5	5.4	21.4	46	22.8

Table 46.1. **Subtypes of stroke observed in epidemiological studies in young patients.**

* Represents the sum of individuals and ALVD ASVD.
** Transient ischemic attack patients were not included.
*** Includes patients with cryptogenic stroke, with more than one possible cause, and incomplete assessments.
ASVD = atherosclerotic small-vessel disease
ALVD = atherosclerotic large-vessel disease
CE = cardioembolic
OC = other known cause
C = cryptogenic
NOMASS = Northern Manhattan Stroke Study
BWCYSS = Baltimore-Washington Cooperative Young Stroke Study

46.3 Stroke Etiology in Young People

Stroke in adult patients is, in most cases, the result of endothelial injury caused by sustained exposure to vascular risk factors. As a corollary of this phenomenon, the vast majority of studies carried out to delineate the causes, evaluation, management and prognosis of cerebral ischemia have been conducted in groups of adult patients. However, as noted above, stroke in young patients differs significantly from that of adults. With a sample of 428 subjects, the Baltimore-Washington Cooperative Young Stroke Study is perhaps the largest epidemiological study carried out in 15 to 44 year-old patients with first stroke. The biracial population analyzed included approximately 60% of African Americans and 36% of Caucasians. In this study, about 50% of patients had at least one probable cause of stroke, 20% had at least one possible cause of stroke, and 30% had no probable or possible causes of stroke. The frequency distribution by cause of stroke seen in the first subgroup is summarized in Figure 46.3. Drug abuse, contraceptive use, thrombophilia and non-atherosclerotic arterial disease (including vasculitis and vascular dissection) are relatively uncommon causes of stroke in adult patients. However, in this study, these conditions were the etiologic factor for approximately 50% of cases of cerebral ischemia.

Like other epidemiological estimates, vascular risk factors and causes of stroke vary with race or ethnic group studied. In a retrospective study including 264 young patients of Chinese origin aged between 15 and 45 years of age, the stroke subtype more frequently observed was the cryptogenic type (Figure 46.4). The most prevalent risk factors were hyperlipidemia (53%), smoking (50%), hypertension (46%) and family history of stroke (29%). Within the subgroup with stroke due to other causes, the most common etiol-

Atherosclerotic arterial disease	
NO-atherosclerotic arterial disease	• Arterial dissection • Moyamoya Disease • Fibromuscular dysplasia • Susac's syndrome
Thrombophilia	
Migraine	
Embolic cardiopathies	• Atrial fibrillation • Myxoma • Patent foramen ovale (with/without septal aneurysm) • Intraventricular thrombosis • Heart failure
Collagenopathies	
Drug Abuse	• Cocaine • Heroin • Amphetamines
Drugs	• Hormones • Erythropoietin
Genetic syndromes	• Fabry Disease • Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) • Homocysteinemia • Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Table 46.2. **Factors that increase the risk of stroke in young patients.**

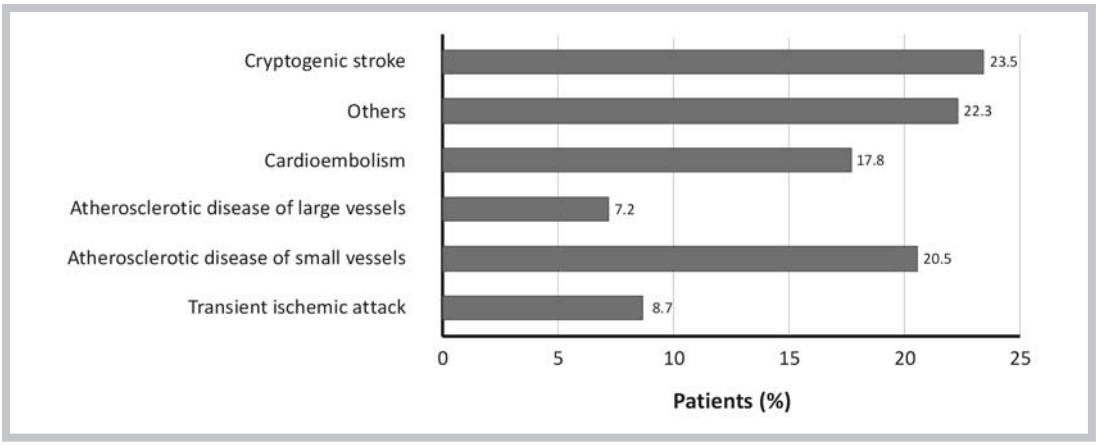

Figure 46.4. **Causes of stroke in young patients (15-45 years) of Chinese origin [Lee, 2002].**

ogies were arterial dissection (39%), antiphospholipid syndrome (17%), and Moyamoya disease (15%). Observed subtypes of stroke in epidemiological studies that include younger patients belonging to certain races or ethnic groups are summarized in Table 46.1.

Table 46.2 summarizes the conditions associated with the development of cerebral ischemia in young patients. The following sections discuss the most relevant pathologies.

46.4 Arterial Dissection

The annual incidence of brain supplying arterial dissection in the general population is 2.6 to 2.9 per 100,000 inhabitants. It is highly probable that the actual incidence is higher than that reported because most of the cases are asymptomatic or present with pain often considered "benign" and not investigated properly. About 70% of cases occur in patients between 35 and 50 years of age. It is estimated that between 10% and 25% of cerebral ischemia in patients under age 45 years are due to this disease, making arterial dissection of the second cause of stroke in young patients.

Traditionally, arterial dissections are divided into traumatic and spontaneous. This subdivision has been questioned because it is considered that a significant number of "spontaneous" dissections are the result of mechanical stress or trauma caused by sudden movements, hyperextension or high-speed acceleration of the neck: 80-90% of cervical-cranial dissections occur in the extracranial portions of the vessel, particularly in its mobile sector. The most vulnerable areas are the portion overlying the carotid bulb and the extracranial segments of the vertebral arteries (segement V3). Intracranial dissections are much less frequent: the affected vessels, in order of decreasing frequency, are the internal carotid artery, the middle cerebral artery, and the V4 segement of the vertebral arteries.

Arterial dissection originates from a tear in the intima which is separated from the rest of the vessel wall and forms a double lumen with an intramural hematoma (Figure 46.5). In other cases, the hematoma originates in the tunica media and subsequently extends into the intima (subintimal dissection), allowing the passage of clots into the bloodstream. The hematoma may also expand into the adventitia (subadventitial dissection), weakening the vessel wall and allowing the development of pseudoaneurysms or dissecting aneurysms. The intracranial vessels are particularly vulnerable to this compli-

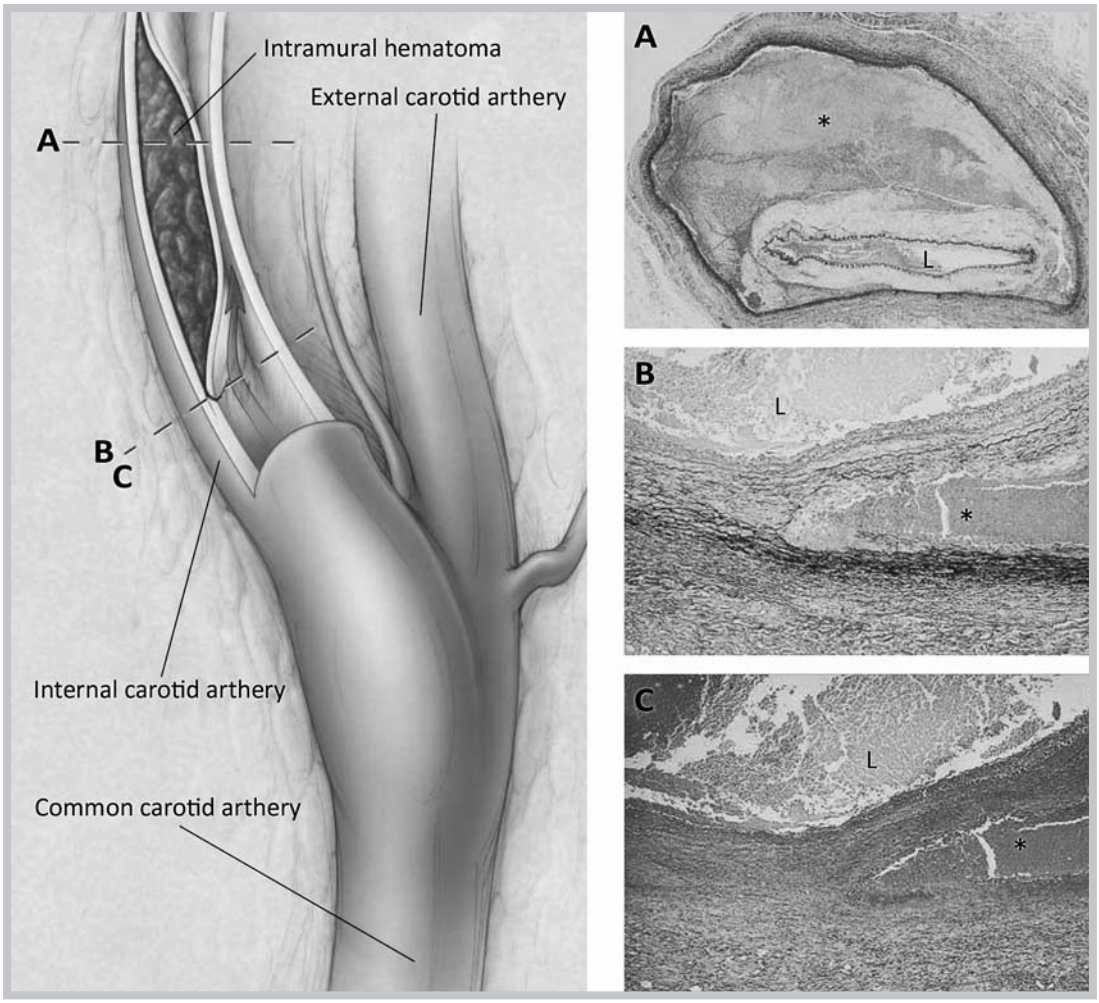

Figure 46.5. **Pathological findings in a 37-year-old patient with carotid artery dissection. The micrograph of the extracranial portion of the right internal carotid artery (panels A, B and C) shows a dissection between the outer layer and the tunica media causing stenosis of the arterial lumen (L). Intramural hemorrhage (asterisk) extends almost completely around the artery (panel A) (van Gieson stain, 4x). At higher magnification, the internal carotid artery shows fragmentation of the elastic lamina (panel b) (van Gieson stain, 25x) with accumulation of a pale substance in the tunica media shown by the blue staining of mucopolysaccharides (panel C) (Alcian Blue, x25). These changes are consistent with the diagnosis of cystic necrosis of the tunica media [Schievink, 2001].**

cation because of the absence of external elastic lamina and the thin adventitia. Once formed, the hematoma expands longitudinally in a proximal and distal way. Compression on the true lumen decreases blood flow, with the consequent risk of cerebral hypoperfusion. While subintimal dissections are associated with ischemic stroke, subadventitial dissections are associated with subarachnoid hemorrhage (SAH). Imaging studies obtained by nuclear magnetic resonance suggests that the pathophysiological mechanism that causes ischemia is, in most cases, thromboembolism.

It has been postulated that arterial dissection is a result of structural instability of the vessel wall. About 15-20% of patients with this disease have fibromuscular dysplasia, and 1-5% have hereditary connective tissue diseases such as type IV Ehlers-Danlos syndrome, Marfan syndrome, autosomal dominant polycystic kidney disease, osteogenesis

imperfecta type 1, pseudoxanthoma elasticum, and α1 antitrypsin deficiency. In addition, arterial dissection has been linked to other arterial diseases such as cystic necrosis of the lamina media and Moyamoya disease. Other risk factors are migraine, recent infection, pregnancy, hyperhomocysteinemia, smoking, hypertension, and use of oral contraceptives.

The clinical presentation is variable but is most often accompanied by ipsilateral or widespread neck pain, facial pain or headache which may precede the occurrence of stroke for days or weeks. Subintimal dissections usually cause transient ischemic attack or stroke; the clinical presentation depends on the infarcted area but most patients present with amaurosis fugax, hemiparesis, or hemiparesthesia. Vascular distension is frequently observed in subadventitial dissections and can cause ispilateral Horner syndrome, pulsatile tinnitus or tinnitus, or cranial neuropathy (most often involving cranial nerves IX-XII). Vertebral dissections usually present with pain located in the neck, occipital region, or trapezius muscle; the pain can also radiate down the arm simulating a radicular neuralgia. The neurological deficits include diplopia, dysarthria, ataxia, and dizziness. The most common presentation is Wallenberg syndrome, which is caused by ischemia in the posterior inferior cerebellar artery territory. Intracranial dissections may present with SAH or ischemia. The latter is rarely transient and evolves into infarction more often than in extracranial dissections.

The diagnosis of arterial dissection has historically been based on radiographic findings obtained from digital cerebral angiography. In the classic form, dissection of the internal carotid artery shows a reduction in vessel calibre, sometimes with total occlusion, with its tapered distal end resulting in a typical “flame” image, followed by a long narrow column of contrast agent which may extend to the skull base (Figure 46.6).

Other typical angiographic findings are arterial dilation in the proximal or distal to the dissection, double lumen, intramural or intraluminal clot formation, and dissecting aneurysm. intraluminal clots and dissecting aneurysm. Magnetic resonance imaging (MRI) and nuclear magnetic resonance angiography (MRA) are non-invasive methods that allow simultaneous evaluation of the major cervico-cerebral vessels and brain parenchyma. MRA reveals the presence of vascular stenosis or occlusion. The T1-fat-saturated sequence shows an expansion of the vascular wall and the presence of intramural hemato-

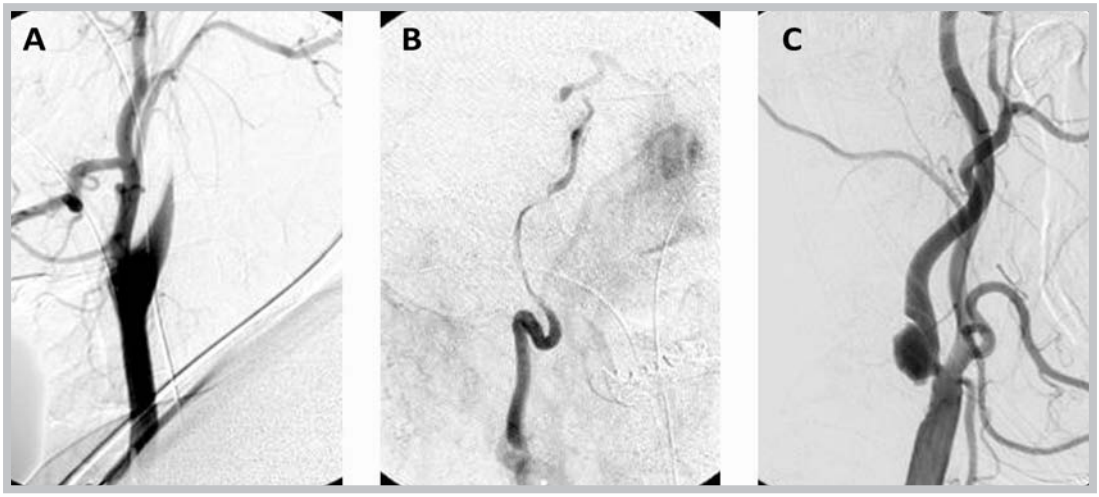

Figure 46.6. **Conventional catheter angiography showing carotid dissection with reduction of the calibre of the internal carotid artery with its distal end forming a “scarf” (A), followed by a long, thin column of contrast material forming the “string sign” (B). A pseudoaneurysm caused by subadventitial dissection (C).**

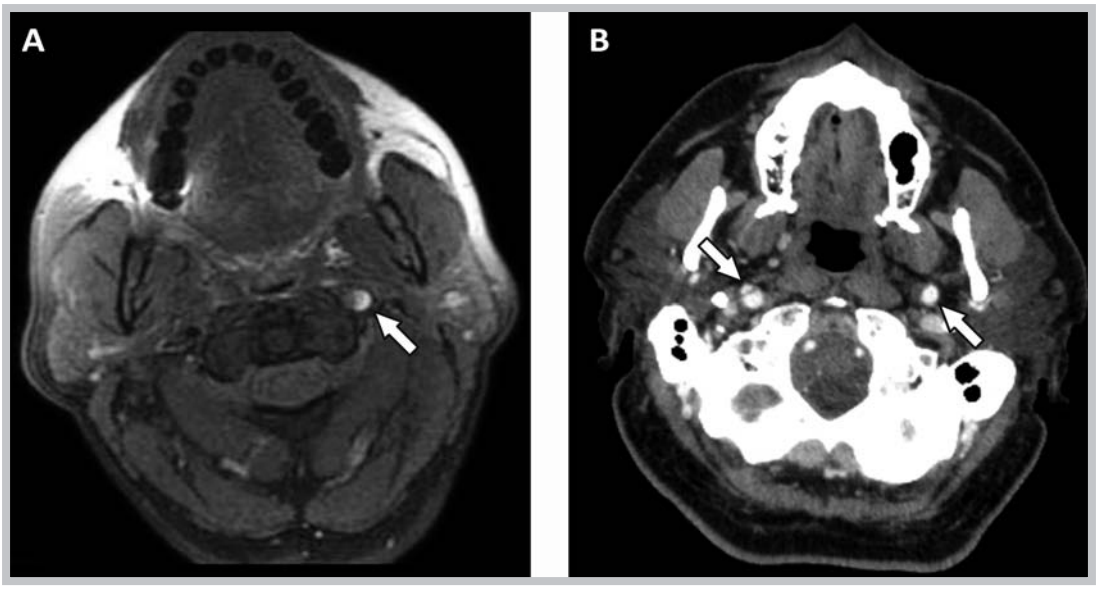

Figure 46.7. **MRI T1 sequence scan with fat saturation showing dissection of the left internal carotid artery with a hyperintense lesion in the wall corresponding to an intramural hematoma (arrow, panel A). CT image showing a double lumen right internal carotid artery (arrow with solid line, panel B) and the normal left internal carotid artery (arrow with dotted line).**

ma, the latter visualized as a hyperintense lesion with a half-moon shape (Figure 46.7). The intensity of the hematoma on T1- and T2-weighted sequences depends on the age of the dissection. In addition, diffusion-weighted imaging, T2-weighted and fluid-attenuated inversion-recovery (FLAIR) sequences can identify parenchymal ischemic lesions. In comparison, vertebral artery dissections most commonly affect the poserioinferior cerebellar artery territory. The sensitivity and specificity of MRI to detect dissection of the extracranial portion of the internal carotid artery is 95% and 99%, respectively, whereas in the portion of the extracranial vertebral artery, the sensitivity and specificity of MRI are 60% and 98%, respectively. Computed tomography angiography (CTA) is a non-invasive method that allows the identification of double lumen (Figure 46.7).

Because it is faster than MRI, CTA has become the radiographic test of choice for evaluating unstable patients. Recent studies suggest that CTA is superior to MRA for detecting vertebral artery dissections, and both techniques are similar for studying the carotid artery. However, MRI allows more detailed assessment of brain parenchyma, thus providing the physician with information of prognostic value. Finally, Doppler ultrasound of the carotid and transcranial Doppler ultrasound are useful in evaluating patients with suspected arterial dissection. The decrease or absence of blood flow in the affected vessel, distal retrograde flow and bidirectional flow in the carotid artery are indirect signs of high degree stenosis or obstruction in the appropriate clinical context and are sugges-

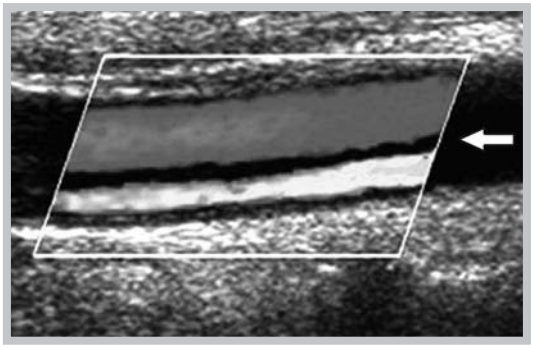

Figure 46.8. **Doppler ultrasound image of the carotid artery in a patient with arterial dissection. The image shows a double lumen, a high flow rate (lower) and a low flow rate (higher), separated by an "intimal flap" (white arrow).**

tive of a diagnosis of dissection. With color Doppler ultrasound the intimal flap and double lumen can be observed (Figure 46.8); usually the flow velocity in the false lumen is lower than that in the true lumen; alternatively, the flow in both compartments may have opposite directions.

The treatment of ischemic stroke associated with arterial dissection is controversial. Currently, there are no randomized trials comparing the efficacy of antiplatelet agents and anticoagulants in the management of this disease. The treatment of intracranial and extracranial dissection differs according to the authors. On the basis of the pathophysiological mechanism of ischemia in patients with extracranial dissections, the use of intravenous heparin is usually recommended, followed by oral anticoagulants for 3-6 months, with the aim of achieving an international normalized ratio (INR) between 2 and 3. More controversial is the use of anticoagulants in patients with intracranial dissection because of the risk (probably low) of SAH in patients with subadventitial dissection. The use of anticoagulants is related to the theoretical risk of intramural hematoma expansion, but the low number of reports describing this complication suggests that it is unusual.

If the use of anticoagulants is contraindicated, we suggest the use of antiplatelet agents that can be continued indefinitely. The use of thrombolytic agents in patients presenting within 3 hours of symptom onset has been described. Most of these reports include a small number of patients. Based on the mechanism underlying the ischemia, it is likely that this treatment is effective in patients who present in the hyperacute state. However, no prospective studies investigating the efficacy and adverse effects of thrombolytics in the treatment of dissection pressure are available. Finally, a few studies describe the use of angioplasty and stenting as alternatives in the management of patients with intra-or extracranial dissections. Manipulation of the dissected vessel may cause blood clots to shed, with the risk of causing further ischemia. Therefore, this treatment is reserved for cases refractory to medical treatment with anticoagulants.

The risk of recurrence of this disease is low. In a retrospective study involving 459 individuals with carotid dissection, the risk of recurrent ischemia at 31 months was 0.9%; half of the cases occurred in the subacute period and the other half was due to recurrent dissection.

46.5 Thrombophilia

It has been estimated that about 5-10% of cases of cerebral ischemia in the general population are caused by thrombophilia; this percentage is even higher in younger patients. Maintenance of homeostasis depends on the combined action of procoagulant and anticoagulant mechanisms, and the deficiency of inhibitory factors as well as the elevated levels of certain mediators of the coagulation system increase the risk of thrombosis. There are numerous inherited and acquired hypercoagulable states, those most frequently encountered in clinical practice are summarized in Table 46.3.

Hereditary	• Resistance to activated protein C due to mutation of factor V Leiden • 20210 mutation, prothrombin gene • Protein C deficiency • Protein S deficiency • Antithrombin III • Polymorphism in the gene for the enzyme methylenetetrahydrofolate reductase
Acquired	• Antiphospholipid syndrome • Thrombotic thrombocytopenic purpura • Myeloproliferative syndromes

Table 46.3. **Hypercoagulable states inherited and acquired more frequently encountered in clinical practice.**

Syndrome	Control group asymptomatic (%)	Patients with deep vein thrombosis (%)	Patients with a family history of venous thrombosis (%)	Patients with ischemic stroke	
				%	OR (95% CI)
PC deficiency	0.14-0.5	3.2	4.9	1.4	0.7 (0.2-3.1)
PS deficiency	0.1	2.2	5.1	0.9	0.9 (0.1-6.7)
ATIII deficiency	0.02-0.2	1.1	4.2	5.2	1.3 (0.5-3.3)
FVL	3-6	19	46	4.6	2.1 (0.6-6.8)
MGP	1-2	6.3	18	3.7	1.9 (0.5-6.2)

Table 46.4. **Prevalence of hereditary hypercoagulablility syndromes in Caucasians.**

ATIII = antithrombin III
CI = confidence interval
FVL = factor V Leiden
MGP = 20210A mutation of the prothrombin gene
OR = odds ratio
PS = protein S

Patients with inherited thrombophilias typically present with venous thrombosis; arterial thrombosis, however, is observed less frequently. Thus, the pathophysiological mechanisms of cerebral ischemia more common in patients with thrombophilia are venous sinus thrombosis and paradoxical embolism of thrombus originating in the veins of the legs or pelvis. The prevalence of inherited hypercoagulable states in Caucasians is low, and the role of these as causative agents of ischemia is controversial (Table 46.4).

A meta-analysis including a total of almost 18,000 cases and 58,000 controls was used to study the role of Factor V Leiden (FVL), the mutation 20210 of the prothrombin gene (PGM), and polymorphism in the gene for the enzyme methylenetetrahydrofolate reductase (MTHFR) in the development of cerebral ischemia. The risk of stroke was 1.33 (95% confidence interval [CI], 1.12 to 1.58) in patients with FVL, 1.24 (95% CI, 1.08 to 1.42) in patients with MTHFR, and 1.44 (95% CI, 1.11 to 1.86) in patients with PGM.

In a meta-analysis including approximately 54,000 subjects studied the association between inherited thrombophilias and arterial ischemia (including myocardial infarction, ischemic stroke and peripheral vascular disease). The risk of arterial ischemia in patients under 55 years with FVL was 1.37 (95% CI, 0.96 to 1.97), 1.66 (CI 95%, 1,13-2, 46) in patients with MTHFR and 1.41 (95% CI, 1.13 to 1.76) in patients with PGM.

Antiphospholipid antibodies are circulating IgG, IgM or IgA antibodies that recognize anionic and neutral membrane phospholipids. From a clinical point of view, the most rele-

Clinical examination	• Arterial thrombosis (cerebral, ocular, peripheral, myocardium, pulmonary, mesenteric) • Venous thrombosis (lower limbs, pelvis, venous sinus, hepatic (Budd-Chiari syndrome), pulmonary) • Intracardiac thrombosis • Repeated spontaneous abortions • Livedo reticularis • Cardiac disorders (valvular disease, verrucous endocarditis, Libman Sacks endocarditis, myxomatous degeneration of the mitral valve) • Pulmonary hypertension • Chorea
Laboratory tests	• False-positive VDRL • Thrombocytopenia • Hemolytic anemia • Elevated antinuclear antibody • Prolonged partial thromboplastin time • Hypocomplementemia (reduced c4)

Table 46.5. **Clinical and laboratory features associated with antiphospholipid syndrome.**

vant are the lupus anticoagulant, anticardiolipin antibodies and β2-glycoprotein antibodies. The phosphatidylserine antibody is seen less frequently and has been less studied. Antiphospholipid antibodies are mostly acquired, although they can sometimes be inherited. Antiphospholipid syndrome (APS) is characterized by the presence of antiphospholipid antibodies in the context of arterial or venous thrombosis. The prevalence of APS in the general population is estimated to be between 1.0% and 6.5% and its presence is suspected in individuals with history of repeated spontaneous abortions, connective tissue diseases (such as lupus), the presence of livedo reticularis on clinical examination, and ischemia of unknown origin in young patients. In laboratory studies, APS is suggested by a prolonged partial thromboplastin time, a false positive venereal disease research laboratory (VDRL) test, and a moderate thrombocytopenia. Other findings that suggest the presence of this condition are summarized in Table 46.5.

APS produces a hypercoagulable state and is observed in approximately 10% of patients with cerebral ischemia. This percentage is even higher in younger patients. The IgG isotype was statistically associated with the occurrence of stroke, and IgM isotype is considered an acute phase reactant whose level increases after certain infections. The role of IgM and IgA in ischemic stroke has not been clarified yet.

The management of venous or arterial thrombosis in patients with hypercoagulablity states is controversial. The presence of deep vein thrombosis (DVT) in the legs, and probably in the pelvis, in individuals with ischemic stroke and inherited thrombophilia, should prompt the assessment for cardiac variants causing right-to-left shunt and paradoxical embolism. If there is no alternative mechanism of ischemia, the use of heparin followed by warfarin sodium is recommended in order to achieve an INR between 2 and 3.

In the WARSS APASS trial (Antiphospholipid Antibodies and Stroke Study - Warfarin Aspirin Recurrent Stroke Study), the effectiveness of warfarin compared to aspirin in preventing the recurrence of cerebral ischemia in individuals with antiphospholipid antibodies was compared. This study included a total of 1770 individuals, 720 had antiphospholipid antibodies and 1050 were controls. The risk of recurrent stroke at 2 years was similar in both groups. Moreover, the frequency of recurrent cerebral ischemia in the individuals with antiphospholipid antibodies was similar. On the basis of these results, there is no evidence to justify the use of oral anticoagulants in patients with first ischemic stroke and antiphospholipid antibodies; in such patients the use of antiplatelet agents is reasonable. Differently, in patient with cerebral ischemia and APS we recommend the use of heparin followed by warfarin sodium in order to achieve an INR between 2 and 3. Due to the autoimmune mechanism underlying the APS, the possible role of iatrogenic immunosuppression with steroids or immunosuppressive drugs such as azathioprine, cyclophosphamide, cyclosporine, intravenous gamma globulin, and plasmapheresis has been suggested. The benefits and potential adverse effects associated with the use of these agents in preventing recurrent ischemic stroke have not been evaluated in clinical trials; therefore, these treatments are considered experimental and reserved for patients refractory to antithrombotic therapy.

46.6 Sickle Cell Anemia

Sickle cell anemia (SCA) is an autosomal recessive genetic disorder caused by a mutation in codon 6 of the β-globin gene. This mutation causes the substitution of a residue of valine for glutamic acid which induces a change in the spatial structure of the hemoglobin molecule (HbS). Two of the most serious complications of this disease are ischemic

stroke (75% of cases) and cerebral hemorrhage (25% of cases). The most frequently affected population is children and young adults. Under low oxygen tension, deoxygenated HbS forms insoluble polymers that precipitate in the microvessels. The endothelial injury that occurs in this condition generates a non-inflammatory arteriopathy affecting the large vessels of the circle of Willis, causing stenosis and ischemia. In areas of severe stenosis, a phenomenon of neovascularization may occur that generates small collateral vessels (moyamoya), which are fragile and increase the risk of cerebral hemorrhage. Other pathophysiological mechanisms of ischemia that can occur in this disease include hypercoagulability, related to an increased production of thrombin, platelet activation, and high levels of inflammatory mediators, and cardioembolic stroke. The latter, however, is rarely observed.

In the early 1990s, Adams showed that the average flow velocity in the middle cerebral artery of patients with SCA as measured by transcranial Doppler ultrasound (TCD) is directly correlated with the risk of stroke. This observation was the starting point for the Stroke Prevention Trial in Sickle Cell Anemia I (STOP I) study. This trial compared medical treatment with regular transfusion in the prevention of cerebral ischemia in patients with SCA. Approximately 2000 individuals with SCA (age range, 2-16 years) were studied by TCD and those with flow velocity in middle cerebral artery >200 cm/sec were randomized to receive medical treatment or periodic transfusions to reduce the level HbS <30%. The annual risk of stroke was 10% in the control group and 0.5-1% in those treated with regular transfusions. Moreover, in the latter group a significant decrease in flow velocity in the middle cerebral artery was observed. This trial was followed by the STOP II trial which investigated whether it was safe to stop periodic transfusion in patients who had normalization of flow velocity in the middle cerebral artery. This study was aborted early after seeing a rapid reversal of the hemodynamic benefit achieved and the occurrence of two cases of cerebral ischemia after regular transfusions were discontinued.

The management of young adult patients with SCA and stroke include the use of antiplatelet agents and the control of classical cardiovascular risk factors associated with the occurrence of cerebral ischemia. The use of regular transfusions can be considered in order to reduce the HbS <30-50%. However, it should be noted that most of the patients analyzed in STOP I and II studies were children and it is unclear whether the results can be extrapolated to adults. In addition, chronic transfusion is associated with complications and carries the risk of causing iron overload which requires the use of oral chelators.

46.7 Patent Foramen Ovale

Based on autopsy studies, it was estimated that the prevalence of patent foramen ovale (PFO) in the general population is 26%. Its pathological value is controversial. The PFO, as well as atrial septal defects, allows communication between venous and arterial blood and increases the risk of paradoxical embolism. Right-to-left shunt may be revealed or increased by manoeuvres or activities that increase intrathoracic pressure, the flow direction also can be reversed in certain pathological conditions.

In a clinical trial in patients <55 years of age, the prevalence of PFO was 40% in those with ischemic stroke and 10% in the control group (P <0.001). Within the group of patients with ischemia, the prevalence of PFO in individuals with known cause of stroke was half of those without an identifiable cause of stroke (20% versus 40%, P <0.10). This study, like others, shows an association between PFO and the presence of ischemia, particularly in individuals with cryptogenic stroke. In addition, several studies show that the

association of this disease with ischemic stroke increases with the size of PFO. On the basis of observations it has been suggested that, besides allowing paradoxical embolism, PFO may be a direct causal agent of cerebral ischemia.

There are several techniques that allow the diagnosis of PFO. Among the echocardiographic techniques, transthoracic echocardiography (TTE) is the most widely used method. Trans-oesophageal echocardiography (TEE) is more invasive, but its sensitivity is higher and it is considered the reference method. Atrial septal defect is a discontinuity in the interventricular septum, whereas PFO has a valve-like structure. In addition, the PFO does not always manifest at rest, requiring in such cases the use of techniques that can provoke it, as the Valsalva manoeuvre. In transcranial Doppler, micro-bubbles are used as a contrast method; they are injected intravenously while the peripheral middle cerebral artery is interrogated. The presence of microbubbles in the arterial system in a "shower" or "curtain" pattern is consistent with a right-to-left shunt. Depending on the clinical context, it can suggest the presence of PFO or arteriovenous fistula. In comparison with TEE, transcranial Doppler has a sensitivity in the detection of PFO of 68-89% and a specificity of 92-100%.

The management of ischemic stroke of unknown cause in patients with PFO alone (without atrial septal aneurysm) has generated controversy. There is no evidence in the literature to suggest that warfarin is superior to antiplatelet agents in preventing recurrent stroke. As an alternative to medical treatment, surgical or percutaneous closure of PFO has been suggested. In a recent prospective study, however, PFO closure in patients with cryptogenic stroke or TIA did not offer a greater benefit compared to medical therapy alone for the prevention of recurrent ischemic events. At present, medical treatment with antiplatelet agents for patients with cryptogenic stroke and PFO is recommended. Treatment with warfarin is reserved for individuals at high risk of recurrence, as those with hypercoagulable states or DVT. Percutaneous closure of PFO is recommended only for recurrent stroke cases unresponsive to medical treatment.

46.8 Retinococleocerebral Artery (Susac's Syndrome)

Susac's syndrome (SS) is characterized clinically by the triad of encephalopathy, fluctuating sensorineural hypoacusia and sudden visual loss. The pathophysiological mechanism is a microangiopathy that affects the vessels of the brain, retina and cochlea producing microinfarcts. The cause of this disease is unknown, although there is evidence suggesting a mechanism of autoimmunity whose target organ is the endothelial cell. Histopathology shows the presence of a predominantly lymphocytic perivascular infiltrate, microinfarcts, adventitial thickening, and endothelial proliferation (Figure 46.9).

Magnetic resonance imaging of the brain shows the presence of microinfarcts with a typical "snowball" appearance located, more often, in the corpus callosum and the supratentorial white matter (Figure 46.9).

The diagnosis of SS is mainly clinical and radiological. Encephalopathy and the motor or sensory deficits have been observed in 80% of cases, vision loss and hearing loss have a frequency of 46% and 52%, respectively. The typical triad is much less common, occurring only in 20% of individuals. In the peripheral blood there is usually an elevation of serum markers of inflammation such as erythrocyte sedimentation rate and C-reactive protein, and the cerebrospinal fluid shows elevated protein and lymphocytic pleocytosis. The ophthalmologic exam is characterized by occlusion of branches of the central retinal artery, and the audiogram shows hearing loss with a predilection for mid and low frequencies.

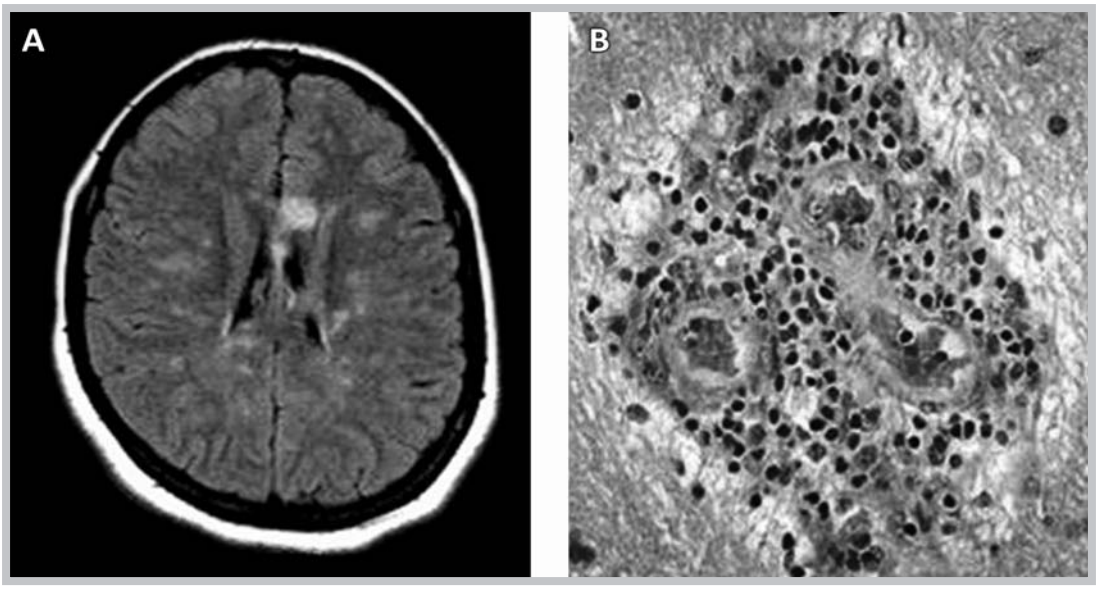

Figure 46.9. **A Magnetic resonance imaging (fluid attenuated inversion recovery [FLAIR] sequence) axial section of a patient with Susac's syndrome showing an ischemic lesion in the form of a "snowball" in the ischemic knee of the corpus callosum. Note the smaller ischemic lesions affecting mainly the white matter. B. Brain biopsy preparation showing adventitial thickening, endothelial proliferation and a predominantly periarteriolar lymphocytic infiltrate (staining: hematoxylin and eosin, 400x) [Fox, 2006].**

Treatment of SS is controversial and is based largely on studies with a small number of patients and the postulated mechanism of autoimmunity. Intravenous steroids are often used in the acute state. In refractory cases, plasmapheresis or intravenous gamma globulin administration are suggested. The use of other immunosuppressive drugs like azathioprine and cyclophosphamide has been reported in the literature, with variable results. Antiplatelet and anticoagulant agents are usually ineffective for treating this condition.

Susac's syndrome has a self-limiting course lasting from a few months to 5 years. Early diagnosis and rapid initiation of immunosuppressive therapy have a direct impact on the prognosis of these patients.

46.9 Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL)

CADASIL is an autosomal dominant systemic arteriopathy caused by a mutation ni the Notch3 gene. This gene is located on chromosome 19p 13.2-13.1 and encodes a membrane receptor involved in signal transduction mechanisms and neural development of Drosophila. In humans, its role is unknown, but it has been postulated that it's important for maintaining the structural stability of vascular smooth muscle cells. In patients with CADASIL, the membrane receptor Notch3 accumulates in the plasma membrane of these cells in the intracranial and extracranial vessels; electron microscopy shows intraneuronal granular osmiophilic deposits. Clinically, CADASIL is associated with migraine (usually with aura) that develops in 40-70% of cases in the third or fourth decade of life. The most severe complication of this entity is recurrent ischemic stroke which occurs in

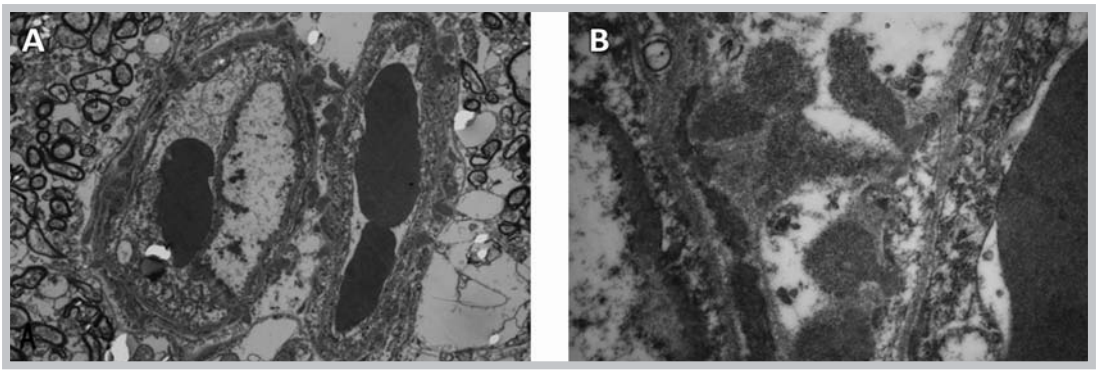

Figure 46.10. **Electron microscopy of skin biopsy preparation from a patient with CADASIL showing arteriolar ultrastructure. Panel A: granular osmeophilic deposits are seen in smooth muscle cells. At higher magnification, these granular osmeophilic deposits are irregularly shaped, 0.2 to 1 mm in size and consist of fine granules [Arima, 2003].**

80-85% of patients 30-50 years of age. Other typical clinical manifestations are psychiatric disorders and subcortical dementia.

Magnetic resonance imaging of brain shows ischemic lesions in the periventricular white matter and around the basal ganglia, with particular focus on the anterior pole of the temporal lobe and external capsule. These changes are not specific to CADASIL and may be absent in initial stages of the disease. The diagnosis of CADASIL is based on the identification of the Notch3 gene mutation. Electron microscopy of skin biopsy shows the presence of granular osmiophilic deposits adjacent to the basement membrane of smooth muscle cells of the arteriolar wall (Figure 46.10). These findings have a sensitivity of 45% and a specificity of 100% in the diagnosis of CADASIL; the immunological staining using anti-Notch3 monoclonal antibody increases the sensitivity of skin biopsy to 100%. Finally, this disease can also be diagnosed by identifying the mutation in the Notch3 gene in a sample of peripheral blood. This method, however, is expensive and laborious.

In the absence of specific treatment for this disease, efforts should focus on identifying and correcting cardiovascular risk factors. Death usually occurs 20 years after the onset of symptoms.

46.10 Fabry Disease

Fabry disease (FD) is a genetic disorder caused by deficiency of-galactosidase α (α-gal). This enzyme is a lysosomal hydrolase involved in the metabolism of glycosphingolipids. Its deficiency causes the intralisosomal accumulation of sphingolipids with α-galactosyl residues, particularly globotriaosylceramide (Gb3). The gene coding for the α-gal is located on the X chromosome and more than 400 mutations have been described. These are de novo mutation; therefore, the lack of family history of FD does not exclude the diagnosis of this condition. The age of onset is variable and depends on the residual enzyme activity. The most frequent manifestations of FD are listed in Table 46.6. Historically, it was considered that FD affected men and women were asymptomatic carriers. However, there are numerous reports indicating that, due to non-random tissue-specific X chromosome inactivation, women may have atypical presentations.

Ischemic stroke is one of the most severe complications of this disease. A study on 721 young adult patients 18-55 years of age with cryptogenic stroke (289 women and 432

men) showed the presence of mutations in the α-gal compatible with FD in 2.4% of women and 4.9% of men. Based on this information, it has been estimated that the FD is responsible for 1.2% of cryptogenic ischemic stroke in young adults. Cerebral ischemia in individuals with FD usually occurs in the posterior circulation. Its pathophysiology has not yet been fully elucidated. In addition to cardioembolic mechanism, patients with FD have vascular disease in the small and large cerebral vessels. It has been postulated that the accumulation of Gb3 in endothelial cells and muscle present in the vascular wall produces progressive stenosis of the small cerebral vessels and great vessels. However, the accumulation of Gb3 causing the weakening of vessel wall and dolichoectasia slowing the blood flow and increasing the risk of thromboembolism. Other proposed mechanisms include accelerated atherosclerotic disease and a possible prothrombotic state.

The diagnosis of FD is based on the determination of the enzymatic activity of α-gal in leukocytes or plasma. However, this technique allows the identification of heterozygotes. In women, in particular, gene sequencing may be necessary.

Dermatologic	• Angiokeratoma • Hypohidrosis or anhidrosis
Renal	• Proteinuria • Lipiduria • Tubular dysfunction (polyuria and isosthenuria) • Progressive kidney failure • Azotemia
Ocular	• Corneal opacities • Vascular lesions of the conjunctiva or retina • Lens opacities
Gastrointestinal	• Recurrent diarrhoea, vomiting or constipation • Postprandial bloating or abdominal pain • Weight loss
Cardiac	• Left ventricular hypertrophy • Syntolic and diastolic dysfunction • Valve disease (mitral regurgitation/insufficiency) • Arrhythmias • Coronary artery stenosis
Nervous system	• Cerebrovascular disease • Acroparesthesias • Hearing loss and tinnitus
Psychiatric	• Depression

Table 46.6. **Manifestations of Fabry disease.**

The treatment of FD is based on the identification and correction of modifiable vascular risk factors. It has been demonstrated that intravenous infusion of α-gal (1 mg/kg 2 times per week) in patients with FD significantly decreases the amount of Gb3 deposited in endothelial cells, and slowed the progression of kidney disease, a reversal of hypertrophic heart disease, resulting in slowed progression of kidney disease, reversal of hypertrophic heart disease, and improvement in autonomic activity and neuropathic pain. Due to the small number of patients studied, it is unclear whether enzyme replacement can reduce the recurrence of cerebral ischemia. In light of the benefits observed in this study, intravenous infusion with early α-gal treatment is recommended for patients with FD. In heterozygous individuals with ischemic stroke the use of antiplatelet agents or anticoagulants (depending on the case) and the correction of vascular risk factors are recommended. Intravenous infusion of α-gal should be considered in refractory cases.

46.11 MELAS Syndrome

The MELAS syndrome (mitochondrial encephalopathy, lactic acidosis and stroke-like episodes) is a progressive neurodegenerative disease caused by mitochondrial dysfunction. Almost 80% of patients with this condition have a mutation in mitochondrial DNA in the

position of tRNA-Leu 3243. However, other mutations in mitochondrial or nuclear DNA can cause the same syndrome.

Table 46.7 summarizes the most frequent manifestations of this disease. Each mitochondrion has a variable number of copies of mutated mitochondrial DNA and the content of dysfunctional mitochondria varies from one cell to another. This variability (heteroplasmy) makes the amount of mutated mitochondrial DNA differ from one tissue to another and makes the presentation of MELAS syndrome heterogeneous. The most susceptible tissues are those with a high metabolic rate. In the nervous system, mitochondrial dysfunction and consequent energy deficit present with stroke-like episodes. Clinically the patient presents with neurological deficits that correlate with parenchymal brain lesions. On magnetic resonance imaging, these are typically hyperintense hyperintense on diffusion-weighed image sequences and apparent diffusion coefficient, suggesting the presence of vasogenic edema. These lesions are not located in a defined vascular area, have a predilection for the posterior regions of the brain and may progressively extend to other areas. Their origin has not yet been established. It has been postulated that mitochondrial failure of intracerebral small vessels causes vascular dysfunction affecting the perfusion of the brain parenchyma (the "mitochondrial angiopathy" theory). Alternatively, it has been suggested that mitochondrial DNA mutation causes intracellular energy failure resulting in tissue hypoxia or anoxia (the "cytopathic" theory).

Treatment of patients with MELAS is based on improving the production of ATP and the transfer of electrons. To this end, substrates, such as coenzyme Q10, are frequently utilized. Coenzyme Q10 is usually used alone or in combination with creatine and lipoic acid. Idebenone is a synthetic analogue of coenzyme Q10 and has the advantage of having a better permeability for the central nervous system. Currently, there are no studies that demonstrate any benefit of these or other substrates of the respiratory chain in patients with MELAS. Dichloracetate indirectly activates the pyruvate dehydrogenase complex increasing the consumption of lactic acid. This enzyme converts the endogenous inhibitor of pyruvate dehydrogenase. Dichloroacetate causes an increase in the activity of pyruvate dehydrogenase, which increases the consumption of lactate and decreases the lactic acidosis observed in these patients. However, this drug is neurotoxic and has not been shown to be beneficial in the treatment of patients with MELAS. More recently it has been reported that L-arginine reduces the symptoms associated with stroke-like episodes, normalizes the levels of lactate and pyruvate, and reduces the recurrence of subsequent episodes. Finally, it has been suggested the use of carnitine in order to improve the β-oxidation of fatty acids and cellular energy homeostasis. Due to the low fre-

Constitutional	• Exercise intolerance • Short stature
Renal	• Nephropathy
Ocular	• Optic nerve atrophy • Pigmentary retinopathy • Ophthalmoplegia
Auditory	• Hearing loss
Gastrointestinal	• Gastrointestinal dysmotility • Vomiting
Cardiac	• Dilated cardiomyopathy • Left ventricular hypertrophy • Arrhythmias
Central nervous system	• Epilepsy • Stroke-like episodes • Encephalopathy/ dementia • Headache (usually migraine) • Elevated protein and lactate levels in the CSF
Peripheral nervous system	• Myopathy • Peripheral neuropathy
Endocrine system	• Diabetes mellitus

Table 46.7. Manifestations of MELAS.

quency of MELAS, the benefit of these and other drugs has not been demonstrated in randomized trials.
MELAS patients often have a progressive cognitive impairment and neurological systems. The latter is related to the occurrence of stroke-like events and recurrent seizures.

46.12 Evaluation in Young Patients With Stroke

In the absence of an established causal mechanism of cerebral ischemia, the assessment of young patients with stroke should include alternative pathologies, some of which are rarely found in elderly patients. Several of these entities have therapeutic peculiarities that can considerably change the prognosis and natural history. For illustrative purposes, Table 46.8 provides a guide for the evaluation of young individuals. It should be emphasized that the evaluation of these cases can be complex, extensive and expensive. Diagnosis and individualized plans for each patient are in the hands of the treating specialist who, according to personal experience, will select diagnostic studies at a reasonable cost.

Initial assessment	• Non-invasive
	  · CT/MRI
	  · CTA/MRA (or Duplex)
	  · Transthoracic
	  · Holter monitoring
	  · Lipid profile
	  · Basic evaluation of hypercoagulable state: red blood cell and platelet count, clotting studies (PT and aPTT), lupus anticoagulant factor, screening for sickle cell anemia, thalassemia
	  · Homocysteine
	  · Toxicology screening (cocaine, alcohol, etc.)
	  · Basic rheumatologic assessment
	  · VDRL
	• Invasive
	  · Cerebral angiography
	  · Transesophageal echocardiogram

Advanced assessment	• Advanced rheumatologic assessment • Advanced hypercoagulability studies • Lactic acid • Serology of genetic diseases (alpha-gal activity, sequencing of Notch-3 and alpha-gal genes) • Skin biopsy • Brain biopsy

Table 46.8. Suggested stroke assessment in young patients. Note: This table simply summarizes the most frequent complementary studies in the etiological diagnosis of stroke in young people. The goal is to simply provide a guide, not an exhaustive reference for the reader. The order of the studies should be individualized depending on the past medical history, family history, and physical exam findings.
CT = computed tomography
CTA = computed tomographic angiography
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging

46.13 Prognosis

The mortality within 30 days of young stroke patients varies between 10% and 34% depending on ethnicity. Nevertheless, these data should be analyzed carefully since the size of the samples is usually small. In the NOMASS trial, for example, among the 924 stroke cases identified, only 74 occurred in patients under 44 years of age; in this study, mortality within 30 days of patients between 20 and 44 years was 17% versus 16% observed in patients older than 45 years. In the group of young patients, the highest mortality was observed in individuals with parenchymal hemorrhage (36%), followed by SAH (12%), and ischemic stroke (6%).
Studies based on administrative data show a lower mortality at discharge in young patients with stroke. For example,

in a study of over 26,000 stroke patients in Canada, the mortality rate was 5.6% in patients under 50 years of age, 6.2% in those aged 51-65 years, 12.7% in those aged 66-80 years, and 24.2 % in those older than 80 years. These data confirm that age is one of the two most important prognostic factors in patients with ischemic stroke (after stroke severity).

As in adults, the prognosis in young patients depends, at least in part, on the degree of complexity of the disease and the experience of the medical team. A recent study com-

Characteristics	Western Europe n=111 (%)	Eastern Europe n=90 (%)	P value
Demographic			
Men	58	57	0.9
Atrial fibrillation	2	11	<0.001
Hypertension	46	54	0.2
Diabetes	11	6	<0.001
Myocardial infarction	5	8	0.03
Smoking (current or previous)	22	39	0.001
Stroke severity indicator			
Language disorder	28	26	0.9
Dysphagia	18	13	0.4
Incontinence	21	26	0.4
Coma	12	17	0.3
Weakness of a member	76	86	0.08
Stroke subtype			
Stroke	80	83	
Cerebral hemorrhage	20	16	
Service			
Admission within 6 h	43	38	0.5
Angiography	24	33	0.2
Carotid doppler	63	52	0.1
Echocardiography	71	22	<0.001
Admission to a centre with expertise in cerebrovascular disease	67	24	<0.001
Stay (days)	13	16	0.3
Time with the doctor (h)	26.9	10.6	<0.001
Nursing time (h)	98.5	45.3	<0.001
Personal time with physical therapy (h)	26.9	20	0.01
Prognosis			
Mortality			
• 7 days	14	2	0.001
• 30 days	18	7	0.003
• 3 months	23	8	0.003
0-14 Barthel index score within 3 months	21	2	<0.001

Table 46.9. **Characteristics of patients younger than 55 years with stroke treated in Eastern and Western Europe. Modified from [Bhalla, 2008].**

pared the mortality and disability (measured by the Barthel Index) at 3 months in patients younger than 55 years with stroke treated in Eastern Europe and Western Europe. A total of 201 cases were detected, which were uniformly distributed in the two study groups. The study results are shown in Table 46.9. In patients treated in Western Europe, where health care services are superior, the prognosis was significantly better than in those treated in Eastern Europe. These results confirm that, as in adult patients, the level of expertise of the medical centre, the intensity of treatment and quality of service provided in the acute post-stroke period all have a direct impact on the prognosis of young patients suffering from this condition.

46.14 Conclusions

The pathophysiological mechanism of stroke in adult patients is closely related to atherosclerotic arterial disease and cardiac conduction disorders. In younger patients, however, about 50% do not have these risk factors, suggesting the existence of alternative pathophysiological mechanisms. Identifying the cause of ischemia is the first step in developing therapeutic plan that will improve the prognosis of individuals with this devastating condition. Additional population studies are needed to precisely delineate the etiology, assessment, management and prognosis of adult patients with cerebral ischemia of different origins.

46.15 Acknowledgements

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47 Extracranial Atherosclerotic Carotid Artery Disease

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This chapter is organized in five sections. The first presents epidemiological, anatomical and pathophysiological concepts, clinical manifestations and a diagnostic approach. The second, third and fourth sections discuss carotid endarterectomy (CEA), carotid angioplasty (CA) and medical treatment, respectively. The fifth and final section analyzes the treatment strategies for the frequent presentation of concomitant coronary and carotid disease.
The approach to carotid artery disease is presented from a practical point of view, addressing problems of clinical relevance and a review of the available scientific literature.

47.1 Introduction

The relevance of the carotid arteries and their relationship with brain circulation was documented in 438 BCE by the Greeks [1]. More than 1500 years later, in 1951, Fisher described a case series of patients with carotid artery disease who experienced a transient ischemic attack (TIA). He mused that "it is conceivable that vascular surgery will some day find a way to bypass the occluded segment of an artery during the period of ominous transient symptoms." [2]. The first randomized studies to assess the utility of CEA were carried out between 1969 and 1970 [3]. Since then, a growing body of scientific evidence endorses both medical treatment and surgical procedures for the reduction of cerebrovascular risks.
According to international series, between 10 and 15% of ischemic strokes occur in a setting of carotid disease [4,5]. An analysis of 10 studies including 5043 patients (personal communication) on the subtype distribution of ischemic stroke in Argentinean hospitals revealed that 11% of cases were attributable to carotid artery disease according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria classification [6]. Of an estimated incidence of 100,000 ischemic strokes per year in Argentina, 11,000 could be due to carotid disease. The epidemiologically significant is that carotid artery disease is a preventable cause of ischemic stroke [7] and that the recurrence rate of ischemic stroke is 26% within 3 months after TIA [4,8].

47.1.1 Basic Anatomy of the Internal Carotid Artery

The internal carotid artery (ICA) can be divided in seven segments (Figure 47.1) [9].
It has its origin in the common carotid artery (CCA) at the level of the C3-C4 or C4-C5 vertebrae. The first segment is the cervical segment (C1), comprising the carotid bulb and the ascending portion. The carotid sinus or bulb is the widest portion (7.5 mm) and the one most frequently affected by atherosclerosis. The ascending portion measures 4.7 mm in diameter on average. The C2 or petrous segment starts where the ICA

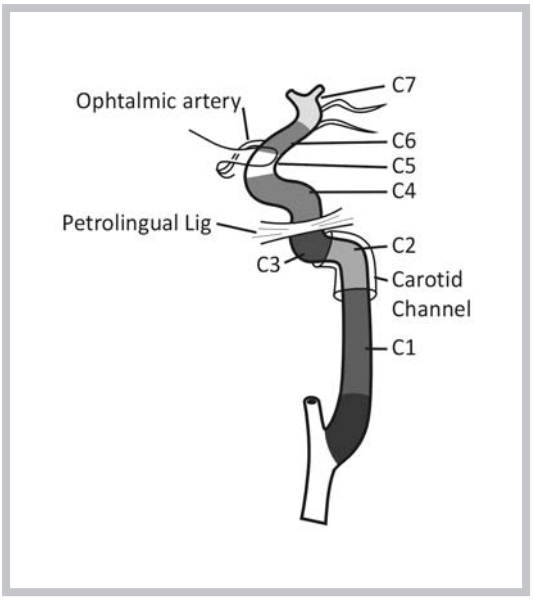

Figure 47.1. Internal carotid artery.

enters the carotid canal in the petrous or temporal bone. It consists of two subsegments: the ascendant and the horizontal. The C3 or lacerum extends from the foramen lacerum to the petrolingual ligament. The C4 or cavernous segment begins at the petrolingual ligament, courses across the cavernous sinus and consists of three subsegments: posterior-ascendant, horizontal and anterior-ascendant. The union of the second subsegment with the first and third form the posterior and anterior genu, respectively. The C5 or clinoid is a short, wedge-shaped segment that begins at the proximal dural ring and ends at the distal dural ring. The C6 or ophthalmic segment originates after the distal dural ring, extending distally to the origin of the posterior communicating artery, and giving rise to the ophthalmic artery.

The final portion is the C7 or communicating segment, which ends where the ICA divides into its two terminal branches, the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). As its name indicates, it gives rise to the posterior communicating artery (PoCA).

47.1.2 Pathophysiology of Carotid Artery Atherothrombosis

Stenosis severity seems to be the most important risk factor for ischemic stroke [10]. This notwithstanding, the relevance of the structural conformation of atheromatous plaque has recently been emphasized [11], which is why it seems more adequate to use the term “carotid artery disease” instead of “carotid stenosis”.

The vascular endothelium is responsible for maintaining the patency of the arterial wall through the balanced release of pro-atherogenic (thromboxane, angiotensin II, endothelin, thrombin, etc.) and anti-atherogenic substances (prostacyclins, nitric oxide, serotonin, histamine, etc.) Vascular risk factors, hemodynamic effects and some specific humoral products may cause endothelial dysfunction, a systemic and potentially reversible process. This dysfunction triggers the formation of carotid atheromatous plaque, which begins with cholesterol internalization and the incorporation of inflammatory cells into the vascular wall [12]. Local rheological factors and shear stress produced by the blood flow on certain regions of the arterial tree such as the carotid sinus favor these pathological phenomena.

Unless there is early intervention to reduce risk factors, the atheromatous plaque becomes increasingly vulnerable: reduced thickness of the fibrous capsule [13], ulceration, intraplaque hemorrhage due to vasa vasorum rupture, large necrotic lipidic core (>40%) [16,17] or in situ thrombosis [18].

Histologically, the vulnerable plaque shows an intense inflammatory-macrophagic infiltrate [19]. An increase in neovascularization of the plaque through the vasa vasorum has recently been described [20]. Each of these factors is associated with a higher risk of arterio-arterial embolic phenomena. Nevertheless, not all vulnerable plaques can generate embolisms. In fact, they can also be found in the carotid arteries of asymptomat-

ic patients [14]. The “vulnerable patient” theory, which draws on the concept of thrombophilia or a transient pro-thrombotic state induced by various triggering mechanisms [21], has been advanced to explain this phenomenon. It has been observed that such patients exhibit elevated levels of C-reactive protein (CRP), leukocytosis, metalloproteinases, proteolytic enzymes and other biological markers [22-24]. These markers are intrinsically related to oxidative stress and inflammatory processes, and might be the mediators in the transformation of non-vulnerable plaques into vulnerable ones.

47.1.3 Ischemic Stroke Etiopathogeny in Patients with Carotid Artery Disease

Ischemic stroke in patients with carotid artery disease can be explained in terms of processes related to the arterial stenosis itself or to unrelated mechanisms such as cardioembolism, small vessel disease or, less frequently, hypercoagulability states. Among the 1021 strokes that occurred in 2885 NASCET patients, 11% were due to cardioembolism, 21% to small vessel disease, and 68% to carotid disease.

When analyzing exclusively the strokes that occurred in asymptomatic patients with stenosis >70% in the ICA territory (contralateral to the treated ICA), 45% were attributable to cardioembolism or small vessel disease [25], which is consistent with the multiple mechanism phenomenon proposed by Caplan [26].

With regard to the mechanisms directly related to carotid artery disease, we must consider hemodynamic phenomena causing severe hypoperfusion (<20% of brain blood flow compared to the contralateral hemisphere) [27], local thrombosis on a vulnerable plaque with subsequent distal embolism [18,28] or microthrombi formation on the surface of macro- and microscopically undamaged endothelial plaques (endothelial dysfunction without structural damage) [29,30]. Infrequently, emboli originating in the heart and impacting on a pre-existent carotid stenosis can be found.

47.1.4 Risk Factors

In general, risk factors for atheromatous plaque formation are the same as those that lead to atherosclerosis of other vessels, such as the intracranial, coronary, inferior limb arteries, etc.: arterial hypertension, dyslipidemia, smoking, diabetes, sedentary lifestyle, obesity, infectious disease and metabolic syndrome among others. Perhaps the most in-

	Asymptomatic carotid artery disease [n=113]	Ischemic stroke or TIA [n=175]	p
Age, years (mean ±SD)	67.3±8.2	67.6 ± 13.0	1.00
Male gender (%)	74.3	64.6	0.08
Arterial hypertension (%)	86.7	83.4	0.45
Diabetes mellitus (%)	32.7	22.9	0.06
Dyslipidemia (%)	75.2	54.3	<0.01
Smoking (%)	58.4	42.3	0.01
Myocardial infarction (%)	35.4	17.1	<0.01

Table 47.1. **Risk factor load in patients with asymptomatic carotid artery disease and in patients with ischemic stroke of non-carotid origin [Data from Stroke Center. Neuroscience Institute, Favaloro Foundation, 01/01/06 to 12/31/08].**

teresting fact is that the cardiovascular risk factor load is higher in patients with carotid artery disease (even asymptomatic) than in those who suffered an ischemic stroke of non-carotid origin. This finding is shown in Table 47.1 which compares the risk factor load of patients with asymptomatic carotid disease to those who suffered an ischemic stroke of non-carotid origin.
Dyslipidemia and smoking seem to be risk factors differentially associated with carotid disease. These data further support the hypothesis that an accumulation of risk factors might be necessary for the formation of atheromatous plaque which may later become vulnerable but not sufficiently so to cause an ischemic stroke.

47.1.5 Clinical Manifestations of Ischemic Stroke due to Carotid Artery Disease

More severe neurological syndromes usually arise in ischemic strokes caused by carotid artery disease than in those doe to such other mechanisms as small vessel disease. Greater severity is related to the large size of infarcts. They have been classically defined as being >15 mm, although this threshold has recently been questioned [31]. Localization is usually cortico-subcortical, with a predominance of the MCA territory. This explains why, aside from the classical motor and/or sensory deficit signs, a patient with an ischemic stroke of carotid origin may present cortical signs such as aphasia, neglect, anosognosia, sensory extinction or visuospatial disturbances.
A distinctive clinical finding is retinal compromise presenting as transient monocular blindness (amaurosis fugax), ipsilateral to carotid disease. Less frequently, irreversible monocular blindness may arise. It usually manifests within a few seconds (described like a curtain coming down or sideways), rapidly affecting vision with possible total visual loss. It may last from a few seconds to minutes (usually <10 minutes). It may also start as a progressive darkening of vision in the affected eye. These transient phenomena are caused by hypoperfusion of the ophthalmic artery or microembolisms from the ICA to the central retinal artery with posterior recanalization mediated by the endogenous fibrinolytic system [32].
Clinical manifestations such as dizziness, vertigo or syncope are not attributable to carotid artery disease [33].

47.1.6 Diagnosis of Carotid Artery Disease

Patients with a history of ischemic stroke should be screened for the presence or absence of both extra- and intracranial carotid disease. In the general population without a history of stroke or TIA, the indication for carotid artery disease evaluation is questionable. According to the U.S. Preventive Services Task Force (USPSTF), the potential benefit derived from the identification and later surgical resolution of a carotid artery stenosis >70% in asymptomatic patients does not outweigh the risk of postoperative brain digital subtraction angiography (DS-A) and the surgery itself. In conclusion, the USPSTF recommends not screening the general population for carotid disease (Level D evidence) [34].
Over the past years, considerable progress in the visualization and identification of the vulnerable plaque components has been achieved with ultrasound techniques such as intravascular Doppler ultrasound (IVUS) and other imaging methods, including magnetic resonance angiography (MRA) and multislice angiotomography. These procedures have become daily practice in specialized national and international medical centres (Figure 47.2).

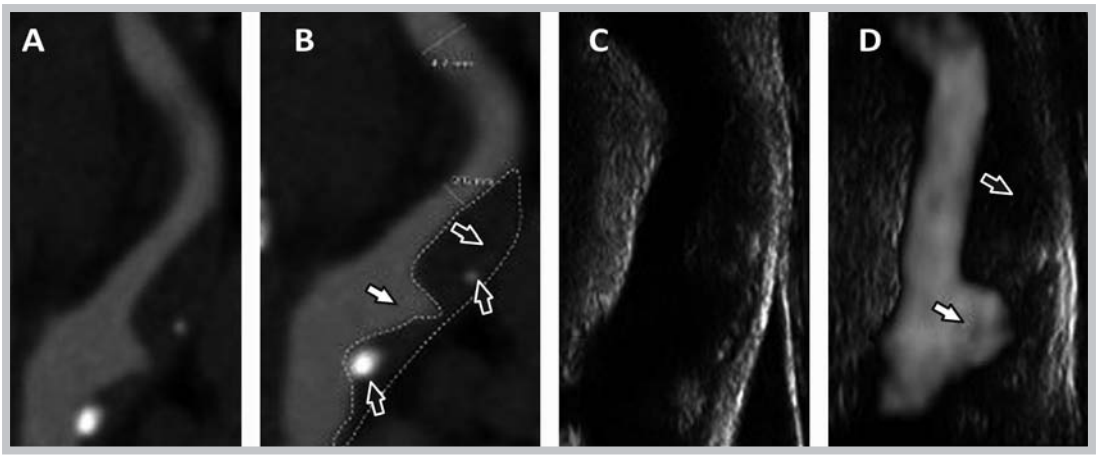

Figure 47.2. **Doppler ultrasound with power doppler and angiotomography of the internal carotid artery. (A, B). CT-A of the ICA showing a bulbar stenosis by a plaque with fibrolipidic component (pointed arrows), scarce calcium component (black arrows) and a large ulcer (white arrows). (C, D). Doppler and power doppler ultrasound scans of the same artery.**

Nevertheless, their real clinical and epidemiological value needs to be confirmed by large prospective studies before they can be formally recommended, given the fact that they still lack a defined role in the algorithm for the evaluation of patients with carotid artery disease (Level B evidence, class IIa) [35]. For the time being, of all the arterial abnormalities that can be documented by diagnostic tests, only the degree of stenosis is consistently significant in multivariate models, yielding the highest predictive value for ipsilateral ischemic stroke [36].

Several strategies or diagnostic algorithms for the evaluation of patients with carotid artery disease have been proposed. The method used for determining stenosis degree is not a minor detail. Many of the discrepancies in the results of randomized studies on the surgical approach to carotid artery disease can be explained by differences in the measurements [37,38].

Carotid artery color Doppler ultrasound (CDUS), because of its relatively low cost and wider availability, is the most widely used technique in clinical practice [39]. Nevertheless, it is highly operator dependent. Another of this method's drawbacks is the impossibility to evaluate proximal CCA and distal ICA, which limits the detection of tandem stenosis [40]. Moreover, by not assessing intracranial circulation, the possibility of detecting aneurysms is lost, these being findings that might radically change the choice of treatment [40]. It should be noted that intracranial circulation could be assessed by transcranial Doppler (TCD). But because the sound beam is hampered by osseous interposition, TCD requires additional training, which results in a lower rate of use. Finally, the quality of the printed images is usually not sufficient for evaluation by a professional who was not present during the test, which is why the attending clinician frequently has to trust the report blindly. These remarks aside, there is a growing tendency to plan surgical treatment based on CDUS scans performed by two different operators or on imaging findings from CDUS and another non-invasive method instead of DS-A. Although excellent correlations between CDUS and DS-A have been reported, they were never perfect, an essential criterion for the choice of surgical strategy [41]. Several studies confirm that surgical choice cannot be made based upon information obtained exclusively from CDUS [42,43].

MRA with time of flight (TOF) requires no use of paramagnetic contrast material. Still, dynamically administered contrast material to visualize the whole arterial tree, from its

beginning in the aortic arch to its terminal branches, has substantially improved image quality. This method is known as contrast-enhanced MRA (CEMRA). Like non-contrast MRA, it overestimates stenosis degree in severe pre-occlusive obstructions. Apart from this, it requires longer acquisition periods (albeit shorter than TOF MRA), which may result in a reduction of image quality if the patient moves. Some authors suggest that it is the most accurate non-invasive diagnostic method, having an excellent anatomic correlation and allowing an adequate evaluation of intracranial circulation [40,44].

Cerebral angio-tomography (CT-A) affords the possibility of obtaining images of the whole arterial tree much quicker than with CEMRA, thus avoiding movement artifacts. It requires the administration of iodinated contrast material by a pump operated by trained personnel, exposing the patient to high doses of radiation. This technique allows more exact visualization of the anatomical features of the arteries, as well as plaque components. Based on our experience, the diagnostic yield seems to be higher when evaluating the images dynamically from the CT console monitor than when analyzing the slides in a negatoscope or through a selection of digitalized images. Image reconstruction, which may entail some hours, is a disadvantage but it allows visualization of the intracranial circulation with remarkable clarity and detail.

DS-A is considered the gold standard for the assessment of extra- and intracranial cerebral arteries. It requires an intra-arterial catheter for the injection of iodinated contrast material and involves a considerable radiation burden. Between 1% (incapacitating and/or fatal) and 4% (mild) of ischemic strokes may arise as complications [45]. Other complications such as catheter insertion site hematoma may occur. Another disadvantage is that, because it can only identify plaque ulceration, it provides no information on plaque morphology. There are several methods for measuring the degree of stenosis. The two most widely used are those described in the NASCET and ECST (European Carotid Surgery Trial) studies (Figure 47.3) [46,47]. The more widely used is NASCET's [48], although both are reliable and correlate well with one another. The following formula must be applied to convert measurements: ECST = 40 + (0.6 x NASCET).

In conclusion, CDUS is an adequate method for carotid artery disease screening in patients with a history of ischemic stroke or TIA. It is preferable over other methods because of its wider availability and lower cost. When the potential presence of intracranial disease may result in therapy modification, appropriate non-invasive tests will be necessary (MRA or CT-A). Both NASCET and ECST used DS-A to confirm the degree of stenosis [46,47]. Extrapolation of the two trials' conclusions to patients evaluated with non-invasive tests such as MRA, Doppler or CT-A may be risky, hastening wrong decisions. Nonetheless, the American Heart Association/American Stroke Association (AHA/ASA) suggests that when consistent results are obtained from two non-invasive methods (CDUS, MRA, CT-A), DS-A is not necessary. This imaging study may be reserved for those cases in which non-invasive methods do not correlate. (Level B evidence, class IIa) [35].

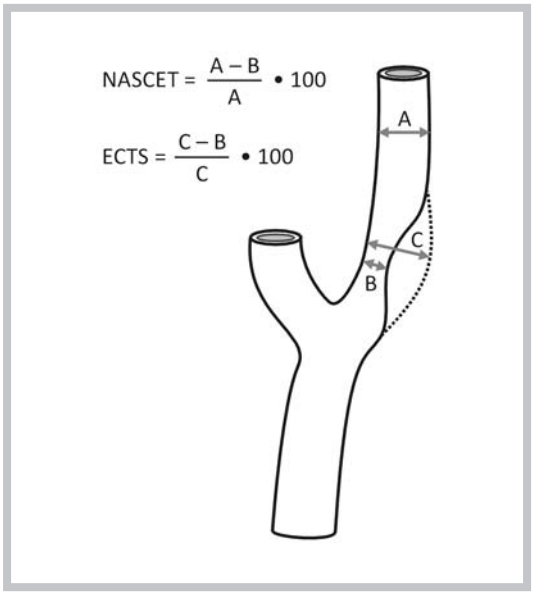

Figure 47.3. **Measurement of extracranial carotid stenosis according to NASCET and ECST.**

The AHA/ASA guidelines for the evaluation of extracranial ICA stenosis degree and selection of candidates for CEA are: a) CDUS should not be used as the only diagnostic method when considering endarterectomy (Level A evidence, class III); b) the method of choice for measuring stenosis degree is DS-A (Level A evidence, class I); c) two non-invasive methods may be used (CDUS, MRA, CT-A) for the assessment of stenosis degree, although less accurate than DS-A, which may increase the chance of indicating an erroneous treatment (Level B evidence, class IIa); d) subocclusive lesions are more accurately detected by DS-A, closely followed by CT-A (Level B evidence, class IIa) [49].

47.2 Carotid Endarterectomy

Just 7 months after Fisher envisaged the first carotid surgery [2], Raúl Carrea performed the first operation on a patient with carotid artery obstruction, removing the atherosclerotic plaque and anastomosing the external carotid artery (ECA) to the ICA[50,51]. The first CEA with the presently used technique (except for slight modifications) was performed by Michal DeBakey in 1953, but the case report was not published until 1975 [52]. The patient had a 19-year follow-up and died from an acute myocardial infarction. In 1954, Eascott performed carotid artery repair by partial resection of a previously thrombotic ICA and CCA and posterior direct anastomosis [53]. With time, the number of endarterectomies gradually increased until the 1980s, when studies began to warn about the increased rates of postoperative stroke and death [54-56]. In the early 1990s, following publication of the NASCET and ECST, enthusiasm for CEA was rekindled, opening a new chapter in primary and secondary stroke prevention [46,47,57].

47.2.1 Endarterectomy

There are two surgical techniques: the classical approach and the eversion technique (Figure 47.4). The first consists of longitudinal resection of the ICA to remove the atheromatous plaque [58]. The second involves transversal resection of the ICA origin around its entire circumference, followed by eversion of the adventitia and tunica media. With this procedure, the ICA atheroma is removed, followed by endarterectomy of the CCA with the classical technique; finally, the ICA bulb is re-anastomosed at the bifurcation [59].

The advantages and disadvantages of both techniques are summarized in Table 47.2. A systematic revision of randomized studies comparing classical endarterectomy to eversion technique endarterectomy (2590 surgeries) showed no significant difference in perioperative stroke, death or local complications [60].

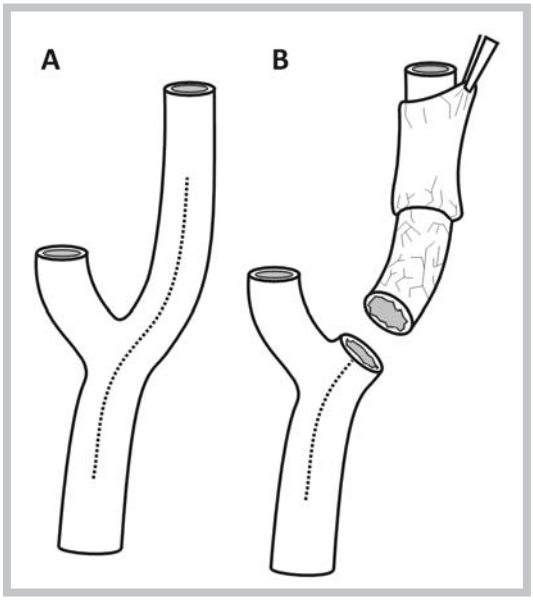

Figure 47.4. **Classic endarterectomy and eversion endarterectomy. (A). Classic endarterectomy with longitudinal resection along the ICA and CCA. (B). Eversion endarterectomy.**

Classic endarterectomy	Eversion endarterectomy
Advantages	
Shunting from the beginning of surgery	Lower re-stenosis rate
Distal atheroma resolution possible	No need for patching
Continuous view of distal intimal segment	Redundant segment resection possible (prevents kinking)
	Shorter surgical time
Disadvantages	
Longer surgical time	Inability to place shunt until plaque is removed
Predisposition to long-term kinking (due to elongation of the ICA during surgery)	Distal intimal segment might not be visualized
	Risk of failure to detect intimal flaps
	Technical difficulties with plaques with distal extension

Table 47.2. **Advantages and disadvantages of classic endarterectomy and eversion endarterectomy.**

47.2.2 Patch Use

One of the risks or potential complications of CEA is re-stenosis. Long-term re-stenosis is usually due to inadequate control of risk factors. On the other hand, re-stenosis during the first year is generally caused by neointimal hyperplasia [61]. Various different patch types have been used to prevent neointimal hyperplasia. Although patches may be associated with infection or hematoma (in case of rupture), their use has reduced the rats of severe complications.

A systematic review of 10 randomized studies comprising 2157 procedures in 1967 patients compared the result of endarterectomy performed with autologous (venous) or synthetic patches vs. primary closure surgeries (without patch) [62]. Patch use was associated with a reduction in the risk of ipsilateral stroke at 30 days (OR 0.31, 95% CI 0.2-0.6; p <0.001). Long-term follow-up also evidenced a lower re-stenosis rate (OR 0.24, 95% CI 0.2-0.3; p <0.00001) and lower risk of stroke or death (OR 0.59, 95% CI 0.4-0.8; p <0.0001).

47.2.3 Intraoperative Shunting

During the surgical procedure, while the atheromatous plaque is being removed, it is necessary to stop ICA circulation. This may be done with or without shunting. With the first option, hemispheric blood flow is maintains by placing a shunt between the CCA and the ICA distal to the clamping site. Without shunting, brain blood flow from the clamped ICA is maintained by collateral circulation from the circle of Willis or through extracranial circulation from the ECA. A study using continuous monitoring of brain blood flow and electroencephalography (EEG) during CEA showed that without the use of shunting, the hemispheric blood flow in some patients was close to zero [63]. This resembles the effect of cardiorespiratory arrest on the brain. Use of intraoperative shunting allows the surgeon more time and might work as a brain protection system to reduce the risk of ischemic stroke due to hypoperfusion. Nevertheless, most post-CEA ischemic strokes are produced by embolism of particulate matter detaching from the arterial walls and not by hypoperfusion. In fact, placing a shunt might favor embolism from the CCA as well as dissection. Two randomized studies assessing the potential benefit of shunting involved 590 patients and showed a non-significant trend toward a reduction in the risk of stroke

or perioperative death [64,65]. Due to the lack of conclusive results, no recommendations on the use of shunt during CEA can be made yet.

47.2.4 Local or General Anesthesia

CEA can be performed with either local or general anesthesia. Local anesthesia has several theoretical advantages. First, shunting might not be necessary because the patient is awake and therefore available for constant evaluation throughout the surgery. This would allow the use of intraoperative shunting only when there is evidence of focal neurological deficits. For the same reasons, continuous brain blood flow monitoring or EEG would not be necessary. Nevertheless, it should be noted that not all patients tolerate the procedure, many requiring conversion to general anesthesia.
Despite the theoretical advantages of local anesthesia, the randomized General versus Locoregional Anesthesia in Carotid Surgery (GALA) study that compared local anesthesia vs. general anesthesia in CEA showed no differences in the risk of stroke, acute myocardial infarction or death at 30 days [66]. A systematic review of 4335 surgeries including the 3526 cases in the GALA study revealed no difference in the risk of stroke or death related to the type of anesthesia used [67]. Based on these results, the choice of anesthetic modality should be at the discretion of the surgical team.

47.2.5 Postoperative Complications

As with any surgical procedure, local, neurological or systemic complications may arise after CEA. Reported complication rates differ across studies [68]. This derives mainly from methodological issues. A relatively reliable approach is to analyze studies under two criteria: a) those on patients with symptomatic carotid disease vs. asymptomatic carotid disease; and b) those in the context of randomized studies vs. observational studies (Table 47.3) [69-74].

Study (no. of subjects)	Stroke	Death	AMI	Stroke or death	Stroke, AMI or death	Hematoma	Local infection	Cranial nerves
Randomized studies in asymptomatic patients								
ACAS (814) [69]	1.2	0.1	0.4	1.5	1.7	ND	ND	ND
ACST (1405) [70]	2.5	1.1	1.0	2.8	3.6	ND	ND	ND
Total (2219)	2.0	0.8	0.8	2.3	2.9	ND	ND	ND
Randomized studies in symptomatic patients								
NASCET (1415) [71]	5.4	1.1	1.0	6.5	7.3	7.1	2.0	8.6
ECST (1729) [72]	6.7	1.0	0.5	7.1	7.3	3.1	0.2	6.4
Total (3144)	6.1	1.0	0.7	6.8	7.3	4.9	1.0	7.4
Observational studies in asymptomatic patients								
NYCAS (6655) [73] (1377) [74]	2.5 [24]	ND	ND	3.0 [73]	ND	4.7 [74]	0.7 [74]	5.3 [74]
Observational studies in asymptomatic patients								
NYCAS (2653) [73] (611) [74]	5.3 [73]	ND	ND	6.4 [73]	ND	6.3 [74]	0.9 [74]	7.7 [74]

Table 47.3. **Complications associated with CEA. All values are expressed as percentage.**
AMI = acute myocardial infarction
ND = no data

47.2.6 Hyperperfusion Syndrome and Revascularization Hemorrhage

Hyperperfusion syndrome (HPS) after carotid endarterectomy or carotid angioplasty is generally reported to be between 0 and 3%. It may present clinically as a diffuse or facial, periorbital or fronto-temporal headache, vomiting, confusion, seizures or focal motor deficits. Hemodynamically, it is defined as an increase >100% in revascularized hemisphere blood flow compared to preoperative values [79]. Endothelial dysfunction mediated by free radicals and the subsequent disruption of cerebral autoregulation are thought to be the central phenomena of the pathophysiological cascade.

The principal risk factors are postoperative hypertension, diminished cerebrovascular reserve, prolonged hyperperfusion (↑cerebral blood flow >100%) after the procedure, contralateral ICA occlusion, scant collateral circulation and severe stenosis of the operated ICA, among others [80]. Thus, the best means of prevention is with strict control of postoperative arterial pressure. Neuroimaging showing diffuse, unilateral cerebral edema is a characteristic feature, although edema can also be observed in the contralateral hemisphere (Figure 47.5).

Less frequently, HPS can be complicated by intracranial hemorrhage (ICH). In a survey including a total of 122,856 endarterectomies and 13,047 angioplasties performed in the United States in 2005, the frequency of ICH was 0.016 and 0.15%, respectively [81], indicating this complication was ten times more frequent in angioplasties than in endarterectomies. In this study, angioplasty was an independent predictor for ICH (OR 5.9, 95% CI 3.1-11.1; p <0.001).

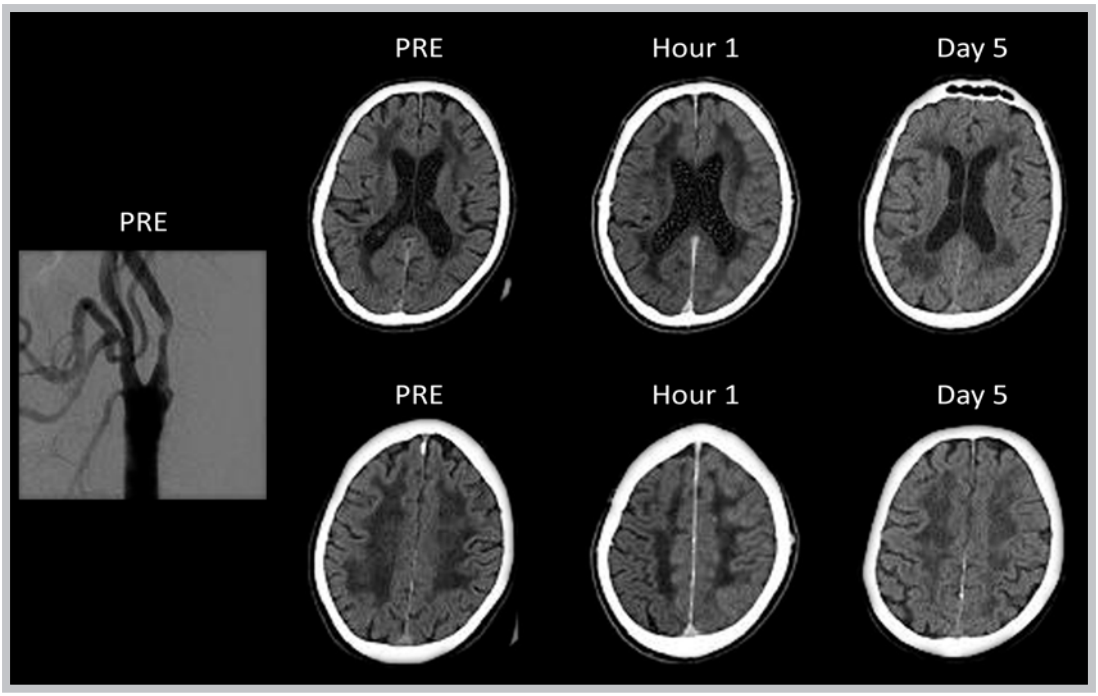

Figure 47.5. **Digital subtraction angiography and non-contrast enhanced computed tomography of a patient with hyperperfusion syndrome after left carotid artery stenting. Digital angiography and the brain computed tomographies of a 65-year-old patient before (PRE), 1 hour, and 5 days after angioplasty with stenting of the left ICA. Note the stenosis in the left carotid. Evident left hemispheric edema on tomographies obtained 1 hour and 5 days after angioplasty.**

47.2.7 Procedural Risk Stratification

The risk of complications secondary to CEA depends on a number of variables. As noted in Table 47.3, complications are more frequent in procedures for symptomatic stenosis than for asymptomatic stenosis. This observation is consistent with a review of 59 studies that revealed a higher risk for symptomatic patients (OR 1.62, 95% CI 1.45 - 1.81; P <0.00001) [82]. Table 47.4 summarizes the main variables influencing the risk of post-CEA complications [83,84].

Based on independent risk predictors, two models for CEA-associated risk stratification have been developed [85,86]. The Halm model seems to be more appropriate for predicting neurological, medical and surgical complications (Table 47.5) [74,86]. The risk score is obtained by adding a point for each of the following factors: a) active coronary disease (grade IV angina or unstable angina); b) stroke (non TIA) related to surgery; and c) ≥50% contralateral ICA stenosis. One point is to be subtracted if local anesthesia is given. The maximum score is 3 and the minimum -1. The model is used to predict the com-

Variable	HR	95% CI	p
Ipsilateral postoperative stroke in stenosis ≥70%, symptomatic [77]			
Female gender	0.79	0.64-0.97	0.03
Age 65 to 74 years	1.23	1.00-1.51	0.001
Age ≥75 years	1.70	1.28-2.56	0.001
Diabetes	1.31	1.05-1.65	0.02
Ulcerated or irregular plaque	1.35	1.11-1.64	0.003
Cerebral TIA vs. retinal TIA	1.88	1.38-2.55	<0.0001
Stroke vs. retinal TIA	2.33	1.74-3.13	<0.0001
Contralateral ICA occlusion	1.30	098-1.88	0.16
Previous stroke or TIA	1.20	0.99-1.46	0.07
Stroke or postoperative death in stenosis 50 to 69%, symptomatic [77]			
Female gender	1.50	1.14-1.97	0.004
Age 65 to 74 years	0.99	0.76-1.32	0.78
Age ≥75 years	0.83	0.49-1.41	0.78
Diabetes	1.45	1.05-2.02	0.03
Ulcerated or irregular plaque	1.37	1.03-1.83	0.03
Cerebral TIA vs. retinal TIA	2.62	1.68-4.09	<0.0001
Stroke vs. retinal TIA	1.91	1.22-3.01	<0.0001
Contralateral ICA occlusion	2.21	1.33-3.67	0.002
Previous stroke or TIA	1.59	1.21-2.09	0.001
Postoperative death in symptomatic and asymptomatic patients [76]			
Age ≥75 years	1.36	1.07-1.68	0.02
Age ≥80 years	1.80	1.26-2.45	<0.001
Postoperative stroke or death in symptomatic and asymptomatic patients [76]			
Female gender	1.31	1.17-1.47	<0.001

Table 47.4. **Variables affecting risk of complications at 30 days post CEA.**
CI = confidence interval
HR = hazard ratio

Halm score	Stroke or death	Cardiac	Medical, non cardiac	Minor neurological	Surgical wound
-1	0.7	2.1	1.4	4.3	3.3
0	1.7	3.0	2.4	6.4	5.3
1	5.9	6.1	4.9	8.7	8.3
≥2	13.0	8.8	7.8	12.8	9.8

Table 47.5. **Halm score for predicting post-CEA complications. All values are expressed as percentage.**

plications until postoperative day 30: a) stroke or death; b) cardiologic complications (ventricular tachycardia, unstable angina, acute myocardial infarction, congestive heart failure); c) non-cardiologic medical complications (assisted mechanical ventilation, postoperative pneumonia, sepsis, kidney failure, pulmonary thromboembolism, deep vein thrombosis or gastrointestinal hemorrhage); d) minor neurological complications (TIA, seizures, cranial nerve damage); e) surgical wound complications (hematoma or infection).

A neurologist is usually consulted to aid in deciding whether a patients with carotid artery disease should undergo endarterectomy. Complication rate and risk stratification is useful in the decision-making process for predicting the likelihood of postoperative complications but not whether a patient should undergo surgery or not. Instead, a decision for or against surgery should be based on two fundamental criteria: a) individual recurrence risk stratification when given the best medical treatment; and b) the applicability of randomized study results to the patient based on such diverse criteria as stenosis degree, age, gender, etc. (see below) [87].

47.2.8 Indications for CEA in Symptomatic Patients

The results of NASCET were published In 1991. This study sought to demonstrate the unequivocal benefit of surgical treatment in reducing stroke recurrence in symptomatic patients [46]. Seven years later, the final results of ECST (the European counterpart) were published with very similar results [47]. That same year, an analysis of the long-term NASCET results was published [88]. The Veterans Affairs Trial 309 (VA309) had to be interrupted when the NASCET results and a preliminary ECST analysis were published in 1991 [88]. To sustain these results, all the studies required compliance to a surgical complications rate <6%.

The three large, randomized studies proved the utility of CEA in symptomatic patients with stenosis >70%. To understand the implications of these conclusions and their applicability to clinical practice, the concept of “symptomatic carotid disease” needs to be clarified, given that not all symptoms should be considered related to the ICA. Both NASCET and ECST defined symptomatic carotid disease as a history of ischemic stroke or TIA in a carotid territory appearing up to 6 months previous to randomization. Although not exactly the same, the definition relevant for clinical practice should be “any ischemic stroke or TIA with clinical manifestations attributable to a carotid territory in the 6 months prior to the first visit”. The temporal parameter, as we will see, is not a minor detail. Although no evidence exists on this subject, we believe that carotid disease in patients with silent ischemic lesions on neuroimaging should not be considered “symptomatic” unless it can be proved (by MRI diffusion-weighted images or by comparison with previous studies) that these lesions have been present for less than 6 months.

47.2.9 Individual Risk Stratification Under Medical Treatment

There are several instruments to predict the risk under medical treatment. The most sophisticated is the Carotid Stenosis Prediction Tool available online (http://www.stroke.ox.ac.uk). This tool was developed by Rothwell and Oxford University collaborators, based on the analysis of ECST data, and later validated with NASCET's. This system classifies patients in quintiles. Those in the three lower quintiles would not benefit from CEA at year 5 (RAR_{5a} [risk-adjusted ratio] 0-2%), those in the fourth quintile would have a moderate benefit (RAR_{5a} 10.8%, 95% CI 1.0-20.6), and those in the highest quintile would have the maximum benefit (RAR_{5a} 32.0%, 95% CI 21.9-42.1). Alternatives to this model are the tables for risk stratification by color available on the same website.

47.2.10 Applicability or External Validity of Randomized Trials

Once the patient's individual risk is assessed, the next question is whether they might benefit from CEA. To answer this question, it is necessary to know if the patient meets the qualifying criteria that emerged from an analysis of the randomized studies. Specifically, we must determine whether age, gender, stenosis degree and other variables in our patient match the characteristics of those subgroups that benefited from CEA in NASCET and ECST.

As stated above, the degree of stenosis remains the most relevant piece of information when deciding on the surgical strategy in patients with carotid artery disease [36]. Nevertheless, it is not the only criterion. Several other variables may significantly interact with stenosis degree, modifying the potential impact of surgery on the reduction of risk for ischemic stroke recurrence [37]. Table 47.6 shows the number needed to treat with CEA to prevent a stroke or postoperative death over the next 5 years after surgery (NNT_{5a}) and the absolute risk reduction for the same outcome for the same follow-up period (RAR_{5a}), stratified by stenosis degree and the interaction with other variables [84].

The data from Table 47.6 should be analyzed cautiously. Except for subocclusive lesions, CEA reduces the risk of stroke or death in all patients with stenosis >70%. Besides the degree of stenosis, to define a lesion as subocclusive it should meet the following angiographic criteria: a) poststenotic ICA collapse; b) faster filling of the ECA than the ICA; and c) preferential filling of intracranial circulation through the collateral circulation [7]. These are usually associated with stenosis >99%. A benefit from CEA could not be proved for this specific group in the combined analysis of NASCET; ECST and VA309 (RAR_{5a} -0.1, 95% CI -10.3-10.2) [37]. Despite this seeming lack of benefit, some patients with subocclusive lesions might benefit from this intervention. Those with recurrent TIA despite optimal medical treatment might be among them. In the ECST, in fact, CEA was associated with a significant TIA RAR_{5a} in patients with subocclusive lesions. (RAR_{5a} 15%, NNT_{5a} 7; p <0.007) [92]. As shown in Table 47.6, patients with stenosis <50% do not benefit from CEA. The group with carotid artery stenosis between 50 and 69% requires further analysis. In such patients the presence of other variables may tilt the balance toward or against surgery. In this subgroup analysis, CEA was not found to be effective in women, diabetics or patients with contralateral ICA occlusion. Nor was it beneficial for those whose qualifying symptom was a retinal event or TIA [84].

These data informed the AHS/ASA recommendations: a) CEA is recommended in patients with ischemic stroke or TIA in the last 6 months and ipsilateral carotid stenosis between 70 and 99%, as long as the surgeon's documented perioperative morbimortality rate is <6% (Level A evidence, class I); b) endarterectomy is recommended in patients with ischemic stroke or TIA in the last 6 months and carotid stenosis between 50 and

Variables	NNT_{5a}	RAR_{5a}
All patients	**24**	**4.1 (2.3-6.0)**
Stenosis >70%	**7**	**13.5 (9.8-20.7)**
Males	6	6.0 (3.8-8.2)
Females	10	9.9 (1.8-18.0)
Age <65 years	10	9.8 (3.8-15.7)
Age 65-74 years	7	13.5 (6.5-20.5)
Age ≥75 years	3	37.2 (22.9-51.5)
History of diabetes	6	16.7 (6.0-27.4)
No history of diabetes	8	12.9 (8.1-17.7)
Ulcerated plaque	6	17.1 (11.6-22.6)
Contralateral ICA occlusion	4	23.6 (3.2-44.0
Without contralateral ICA occlusion	8	12.7 (8.3-17.1)
<14 days between symptoms and surgery	4	23.0 (13.6-32.4)
14-30 days between symptoms and surgery	6	15.9 (6.6-25.2)
30-90 days between symptoms and surgery	13	7.9 (1.3-14.4)
<90 days between symptoms and surgery	14	7.4 (-3.3-18.1)
Ocular symptoms (amaurosis fugax or infarction)	18	5.5 (-1.2-12.1)
Qualifying symptom = TIA	7	15.4 (7.7-23.1)
Qualifying symptom = stroke	18	17.7 (9.9-25.5)
Stenosis 50-69%	**13**	**7.8 (3.1-12.5)**
Males	13	8.0 (3.4-12.5)
Females	NA	-2.7 (-8.8-3.5)
Age <65 years	77	1.3 (-4.0-6.7)
Age 65-74 years	19	5.4 (-0.4-11.2)
Age ≥75 years	9	10.7 (-0.2-21.6)
History of diabetes	16	6.2 (-4.1-16.5)
No history of diabetes	23	4.3 (0.4-8.2
Ulcerated plaque	18	5.7 (0.7-10.6)
Contralateral ICA occlusion	NA	-16.0 (-34.8-2.8)
No contralateral ICA occlusion	18	5.7 (1.9-9.5)
<4 days between symptoms and surgery	7	14.8 (6.2-23.4)
14-30 days between symptoms and surgery	30	3.3 (-6.3-13.0)
30-90 days between symptoms and surgery	25	4.0 (-1.7-9.7)
<90 days between symptoms and surgery	NA	-2.9 (-10.2-4.3)
Ocular symptom (amaurosis fugax or infarction)	67	1.5 (-5.5-8.4)
Qualifying symptom = TIA	26	3.8 (-2.6-10.1)
Qualifying symptom = stroke	13	7.5 (1.6-13.5)
Stenosis <50%	**39**	**2.6 (-1.7-6.9)**

Table 47.6. **NNT_{5a} and RAR_{5a} of CEA to prevent postoperative stroke or death in symptomatic patients stratified according to degree of stenosis and other variables. RAR_{5a} (**risk-adjusted ratio) **values are expressed as percentage with 95% confidence interval.**

NA = not applicable
NNT = number need to treat

69%, depending on patient-specific factors such as age, sex, co-morbidities and severity of initial symptoms (Level A evidence, class I); c) CEA is not recommended when carotid artery stenosis is <50% (Level A evidence, class III) [93].

47.2.11 Age and CEA

The relationship between the age of a patient with symptomatic carotid disease and the potential benefit of endarterectomy deserves specific mention. On the one hand, postoperative mortality is higher in patients between 75 years (OR 1.36, 95% CI 1.07-1.68; p=0.02) and 80 years of age (OR 1.80, 95% CI 1.26 - 2.45; p <0.001) [83]. A similar though not significant trend has been observed for the risk of stroke and postoperative death in both age groups. Nonetheless, as shown in Table 47.6, the benefit of endarterectomy increases with age. These data might seem contradictory. The higher benefit of surgery in patients aged 75 years and older is explained by the fact that, in the long run, the recurrence rate for medical treatment overweighs the risk of perioperative stroke or death. Based on this, there are no reasons to contraindicate CEA in patients aged older than 75 years with a life expectancy >5 years.

Despite this consideration, some guidelines (see section on angioplasty) recommend carotid angioplasty in patients >80 years. An interesting meta-analysis reports the following risk factors for patients >80 years who underwent carotid angioplasty and CEA, respectively: acute myocardial infarction 0.93 vs. 2.20% (p=0.083), mortality 1.98 vs. 1.11% (p=0.253), and 7.04 vs. 1.91% (p <0.01), According to the authors, the only significant difference was evidenced in stroke frequency in patients who underwent carotid angioplasty [94]. This notwithstanding, reanalyzing the study data, the OR of CEA for different outcomes shows a lower risk of stroke and death but a higher risk of acute myocardial infarction with CEA. In summary, CEA seems to be associated with a lower risk for stroke and death but a somewhat higher frequency of acute myocardial infarction in the elderly.

47.2.12 Relevance of Time Elapsed Between Symptom Presentation and Surgery

The time between symptoms onset and surgery influences the expected benefit, which will be higher the earlier the procedure is performed. An inverse relation between time to surgery and intervention benefit documented in randomized studies since the 1990s can be explained by several mechanisms.

On the one hand, the recurrence risk is highest during the first days after the first neurological event and then decreases with time, possibly due to the effect of medical treatment on atheromatous plaque stabilization [14,95]. On the other, it is reasonable to presume that time might also favor the development of collateral circulation. Finally, and after some weeks, by balancing the potential beneficial effect of CEA with the recurrence risk, the result is neutral, counterbalancing the usefulness of surgical intervention. As shown in Table 47.6, the most beneficial period for CEA is the first 14 days. In patients with symptomatic carotid stenosis >70%, the favorable effect of CEA is lost if deferred beyond 90 days, while in those with symptomatic stenosis 50 to 69%, it is lost after the first 14 days, making it not reasonable to indicate surgery beyond these time windows.

The meaning of “the first 14 days” warrants careful analysis. First, this period corresponds to the time between randomization and surgery in studies such as NASCET and ECST. This time window should not be considered as a synonym for a “period between

initial symptoms and surgery". In both NASCET and ECST, the patients were randomized by symptoms occurring up to 6 months earlier. This means that the period between the occurrence of symptoms and randomization (up to 6 months) should be added to the randomization-surgery time the studies reported. Hence, we could assume that the real time window in which CEA was beneficial in the randomized studies was more than 14 days.

Second, the fact that CEA might be more effective during the first 14 days does not necessarily imply that all patients should undergo surgery during that period. Paradigmatic cases that escape the standard of immediate surgery are **crescendo TIA** and **stroke in evolution**. Crescendo TIA can be defined in several ways but such events usually fit into one of the following categories: a) 2 or more episodes in the last 24 hours [96]; b) 3 or more episodes in the last 3 days [73]; and c) 3 or more episodes in the last 7 days [97,98].

Nevertheless, a systematic review revealed that urgent CEA in crescendo TIA or stroke in evolution was associated with a higher risk of stroke and perioperative death than delayed surgery (OR 4.6, 95% CI 3.4-6.3; p=0.001) [101]. The absolute risk for stroke or postoperative death attributable to urgent CEA was 20.2 (95% CI 12.0-28.4) for stroke in evolution and 11.4 (95% CI 6.1-16.7) for crescendo TIA (95% CI 6.1-16.7). Emergency surgery in patients with minor stroke or TIA with stable neurological syndromes was not associated with a higher perioperative risk (OR 1.2, 95% CI 0.9-1.7, p=0.17).

47.2.13 Indications for CEA in Asymptomatic Patients

The annual risk for ipsilateral stroke in patients with carotid stenosis >50% varies between 2 and 3% [102], increasing to 16.6% (95% CI 1-32) [103] during for a 15-year follow-up period. Acute myocardial infarction and nonvascular-related death risk also seem to be higher: 24% (95% CI 14-34) [103]. Age and presence of diabetes increase the risk [103].

Analyzing the results of large randomized studies on CEA in asymptomatic patients is much less complex than studies on symptomatic patients. The most relevant are the Asymptomatic Carotid Atherosclerosis Study (ACAS) [104] and the Asymptomatic Carotid Surgery Trial (ACST) [70]. The Veterans Affairs Cooperative Study (VACS) recruited only a male population [105]. The design of CASANOVA (Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Vs. Aspirin) was criticized for its low number of patients and for excluding those with >90% carotid artery stenosis [106]. Finally, MACE (Mayo Clinic Asymptomatic Carotid Endarterectomy), comparing aspirin vs. CEA, had to be suspended for safety reasons when an excess of deaths due to acute myocardial infarction was detected in the randomized endarterectomy arm [107].

ACAS enrolled asymptomatic patients with carotid stenosis between 60 and 99% [104]. ACST enrolled patients with no history of stroke or TIA in the previous 6 months and with stenosis ≥60% [70]. Both studies showed a reduction in stroke risk in CEA patients. Although both ACAS and ACST formed the basis for the analysis of the utility of CEA in asymptomatic patients, they are not identical. The most controversial discrepancy was that in the ACAS, the participating surgeons had to demonstrate results with a perioperative morbimortality rate <3%, whereas in the ECST, NASCET and ACST the surgeons were required to report a complication rate <6% Moreover, some of the surgeons who were originally selected were later excluded from the study due to the adverse outcomes in their first patients [108].

Noteworthy is that the ACAS reported a strikingly low rate of surgical complications. Table 47.7 compares stroke and postoperative death rates in this study with those of ACST

(1.5 vs. 2.8%; p=0.07) and those of an observational study involving 6655 asymptomatic patients in New York (1.5 vs. 3.0%; p=0.02) [73]. As shown in the table, the postoperative mortality rate in the ACAS was 8 times lower than that of the two other studies. A meta-analysis of outcome after CEA not performed in randomized trials also showed a complications rate 8 times lower than that reported for ACAS [109]. The low complications rate observed in the latter might limit the reproducibility of its conclusions in clinical practice, particularly when considering the lack of information from many centres about their surgical complications rates.

In the ACST, the most questionable fact is that patients were randomized and underwent surgery with a non-centrally audited carotid artery CDUS [110]. This might have resulted in increased underreporting of subocclusive lesions, as well as mistakes in estimating the degree of stenosis [111].

Unlike symptomatic carotid studies, both the ACAS and ACST concluded that increasing degrees of stenosis are not related to a higher benefit from endarterectomy. This merits careful interpretation. Based on these data, the only variable related to stenosis degree that should be considered in the surgical indication is whether it is higher or lower than 60%.

As with symptomatic carotid disease, other variables can tilt the decision for or against surgical intervention. Gender seems to be a determinant with a higher impact on CEA outcome in asymptomatic patients. A meta-analysis of the ACAS and ACST results evidenced a reduction in the risk of perioperative stroke and death at 2.3 years in men (OR 0.49, 95% CI 0.36-0.66) but not in women (OR 0.86, 95% CI 0.63-1.45) [112]. Hence, CEA would not be advisable in asymptomatic women.

Carotid atheromatous plaque progression can occur in approximately 9% of patients within 6 to 9 months. It is defined as moving from a lower to a higher category on a scale that stratifies the degree of stenosis according to 6 levels: 0 to 29%, 30 to 49%, 50 to 69%, 70 to 89%, 90 to 99%, and 100%. It is not only associated with a higher risk of ipsilateral stroke (HR 2.0, 95% CI 1.0-4.1; p=0.04) [113-115] but also with a higher risk of acute myocardial infarction (HR 2.4, 95% CI 1.1-5.4; p=0.04) and cardiovascular death (HR 1.8, 95% CI 1.0-3.0; p=0.04) [113]. Although the postulated association is clear, there is still no evidence to recommend endarterectomy solely on the criterion of carotid plaque progression, although it might be an element to be considered in the decision process.

With regard to age, according to the ACST, the difference in the risk of stroke in the carotid territory between those who underwent surgery and those who did not was 7.8% (95% CI 4.3-11.3, p <0.0001) in patients <65 years and 7.5% (95% CI 4.7-10.3; p <0.0001) in patients 65 to 74 years of age [70]. Due to the low number of patients involved, determining whether endarterectomy might have been of benefit for patients >77 years was impossible. The way in which these data were presented should be carefully considered, given that the RAR_{5a} for the combined outcome of stroke of any cause and perioperative death were not reported.

Another risk marker in asymptomatic patients is the presence of microemboli detected by carotid artery ultrasound or TCD imaging. In a recent study, the annual event rate in

Endpoints	ACAS			ACST		
	NNT_{5a}	RAR_{5a}	p	NNT_{5a}	RAR_{5a}	p
Stroke	17	5.9	0.004	19	5.4	0.0001
Disabling stroke or death	37	2.7	0.26	40	2.5	0.004

Table 47.7. **NNT_{5a} and RAR_{5a} of CEA to prevent different endpoints in asymptomatic patients.**

asymptomatic patients with carotid stenosis between 60 and 99% and microemboli was 4.6%, while the rate was 2.4% (p=0.032) [116] for those without microemboli. The value of microemboli detection in clinical practice is yet to be determined.

In conclusion, CEA in asymptomatic patients should be reserved for a select subgroup. So far, this group has been defined as men <75 years of age, with stenosis >60%, as long as the surgical team's documented morbidity and mortality rate is <3%. It is highly likely that more evidence supporting non-surgical medical treatment over surgery will emerge very soon. In that eventuality, CEA might not be the first option for a great majority of asymptomatic patients and the most important approach will be to optimize medical treatment and interventions to reduce the risk of coronary disease, which remains the leading cause of mortality in this population.

47.3 Carotid Angioplasty

Although CEA is the most commonly performed procedure to reduce stroke risk in patients with symptomatic and asymptomatic carotid stenosis, the advent of percutaneous techniques has lead to the development of carotid angioplasty (CA) and CA with stent (SCA) techniques. The first CA procedure was described by Mathias in 1977 [117,118].

Among the potential advantages of CA and SCA are their less invasive nature is emphasized (they can be performed under local anesthesia and sedation), shorter hospital stay, and lower probability of complications associated with concomitant coronary disease. Unlike CEA, which is limited to the cervical carotid, endovascular procedures can be performed on much more cephalic lesions, and even in the intracranial carotid. A subgroup of patients who might benefit from CA and SCA are those with "tough or hostile necks", presenting a higher risk of complications with CEA. Patients with a history of radiotherapy or cervical surgery or tracheostomy are included in this group [119,120].

Notwithstanding its advantages, percutaneous procedures also carry the risk that mobilization and eventual displacement of the atherosclerotic plaque might result in a higher incidence of neurological events [121].

For CA and SCA, some other considerations should be taken into account:

- CEA benefits in symptomatic patients have been demonstrated, and the rate of complications is low when performed by experienced surgeons. Therefore, results, complications and hospital stay in percutaneous techniques should be compared to those of CEA.
- Morbidity and mortality associated with the use of intravascular devices remains to be clearly defined.
- Acute intraoperative carotid occlusion, unlike acute occlusion in other territories, might not be surgically corrected in an emergency procedure.
- Re-stenosis after a percutaneous procedure might be very hard or even impossible to repair surgically.

47.3.1 Angioplasty

Percutaneous angioplasty has been extensively used in the treatment of peripheral and coronary vascular diseases, whereas it has been much more cautiously applied to carotid disease due to the risk of dissection and embolic stroke. Moreover, because the main etiology in stroke of carotid origin is predominantly embolic, the increase in carotid diameter with CA has a less attractive biological approach than removal of the embolic source. Initial studies reported a rate of major or minor stroke of 1.4% and 2.7% respec-

tively, while other series demonstrated embolic complications in up to 12% of cases. In some series, re-stenosis occurred in up to 15% of patients and dissection in up to 5% (complications that were significantly reduced with the increasing use of stents).
CA is performed in a conscious patient, allowing for real-time intraoperative neurological monitoring. Nevertheless, unlike CEA in which intolerance to clamping can be treated with shunt placement, options are limited when ischemia of embolic origin occurs during CA or SCA, which is why all efforts have been directed to minimizing the risk of intraoperative embolism. On the other hand, ischemia time during CA or SCA is <1 minute is attractive compared to the much longer arterial clamping time in CEA. Since the advent of modern stents, CA is rarely performed without them.

47.3.2 Stents

The first balloon-expandable stents were replaced very favorably by self-expandable-stents. The first cobalt-chrome alloy stents (Wallstent®) were later replaced by current stents made of nitinol, a nickel-titanium alloy with a thermal memory and greater adaptability to the vessel wall. According to stent design configuration of cell opening, stents are classified as **open-cell** (more navigable and adaptable to vascular tortuosities), **closed-cell** (with a higher radial tension, better plaque containment and probably less emboligenous potential), and **hybrid stents** (a central closed cell with open cells at the edges).

47.3.3 Protection Systems

Filters, proximal occlusion balloons and distal occlusion balloons are used to minimize embolism risk. Distal protection filters are wires that pierce the lesion and have a bag-shaped receptacle with 80 to 140 micron perforations at its ends designed to capture the detached particles. Easy to use, they are the most widely employed system [125]. Its main disadvantage is the need to pierce the lesion without the system in function, which is why they are not readily used in critical lesions, with visible thrombi or in patients with recurrent symptoms.
Proximal occlusion balloons block blood flow through the vessel by balloon-mediated occlusion of the ECA and CCA under the obstruction [126]. In the system created by Parodi, the guide catheter has an auxiliary port from which an inverted flow from the internal carotid to the femoral vein is created. In both cases, the lesion is pierced and the stent is advanced with no active flow through the carotid, removing as much residual material as possible before finishing the procedure [127]. These systems are useful in critical lesions, with visible thrombi or with recurrent symptoms. Its disadvantages are its wider diameter and longer learning curve.
Lesion piercing by the guide (with consequent embolic risk) is necessary when using distal occlusion balloons as well. A balloon distal to the stenosis is then inflated to force flow to detour into the ECA while the plaque is treated. Although simpler in use, its use is becoming increasingly restricted [128].

47.3.4 Comparative Studies

A systematic review of 10 randomized controlled studies published as of March 2007, which compared CEA versus SCA in 3178 symptomatic and symptomatic patients, reported [129]: a) primary outcome for a new stroke or death at 30 days favored CEA according

to a fixed-effect model, but the result was not statistically significant in a randomized-effect model (which is less likely to underestimate confidence intervals); b) there were no significant differences between CEA and endovascular treatment in stroke risk or death on long-term follow-up; c) data interpretation was difficult due to the wide confidence intervals, significant heterogeneity in the studies, some of which were preliminarily interrupted. The reviewers concluded that there was insufficient evidence to recommend a change in recommending CEA as the treatment of choice for carotid artery disease.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) enrolled 504 patients with carotid or vertebral artery stenosis. There were no significant differences in the incidence of mortality or severely disabling stroke (10% for each group) or any type of stroke (6% for each stroke) between the procedures [130] at 30 days or after a 3-year follow-up period. No differences were found in the risk of procedure-related stroke or death between angioplasty and endarterectomy. Nevertheless, the conclusions were limited by the heterogeneity of the study population (stents were used in only 25% of patients). Recent follow-up studies have shown that the rate of re-stenosis in patients with CA is three times that of the CEA group, although the risk of ipsilateral stroke is low [131,132].

The SPACE (stent-protected angioplasty versus carotid endarterectomy) study was a European study involving 1183 patients and designed to demonstrate the non-inferiority of SCA compared to CEA for severe symptomatic carotid stenosis treatment. Patients with a high risk, non-controlled hypertension or re-stenosis were excluded [133]. At day 30, combined ipsilateral stroke or death outcome were equal in both groups (6.8 vs. 6.3%), although it did not statistically prove the non-inferiority of SCA vs. CEA. In a post hoc analysis, old age in the SCA group (but not in CEA) was associated with a higher risk of ipsilateral stroke or death [134]. There were no significant differences during the 2-year follow-up for the combined risk of perioperative ischemic stroke and death [135]. The criticisms raised against SPACE were that the use of embolism protective devices was optional and that they were used in only a 27% of cases, although there were no differences in the results at 30 days (when the perioperative factor was assessed).

The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis study (EVA-3S) conducted in France also evaluated the hypothesis that SCA was not inferior to CEA in patients with severe symptomatic carotid stenosis [136]. This study excluded high-risk patients with unstable angina, unstable diabetes or non-controlled hypertension, as well as patients with a history of revascularization procedures. Incidence of any stroke or death at 30 days was higher with SCA than with CEA (9.6 vs. 3.9% with a relative risk (RR) of 2.5). The study was prematurely discontinued due to excess mortality in the SCA branch. The 4-year follow-up results also showed a higher incidence of negative combined outcome for SCA vs. CEA (11.1 vs. 6.2%) [137]. The difference was mainly due to the high number of perioperative strokes, while during later follow-up there were no significant differences. The main criticism raised against this trial was the lack of experience of many of the operators, the use of different classes of stents and protective devices. The use of the latter was also optional.

Unlike previous studies, SAPPHIRE evaluated non-inferiority of SCA vs. CEA in patients with symptomatic (>50%) and asymptomatic carotid stenosis (>80%) considered to have a high surgical risk [138,139]. Over 70% of patients were symptomatic. All patients received a stent with an embolic protection device. Results at 1 year showed that SCA was not inferior to CEA and a reduction in the combined endpoint for stroke, acute myocardial infarction, and death in the SCA vs. the CEA-treated group. Non-inferiority of SCA vs. CEA could not be proved beyond 1 year, and there were no significant differences in the secondary endpoint (primary endpoint plus ipsilateral stroke or death between the first

ICCS-SPREAD	SAPPHIRE
Contralateral laryngeal nerve paralysis	Contralateral laryngeal nerve paralysis
Cervical irradiation history	Previous cervical irradiation
Previous CEA with recurrent stenosis	Previous CEA with recurrent stenosis
	Previous radical neck surgery
High ICA lesion	
Infraclavicular CCA lesion	
Tandem severe lesions	
Age >80 years	Age >80 years
Severe pulmonary disease	Severe pulmonary disease
Severe vascular or cardiac co-morbidities	
Congestive heart failure (NYHA class III-IV) and/or severe left ventricle function dysfunction	Congestive heart failure
Need for heart surgery in the next 6 weeks	Need for heart surgery
Recent acute myocardial infarction (>24 hours and <4 weeks)	
Unstable angina (Canadian Cardiovascular Society Class II-IV)	Abnormal stress test
Contralateral carotid occlusion	Contralateral carotid occlusion

Table 47.8. **High-risk conditions for CEA.**

and third year). Despite difficulty in interpreting these analysis, the conclusion that SCA might not be inferior to CEA in patients with high risk should probably be considered valid for this study group (Table 47.8) [140].

47.3.5 Recommendations

The ICCS-SPREAD Joint Committee, a collaborative initiative by Italian scientific societies for the treatment of vascular disease, issued recommendations for the organization of multidisciplinary teams involved the decision-making in the treatment of patients with carotid stenosis, as well as the knowledge and training requirements for an operator to be certified for performing a revascularization procedure, emphasizing that guidelines should be adjusted to evidence emerging from ongoing studies [141].
Table 47.8 lists the "high-risk" conditions for CEA according to the ICCS-SPREAD Joint Committee and SAPPHIRE [138,141]. In patients with such characteristics treated by team with certified qualifications, SCA might be prioritized over CEA.
Nevertheless, Roghwell and Roffi, in two recent independent comments, called for a reconsideration of the lack of evidence for SCA results in patients eligible for CEA. Therefore, CEA should be still considered the first choice when attempting carotid revascularization [142,143].

47.4 Medical Treatment

The growing body of data on the importance of medical treatment as a primary and secondary prevention strategy will be examined in this section. We shall also discuss the use of antithrombotics before, during and after CEA.

47.4.1 Current Status of Medical Treatment

Medical (non surgical) treatment of vascular disease is the basis on which prevention measures are built. It includes: a) risk factor assessment; b) cessation of harmful habits and unhealthy lifestyle (smoking, excessive alcohol intake, recreational drug use, sedentarism); c) diet (risk-profile specific) and weight loss; d) use of antiplatelet therapy; e) antihypertensives; and f) statins [144]. An important feature of medical treatment for carotid artery disease is that, exceptions aside, it helps prevent general vascular risk. Not only does it prevent stroke but also acute myocardial infarction, heart failure and peripheral vascular disease. Moreover, unlike endarterectomy or angioplasty (which are aimed to prevent mainly hemodynamic and arterio-arterial mechanisms), medical treatment reduces the risk of stroke across the entire spectrum of stroke subtypes and, apart from preventing carotid artery events, it also reduces small vessel and cardioembolic strokes.
Over the past years an intriguing question has arisen: Can the best medical treatment replace CEA and CA in patients with carotid disease? We have already pointed out that no randomized study endorses SCA as the best **prevention strategy** [142,143]. Therefore, this treatment is just an option for well selected cases in which the patient does not meet the criteria for CEA. Based on this observation, throughout the rest of this section we will examine the relationship between medical treatment and CEA in symptomatic and asymptomatic patients.
Based on the results of studies such as NASCET and ECST, it seems unlikely that current best medical treatment could be better than CEA in symptomatic patients. Therefore, the current role for best medical treatment in patients with symptomatic carotid disease is to enhance the demonstrated benefit of CEA.
For asymptomatic carotid disease, the picture is different. If we consider the marginal benefit of CEA in asymptomatic patients, best medical treatment–as developed so far--might probably be better than surgical intervention [145].

47.4.2 Current Best Medical Treatment vs. CEA in Symptomatic Patients

Randomized studies assessing CEA benefits in symptomatic patients started in 1983 [105] and were completed by July, 2003 [70]. These studies proved that surgery plus best medical treatment initiated at randomization time and maintained during the follow-up period is superior to best medical treatment alone. Nonetheless, in the last 25 years medical treatment has evolved spectacularly with development of new drugs and the discovery of new properties for old ones. This has led to recent questioning of the current applicability of conclusions from studies such as the ACAS and ACST.
A recent systematic review set a turning point in the history of CEA vs. best medical treatment in asymptomatic patients with carotid stenosis >50% [146]. The relevance of this article, with its exceptional analysis of evolution and impact of best medical treatment on stroke rates in patients with asymptomatic carotid disease over the last 25 years justifies a detailed discussion of its results and most interesting findings.
The most significant finding was evidence for a progressive reduction in the rate of cerebrovascular events in patients under best medical treatment included in hospital observational studies between 1985 and 2007: ipsilateral stroke -1.4% ($p < 0.0012$) and any-territory stroke -2.5% ($p < 0.00012$). According to the author's analysis, when comparing the effect of best medical treatment to that of CEA performed in randomized studies in the following years, surgical intervention stopped being better than best medical treatment by the 1980s for ipsilateral stroke, by 1990 for any territory stroke, and by 2001 for

stroke or TIA in any territory. This occurred despite an increase in the prevalence of arterial hypertension (↑5%) and average patient age (↑5.5%), although there was a significant reduction in smokers (↓15%), men (↓8%), coronary disease (↓37%) and peripheral vascular disease (↓11%). The main conclusion is that since 2001, best medical treatment is at least as effective as CEA combined with best medical treatment 10 to 20 years ago. If we also consider that best medical treatment is 3 to 8 times less expensive (another conclusion of this study) for stroke prevention, the balance certainly shifts toward the use of the first option.

At least two observations on Abbott's work can be made. Based on his study, we know that for symptomatic patients with carotid stenosis >50%, current best medical treatment is at least as good as CEA plus best medical treatment 10 to 20 years ago. However, to determine best therapeutic option for 2010 we should compare current (2010) best medical treatment with CEA plus best medical treatment 10 to 20 years ago. A randomized trial for this purpose would require a very large number of patients due to effectiveness parity between both therapeutic interventions. Therefore, the cost would be hard to justify, even more so when considering applicability obstacles or external validity. One way to shed light on this matter would be to create large multicentre registries. In Abbott's study, since the analysis was performed on data from socioeconomically developed countries (the Netherlands, Canada, the United States and Australia), it might be risky to extrapolate this study's conclusions to other countries [147]. What we can certainly suggest is that the introduction of health policies aimed to optimize vascular prevention programs may have an enormous impact. Meanwhile, CEA will remain an option for a small, selected patient subgroup.

Whatever the conclusion regarding this question, patients with symptomatic or asymptomatic carotid artery disease should be treated with the currently available best medical treatment. Further information on this subject can be obtained from the AHA/ASA secondary prevention guidelines [93].

47.4.3 Antithrombotic Therapy Before, During and After CEA

Platelet adhesion and aggregation increase during CEA, especially during clamping and unclamping of the ICA [148]. This phenomenon may be boosted by a reduction in the antiaggregant effect of aspirin during surgery [149]. As a result, thrombosis at the surgical site can be postoperatively detected in 2.7% of cases [150]. Aside from local thrombosis, 5% of CEA patients develop an increased degree of microembolization detected by ultrasound in the first 2 hours after surgery [150] and 30-60% of these patients will suffer an ischemic stroke in the subsequent hours [150,151].

47.4.4 Antithrombotics During CEA

The combined use of aspirin (330 mg/day) and dipiridamol (75 mg/day) has significantly reduced platelet accumulation at the endarterectomy site [153]. These data are consistent with the positive effect shown by aspirin, when administered in 75 mg/day doses before surgery, on the reduction of severe stroke in the first month as compared against placebo [154]. The ACE (Aspirin and Carotid Endarterectomy) Trial showed that lower doses of aspirin (81 mg/day and 325 mg/day) administered before and after CEA were associated with a reduced risk for stroke, acute myocardial infarction and death at 3 months (6.2 vs. 8.4%; p=0.03) compared to higher doses (650 mg/day and 1300 mg/day) [155]. Combination therapy with aspirin (150 mg/day) and clopidogrel (75 mg/day) administered 5 days prior to CEA also reduced the number of microemboli detected dur-

ing the first 3 postoperative hours (OR 0.10, 95% CI 0.01-0.79) compared to aspirin alone (150 mg/day) without an increase in bleeding complications [156]. With regard to the specific use of clopidogrel, although small studies have shown it has a relative safe profile when administered before surgery [157], the company that markets the drug recommends its discontinuation 5 to 7 days before any elective surgery [158].

A patient with a crescendo TIA or a progressive stroke due to carotid artery disease is relatively often encountered in clinical practice. Although the utility of i.v. sodium heparin (with or without a previous bolus) and low-molecular-weight heparin have been investigated, with none of these have proved useful in the reduction of neurological damage due to stroke or the prevention of early recurrence [159]. Based on these data and the higher risk of cerebral and non-cerebral bleeding, the AHA/ASA advises against its use after TIA or acute ischemic stroke [159].

In summary, aspirin use (75-100 mg/day) before CEA seems safe and necessary to reduce the risk of microembolization and postoperative stroke (recommendation grade IA from the American College of Chest Physicians) [160]. Until strong evidence supporting the benefits and safety of clopidogrel emerge, its use is not recommended in the perioperative period; nevertheless, there is no evidence to support deferred surgery in patients previously receiving this drug. Finally, patients should not be treated with anticoagulation while awaiting CEA.

47.4.5 Antithrombotics During CEA

Different therapeutic attempts to reduce the risk of embolization during CEA have been tried, especially before clamping and unclamping. Although some studies have shown a reduction in the microembolic load and risk of perioperative stroke with Dextran administration in patients undergoing CEA, its use has not been widely accepted due to the risk of heart failure and other complications [161,162].

The American College of Chest Physicians' recommendation for intraoperative antithrombotic management is the use of i.v. non-fractionated sodium heparin [160]. Close control with intraoperative coagulation tests is also advisable.

Controversies surround whether intraoperative i.v. anticoagulation should be reversed with Protamin after the procedure. Protamin is usually associated with hemodynamic alterations and does not necessarily reduce the risk of postoperative bleeding [160,163]. On the other hand, anticoagulation reversion with Protamin may be associated with a higher risk of local thrombosis [164].

In conclusion, anticoagulation with i.v. non-fractionated heparin should be started before ICA clamping and there is not enough evidence to advice for or against anticoagulation reversion with Protamin.

47.4.6 Antithrombotics After CEA

A recent meta-analysis evidenced that platelet antiaggregants reduce stroke risk (OR 0.58, 95% CI 0.34 - 0.98; P=0.04) after CEA but do not seem to have a significant effect on mortality (OR 0.77, 95% CI 0.48 - 1.24) or perioperative bleeding (1.71, 95% CI 0.73 - 4.03) [165]. The antithrombotic of choice should be selected according to each patient's risk profile. The American College of Chest Physicians recommends aspirin use (81-100 mg) indefinitely. Given that up to 30% of patients with large vessel disease may also present a cardioembolic source, we recommend their systematic investigation with transoesophageal echocardiography (TOEE), since in such cases, and after CEA, the an-

tithrombotic treatment of choice would then be oral anticoagulation instead of platelet antiaggregation [166].

47.4.7 Antithrombotics Before, During and After CA

The rationale for antithrombotic use in patients undergoing CA is to prevent thrombi formation during the immediate postoperative period and to reduce early (first 30 days) or late re-stenosis risk. Intimal damage due to mechanical trauma during SCA causes the release of collagens and other endothelial proteins which stimulates platelet aggregation and adhesion. Subsequent endothelial repair involves intense cellular infiltration of the parietal thrombus, with smooth muscle cell proliferation and migration. The exacerbation of this process is referred to as "neointimal hyperplasia" and is the main cause of re-stenosis during the first 30 days [167]. Late re-stenosis usually refers to atherosclerotic phenomena related to inadequate control of vascular risk factors [168].

47.4.8 Antithrombotics Before CA

Asymptomatic microemboli detected on carotid artery CDUS have become progressively relevant as predictors of stroke and TIA [169] and are more frequent in symptomatic than asymptomatic carotid disease [170]. The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis Trial (CARESS) is a randomized study that compared aspirin-clopidogrel therapy (300 mg loading dose plus maintenance with 75 mg/day for 7 days) vs. aspirin alone (75 mg/day) in 107 patients with carotid stenosis >50%, that had been recently (last 3 months) symptomatic [171]. The number of asymptomatic microemboli were lower in the dual therapy group (reduced RR of 39.8%, 95% CI 13.8-58.0; p <0.005). The recurrent stroke frequency was 0.0% in the dual therapy group vs. 7.1% in the only-aspirin group (P=0.44). major bleeding Neither group experienced. We did not discuss CARESS results in the section on CEA and antithrombotics because it has already been mentioned that clopidogrel use in the days prior to surgery is not recommended. However, combination therapy with clopidogrel and aspirin might indeed be an interesting option in a small and properly selected group of patients with symptomatic carotid stenosis >70% awaiting angioplasty.

47.4.9 Antithrombotics During CA

Routinely, after a diagnostic angiography confirming previous findings and before introducing a guide wire through the stenotic site, 5000 to 7500 units of non-fractionated sodium heparin are administered through the intra-arterial catheter [172], then and throughout the procedure, heparinized saline is infused [172]. Some centres use abciximab during the procedure.

47.4.10 Antithrombotics After CA

Based on experience with coronary angioplasty, all randomized CA studies have used a combination of aspirin and clopidogrel in variable doses and timing. Randomized studies and angioplasty registries have shown the utility of this therapeutic approach [173,174]. Table 47.9 summarizes dual therapy schemes after CA as used in the principal randomized studies. Currently, patients undergoing CA should receive a combination of aspirin and clopidogrel for at least 30 days.

Study	Post-stenting dosis	Duration
ARCHeR [175]	Aspirin* 325 mg/day + clopidogrel** 75 mg/day or ticlopidine** 500 mg/day	*12 M **14 D
BEACH [176]	Aspirin* 325 mg/day + clopidogrel** 75 mg/day or ticlopidine** 500 mg/day	*12 M **30 D
CAVATAS [130]	Aspirin* 150 mg/day + Non-fractionated Heparin for just 24 hours	*>12 M
EVA-3S [137]	Aspirin 100 to 300 mg/day + clopidogrel 75 mg or ticlopidine 500 mg/day	30 D
SPACE [134]	Aspirin 100 mg/day + clopidogrel 75 mg/day	30 D
SAPPHIRE [138]	Aspirin 81 to 325 mg/day + clopidogrel 75 mg/day	14 - 28 D

Table 47.9. **Dual therapy schemes used in the main randomized studies on carotid angioplasty.**
D = days
M = months

47.5 Carotid Artery Disease and Coronary Disease

47.5.1 Epidemiology

Given that atherosclerosis predominates in older patients, gradual population aging has led to a proportional increase in the number of patients with coronary disease, carotid disease or both [177]. The prevalence of carotid artery disease in patients undergoing surgical myocardial revascularization (SMR) varies according to different series. In five studies reporting carotid artery CDUS results of patients undergoing SMR, the prevalence of carotid stenosis >80% was 6.0% (CI 95% 5.4-6.6) [178-183].
In a cohort of 176 patients who underwent CEA at the University Hospital of the Favaloro Foundation in Buenos Aires between 2006 and 2008, 54.5% (95% CI 47.2-61.7) had a history of coronary disease defined as stable chronic angina, unstable angina, or a previous SMR, coronary angioplasty or acute myocardial infarction. These data are consistent with those published by other authors [183,184].
Carotid artery disease and coronary disease are predisposing factors for complications in patients undergoing SMR [185] and CEA [186], respectively. Some 17% of patients with untreated coronary disease suffer a myocardial infarction during the perioperative CEA period [186]. The risk of ischemic stroke after SMR with on-pump or off-pump surgery is 3.8 and 1.9%, respectively [187].

47.5.2 Screening for Carotid Artery Disease in Patients Undergoing SMR

Screening for carotid artery disease in patients undergoing SMR can be done selectively or non-selectively. The predictive factors for carotid artery disease are: age [188-190]; carotid bruit [190-192]; previous stroke or TIA [190-192]; CEA history [191]; peripheral vascular disease [190,191]; and history of smoking, arterial hypertension and diabetes [189,190]. The American College of Cardiology and the American Heart Association management guidelines for patients undergoing SMR recommend screening for carotid disease in patients >65 years, with left main coronary artery trunk disease, peripheral vascular disease, smokers, with a history of stroke or TIA or with a carotid bruit (Level C evidence) [193].

47.5.3 Screening for Carotid Disease in Patients Undergoing CEA

According to studies using SPECT or graded exercise testing, 25% of patients undergoing CEA are asymptomatic coronary disease carriers [194,195]. However, when assessment is performed with coronary angiography, this proportion can be 84% [196]. Based on this evidence, the AHA/ASA guidelines recommend searching for coronary artery disease in patients with a history of stroke or TIA of carotid origin, emphasizing that randomized studies are needed to confirm this suggestion [197]. To date, there are no specific strategies for coronary disease screening before CEA in patients with asymptomatic carotid disease.

Finally, we will present some questions for which we have no definitive answers: a) Is it hazardous to perform a stress test on a patient with severe carotid disease? b) Is it relevant if the patient has bilateral carotid artery disease? c) Given that CEA must be performed as soon as possible in symptomatic patients, is it advisable to delay the surgical schedule to disclose coronary disease? d) If the patient has concomitant coronary disease, which would be the adequate approach?

47.5.4 Therapeutic Approach to Patients With Concomitant Carotid and Coronary Disease

The three most serious complications associated with SMR and CEA are stroke, acute myocardial infarction and death. Owing to the lack of definite scientific evidence, the best therapeutic strategy for patients with concomitant carotid and coronary disease has the subject of ongoing debate.

Before analyzing the evidence, it is necessary to identify two possible scenarios: a) the patient scheduled for SMR, diagnosed with carotid stenosis ≥50% during preoperative evaluation; and b) the patient scheduled for CEA for symptomatic carotid disease, who is preoperatively diagnosed with coronary artery disease.

With regard to the first scenario, a recent systematic review that compared SMR plus best medical treatment versus SMR plus best medical treatment plus CEA found no study that could be selected for analysis [198]. Despite the lack of evidence, it is interesting to mention a study involving 3942 patients undergoing cardiovascular surgery [199]: 6% (239) had carotid disease ≥50%; the stroke frequency was higher in this group than in those without carotid disease ≥50% (7.5 vs. 1.5%; P <0.001) The most striking feature of this study is that, of the 18 ischemic strokes in patients with carotid disease ≥50%, only 4 (20%) occurred in the territory ipsilateral to the affected carotid. The rest happened in other or multiple territories. This finding underscores that strokes in patients undergoing SMR are more often in those with carotid artery disease, although the mechanism is not directly related to the surgery. In fact, the most frequent stroke mechanism in these patients is particulate embolism from the thoracic aorta at the moment of clamping and unclamping, as well as from extracorporeal circulation [200]. This study contributes to the controversy on whether or not to treat carotid artery disease in patients who are scheduled for SMR.

In the second scenario (a patient undergoing CEA for symptomatic carotid disease, diagnosed with coronary artery disease), various different strategies can be considered: a) CEA followed by SMR; b) SMR and posterior CEA; c) synchronous CEA and SMR (on-pump); d) synchronous CEA and MRS (off- pump); and e) CA followed by SMR. We present the available evidence for each option in Table 47.10 [201-203].

	CA then SMR		Synchronous CEA and SMR *		Synchronous CEA and SMR **		CEA then SMR		SMR then CEA	
	Risk % (95% CI)	N	Risk % (95% CI)	N	Risk % (95% CI)	N	Risk % (95% CI)	N	Risk % (95% CI)	N
Ipsilateral stroke	-	760								
Any stroke	4.2 (2.4-6.1)	760								
Death	5.5 (3.4-7.6)	760	4.6 (4.1-5.1)	6230	1.5 (0.3-2.8)	324	3.9 (1.1-6.7)	917	2.0 (0.0-6.1)	302
AMI	1.8 (0.5-3.0)	760	3.6				6.5		0.9	
Ipsilateral stroke or death	ND	ND	7.2 (6.5-7.9)	4996	1.6 (0.4-2.8)	318	4.8 (2.8-6.8)	809	3.4 (0.0-9.8)	87
Stroke or death	9.1 (6.1-12.0)	760	8.2 (7.5-8.9)	6230	2.2 (0.7-3.7)	318	6.1 (2.9-9.3)	917	7.3 (1.7-12.9)	302
Stroke, AMI or death	9.4 (7.0-11.8)	760	11.4 (10.4-12.5)	3699	3.6 (1.6-5.5)	309	10.2 (7.4-13.1)	709	5.0 (0.0-10.6)	221

Table 47.10. **Outcome after different surgical strategies according to meta-analysis.**
AMI = Acute myocardial infarction
ND = No data

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48 Intensive Care Management in Space-Occupying Middle Cerebral Artery Stroke

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48.1 Definition, Risk Factors and Clinical Signs

Space occupying middle cerebral artery (MCA) infarction – also termed malignat MCA infarction – develops in around 1 to 10% of patients with supratentorial infarcts. Up to 80% mortality has been reported in older series [1]. In patients with malignant MCA infarction severe brain edema develops due to a vicious circle starting from unsuccessful or too late recanalization, followed by large brain ischemia and cytotoxic edema, leading to impaired substrate supply in the areas adjacent to the infarct, promoting further ischemia and brain swelling. Recently, a novel phenomenon, spreading depolarization, has been recognized to cause secondary brain injury including edema formation in malignant ischemic stroke [2]. In the course of these events, intracranial pressure raises and may lead to lethal brain herniation.

The early identification of patients at risk for developing a malignant course in large MCA infarction is of great importance for therapeutical decision making. Several clinical and radiological parameters have been suggested to predict the development of life thretatening brain edema. They however, lack sufficient predictive power to reliably guide potential surgical therapy [3]. So far, solely the size of ischemic lesion seems to be a reasonable sensitive and specific parameter to predict the development of a malignant course [4]. Patients at risk for malignant brain edema usually present with a severe stroke syndrome with hemiplegia, hemisensory symptoms, frequently ipsilateral gaze devation, followed by impaired consciousness. Patients with carotid artery or proximal MCA occlusion in whom respective large MCA and/or anterior cerebral artery (ACA) territory infarction is suspected should be monitored closely. An alarming sign for development of malignant brain edema with an increase in intracranial pressure is a gradual decrease in consciousness. Respiratory insufficiency and pupillary enlargement are “late” signs and indicate brainstem dysfunction due to mass effects and require immediate attention. Severe brain edema usually develops around day 2 to 5 after the ictus.

- Risk factors for development of a malignat course:
  - Severe neurological deficit on admission
  - Impaired consciousness on admission (LOC > 0)
  - Large infarct on CT or MRI (>145 cm^3), including the basal ganglia
  - Proximal MCA occlusion, ICA occlusion
  - Tandem ICA and MCA occlusion
  - Unsuccessful recanalization
  - Young patients
- Clinical red flag: decrease in consciousness!

48.2 Conservative Management

Approximately 5% of all ischemic stroke patients undergo mechanical ventilation, mainly due to impaired consciousness and/or diminished protective airway reflexes. Further

indications for mechanical ventilation include tachypnoe >25-30/min, bradypnoe <4-6/min, paO_2 <60 mmHG, paCO2 >55-60 mmHg or $Sa0_2$ <85-90% despite 100% oxygen mask therapy. Ventilation, preferably with pressure control mode, should be initiated with tidal volumina of 6-10 ml/kg and respiratory frequency of 12-15/min. PEEP levels of 5-8 mbar are considered safe. Higher PEEP levels should be delivered under close MAP, ICP and CPP monitoring due to the concerns that increased intrathoracic pressure by PEEP may critically lower MAP and CPP. I:E ratio seems not to have effects on ICP or CPP. Ventilation and oxygenation goals include $paC0_2$ 35-45 mmHg, paO_2 > 80 mmHg and SaO_2 >95%. Accurate blood pressure (BP) management in ischemic stroke is essential. Current guidelines advice not to lower BP until 220 mmHg systolic and/or 120 diastolic blood pressure is reached [5]. However, in severe brain edema with significantly increased ICP and impaired autoregulation, lower thresholds may be applied, dependent on the actual state of autoregulation, ICP a CPP levels. Common intravenous BP lowering agents include urapidil, propranolol, labetalol, enalapril and clonidine. Caution should be applied in vasodilatators as nitroglycerin and dihydralazine or calcium-channel blockers nifedipine and nimodipine as these agents may potentially increase the ICP by vasodilation. However, no study exists confirming these assumed effects in human stroke. Following the acute phase, usual enteral antihypertensive therapy including combinations of angiotensin receptor blockers, angiotensine-converting enzyme inhibitors, beta-blockers, calcium antagonists and diuretics should be initiated.

Best medical treatment for increased intracranial pressure (ICP) in malignant stroke does not differ from standard ICP management as performed in patients suffering from other causes of cytotoxic brain edema. In contrast to vasogenic edema, steroids are not recommended. When brain edema has progressed to the point that the patients need to be intubated and mechanically ventilated, placement of an ICP probe is advisable in order to monitor patients. Therapeutic targets are to maintain ICP below 20 mmHg and CPP around 60-70 mmHg. However, there is no clear evidence to support these thresholds. First steps to combat increased ICP include proper analgosedation, using standard medications such as continuous intravenous benzodiazepines or propofol in combination with opiates. Ketamine may also be used as long as arterial CO_2 and mean arterial pressure are controlled. Mild hyperventilation with an arterial CO_2 target around 30-35 mmHg may be applied but the possibility of unwanted side effects of vasoconstriction have to be taken into account, in particular in the yet uninjured areas. Long-term hyperventilation leads to compensatory mechanisms which counteract the effect of vasoconstricion and may trigger a rebound effect. Therefore, mild hyperventilation is only an option for short interventions. Elevation of the head to 30° may be considered but the effect on CPP has to be monitored.

Standard drugs include osmotherapeutics such as mannitol or glycerosteril. Long term application has been associated with a rebound phenomenon triggered by the osmotic substrates crossing to the brain parenchyma due to a damaged blood brain barrier. Hypertonic saline may be applied as well. Other options include tromethamine which via reduction of cerebral acidosis leads to vasoconstricsion or barbiturates as last tier therapy, leading to a decrease in cerebral metabolism and blood flow. Above mentioned measures frequently are used to bridge the time until the patient will be operated.

48.3 Decompressive Surgery

Decompressive hemicraniectomy represents the treatment of choice in malignant MCA infarction. Evidence for the benefical effect of decompressive surgery in patients be-

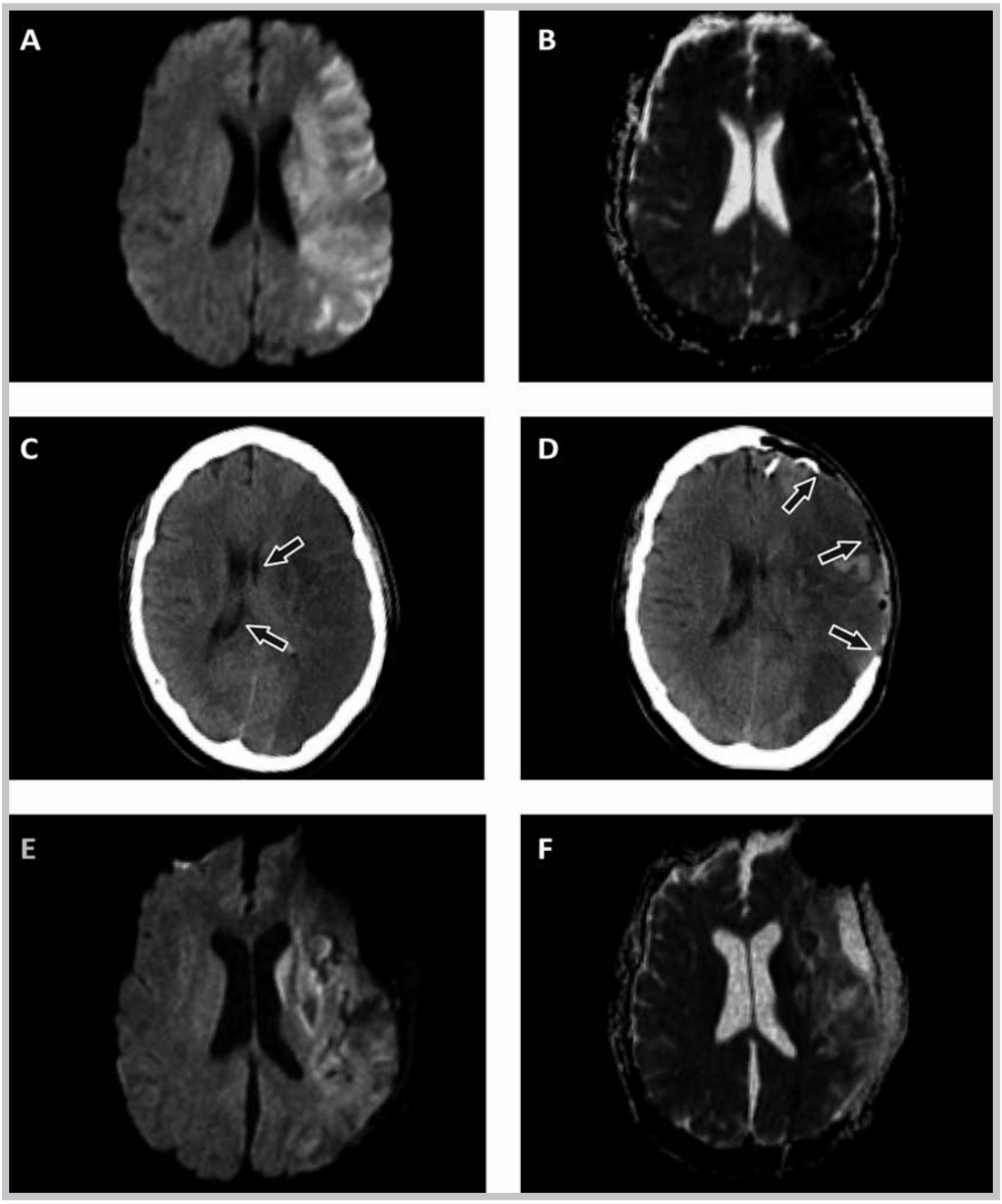

Figure 48.1. **Diffusion-weighted MRI (A) and corresponding ADC map (B) of a 53-year-old patient with aphasia and right-sided hemiparesis (NIHSS 19) show signs of cytotoxic edema indicating acute left-sided MCA infarction on admission. MRI-based thrombolysis was performed with 80 mg rt-PA 1 hour after symptom onset. (C) The follow-up CT scan at 24 hours shows signs of raised ICP with midline shift, compression of the lateral ventricles, and impending subfalcial herniation (arrows). Hemicraniectomy was performed 30 hours after symptom onset. (D) Postoperative CT scan: the vector of brain extension is reverted to the newly created compensatory space to relieve the pressure on midline structures. Follow-up diffusion weighted MRI scan (E) and ADC map (F) 16 days after hemicraniectomy show signal normalization and reduction of mass effect of the MCA infarction. The patient was transferred to a rehabilitation clinic 21 days after the infarction. At that time he was awake, had nonfluent aphasia, and brachio-facial hemiparesis on the right side (NIHSS 13). [Courtesy of M. Blatow, Department of Neuro-Radiology, University of Heidelberg].**

tween 18 to 60 years in malignant MCA stroke has been provided by three randomized trials including 93 patients (52 surgery with 48 hours, 41 conservative treatment) [6]. The primary outcome measure in these trials was the modified Rankin scale (mRS) at one year. The distribution of the mRS at one year differed significantly between the conservative and the operative group: 75% of patients in the surgery group had a mRS ≤4 compared to 24% in the conservative group. 43% of patients attained a mRS ≤3 in the surgery group versus 21% in the conservative arm. Mortality at one year was significantly different between groups: 78% of patients who underwent surgery versus 29% in the conservative group survived ($p<0.0001$). The number needed to treat (NNT) was 2 for survival with mRS ≤4, 4 for survival with mRS ≤3, and 2 for survival irrespective of functional outcome. However, despite a level 1A evidence recommendation in European guidelines, the potential neurological deficits should be discussed with the patient and/or the family and one should always consider the individual opinion of a patient facing survival with a severe neurological deficit.

Based on these persuading results, the DESTINY II study had been undertaken, assessing the benefits of decompressive surery in patients older than 60 years. The study has not been published yet, however, the preliminary results clearly suggest that also elderly patients may benefit from decompressive surgery.

Above mentioned studies have performed surgery within the first 48 hours after ictus. While several studies had suggested that early hemicraniectomy may be preferable, in a larger case series of 138 patients, age however has been the only factor relevant for outcome, while time to surgery had no effect [7]. Still, it seems advisable to identify patients at risk for maligant stroke as early as possible in order to minimize the risk of further brain injury. If a malignant course seems predictable and a consent regarding surgery is gained, the operation should be performed rapidly since waiting for further clinical deterioration carries no benefit.

48.4 Hypothermia

Due to the evidence from randomized trials for the benefit of decompressive surgery, application of mild (>33°C) or moderate hypothermia (29-33°C) for malignant brain edema following ischemic stroke has so far been abandoned. This is in line with the result of one study comparing decompressive surgery and hypothermia, concluding that hemicraniectomy was associated with lower mortality rates and complications than hypothermia [8]. The combination of hemicraniectomy with hypothermia is recently under investigation (DEPTH-SOS).

In contrast, the neuroprotective effects of mild hypothermia in the early phase after stroke have not been properly explored. Data from patients following cardiac arrest seem promising [9]. It is unknown and subject of current studies if early application of hypothermia may impede the development of malignant brain edema. At the moment, the use in awake stroke patients is being assessed.

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49 Acute Management of Cerebral Venous Thrombosis

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49.1 Introduction

Thrombosis of the dural sinus and cerebral veins is less common and has a more varied clinical presentation than other types of stroke. CVT is also more difficult to diagnose, as magnetic resonance imaging (MR) and venography are needed to confirm the diagnosis. Furthermore, CVT can be a manifestation of several systemic diseases, a complication of other central nervous system (CNS) disorders, of pregnancy or of the use of drugs with thrombogenic proprieties.

The most frequent symptoms of CVT are headaches, seizures, motor, sensory or language deficits, and altered consciousness. Acute seizures are more frequent in patients with supratentorial parenchymal lesions, sagittal or cortical vein thrombosis and motor or sensory defects.

Symptoms and signs can be grouped in four major syndromes:

- Isolated intracranial hypertension: headache with or without vomiting, papilledema and visual symptoms.
- Focal syndrome: focal deficits, seizures or both.
- Encephalopathy: multifocal signs, mental status changes, stupor or coma.
- Cavernous sinus: diplopia, ocular pain, cheimosis, proptosis, oculomotor palsies

The clinical presentation is influenced by:

- Site and number of occluded sinuses and veins:
  - Cerebral cortical vein thrombosis without dural sinus involvement can cause focal seizures, motor or sensory deficits with or without headache.
  - In occlusion of the sagittal sinus, motor deficits, bilateral deficits and seizures are frequent.
  - Patients with isolated thrombosis of the lateral sinus often present with isolated intracranial hypertension or isolated headache; aphasia is frequent if the left transverse sinus is involved.
  - If the deep cerebral venous system is occluded, the clinical picture is usually more severe, with coma, mental symptoms and bilateral motor deficits.
- Presence of parenchymal lesions:
  - Patients with parenchymal lesions are more likely to be comatose or to have motor deficits or aphasia and seizures.
- Age of the patient:
  - Decreased vigilance and mental symptoms are more common in elderly patients.
  - Headaches and isolated intracranial hypertension are more frequent in younger patients.
- Gender: headaches are more common in women.
- Interval from onset to presentation:
  - Patients with a chronic or subacute course are more likely to present with isolated intracranial hypertension and to show papilledema.

Concerning prognosis, several recent prospective series and systematic reviews consistently established the current vital and functional prognosis of patients with acute CVT, showing a 15% overall death or dependency rate. The predictors of poor long-term prognosis derived from the ISCVT cohort were:

- Age >37 years.
- Male gender.
- Glasgow Coma Scale (GCS) score on admission <9.
- Mental status disorder.
- Deep cerebral venous system thrombosis.
- Hemorrhage on CT/MR.
- CNS infection.
- Malignancy.

This predictive model was validated in two other cohorts.

The acute case-fatality is low (4%). Predictors of mortality at 30 days are depressed consciousness, mental status disorder, thrombosis of the deep cerebral venous system, right hemispherical hemorrhage and posterior fossa lesions. The main cause of death is transtentorial herniation secondary to a large hemorrhagic lesion. Other causes include herniation due to multiple lesions or to diffuse brain edema, status epilepticus, medical complications and pulmonary embolism.

Recanalisation occurs in 40-90% of patients, mostly within the first 4 months, but is not related to outcome. Long-term complications of CVT include seizures, headaches, vision loss, dural arteriovenous fistulae and recurrent venous thrombosis of the brain, extremities or pelvis. Recurrent CVT is rare (2-7%) and also difficult to document, particularly if a previous follow-up MR/MRV is not available. In the Rochester Mayo Clinic series, the likelihood of recurrent venous thrombosis was the same after CVT and lower extremity deep venous thrombosis. Recurrence of CVT was not influenced by warfarin therapy. In children, age at CVT onset (>2 years), persistent venous occlusion, the G20210A mutation and non-administration of anticoagulation predict recurrent CVT or systemic venous thrombosis.

49.2 Confirmation of Diagnosis by Neuroimaging

Confirmation of diagnosis of CVT by neuroimaging implies the visualization of an occluded sinus or vein and of the thrombus. MR combined with MR venography (MRV) is the most sensitive examination technique for the diagnosis CVT. However, even using MR plus MRV, there are some diagnostic difficulties particularly concerning the diagnosis of cortical vein thrombosis, which has a low interobserver reliability. Gradient echo (GRE) T_2* weighted sequences with thrombus susceptibility effect (SE) should always be performed if the working diagnosis of CVT is raised. T2* SE images show the thrombus, including an isolated cortical vein thrombosis, as a hypointense area. Multidetector CT venography (CTV) can be used as an alternative to MRV, with an excellent sensitivity and specificity for the diagnosis of CVT.

49.3 Etiological Investigation

The most frequent causes or associated conditions with CVT are listed in Table 49.1. The relative weight of these causes varies accordingly to world regions. In countries with low

Gross National Income, infection, anemia and puerperium-related CVT are more common.

More than half of patients have more than one cause for their CVT, while in about 15% no cause can be found despite extensive investigation. Some rules of thumb are suggested during the etiological workup:

- Systematic prothrombotic screening must always be performed, even when an "obvious" cause is already detected.
- Prothrombotic screening includes: protein S, C, anti-thrombin III, factor V Leiden and prothrombin G20210A mutations, homocysteine, lupus anticoagulant, anticardiolipin and anti-phospholipid antibodies.
- In middle aged and elderly patients a comprehensive search for a malignancy should be performed.
- When no underlying cause can be found, a high anticardiolipin antibody titre, a vasculitis or a malignancy can be found in a repeated evaluation 3 to 6 months after the acute phase of CVT.

Series	ISCVT	Pakistan and Middle East
Nr. of patients	624	109
Genetic thrombophilia	22%	12%
Antiphospholipid antibodies	6%	1%
Hyperhomocysteinemia	5%	9%
Malignancy	7%	4%
Anemia	9%	NA
Pregnancy*	6%	NA
Puerperium*	14%	31%
All infections	12%	18%
ENT, face and neck infections	8%	12%
Oral contraceptives*	54%	12%

Table 49.1. Common (>5%) causes of cerebrovenous thrombosis [Ferro, 2004; Khealani, 2008].

* among women
ENT = ear, nose and throat
ISCVT = International Study on Cerebral Vein and Dural Sinus Thrombosis
NA = not available

49.4 Treatment in the Acute Phase

Management of acute CVT includes:

- Treatment of the underlying condition.
- Antithrombotic treatment.
- Symptomatic treatment.
- Prevention and treatment of complications.

Antithrombotic and symptomatic treatment are discussed in the following paragraphs.

49.4.1 Antithrombotic Treatment

Anticoagulation

Currently, there is broad consensus on the use of either IV heparin or SC low-molecular-weight heparin (LMWH) in acute CVT to prevent thrombus propagation and pulmonary embolism and to increase the chances of recanalisation. The use of heparin in acute CVT is supported by three clinical trials and a meta-analysis of two of these trials which showed a relative risk of 0.46 (95% CI 0.16-1.31) of death or dependency after anticoagulant therapy as compared to placebo. Several observational series showed that heparin is safe and can be used in acute CVT patients with intracranial hemorrhagic lesions. Limited data suggest that anticoagulant therapy is also safe in children with CVT.

Procedure	• Catheterization of the sigmoid, transverse and superior sagittal sinuses via the femoral venous or jugular approach • Chemical thrombolysis: ▪ Urokinase, suggested dosage: bolus 100,000 to 600,000 IU, followed by infusion of 100,000 IU/h during 24 hours or longer if needed or ▪ rtPA Bolus: 1-5 mg followed by infusion: 1-2 mg/h during 24 hours or longer if needed • Mechanical thrombolysis by disruption (guiding catheter), removal (balloon catheter) or suction (rheolytic catheter) may be performed according to local experience and preferences
Contraindications	• Documented bleeding disorder • Thrombocytopenia (<100,000/l) • Severe liver or renal dysfunction interfering with coagulation • Acute pancreatitis • Oesophageal varices • Uncontrolled severe hypertension (diastolic >120 mmHg) • Recent bleeding diathesis (<3 months) • Recent (<24 h) surgery
Main side effects	• Risk of bleeding, including puncture site* • Hemorrhage from tissue or organ* • Pain due to dural sinus manipulation • Hypofibrinogenemia • Nausea and vomiting

Table 49.2. **Local thrombolysis with urokinase or rtPA (treatment may be modified according to local procedures).**
* In case of serious bleeding, thrombolytic administration should be discontinued and administration of coagulation factors may be required

Endovascular Thrombolysis

Endovascular thrombolysis, with or without mechanical thrombus disruption, is used in some centres as an alternative to heparin in severe cases or in patients who fail to improve on anticoagulation. Direct thrombolysis aims to dissolve the venous clot by delivering a thrombolytic substance (urokinase or rtPA) within the occluded sinus through an intravenous catheter. In some cases, mechanical endovascular disruption of the thrombus may also be used. No randomized trials of endovascular treatment for sinus thrombosis have been done. In a systematic review, new symptomatic intracranial hemorrhages were reported in 5% of patients and a poor outcome in 13% of those treated with thrombolytics (mortality 9%, dependency 4%). Intracranial hemorrhage after thrombolysis was reported in 17% of cases, and was associated with clinical worsening in 5%. However, the possibility of publication bias must be kept in mind. In a recent Dutch series of 20 patients treated with IV local thrombolysis, 12 recovered to independent living and 6 died. Local thrombolysis was not useful in patients with large infarcts and impending herniation. A randomized trial to compare endovascular treatment vs. heparin in acute CVT was recently launched. Before such a trial is completed, endovascular treatment cannot be routinely recommended and should be reserved for critical cases which fail to improve on anticoagulation and do not have an indication for decompressive surgery.

49.4.2 Symptomatic Treatment

Treatment of Intracranial Hypertension

In patients with severe headache and papilledema, intracranial hypertension can be reduced and symptoms relieved through a therapeutic lumbar puncture. Despite the lack

In all cases	• Anticoagulation in therapeutic dosages with IV heparin or SC LMWH, except in patients with systemic contraindications for anticoagulation • Headache relief with paracetamol or tramadol • Treatment of underlying and associated systemic or CNS conditions
In cases presenting with isolated headache or intracranial hypertension syndrome	All the above plus: • Headache relief if needed with acetazolamide or therapeutic lumbar puncture
Cases with seizures	• Start valproate
Cases with symptomatic large hemispheric ischemic or hemorrhagic lesions with mass effect	• Osmotherapy with mannitol • Consider hemicraniectomy, if impending transtentorial herniation
Cases with encephalopathy or comatose, with diffuse brain edema or bilateral ischemic or hemorrhagic lesions	• Osmotherapy with mannitol • Consider hemicraniectomy, if impending transtentorial herniation due to one unilateral lesion • Intensive care unit admission with sedation, hyperventilation to a target $PaCO_2$ of 30 to 35 mmHg, and ICP monitoring • Consider local endovascular thrombolysis with urokinase or rtPA

Table 49.3. **Treatment of CVT according to clinical presentation and neuroimaging findings.**

of randomised trials, acetazolamide is also used in some centres to relieve symptoms (headache, vision loss) of increased intracranial hypertension.

General recommendations to control acutely increased intracranial pressure (ICP) include elevating the head of the bed, osmotic diuretics such as mannitol, intensive care unit admission with sedation, hyperventilation to a target arterial carbon dioxide tension ($PaCO_2$) of 30 to 35 mmHg, and ICP monitoring. Corticosteroids are not indicated, unless they are needed to treat the underlying condition.

Hemicraniectomy may be life-saving in patients with parenchymal lesions producing impending herniation. The surgical procedure should include the removal of a large cranial bone flap over the whole area of the parenchymal lesion, opening of the dura and insertion of a dural patch. Cranioplasty is performed after at least 6 weeks with the stored bone flap or acrylate.

A recently published retrospective registry and systematic review of published cases indicates that decompressive surgery (hematoma evacuation or hemicraniectomy) is life saving in acute CVT patients with large hemispherical or posterior fossa lesions and impeding herniation, even in patients with severe neurological condition, such as coma or fixed pupils. Complications of hemicraniectomy include intracranial bleeding, infection, hydrocephalus and depressed skull bone defect.

A lumboperitoneal shunt (at the L2-3 or L3-4 level) is indicated in patients with persistent symptoms of increased intracranial hypertension and/or vision loss who do not improve with repeated lumbar punctures. Complications of this procedure include shunt block or other malfunctioning, infection, cerebrospinal fluid (CSF) leakage with intracranial hypotension and radiculopathy.

Treatment and Prevention of Seizures

Acute seizures and supratentorial lesions are the risk factors for subsequent early seizures. Patients with both risk factors should be prescribed antiepileptic drugs. Prophylactic antiepileptics can also be considered in patients with one of these risk factors and should be avoided in patients with neither of the two. Concerning the choice of the antiepileptic, phenytoin, carbamazepine or valproate are possible first-line options. Val-

proate is preferred because it causes less interference with oral anticoagulants and can be used intravenously. If phenytoin, carbamazepine or valproate is not tolerated, lamotrigine, topiramate or leviracetam can be used as alternatives.
Patients with status epilepticus should be treated according to guidelines for this epileptic condition: 3-stage approach with immediate administration of diazepam or lorazepam IV, followed by phenytoin or phosphenytoin IV and by barbiturate coma if the epileptic activity does not stop.
As described above, CVT has a wide spectrum of clinical and symptomatic presentations. Management in the acute phase should be tailored to the severity, clinical syndrome and neuroimaging findings of the individual patient (Table 49.3).

49.5 Education and Medication Upon Discharge

To reduce the risk of recurrent thrombotic events, namely, deep venous thrombosis of the limbs, treatment with oral anticoagulants, aiming at an international normalized ratio (INR) between 2 and 3, is given for a variable period depending on the patient's inherent thrombotic risk. Anticoagulants can be prescribed for only 3 months if CVT was related to a transient risk factor (e.g., pregnancy, infection). In patients with idiopathic CVT or CVT associated with "mild" thrombophilia, the period of anticoagulation must be extended for 6 to 12 months. In patients with "severe" thrombophilia (e.g., two or more prothrombotic abnormalities; antiphospholipid syndrome), anticoagulants should be given for life.
Patients with persistent symptoms of increased intracranial hypertension and/or vision loss can be treated with repeated lumbar punctures or a lumboperitoneal shunt.
Antiepileptics are recommended for patients with seizures in the acute phase and for those who experience a seizure after the acute phase. Antiepileptics can also be considered for patients without seizures but with either supratentorial hemorrhagic lesions or motor deficits.
Oral contraception and hormonal replacement therapy should be stopped. Emergency contraception is also contraindicated. Women of reproductive age should not become pregnant while on oral anticoagulants because of the teratogenic effects of these drugs. CVT and pregnancy or puerperium-related CVT are not a contraindication for future pregnancy. Although pregnancy and the puerperium are risk factors for CVT, the risk of complications during a subsequent pregnancy among women who have a history of CVT is low.

49.6 Key Concepts

Consider the possibility of CVT in patients with unexplained severe headaches of recent onset, new seizures or encephalopathy.
Use MR with T2* sequences and veno-MR to confirm the diagnosis of CVT.
Always perform thrombophilic screening, even when CVT is associated with a transient risk factor.
Anticoagulation is indicated in all cases, even if there are intracranial hemorrhages, except if there are systemic contraindications.
Endovascular thrombolysis should be reserved for critical cases which fail to improve on anticoagulation and do not have an indication for decompressive surgery.
Hemicraniectomy may be life-saving in patients with large venous infarcts or intracerebral hemorrhages causing eminent herniation.

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50 Diagnosis and Treatment of Intracerebral Hemorrhage

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50.1 Introduction

Intracerebral hemorrhage (ICH) occurs in 1 or 2 out of 10 patients with cerebrovascular disease (CVD), being more frequent in adults with hypertension. ICH is the less studied type of CVD and generally the most stigmatized by nihilism and fatalism; for that reason it is considered by some authors as "the great forgotten one", in spite of its high (50%) mortality observed in the acute phase and the incapacitating sequelae at 6 months in 20 to 30% of survivors.

Cranial computed tomography (CT) is still the best basic tool to guide ICH diagnosis, its etiology, therapeutic approach and prognosis. Current and future topics in the management of ICH include a rigorous versus standard control of blood pressure, pharmacologic and non-pharmacologic neuroprotection, the handling of peri-hematoma edema and the use of hemostatic therapies. The role of surgery in ICH is uncertain; however, clot fibrinolysis and minimal invasion drainage system are promising approaches.

50.2 Definition

ICH, also known as intraparenchymal brain hemorrhage, spontaneous intracerebral hemorrhage or nontraumatic intracerebral hemorrhage, refers to a hematic collection within the parenchymal tissue ensuing from the irruption of blood, the etiology, location and volume of which depend largely on patient age and other risk factors [1].

ICH occurs most often as a sudden nonconvulsive neurological deficit, with increasing severity after the onset. CT findings of ICH can appear as a hyperdense parenchymal area of variable dimension, with a supra- or infratentorial location, with or without mass effect over the cerebral structures, midline deviation with or without irruption into the ventricular system. Primary or spontaneous ICH occurs in the absence of trauma or pre-existing cerebrovascular malformations (CVM); in adults and the elderly almost 85% is due to hypertension or amyloid angiopathy.

50.3 Epidemiology

The frequency of ICH has been reported in 5 to 19% of all CVD types, predominantly in adult males [2]. In the United States, the highest incidence is among Blacks (50/100.000 habitants), Asians, and Hispanics as compared to Whites (incidence of 25/100,000 habitants) [2-5].

In Latin America, owing to the lack of ICH data from hospital registries, its frequency is estimated to be 19 to 50% [6-9]. Lavados et al., in their study in Chile, reported an incidence of 27.6/100,000 habitants, with an increase related to age; in people <35 years of age it was reported in 4.3/100,000 habitants, it increases up to 84.4/100.000 in patients aged 55 to 64 years, and reaches 204.2/100,000 in those >75 years [10].
Notwithstanding the lack of data, the frequency of ICH is projected to double by the year 2050, due to shifts in racial demography and the aging population [11-13].

50.4 Risk Factors

Hypertension, the leading risk factor for ICH, is reported in over 60% of cases, mainly when untreated or treatment is irregular, associated with smoking, and occurs before 55 years of age [1,12]. Alcoholism is associated with ICH by altered coagulation mechanisms and blood vessel integrity resulting from chronic alcohol consumption or acute intense intake [1,12]. Smoking has been associated more frequently with subarachnoid hemorrhage; nevertheless, it has also been associated with ICH [14].
The role of hypocholesterolemia as an independent risk factor for ICH is controversial, being apparently relevant only in hypertense subjects with factor XIII-alpha coagulation system mutation [15]. Congophilic angiopathy is associated with ICH due to β-amyloid protein deposition in the walls of the cortical-leptomeningeal vessels [1,12], usually occurring in persons over 55 years of age without hypertension, predominates in lobar topography, is highly recurrent, and can be multiple when ICH is present. Apolipoprotein-E seems to play a key role in the pathogenesis of amyloid angiopathy and the genotype in its recurrence (Figure 50.1).
Other risk factors for ICH such as caffeine consumption and illicit drugs use, obesity and antiplatelet therapy are areas of recent analysis. Anticoagulants usually are associated with large hemorrhages and high mortality.

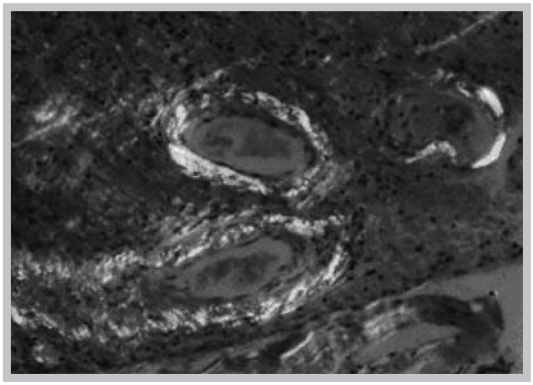

Figure 50.1. **Congophilic deposits characteristic of amyloid angiopathy.**

50.5 Clinical Diagnosis

Clinical manifestations of ICH depend on the location of the hematoma, its initial volume and growth, aperture to the ventricular system, as well as mass effect and midline deviation. Patients with ICH usually present with severe neurological impairment after the onset and can worsen in the first hours. Headache, altered consciousness, motor or sensory deficit and seizures are frequent in supratentorial ICH, whereas headache, dizziness, vomits, ataxia, ophthalmoparesis and deterioration of consciousness with or without motor signs are proper to infratentorial ICH. Because its clinical presentation can also occur in ischemic CVD, neuroimaging studies are essential to differentiate between these possibilities.

50.6 Neuroimaging Diagnosis

50.6.1 Computed Tomography

Simple phase CT easily distinguishes ICH from cerebral infarct (Figure 50.2). It practically detects 100% of hematomas, except when <1 cm, located in the posterior fossa or in those patients with severe anemia (hematocrit <20) [16].
Contrast-enhanced CT is not necessary in acute stage ICH and its indication should be reserved for specific cases depending on hematoma location, the presence of edema and other features suggestive of vasculitis, rupture of CVM or intra-tumor bleeding [1,16].
Besides its utility in determining hematoma size and location, CT also allows the follow-up of complications, including cerebral herniation, midline displacement, cistern and brainstem compression, opening to the ventricular system, hydrocephalus, rebleeding, peri-hematoma and delayed edema.

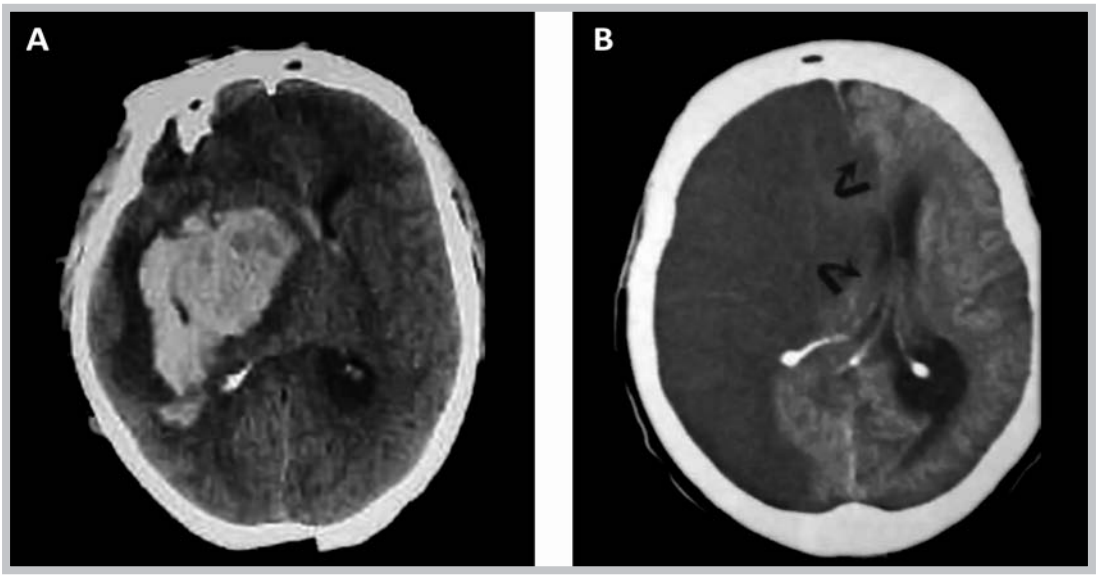

Figure 50.2. **(A) CT scan with massive right ganglia hemorrhage. (B) Right hemispheric infarct. Both images show pronounced mass effect and midline displacement.**

Location

Topography considers the epicentre as the site where the hematoma originates. For a more precise location, we must clarify whether the ICH is supra- or infratentorial. In supratentorial ICH, a lobar hematoma (frontal, temporal, parietal, occipital); basal ganglia (putamen, caudate nucleus, thalamus, striato-insular) or intraventricular location must be specified. Infratentorial ICH is localized in the brainstem (midbrain, pons, medulla) or the cerebellum (Figure 50.3).

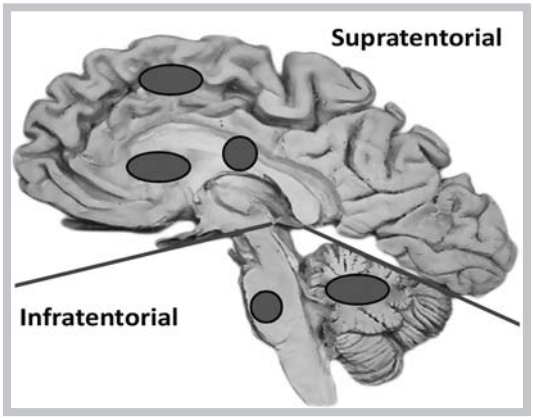

Figure 50.3. **Supra- and infratentorial locations of intracerebral hemorrhage.**

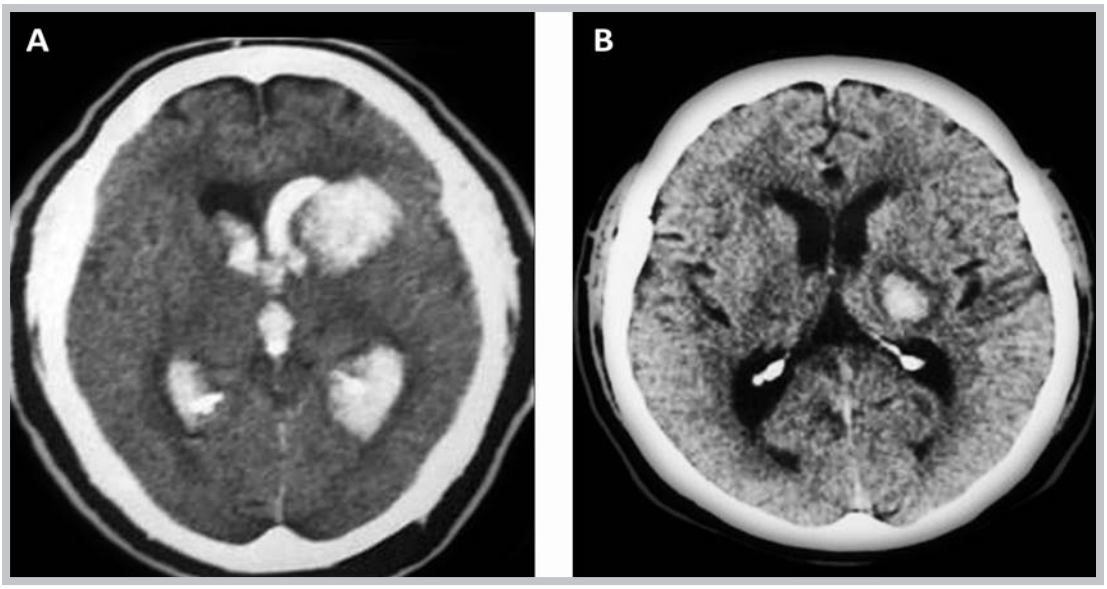

Figure 50.4. (A) Intracerebral hemorrhage with and (B) without ventricular aperture.

Ventricular Opening

Irruption of blood into the ventricular system has been associated with poor prognosis, which is why it is important to establish its presence or absence, to identify the ventricles involved, and determine its volume if possible [17] (Figure 50.4).

Intraventricular hemorrhage volume can be measured with the use of sophisticated CT scan software; however, because of its infrequent use, it is recommended to calculate the Graeb´s index [17]. Mild=1-4; moderate=5-8; severe=9-12 (Table 50.1).

	Score
Lateral ventricles (each ventricle apart)	
Blood traces in the ventricle	1
Blood fills less than half of the ventricle	2
Blood fills more than half of the ventricle	3
Lateral ventricle is full and expanded	4
Third and fourth ventricle (each ventricle apart)	
Blood is present in the ventricle	1
Ventricle is full and expanded	2

Table 50.1. Graeb's index to calculate intraventricular hemorrhage extent.

Volume

Hematoma volume is an important predictor of mortality, making its measurement necessary. As in intraventricular hemorrhage, the use of CT software allows the quantification of hematoma volume; however, since institutions may lack CT scan tools, a knowledge of alternative methods to calculate hematoma volume is needed. The most useful and common method is the ABC/2 formula (considering ICH as an ellipsoid or a football) [18,19]. The major diameter of hemorrhage (A) is multiplied by its perpendicular major diameter (B), times the number of sections (in cm) in which the hemorrhage appears on the CT scan (C), and the final product is divided by two. To calculate the value of C, the CT

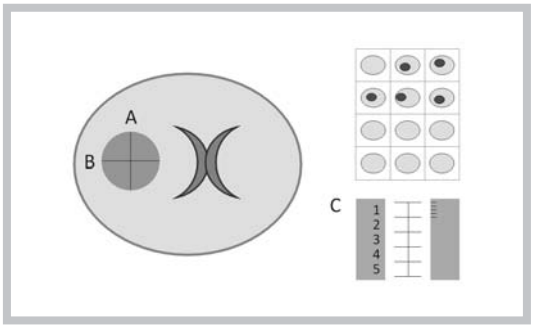

Figure 50.5. Calculation of hematoma volume with the ABC/2 formula.

slice showing the largest hematoma is taken as a reference (100%) and the smallest as 25%, because the size of the hematoma will appear different on the sequence of CT scans; if a subsequent section of the reference slice shows a hematoma half its size, the value is corrected by giving this section 0.5 cm (Figure 50.5).

Density and Shape

A recent analysis of the treatment of ICH with activated Factor VII proposed that a strong predictor for hematoma expansion is irregularity in the shapes and edges of the hemorrhage, as well as heterogeneity in its density [20]. This issue will be discussed later.

Other Tomographic Characteristics of ICH

Imaging findings vary depending on the evolution of the hemorrhage over time. In the hyperacute stage (first 4 hours), the extravasated blood has not yet formed a clot, producing an irregular hyperdense collection within the cerebral parenchyma. The presence of a blood-fluid level suggests an ICH in a very early phase, hemorrhage within a pre-existing cavity, or a hemorrhage due to coagulopathy or fibrinolytic therapy. In the acute phase (5 to 72 hours), a pre-existing hematoma becomes dense due to clot formation [21].

50.6.2 Computed Angiotomography (CTA)

CTA is an alternative non-invasive tool to angiography and magnetic resonance angiography (MRA), with the disadvantage that it requires contrast material and prolonged processing time. Nevertheless, a recent finding during the procedure (within the first 3 hours of ICH) termed “spot sign”, has been proposed as a strong predictor of hematoma expansion. The sign consists of a small “spot” or “point” inside the hematoma and suggests active bleeding from Charcot microaneurysms or from vessels with vascular damage [22].

50.6.3 Angiography

Angiography should be reserved for patients without a clear cause of ICH, especially in young normotensive patients, subjects with hemorrhage opened to the subarachnoid space, in those with prominent vessel structure as evidenced by CT or MR, when a vasculitis is suspected or in cases of sympathomimetic drug use [16,23,24]. Angiography is also recommended in patients with primary intraventricular hemorrhage and in those with perisylvian sulcal or fronto-orbital hemorrhage to dismiss the presence of aneurysms [16,23].

50.6.4 Magnetic Resonance and Magnetic Resonance Angiography (MRI, MRA)

These imaging studies are recommended in aged patients with absolute or relative contraindications to angiography due to blood dyscrasias, anticoagulant use, absent femoral pulse, severe atherosclerosis, as well as contraindication of the use of contrast material in patients with renal failure or multiple myeloma [16,23].
MR provides more information than CT about the hematoma borders, peri-hematoma edema and mass effect over other structures. It also helps to evaluate the dam-

age associated with the hematoma and to define its possible mechanism, for example: arteriovenous malformation (heterogeneous image with empty signals and calcifications), intratumoral bleeding or cavernous angioma [16,23-27]. The disadvantages of MR include long procedural time, contraindication in persons with metal prosthesis, pacemaker wearers, or in those under mechanical respiration or multimonitoring.

MR with gradient-echo (also T2*) has proved an important tool in the study of quiet focal damage that corresponds histopathologically to hemosiderin deposits, termed micro-hemorrhages or microbleeds. Lobar microbleeds have been related to amyloid angiopathy, whereas ganglionar microbleeds have been associated with hypertension [28].

50.6.5 Histopathologic Study

In all patients with hematoma evacuation or autopsy, it is mandatory to confirm the etiologic diagnosis. The sample must include the wall of hematoma and blood vessels. Congo red tissue staining is necessary in elderly subjects to confirm amyloid ICH [29].

50.7 Etiology of Intracerebral Hemorrhage

Hypertension is the main cause of ICH, explaining 60-80% of cases. Hypertension places arterioles (100 to 300 microns in diameter) under constant mechanical stress, leading to hyperplasia of smooth muscle cells which results in atherosclerosis [1,12] (Figure 50.6).

Over time, the muscle cells die and are replaced by collagen tissue (lipohyalinosis), leading to ectasia and occlusion (principal substrate of infarcts) and the formation of Charcot-Bouchard microaneurysms (considered today as the origin of ICH) (Figure 50.7) [1,12].

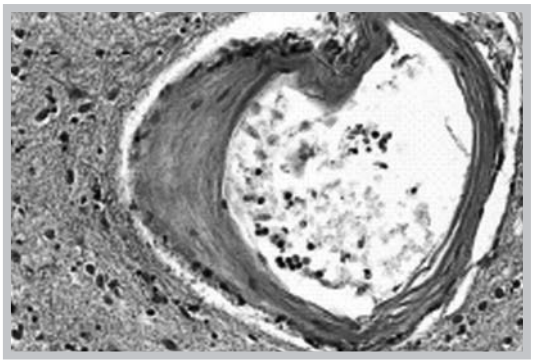

Figure 50.6. **Arteriole in which the muscle wall has been replaced by collagen.**

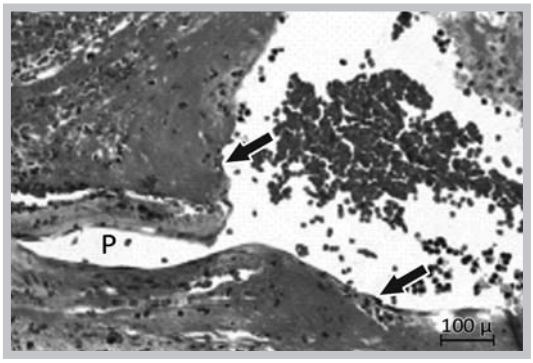

Figure 50.7. **Charcot-Bouchard aneurysm evidenced from tissue obtained after putaminal hematoma evacuation.**

P = vessel of microaneurysm origin

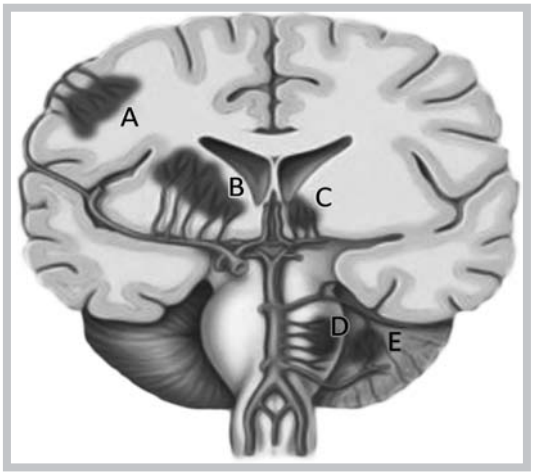

Figure 50.8. **Location of hypertensive ICH hemorrhage. Reproduced with permission of Qureshi [12].**

A = lobar
B = basal ganglia
C = thalamus
D = protuberance
E = cerebellum

The most common sites for arteriolar damage are the bifurcation of penetrating vessels such as the lenticulostriatal, the thalamic perforating arteries, and the brainstem penetrating arterioles. Previous changes match the common topography of ICH in the basal ganglia (35-45%), cerebral lobes (20-25%), thalamus (10-15%), cerebellum (5-10%) and pons (5%) (Figure 50.8).

Other ICH-associated conditions are CVM rupture, hematological dyscrasias, anticoagulants or antiplatelet use, intratumoral bleeding, cerebral venous thrombosis, alcohol intake, legal or illegal use of sympathomimetic drugs, primary or secondary vasculitis of the central nervous system (CNS) and endocarditis [1,12]. When the cause cannot be defined due to inconsistent or insufficient findings, ICH is considered as undetermined. When all diagnostic procedures are negative, the etiology is considered cryptogenic or idiopathic. Uncommon causes of ICH are listed in Table 50.2 [1,12].

In a daily practice, ICH location, patient age plus other associated conditions may suggest a possible etiology. For example, lobar ICH in a young patient is strongly suggestive of a CVM rupture; whereas lobar ICH in a non-hypertensive aged subject leads to consider amyloid angiopathy [1,12,30,31].

In a fronto-orbital ICH, it is mandatory to discard aneurysmal rupture, mainly in the presence of interhemispheric or basal subarachnoid hemorrhage. A hematoma with important perilesional edema will orientate toward discarding brain tumor as a cause of ICH. Basal ganglia hemorrhage in a young pregnant woman with pre-eclampsia is highly suggestive of a hypertensive cause or puerperal vasculopathy; in such patients a lobar ICH location must orientate toward considering cerebral venous thrombosis (Table 50.3).

- Associated with “cold”
- Associated with migraine
- Electroconvulsive therapy
- Human Immunodeficiency virus (HIV) infection
- Toxoplasmic encephalitis (in patients with HIV)
- Diabetic ketoacidosis
- Disulfiram (Antabuse) effect
- Scorpion sting
- Electrocution
- Neurocysticercosis (intracyst bleeding or vasculitis)
- Dental procedure (“dentist chair hemorrhage”)
- Puerperal vasculopathy
- Moya-moya disease
- Methanol intoxication
- Marijuana
- Associated with nightmare
- Cerebrospinal fluid overdrainage

Table 50.2. Uncommon causes of ICH.

Age	Location	Etiology
Young age	Lobar	CVM
Age >55 not hypertensive	Lobar	Amiloid angiopathy
Adult patient	Ganglionar	Hypertension (78-88%)
Young age	Ganglionar	Hypertension (11%)
Adult hypertensive	Lobar	Hypertension (20-30%)
Young age	Cerebellum	CVM
Adult hypertensive	Cerebellum	Hypertension
Young/toxemia	Ganglionar	Hypertension
Young/puerperium	Lobar	Cerebral venous thrombosis
Elderly subject	Any location	Tumor

Table 50.3. Etiology by age and location of ICH plus perilesional edema.

50.8 Pathophysiology of ICH

ICH is a dynamic and complex process of simultaneous or consecutively interrelated events which can be grouped into the following phases:

a. Hematoma formation. This occurs whitin the first 60 minutes. Irruption of blood into the brain destroys the parenchymal tissue, alters intracerebral homeostasis, triggers an increase in local pressure with mass effect, leading to displacement of vectors and distortion of intracranial structures. In addition, the hemorrhage by itself is the source of three other deleterious events: cellular death by necrosis and apoptosis, inflammation and vasogenic edema [32-42].

b. Hematoma expansion. In 38% of patients, hematoma continues to grow after the initial event in the first 3 hours, which is associated with neurological deterioration and poor prognosis. In two thirds of such cases, hemorrhage expansion is already evident in the first hour (Figure 50.9) [43].

Hematoma expansion occurs in the absence of coagulopathies. Although the mechanisms by which this occurs are not yet fully understood, it seems to be due to continuous bleeding from the initial site of the ICH or by small "satellite" hemorrhages in the periphery of the clot [44,45].

Other risk factors or conditions contributing to hematoma growth are issues of meticulous analyses, both in clinical and molecular scenarios, and they represent an opportunity area for therapeutic interventions. Alcohol abuse, hyperglycemia, reduced prothrombin activity, hypofibrinogenemia and liver diseases have all been associated with this phenomenon [43,46]. The "spot sign" as evidenced by CTA, early hematoma density and shape are predictors of hematoma expansion that require further studies to confirm its precise value [20,28].

c. Edema. It appears after 24 hours around the hematoma and reaches its major expression at the fourth day, before slowly decreasing [32,33,35-37,39-42,45]. Severe edema develops mainly in the white matter, is primarily vasogenic, and results from increased blood-brain barrier permeability due to its destruction or dysfunction and the action of

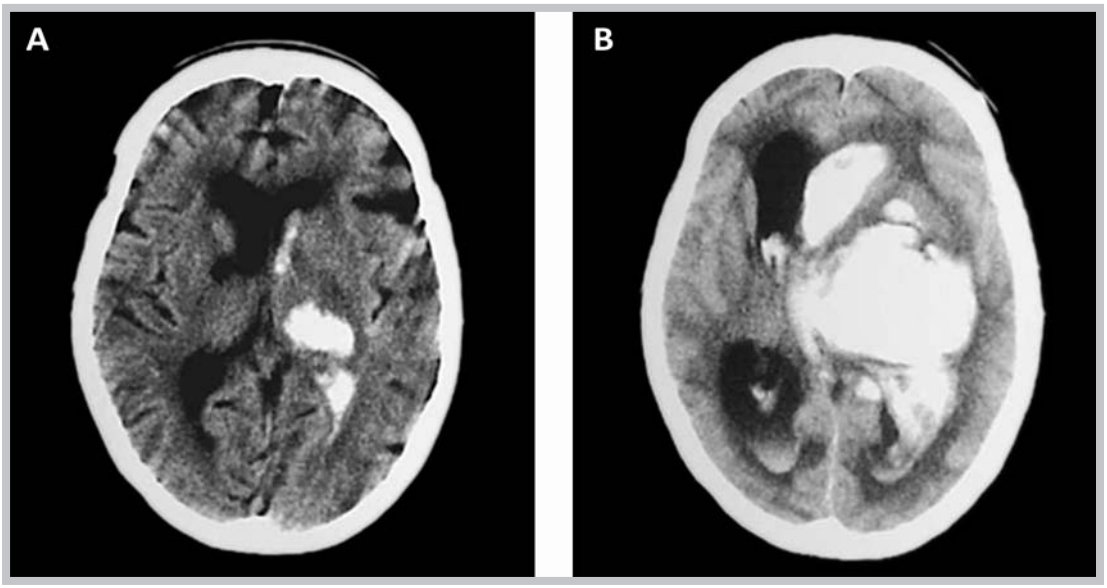

Figure 50.9. Hematoma expansion observed in the first hours.

neurotoxic substances like thrombin or metalloproteinases released from the extracellular matrix.

For many years, "peri-hematoma'' edema was considered as an "ischemic penumbra'' area, similar to that present in cerebral infarcts; nevertheless, SPECT (single-photon

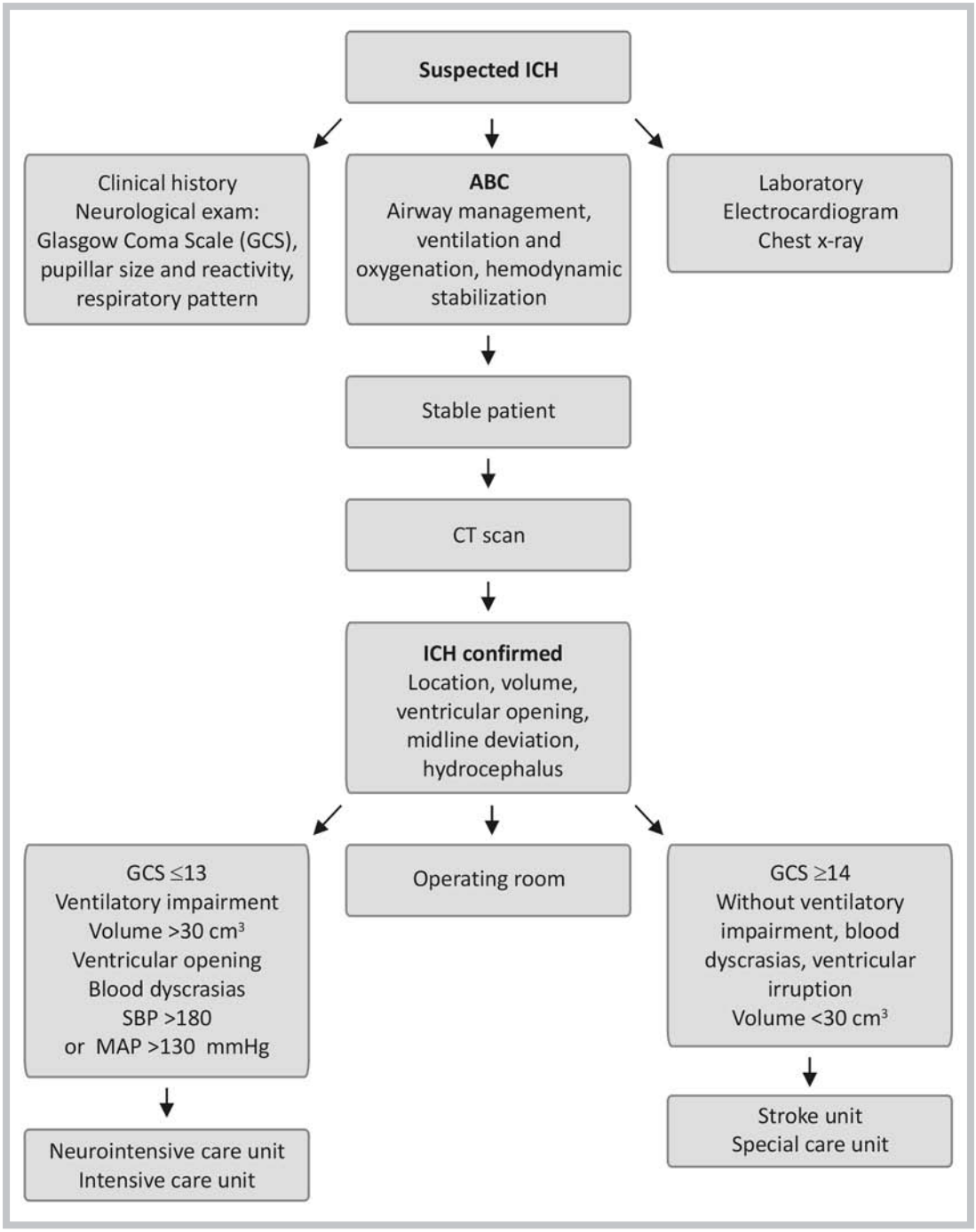

Figure 50.10. **Initial management of intracerebral hemorrhage.**
SBP= systolic blood pressure
MAP= mean arterial pressure

emission computed tomography), PET (positron emission tomography), diffusion-perfusion MRI techniques and microdialysis have all reliably concluded that this zone corresponds to a regional reduction in brain blood flow resulting from the concomitant decrease in metabolic demand or the presence of mitochondrial dysfunction [35,36,41,47].

50.9 Medical Treatment of ICH

The treatment for all types of ICH is medical, possibly surgical, and will preferably be carried out in a neurointensive care unit [48]. For surgical approaches, patient age and co-morbidities are important issues, as are the neurological status at emergency room arrival, hematoma location and volume, displacement of midline structures, ventricular irruption, hydrocephalus, etiology and patient or family end-of-life preferences [1,12,23]. In spite of these variables, some of which easily measurable, ICH treatment remains uncertain [49,50].

50.9.1 Initial Treatment of ICH

The objective is to reduce intracranial pressure and to avoid neurological and systemic complications [23,27]. Management begins with general measures (ABC approach), airway control for optimal ventilation and oxygenation for hemodynamic stabilization. A brief neurological examination must include assessment with the Glasgow Coma Scale (GCS) or the National Institutes of Health Stroke Scale (NIHSS), as well as the evaluation of pupillar form, size and reactivity, together with the respiratory pattern. The decision whether to institute endotracheal intubation is based on clinical judgment, since its delay aggravates the pre-existing neurological damage and increases morbidity and mortality as a result of the secondary insult from hypoxemia, hypercapnia or aspiration pneumonia [11,39,43,44,51-59].

Hypotension needs to be immediately corrected with iso- or hypertonic fluids, colloids and amines such as phenylephrine, dopamine or norepinephrine to maintain adequate cerebral perfusion pressure. The following laboratory parameters must be obtained: hemogram, glycemia, urea, serum creatinine, electrolytes, coagulogram (including platelet count, prothrombin time, partial thromboplastin time and INR), serum cardiac enzymes, arterial gasometry and toxicological profile (in cases of suspected drug abuse). The electrocardiogram and chest x-ray are useful to evaluate cardiovascular function in patients with or without a history of arterial hypertension in the preoperative work-up, and also to detect early non-neurological complications (arrhythmias, pneumonia) [23]. Under no condition should an unstable patient be transferred for complementary studies.

Once obtained, cranial CT findings must be analyzed jointly by the neurosurgery team to decide the initial management according to the flowchart shown in Figure 50.10.

50.9.2 Medical Treatment of ICH in Critical Care Units

General Measures

The general measures of care for ICH patients are similar to those for other acute cerebral insults [23,51,58]. It is recommended to establish a central venous route, high calibre peripheral pathways and an arterial line. The advantages of this approach are that it allows for the precise monitoring of volemia and average arterial tension for easy se-

rial extraction of blood samples without the need for extra procedures on the patient; it also helps when volume expanders are required, colloids, mannitol, plasma or total blood without interfering with the simultaneous administration of sedatives, analgesics, antihypertensives or other drugs.

With regard to the use of intravenous solutions, isotonic sodium chloride 0.9% (physiological solution) or slightly hypertonic solution (3.5%) is recommended, depending on various different factors, including natremia, cerebral salt-wasting syndrome, inappropriate antidiuretic hormone secretion syndrome, endocranial hypertension, volemia, mass effect on CT (midline deviation, cistern effacement), etc. Under no circumstances (except in hypoglycemia) should hypotonic solutions such as dextrose or Ringer´s lactate be given because they worsen the cerebral edema, promote the synthesis of neurotoxic neurotransmitters such as glutamate, produce local tissue acidosis (a powerful stimulator of cerebral vasodilatation), and increase cerebral blood volume with elevation of intracranial pressure [23,51,58]. The "6 N" or "six normalities'' serves as a mnemonic rule (Figure 50.11).

Fever must be aggressively treated because of its deleterious effects on neurons and the blood-brain barrier: stimulation of the production of free radicals and elevation of excitatory amino acid levels. Fever also increases the cerebral metabolic demands of oxygen, with repercussions on intracranial pressure, in addition to decreasing the seizures threshold [60].

Hyperthermia has been associated with poor prognosis [61]. Studies by Godoy et al. have demonstrated a close relationship between the systemic inflammatory response syndrome (SRIS) as a predictor of worse prognosis and mortality in ICH, with fever being a component of the syndrome [62]. The authors recommend its management by physical means, thermal blankets, and the administration of acetaminophen in doses of up to 2 g daily when rectal temperature exceeds 37.5°C. This practice is in line with recent results of a multicenter study on acetaminophen in stroke [63].

Assisted mechanical ventilation is indicated in patients with one or more of the following criteria: GCS ≤8; neurological deterioration (defined as worsening of 2 or more GCS points); endocranial hypertension; respiratory insufficiency; abnormal ventilatory pattern; inability to obtain normoxemia and normocapnea, in spite of additional airway support; and immediate postoperative measures.

If a tracheotomy is created, independently of the time at which it is indicated, it should be done by the percutaneous route. On the other hand, due to the hypercatabolic state

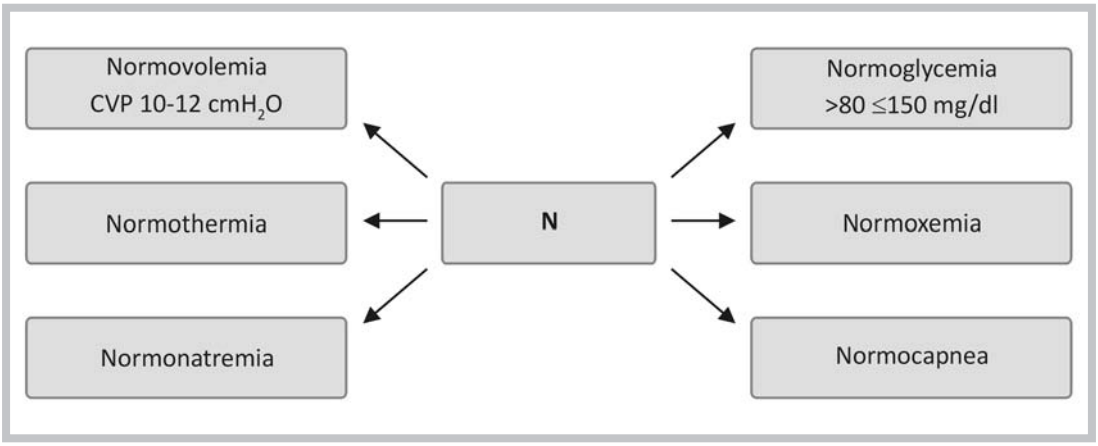

Figure 50.11. **The "6 N", the mnemonic rule to keep in mind when taking care of ICH patients.**
CVP= central venous pressure

and to the difficulty in swallowing in these patients, feeding must be initiated early, within the first 48 hours and preferably by the enteral route with a nasojejunal tube. Gastrokinetics (e.g., methoclopramide or cinitapride) are recommended for concomitant gastroparesis caused by the primary brain damage, the release of cytokines and other mediators, as well as the routine use of opioids or phenytoin, [23,51,58].

Additionally, and despite recent controversies, the head should be maintained 30 degrees from the horizontal plane in a "neutral" position, i.e., without anteroposterior or lateral flexion-extension, to improve the volume-pressure ratio of the cranial cavity, venous drainage, and the redistribution of cerebrospinal fluid; this measure also reduces the probability of mycroaspiration and mechanical ventilation-induced pneumonia.

Other equally important measures [58] include the use of artificial eye drops and frequent eyewashes, frequent oral hygiene with clorhexidine or other similarly effective mouthwashes. To prevent the development of pressure ulcers, the patient's position should be regularly changed - an air or water mattress is not a substitute for this basic care practice. Stress ulcer prophylaxis can be achieved with H_2 blockers, proton pump inhibitors or contact antacids such as sucralfate. Deep venous thrombosis prophylaxis can be achieved by using elastic bandages or pneumatic sleeves with sequential compression. In patients at high risk for thrombembolism such as those with obesity, prolonged immobilization, or hip fracture among others, subcutaneous heparin administration or low-molecular-weight heparinoids are recommended after first 24 hours of ICH.

Specific Measures

Normoglycemia

The strict control of glycemia levels is associated with multiple benefits, including the prevention of osmotic diuresis, maintenance of neutrophil and macrophage function, reduced free radicals production, increased nitric oxidase production and improved erythropoiesis [44,54,55,58]. Nevertheless, studies suggesting an aggressive control of hyperglycemia have not been conducted in ICH. Godoy and his group recommend strict glycemia monitoring and treatment with current insulin therapy if glycemia >150 mg/dl levels [64-66].

Anticonvulsants

Seizure frequency in ICH varies from 5 to 28% depending on the diagnosis method, being the highest when continuous electroencephalography is conducted [23,43,46,52]. Although anticonvulsive prophylaxis in ICH is controversial, the use of anticonvulsants is recommended in the following conditions: seizures as the presenting symptom of ICH, history of epilepsy or seizures with or without anticonvulsants use, lobar ICH with cortical extension and during the postoperative period [54-59,66-69]. Anticonvulsants are indicated in the first month and should be increased later. If seizures recur, the condition must be treated as an epileptic form.

Hemostatic Therapy

Recombinant activated factor VII (rFVIIa or NovoSeven®) is a powerful hemostatic activator used in the treatment of hemophilia [43]. rFVIIa acts primarily in endothelial damaged sites, promoting complexes formation with exposed tissue factors [43,46]. These properties were initially promising for ICH patients, especially in the expansion phase of hematoma in the first hours of evolution [46,66,69-71]. Nevertheless, the high expectations generated by a rFVIIa phase II study were not supported by the results of a recent phase III study [71,72]. Although the expansion of hematoma was reduced in the patient group treated with rFVIIa, no functional benefit was observed at 90 days. On the other hand, the high frequency of venous and arterial thromboembolic adverse events ob-

served in the rFVIIa arm, in both the phase II and III studies, are an important issue for its present recommendation [71,72].

Management of Coagulopathies

Patients anticoagulated with coumarin or warfarin have a 5 to 10 times higher risk of a life-threatening ICH, making the reversion of their effects urgent, with both intravenous vitamin K at a daily dose 2 mg; fresh frozen plasma of up to 15 ml/kg body weight (4 or 5 units), or the concentrated infusion of coagulation factors II, VII, IX and X [11,54,58,66,67,71]. Management should never be delayed while waiting for coagulation tests, the combined use of all available therapeutic tools being frequent in daily practice.

Heparin is inactivated by its antagonist, the sulfate of protamine at 1 mg for every 100 units of heparin. Patients with thrombocytopenia or platelet dysfunction can be treated with platelet concentrate infusion or with a unique dose of 0.3 μg/kg of desmopresine acetate.

Blood Pressure Management

Few aspects in the acute phase of ICH management have generated as much controversy as the handling of blood pressure. Some authors consider that high values are associated with hematoma expansion, greater peri-hematoma edema, and an increased risk of recurrence. Others have argued that its decrease is associated with ischemia due to reduced brain perfusion [11,73,74]. Although the American Heart Association (AHA) guidelines suggest the blood pressure values for which treatment must be initiated, their recommendations lack evidence (level V, degree C), since they were reviewed in patients with ischemic stroke and did not undergo substantial modifications [23,51].

Recent works propose a systolic blood pressure <160 mmHg which, besides being safe, reduces the probability of rebleeding [73-75]. Based on class IV evidence, the 2005 European Stroke Initiative (EUSI) recommends the following [58]: the blood pressure reduction as a routine is not recommended; in chronic hypertensive patients, blood pressure must be treated when systolic and diastolic values exceed 180/105 mmHg, respectively, with a mean arterial pressure (MAP) of 125 mmHg as a target; in non-hypertensive patients, blood pressure values >160/95 mmHg must be treated with the objective to reach to reach a blood pressure of 150/90 mmHg or a MAP of 110 mmHg. Reductions >20% of basal values must be avoided.

Both guidelines agree on early and aggressive treatment of blood pressure when one or more of the following conditions exist: acute pulmonary edema; aorta dissection; acute myocardial infarction; hypertensive encephalopathy; and acute renal failure [51,58].

With regard to antihypertensive drugs use, the literature recommends labetalol as a first-line election, followed by esmolol or nicardipine. The use of nitroprusside sodium and nitroglycerin must be avoided since they have a remarkable vasodilator effect on the cerebral vasculature [51,58]. Clonidine, a low-cost drug accessible and available in almost all intensive care units, is safe in spite of a weak evidence of use [54]; a load drug administration must be avoided, since it can stimulate peripheral receptors with a rebound effect. Clodinine is a presynaptic alpha-agonist that, in addition to its antihypertensive effects, also contributes to mitigate the sympathetic hyperactivity observed in these patients, besides having the advantage of an antiemetic, analgesic, and mild sedative effects. The conventional dose is 0.2 to 0.5 μg/kg/min.

The ATACH (Antihypertensive Treatment of Cerebral Acute Hemorrhage) study of safety and feasibility demonstrated that nicardipine by the intravenous route is viable in the strict control blood pressure [75]. However, we must await the results from the larger scale study (ATACH-2) to confirm these findings and to know its impact on mortality and disability in the short, medium and long term.

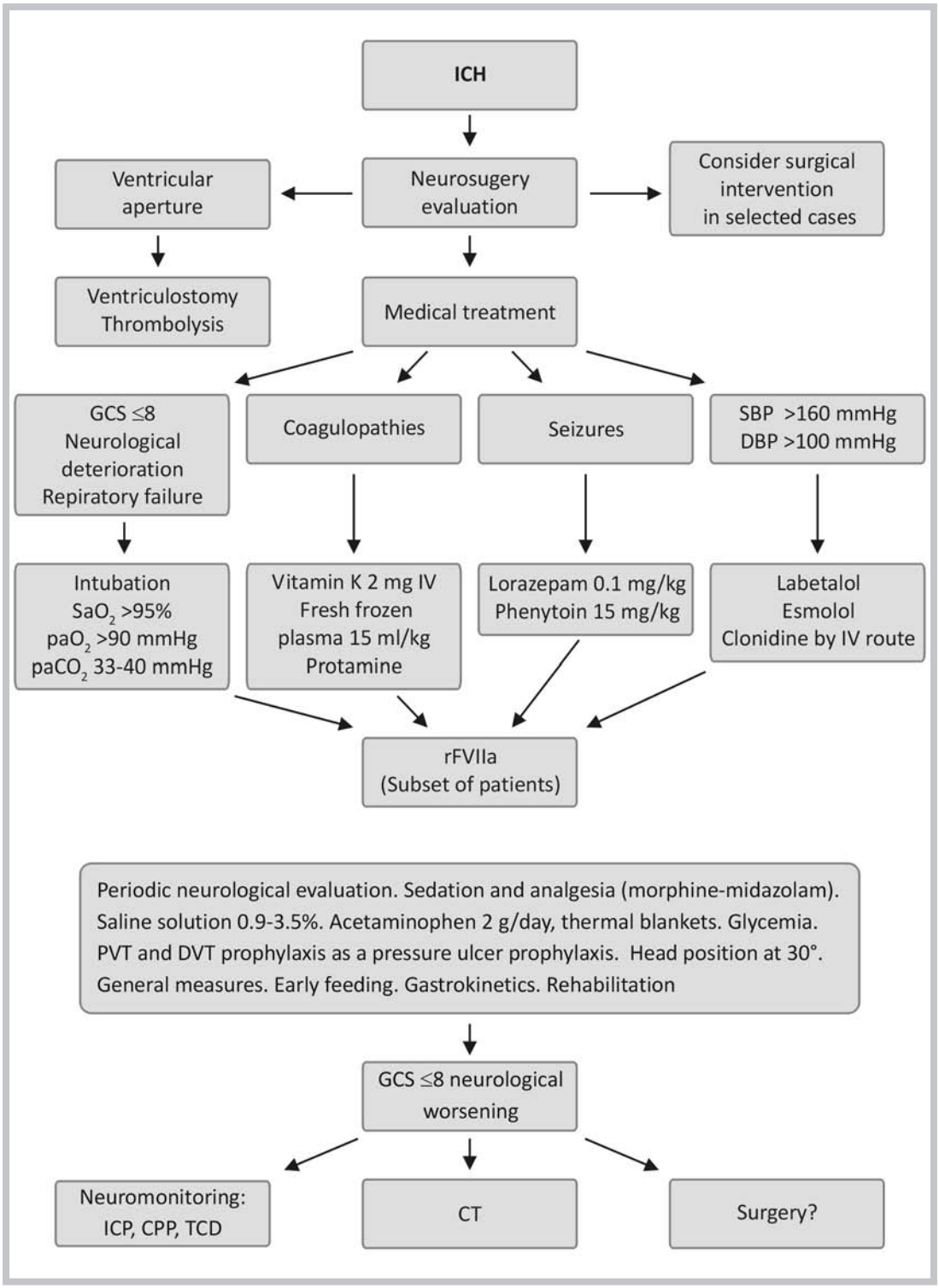

Figure 50.12. **Medical treatment of ICH in the neurointensive care unit.**

CPP = cerebral perfusion pressure
CT= computed tomography
DBP = diastolic blood pressure
DVT = deep venous thrombosis
GCS = Glasgow Coma Scale
ICP = intracranial pressure
PVT = pulmonary venous thrombosis
SBP = systolic blood pressure
TCD = transcranial doppler

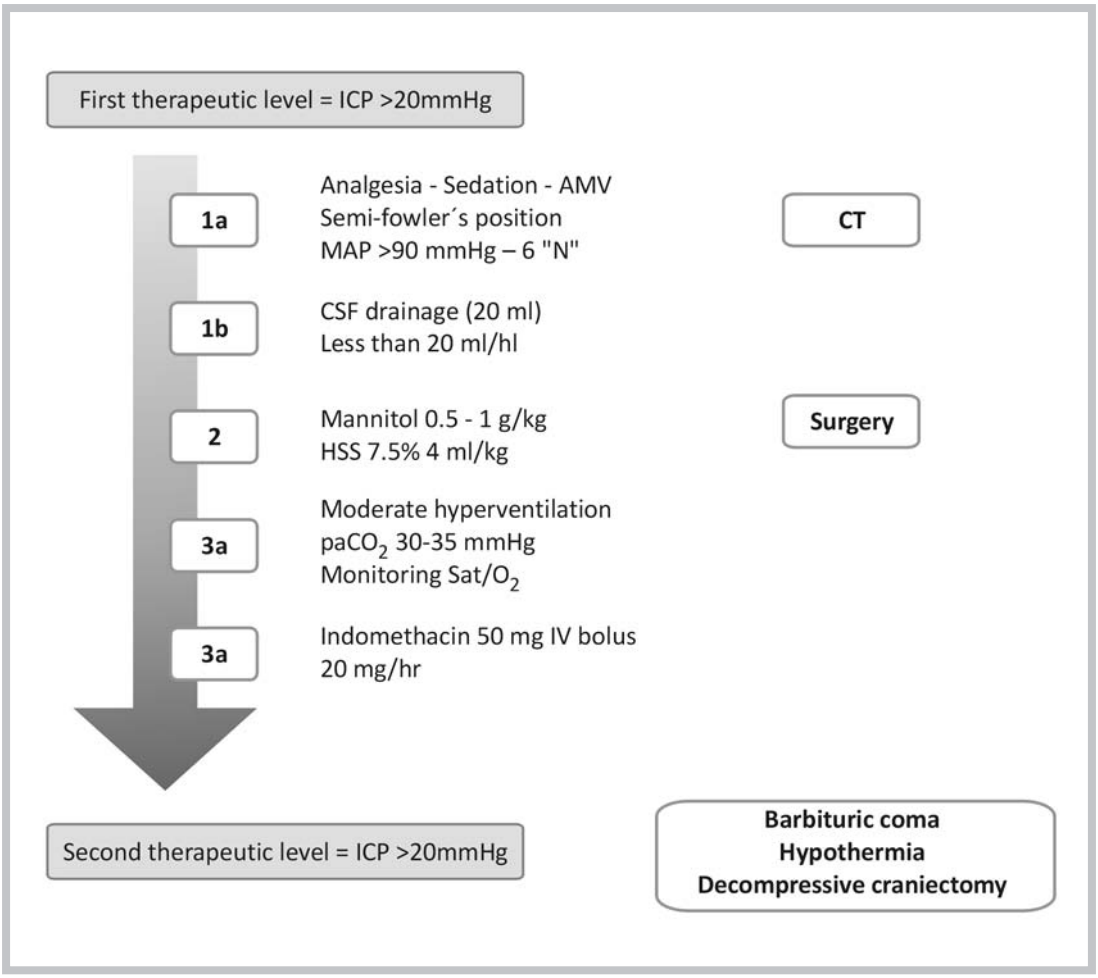

Figure 50.13. **Flowchart for intracranial hypertension management in the neurointensive care unit.**

AMV = assisted mechanical ventilation
CSF = cerebrospinal fluid
CT = computed tomography
HSS= hypertonic saline solution
ICP= intracranial pressure
MAP = mean arterial pressure

A similar pilot study, titled INTERACT (Cerebral Intensive Blood Pressure Reduction in Acute Hemorrhage Trial), showed the safety in the intensive management of systolic blood pressure values when they are reduced up to 140 mmHg [76]. The clinical impact is now analyzed under the scope of another study (INTERACT-2). The medical treatment of ICH in the neurointensive care unit is summarized in Figure 50.12.

Independently of surgical hematoma drainage or not, sequential intracranial hypertension management is indicated (Figure 50.13). It begins with general measures (sedation, analgesia, hyperthermia and seizures control while avoiding hypoxemia, and hypercapnia). If intracranial hypertension persists, ventricular drainage up to 20 ml/h is recommended, in addition to the use of 7.5% hypertonic saline solution as osmotherapy, together with mild hyperventilation, maintaining CO_2 levels between 30 and 35 mmHg. The use of muscle relaxants is not mandatory unless strictly needed. A new CT can be obtained at any time as deemed necessary by the neurosurgery staff. All these therapeutic approaches are considered “first level measures” and a poor response is associated with poor prognosis [23,52,54,56,77].

50.10 Surgical Treatment of ICH

The surgical treatment of the ICH is highly controversial, especially for supratentorial hematomas [34,49,77]. The hypothetical benefits of surgical drainage are that it decreases the hematoma mass effect, avoiding the release of neurotoxic products and preventing prolonged tissue-blot interaction, besides improving regional blood flow and peri-hematoma brain metabolism [78]. Nevertheless, these theoretical advantages must be weighed against the inevitable damage of normal parenchyma to access the hemorrhage [40,79-81]. Most neurosurgeons agree on the need to drain lobar or cerebellar hematomas in patients with clinical deterioration. What remains uncertain is the appropriate surgical approach to a ganglionic ICH [40,79,80].

The AHA guidelines [23,51] recommend surgical treatment in the following conditions: cerebellar hematomas >3 cm in diameter in patients who clinically deteriorate, have hydrocephalus, secondary brainstem or fourth ventricle compression (evidence C); secondary CVM hematomas; medium to larger volume lobar hematomas in young patients with neurological worsening.

The lack of studies with suitable methodology had lead mainly to low-evidence studies, some of which date from the pre-CT era or were derived from a few patients series [82-85]. Recent studies such as the STICH (International Surgical Trial in Intracerebral Hemorrhage) could not satisfy this question [50]. In this multicentre, international study, 1033 patients with supratentorial ICH within the first 72 hours were recruited and randomized to medical versus surgical treatment. Based on the uncertainty or doubt principle with respect to the utility of surgery, all those patients in which neurosurgeons were convinced of the benefits of surgery were operated and not included in the study. The average time from ICH onset to surgery was 30 hours. The results showed no difference in mortality or incapacity at 3 months, which is why the results of this study do not change the present practice [50].

A small subgroup of STICH patients with a better evolution was, however, identified: those with a GCS score between 9 and 12, with more superficial hematomas located to ≤1 cm of the brain cortex. An ongoing collaborative study in lobar ICH (STICH-2) is now comparing medical versus surgical treatment.

50.10.1 Ventricular Extension of ICH

Ventricular extension of ICH occurs in about 40% of patients, mainly when located deep in the thalamus, caudate, putamen or cerebellum [43,44,56,86-91]. Intraventricular hemorrhage carries a poor prognosis, nevertheless, it is the volume and not just its presence that determines the predictive value, being invariably fatal when >20 ml [67,86,88-92]. Its deleterious effects are associated with the development of hydrocephalus, intracranial hypertension, and ischemia of the cortical structures [86,87,91,93]. External ventricular drainage is a therapeutic option; however, its beneficial role remains uncertain.

The permeability of ventriculostomy is difficult to maintain due to frequent obstruction by clots, which is why different studies have used fibrinolytics like urokinase, streptokinase and rtPA [86,88]. Various studies in small series have shown good results related to a minor use of permanent peritoneal derivations and a reduction in mortality with acceptable functional prognosis; nevertheless, despite the high risk of complications such as infections or hemorrhages, prospective multicentre trials, have validated the effectiveness of this approach.

50.10.2 Hydrocephalus

Hydrocephalus develops due to the external compression of the ventricular system by the mass effect of hematomas, mainly those located in the thalamus or putamen which deviate the midline and compress the foramen of Monro, and also by small hemorrhages near of ventricular system as occur in the cerebellar vermis. The second mechanism is by clots obstructing the normal circulation of cerebrospinal fluid [93,94].

Independently of its cause, hydrocephalus leads to intracranial hypertension, cerebral ischemia and neurological deterioration. In addition, it is an independent predictive factor of mortality and inauspicious evolution, mainly when associated with supratentorial hemorrhages. Hydrocephalus is frequently treated with ventriculostomy; nevertheless, the benefit of this therapeutic modality has not been established. New alternative approaches utilizing minimally invasive procedures such as simple drainage by stereotaxia and thrombolysis with hematoma aspiration are technically promising but lack sufficient evidence for their generalized use.

Surgical treatment of secondary ICH due to rupture of arteriovenous malformations (AVMs), cavernous or venous angiomas is not usually urgent. A relatively low mortality in the acute phase of ICH due to AVMs (8.9-19.2%), associated with the reduced risk of immediate recurrence (3-17% for the first year and 2-6% thereafter), as well as the ab-

Reference	n	Scale components	Mortality within 30 days (%)
Hemphill JC et al, 2001	152	1. Glasgow Coma Scale at entrance 2. ICH volume 3. Irruption to the ventricular system 4. Infratentorial lCH 5. Age	45
Cheung RTF et al, 2003*	142	1. NIHSS at entrance 2. ICH volume 3. Irruption to the ventricular system 4. Infratentorial ICH 5. Age**	22
Shaya M et al, 2004	50	1. ICH volume 2. Hydrocephalus 3. Neurological focal deficit	18
Weimar C et al, 2006*	340	1. Age 2. NIHSS at entrance 3. Consciousness level on NIHSS	37
Godoy DA et al, 2006*	153	1. Glasgow Coma Scale at entrance 2. ICH volume 3. Irruption to the ventricular system 4. Intraventricular ICH (Graeb's scale) 5. Age	35
Ruiz-Sandoval JL et al, 2007*	378	1. Glasgow Coma Scale at entrance 2. ICH volume 3. Irruption to the ventricular system 4. Infratentorial lCH 5. Age	47

Table 50.4. **Prognostic scales for mortality in ICH.**

* Scales designed in addition for predicting good functional outcome

** Other variables also were proved

sence of vasospasm, makes time a non-critical condition for their treatment [95]. Mortality associated with ICH due to cavernous angiomas is similar that from AVMs; nevertheless, the risk of recurrence of bleeding is less (0.25-0.7% per year for non-familiar supratentorial cavernous angiomas and up to 6.5% per year for familiar cases) with a risk of recurrence of bleeding of 1.3% depending on the number of lesions per year [96]. The better prognosis relies on closer follow-up, waiting for clot reabsorption, with control studies (MRI) and careful planning of an eventual surgery in candidate cases.

50.11 Mortality and Prognosis in ICH

Acute mortality in ICH varies from 20 to 70%, being many factors its determinants [1,9-11]. A wide range of clinical, molecular and tomographic markers have been identified as predictors of mortality. The GCS score and the volume of the hematoma are variables with the highest weight and consistency in different cohorts. Recently, and by coincidence with this so called "forgotten pathology", there has been renewed interest in the proposal of several systems for predicting mortality in-hospital and at 30, 90 and 180 days after ICH. Table 50.4 shows the prognostic scales for 30-day mortality [91,92,97-99].

Some of these scales also were developed for predicting a good evolution and none of them have been validated in cohorts independently. The scale proposed by Hemphill [92] is one of the most accepted at the moment, since is simple to apply and is reproducible and highly predictive (Table 50.5). The scale has been validated and modified by others in different scenarios, including the proposals by the authors of this chapter [97-99].

The predictive good prognosis at 3 months after ICH is similar to the findings at in-hospital or at 30 days evolution. A recent scale, denominated the FUNC score (Functional Prediction of Outcome in Patients with Primary Intracerebral Hemorrhage) demonstrated that at 3 months, poor or good prognosis is associated with age, GCS at emergency room arrival, hemorrhage location and volume, in addition to previous cognitive deterioration (a good prognosis was based on a GCS >4) [100].

		Points
Glasgow score	3-4	2
	5-12	1
	13-15	0
Volume (cm^3)	≥30	1
	<30	0
Ventricular opening	Yes	1
	No	0
Infratentorial	Yes	1
	No	0
Age (years)	≥80	1
	<80	0
Total		0-6
Death probability at 1 month (ICH score)		
Points	**%**	
0	-	
1	13	
2	26	
3	72	
4	97	
5	100	
6	0	

Table 50.5. **Hemphill's prognostic scale for ICH (ICH score).**

50.12 Conclusion

ICH is the most catastrophic of all forms of CVD. It still is "the great forgotten one" in spite of recent interesting studies. It

seems to be more frequent in Latin America than in other countries, calling for the need to design incidence studies that could confirm it. Risk factors, clinical presentation and radiological findings are uniform in all scenarios. The best medical and surgical management remains uncertain. There is an urgent need for the initiation, termination and validation of all local or multicentre studies that could confirm or reject currently proposed therapeutic options such as neuroprotection, hemostatics use, blood pressure control, and the best surgical instrumentation with consequent safe and effective access.

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51 Non-traumatic Subarachnoid Hemorrhage

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51.1 Introduction

Non-traumatic subarachnoid hemorrhage (SAH) is a neurological emergency caused by the extravasation of blood into the space normally occupied by cerebrospinal fluid. Its most common cause is the non-traumatic rupture of intracranial saccular aneurysms, accounting for over 80% of cases. The remaining 20% are due to pre-truncal or perimesencephalic hemorrhage (10% of cases) or remote etiologies such as rupture of cavernous malformations, spinal arteriovenous malformations or mycotic aneurysms among others (Table 51.1).

The annual global incidence of SAH has been estimated at 6-7 cases per 100,000 inhabitants, and the risk is 1.6 times higher in women. SAH is implicated in <10% of strokes after 45 years of age and in about 50% of those occurring before age 35 years. The fatality rate is 51%, and at least 46% of survivors have long-term cognitive deficits which significantly impact their quality of life. The prognosis is strongly related to the state of consciousness on admission, the patient's age and the amount of bleeding evidenced on the initial brain scan. These variables have been used to develop different scales to enable rapid stratification of patients. Those most commonly used in clinical practice are the Fisher (Table 51.2), the World Federation of Neurosurgeons (World Federation of Neurological Surgeons, Table 51.3), and Hunt and Hess (Table 51.4). The last, in particular, has important prognostic value.

Inflammatory injury of the cerebral arteries	• Mycotic aneurysms • Behçet's disease • Primary CNS angiitis • Churg-Strauss vasculitis • Wegener's granulomatosis
Non-inflammatory injury of the cerebral arteries	• Arterial dissection • Cerebral arteriovenous malformation • Fusiform aneurysms • Dural arteriovenous fistula • Cerebral cavernous angioma • Cerebral amyloid angiopathy • Moyamoya disease • Reversible cerebral vasoconstriction syndrome • Cerebral amyloid angiopathy
Spinal vascular lesions	• Saccular spinal aneurysm • Spinal arteriovenous malformation • Spinal cavernous angioma
Hematological	• Sickle-cell disease • Coagulopathy
Tumours	• Pituitary apoplexy • Malignant glioma • Acoustic nerve tumour • Angiolipoma • Schwannoma • Cervical meningioma • Spinal cord hemagioblastoma • Meningeal carcinomatosis • Cauda equina melanoma
Drugs	• Cocaine • Antithrombotics
Hereditary causes	• Polycystic kidney disease • Ehlers-Danlos type IV • Pseudoxanthoma elasticum • Fibromuscular dysplasia • Neurofibromatosis

Table 51.1. Uncommon causes of non-traumatic SAH.

Grade	Volume of blood on admission head CT
I	No detectable blood
II	Diffuse subarachnoid blood without localized vertical clots <1 mm wide
III	Localized clots in the subarachnoid space or with a vertical blood layer ≥1 mm
IV	Bleeding with extension into the intraventricular or intraparenchymal compartments

Table 51.2. Fisher's scale.

Grade	Glasgow Coma Scale	Clinical picture
I	15	Without motor deficit
II	13-14	Without motor deficit
III	13-14	With motor deficit
IV	7-12	With or without motor deficit
V	3-6	With or without motor deficit

Table 51.3. World Federation of Neurosurgeons Scale.

Grade	Clinical picture	Prognosis
I	Asymptomatic, mild headache or nucal rigidity	75-90% with good outcome 5-15% mortality and/or vegetative state
II	Moderate to severe headache, nucal rigidity, cranial nerve paresis	
III	Obtunded, confusion, mild motor deficit	55-75% with good outcome 15-30% mortality and/or vegetative state
IV	Stupor, moderate to severe hemiparesis early decerebrate posture or neurovegetative imbalances	30-50% with good outcome 35-45% mortality and/or vegetative state
V	Coma, decerebrate posture	5-15% with good outcome 75-90% mortality and/or vegetative state

Table 51.4. Hunt and Hess scale.

Low clinical suspicion	• Limited evaluation of patients presenting with acute severe headache • Ignoring that headache associated with SAH can improve spontaneously • Not knowing that the SAH can present with atypical characteristics • Ignoring that hypertension and ECG changes can accompany SAH
Limitations of computed tomography	• Patient with SAH presenting late in its course • Anemia • Low-volume bleeding • Technical limitations (suboptimal images, thick cuts at the skull base)
Limitations of the lumbar puncture	• Not performing a lumbar puncture in patients with suboptimal, normal or non-diagnostic head CT • Not recognizing xanthochromia in the CSF • Ignoring that the sensitivity of spectrophotometry of CSF is superior to direct observation with the naked eye • Lumbar puncture performed very early in the course (<12 h) or very late (>2 weeks) • Failure to recognize the difference between the results of a traumatic tap and bleeding from a real SAH

Table 51.5. Frequent causes of misdiagnosis of SAH.

51.2 Diagnosis

Retrospective studies have suggested that approximately 1-4% of patients presenting to the emergency room with headache have SAH. The initial hemorrhage can be fatal or cause severe neurological sequelae, and early treatment of the aneurysm reduces not only short-term complications but also improves medium- and long-term prognosis. This makes the early diagnosis of SAH a key factor, which is based on the triad of clinical symptoms, lumbar puncture and the use of complementary diagnostic imaging studies. A study by Vermeulen and Schull in Toronto, Canada, reported that 5.4% of patients presenting to the emergency room with SAH are misdiagnosed; this rate rises to around 20% for patients with low-grade bleeding. Therefore, high clinical suspicion is essential to avoid diagnostic errors that might delay the implementation of appropriate treatment plans (Table 51.5).

51.2.1 Clinical

Typically, SAH presents with severe diffuse headache of acute onset which reaches its peak in seconds. Patients describe the headache as “the worst in their life.” However, it is the acute onset and not the severity that characterizes the headache of SAH. In some cases, the headache completely ceases within minutes or hours and is called “sentinel headache”. It has been shown that many patients with sentinel headache can develop SAH within the 3 weeks following the episode. Other symptoms frequently found in these patients, such as nausea, vomiting and photophobia, are nonspecific and of limited diagnostic value. Two thirds of patients with SAH present with impairment of consciousness, and half of these are already in a coma. Meningismus, which is often observed, is secondary to meningeal irritation caused by blood in the subarachnoid space. This takes place between 3 and 12 hours after the bleeding but it may be absent in deeply comatose patients or in those with mild SAH. Fundoscopic examination is of paramount importance: 1 in 7 patients develop intraocular hemorrhage, which is more common in those presenting with impaired consciousness. The pathophysiological mechanism of these hemorrhages involves a sustained increase in intracranial pressure that blocks the drainage of the central retinal vein in its course through the optic nerve sheath, causing preretinal flame hemorrhages (subhyaloid hemorrhage) located near the optical disc. When there is a sudden increase in intracranial pressure, intraocular bleeding can be more severe and extend to the vitreous humour, causing the so-called Terson syndrome.

Frequently seen are focal neurologic deficits which can have a localizing value of the bleeding site (Table 51.6).

These occur when the aneurysm compresses a cranial nerve or when the bleeding extends into the brain parenchyma. Alternatively, aneurysm rupture can lead to severe va-

Neurological deficit	Localization of the aneurysm
Partial or complete paresis of the oculomotor nerve	Posterior communicating artery
Paraparesis or abulia	Anterior communicating artery
Hemiparesis and aphasia	Middle cerebral artery
Paresis of the VI nerve	Limited localizing value
Ataxia and nystagmus	Posterior fossa

Table 51.6. **Localization of the aneurysm based on the clinical picture.**

soconstriction, and eventually, localized ischemia. This explains why the clinical manifestations of SAH are sometimes indistinguishable from those of an ischemic stroke or intraparenchymal hemorrhage.
In the acute phase of SAH systemic findings such as severe hypertension, hypoxemia, or electrocardiographic changes including depression or ST segment elevation, T wave flattening, presence of Q wave, QT prolongation and bundle-branch block can be observed. In addition, about 3% of cases can evolve into a cardiac arrest.

51.2.2 Lumbar Puncture

About 3% of patients presenting within 12 hours of the onset of symptoms of SAH have normal imaging studies. Since lumbar puncture demonstrates the presence of blood in the cerebrospinal fluid, it is important to have a high degree of clinical suspicion and have a lumbar puncture performed in all patients presenting with acute onset headache suggestive of SAH with a normal computed tomography (CT) of the head. Typically, lumbar puncture in patients with SAH has a high cerebrospinal fluid opening pressure with a xanthochromic appearance and abundant red blood cells. Xanthochromia occurs when the hemoglobin from red blood cells extravasated into the subarachnoid space is metabolized to bilirubin. The latter has a spectrophotometric maximum wavelength absorption at 450-460 nm, allowing its quantification with high sensitivity. This method, in turn, allows to differentiate the presence of bilirubin from other pigments derived from the blood such as oxyhemoglobin or iodinated antiseptics used to disinfect the skin.
In patients with significant bleeding, the cerebrospinal fluid may have a bloody aspect. In such cases, the cerebrospinal fluid should be centrifuged, and a yellowish supernatant will confirm the presence of xanthochromia. In doubtful cases, the presence of bilirubin can be demonstrated spectrophotometrically in the laboratory. Since the enzymatic metabolism of hemoglobin to bilirubin can only occur in vivo, the cerebrospinal fluid should be stored protected from light and ultraviolet radiation which can degrade bilirubin and give false negative results.
Because the metabolism of hemoglobin to bilirubin requires 6 to 12 hours, it is advisable to perform a lumbar puncture 6 or, if possible, 12 hours after the onset of SAH symptoms. The cerebrospinal fluid obtained before 6 hours usually shows a high count of red blood cells without xanthochromia, as observed in traumatic lumbar punctures.
In clinical practice, a widespread technique to differentiate traumatic puncture from SAH is the comparison of the number of red blood cells present in the cerebrospinal fluid obtained at the beginning and end of the lumbar puncture; however, this observation can be unreliable.

51.2.3 Ancillary Radiographic Tests

Computed Tomography

Brain CT without contrast material is one of the most useful studies for investigating SAH and the first to be ordered when the diagnosis is suspected. Subarachnoid

Figure 51.1. Non-contrast enhanced head CT obtained in a patient with SAH.

bleeding appears on the CT scan as a hyperdensity localized to the subarachnoid space, more commonly in the basal cisterns and the Sylvian fissure (Figure 51.1). The sensitivity of this technique depends on several factors:

- **Technique**. The scan plane should be parallel to the hard palate. It should be noted that the sensitivity of CT depends directly on the amount of blood extravasated into the subarachnoid space. If there are only small amounts of bleeding, the sensitivity of CT can be increased by cutting thin slices (3 mm) from the base of the skull.
- **Time since the onset of symptoms**. In the first 12 hours, CT can reveal extravasation of blood into the subarachnoid space in approximately 100% of cases; however, this percentage decreases to 93% between 12 to 24 hours. Over the following days, the blood circulation and elimination from the subarachnoid spaces causes the sensitivity of CT to decrease markedly. It is estimated that the sensitivity of a CT scan performed on the seventh day post-bleeding is only 50%.
- **Hematocrit**. The blood density appearing on CT depends directly on its hemoglobin concentration. Blood hemoglobin <10 mg/dl may be isodense on CT.
- **Scanner resolution**. The sensitivity of third-generation CT scanners to diagnose SAH is around 92-98%. It has been suggested that fifth-generation equipment has superior sensitivity which would approach 100%.

In some uncommon cases, blood doesn't extravasate into the subarachnoid space but into the brain parenchyma, ventricular system or subdural space instead, causing intracerebral, intraventricular or subdural hemorrhages, respectively. A CT scan can also show false positive results as in cases of diffuse cerebral edema where congestion of the cerebral vessels occurs and appears on the scan as hyperdensity of the basal cisterns. This radiographic finding, called pseudo-subarachnoid hemorrhage, must be considered in the appropriate clinical context.

Magnetic Resonance Imaging

Brain magnetic resonance imaging (MRI) is an important ancillary study in the evaluation of patients with SAH. In MRI, unruptured aneurysms are hypointense on T_1 and T_2-weighted images and FLAIR (fluid attenuated inversion recovery) (Figure 51.2).

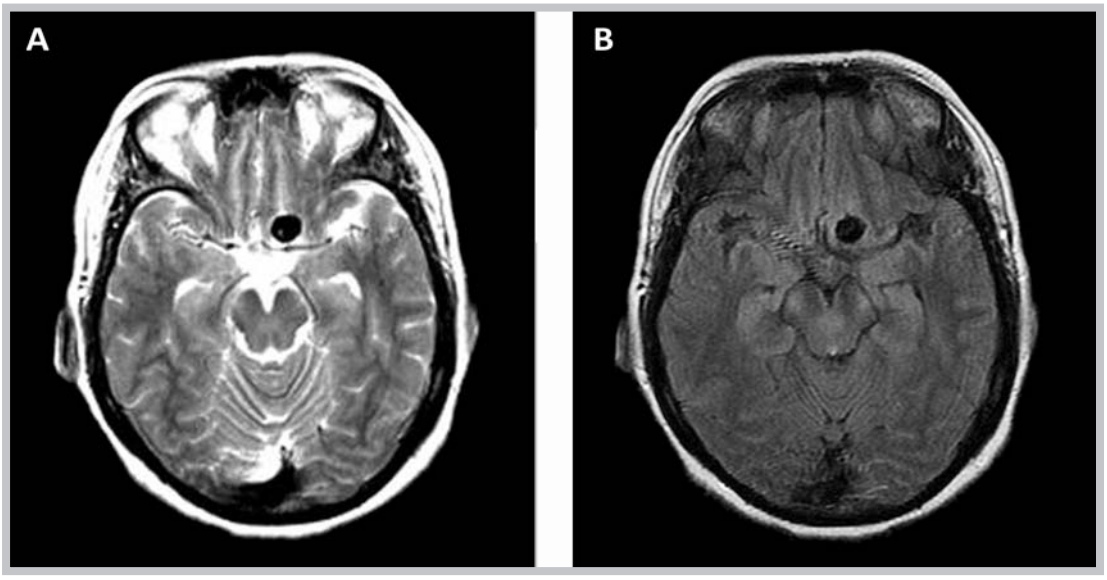

Figure 51.2. **MRI obtained in a patient with an unruptured left internal carotid artery aneurysm. Axial T_2-weighted-image (A) and FLAIR image (B).**

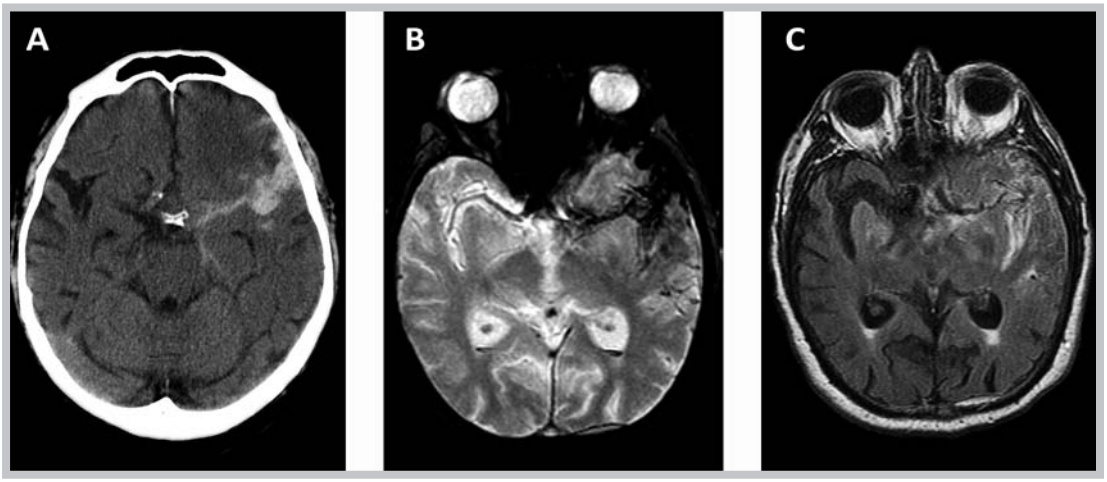

Figure 51.3. **CT images (A) and MRI – GRE sequence (B) and FLAIR sequence (C) – obtained in a patient on day 4 after the rupture of a left middle cerebral artery aneurysm.**

It has been suggested that in the first 5 days, the sequences of proton density and FLAIR are as sensitive as CT for diagnosing the presence of blood in the subarachnoid space. In addition, FLAIR and GRE (gradient echo) sequences can demonstrate the presence of blood after day 4 with a sensitivity of 100% and 85%, respectively (Figure 51.3), a period in which the sensitivity of CT decreases significantly. The undisputed superiority of MRI over CT is that the former can locate not only the aneurysm responsible for SAH but also rule out other etiologies that make up the differential diagnosis, such as tumours or cerebral venous thrombosis which often go completely unnoticed on a CT scan.
MRI requires patients to remain motionless for a considerable amount of time. This limits its use in patients with an altered level of consciousness. In addition, MRI is contraindicated in patients with pacemakers or other implanted metallic devices which are incompatible with magnetic radiation.

Ancillary Angiographic Studies

Ancillary angiographic studies such as magnetic resonance angiography (MRA) and three-dimensional computed angiotomography (CTA) are non-invasive diagnostic mo-

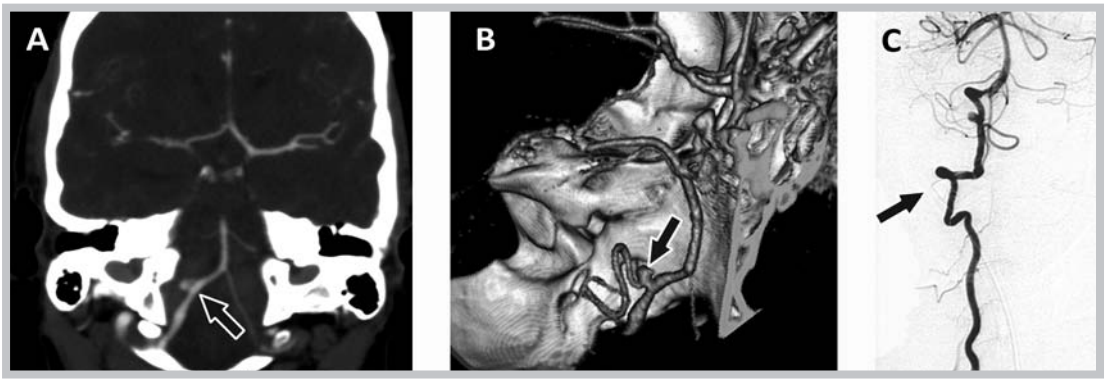

Figure 51.4. **Images obtained in a patient with an aneurysm at the branching of the right postero-inferior cerebellar artery (PICA). A coronal reconstruction obtained by CTA (A), its digital 3D reconstruction (B), and the image obtained by DSA after the injection of contrast material in the right vertebral artery (C). The arrow indicates the location of the aneurysm.**

dalities that allow the identification of the vessel in which the aneurysm originates, the study of its anatomical configuration, and its anatomic relationship with other brain structures. These considerations are of vital importance when choosing the treatment modality (see below).

Three-dimensional computed angiotomography. 3D CTA has considerably evolved recently. To visualize the intracranial vessels, a volume <100 ml of iodine contrast material is injected at a rate of about 4 ml/sec, and the area between the first cervical vertebra and the vertex is scanned. A 3D reconstruction of the intracranial vascular tree is created from the source images. The sensitivity of CTA varies with the size of the aneurysm. Compared to digital subtraction angiography (DSA), considered the gold standard for the detection of cerebral aneurysms, CTA has an average sensitivity of 95% (Figure 51.4). Correct evaluation with CTA will include not only a careful review of the vascular reconstruction but also the source images (Figure 51.5).

Magnetic resonance angiography. The three basic techniques used by MRA for the study of the cerebral vascular tree are the time of flight, phase contrast magnetic resonance angiography, and gadolinium infusion. They allow the visualization of the intracranial vasculature by acquiring two-dimensional or three-dimensional flow-sensitive imaging with background suppression. Three-dimensional images have better resolution and are therefore superior to two-dimensional images. Like CTA, MRA sensitivity

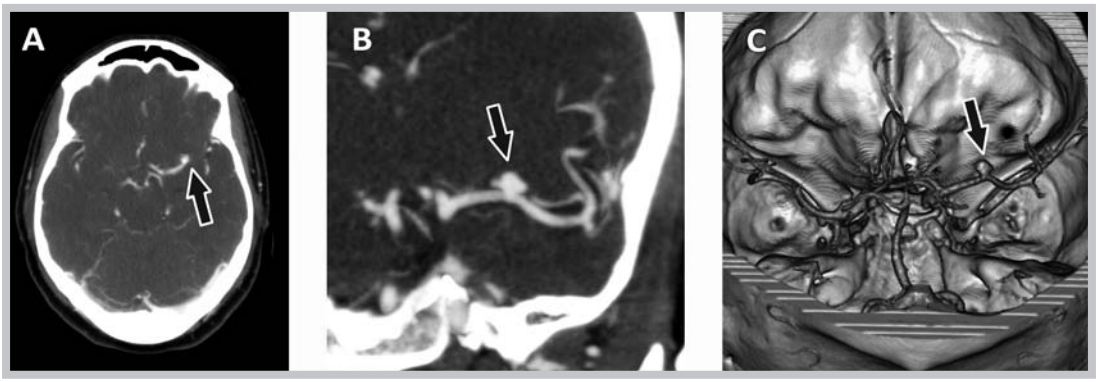

Figure 51.5. **CTA images in a patient with an aneurysm of the left middle cerebral artery. Axial cut from the CTA source images (A), a coronal cut (B), and the digital 3D reconstruction (C). The arrow indicates the location of the aneurysm.**

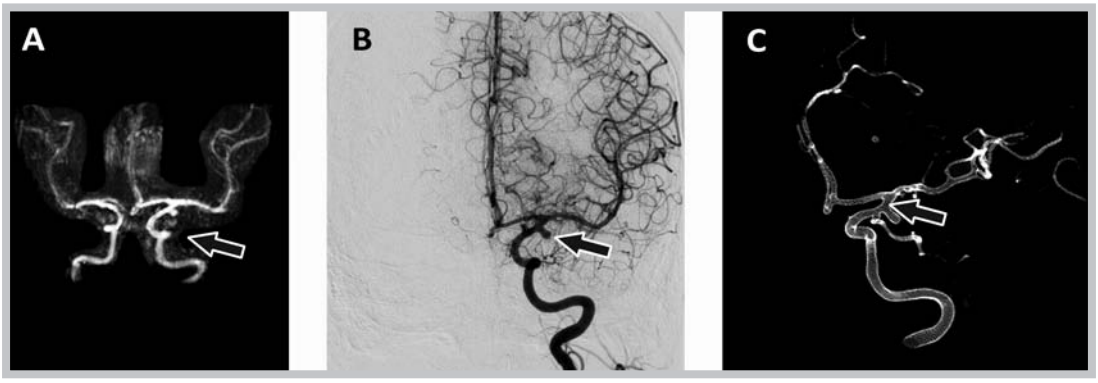

Figure 51.6. **Images obtained in a patient with a left internal carotid artery aneurysm. MRA antero-posterior view after 3D reconstruction (A), DSA after the injection of contrast material in the left internal carotid artery (B), and DSA digital reconstruction (C). The arrow indicates the location of the aneurysm.**

depends on the size of the aneurysm. Compared to digital subtraction angiography, the average sensitivity of MRA is about 90-95% (Figure 51.6). MRA has the advantage of not exposing the patient to the potentially adverse effects of radiation and intravenous iodine contrast. However, the procedure requires the patient to remain motionless for a considerable amount of time, which limits its use in patients with psychomotor agitation. As in CTA, the interpretation of MRA should include a careful review of the vascular reconstruction and source images.

Digital subtraction intra-arterial angiography. DSA is considered the gold standard for detecting aneurysms. It should ideally be done within 24 hours of bleeding and should include the four large vessels (both internal carotid arteries and both vertebral arteries). As a general rule, when multiple aneurysms are observed, the largest, more irregular one is generally considered e the one responsible for the SAH as long as it matches the location suggested by the intracranial bleeding pattern. One of the main advantages of DSA is that, depending on the anatomical features, the same procedure can be used for endovascular treatment (see below). However, the technique is not devoid of potential complications. Its limitations include the use of radiation and contrast material, the risk of transient or permanent ischemic neurological complications, and re-rupture of the aneurysm, which are estimated at around 2% altogether.

Whatever the method chosen to investigate the source of SAH, it should carefully evaluate all cerebral vascular beds, given that up to 15% of patients will have multiple an-

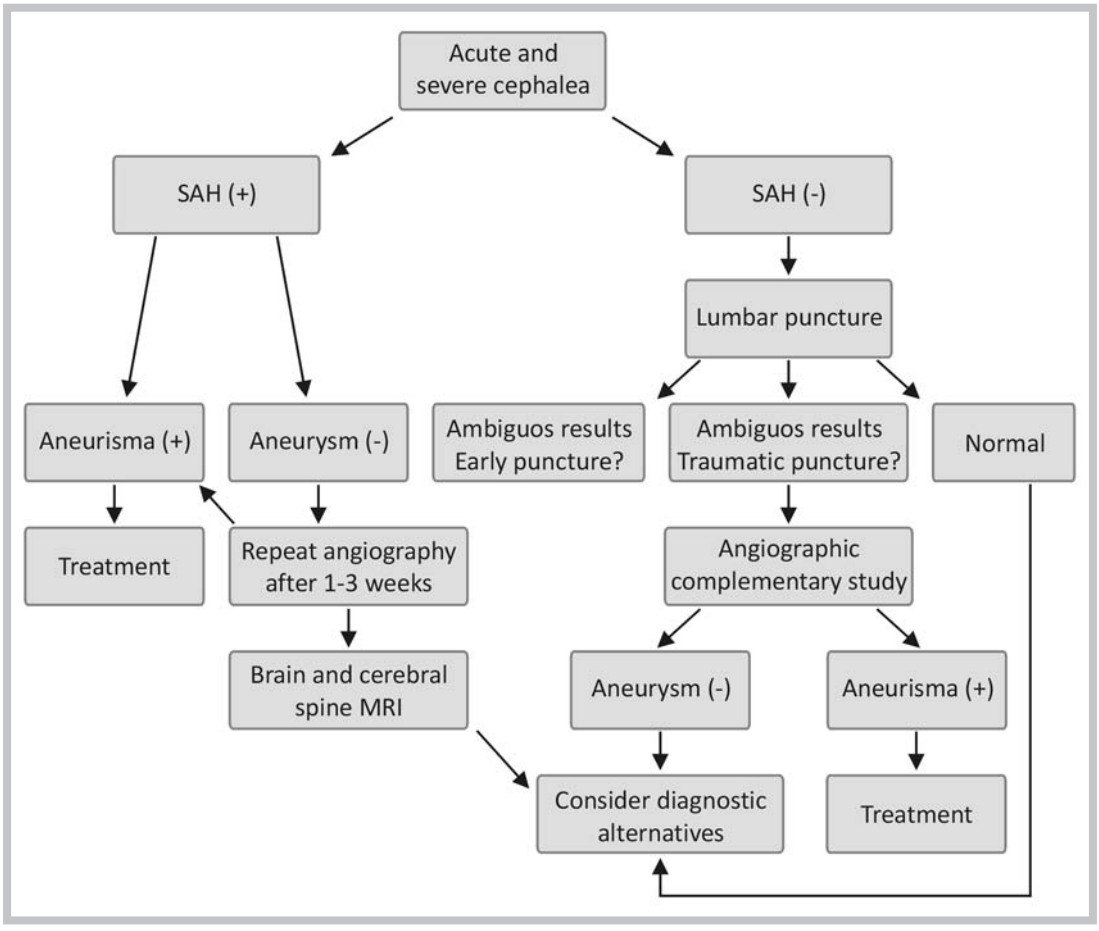

Figure 51.7. Suggested algorithm for the diagnosis of SAH.

eurysms. In those cases where angiographic studies fail to identify the source of the subarachnoid bleeding, we recommend repeating the study in 1 to 2 weeks. If in this instance an aneurysm is not found, an MRI study of the brain and cervical spinal cord should be obtained to investigate the possibility of vascular malformations of the brain, brainstem or spinal cord which may be partially thrombosed and hidden in the angiographic studies. The suggested diagnostic algorithm is shown in Figure 51.7.
Finally, it is important to note that a large percentage of the population over age 50 has small aneurysms (<5 mm) that are found incidentally and do not necessarily require treatment. Therefore, additional angiographic studies must be interpreted within the appropriate clinical context and reserved for the evaluation of patients in which SAH has been diagnosed.

51.3 Treatment and Management

In the approach to management of aneurysmal subarachnoid hemorrhage (SAH), consideration should be given to the clinical grade and initial presentation in each case. Resuscitative measures, airway, breathing and circulation, should be followed emergently with greater attention to unstable patients with worse neurological grades. Typically, all patients with aneurysmal SAH, irrespective of its grade, are admitted to our specialized ICU (Neurocritical Care Unit) where a combination of frequent neurological evaluation in addition to ICU monitoring protocols are instituted. It should be emphasized that patients with a low-grade SAH on presentation may rapidly deteriorate, making frequent neurological evaluation of paramount importance. Once the clinical suspicion of SAH is confirmed by CT or lumbar puncture, initial medical management should follow while diagnostic measures are being carried out. This helps to identify and treat potential medical factors that may contribute to neurological deterioration.
Airway. Low-grade SAH may manifest from a mild depressed mental state to a comatose state and in this setting there is a high risk of respiratory compromise due to poor or absent protective airway reflexes. Other factors that may compromise respiratory function include neurogenic pulmonary edema (discussed below) and trauma after falls due to sudden loss of consciousness or seizures. There should be a low threshold to intubation and initiation of mechanical ventilation in this setting. Attention should be paid to hypercapnia as this may worsen a frequent finding of raised intracranial pressure in this group of patients. Following intubation, anesthetic agents that decrease cerebral metabolism and also assist in blood pressure control such as propofol are reasonable. Other options include midazolam and fentanyl.
Blood pressure control. Most patients with aneurysmal SAH will present with elevated blood pressure due to pain, anxiety and sympathetic activation. A systolic pressure >160 has been associated with rebleeding or re-rupture, with an estimated mortality >50% in this sub-population. Several antihypertensives are available in the ICU setting, however, it is important to recognize the effects of each agent on cerebral autoregulation, predictable dose-response pattern, and safety profile. Continuous infusion of an antihypertensive such as nicardipine, a calcium channel antagonist, is our drug of choice in the initial acute setting, which is titrated to a set blood pressure range. The low end goal is to maintain adequate cerebral perfusion without increasing (high end goal) the risk of re-rupture or worsening intracranial pressure (ICP). Other options include labetalol and esmolol infusions. In cases where the blood pressure are relatively low (140-160 mmHg), intermittent intravenous labetalol and occasionally hydralazine (if there are no concerns of marked ICP elevations) are reasonable options. The use of nitroprusside is usually

avoided in neurological emergencies due to its potential of worsening raised ICP and its toxicity with prolonged infusion, which is sometimes necessary in these clinical settings.

Bed rest. Historically, bed rest in a quiet surrounding has been prescribed in patients with aneurysmal SAH under the assumption that any form of excitement would increase the risk of rebleeding due to surges in blood pressure. In addition to the management of pain and anxiety, it constitutes part of our treatment protocol.

Pain and anxiety. Acute SAH presents as a sudden severe headache and has been described as "the worst headache in my life". Therefore, it seems reasonable that the accompanied surge in catecholamines results in an increase in sympathetic activity with an antecedent rise in blood pressure. In non-intubated patients we have found low-dose opioids (e.g., morphine) to be helpful in this regard. We specifically avoid non-steroidal anti-inflammatory drugs (NSAIDs) due to the increased risk of bleeding from their antiplatelet effect.

Antifibrinolytic therapy. Studies of antifibrinolytic agents, such as epsilon aminocaproic and tranexamic acid, in aneurysmal SAH demonstrated a reduction in rebleeding; however, an increased incidence of thromboembolic events offset any benefit. In the majority of studies, antifibrinolytic agents were used for at least 96 hours. In a Swedish study comparing the use of tranexamic acid initiated within a mean of 4.9 hours from symptom onset, until the aneurysm was secured, and given for <72 hours, the incidence of rebleeding was lower in the treatment group. There was no difference in thromboembolic events or delayed cerebral ischemia in this study. We have occasionally used short-term antifibrinolytic agents in highly selected patients for a short duration if a delay in securing the aneurysm is anticipated as may occur in medically unstable patients or in the long-distance transfer of SAH patients. These agents are then held 6-8 hours prior to securing the ruptured aneurysm. However, our preference is to achieve aneurysm occlusion within 24 hours of symptom onset, obviating the need for antifibrinolytic agents in most cases. It seems that this approach accomplishes the goal of preventing rebleeding and obviates the need for antifibrinolytic agents and their potential complications.

Seizure treatment and prophylaxis. The frequency of seizures after SAH is reported to be 6-20%, with about half of episodes occurring during the perioperative period. Risk factors associated with seizures in retrospective series include middle cerebral artery aneurysm, intraparenchymal or subdural hematoma, cerebral infarcts, thickness of the SAH clot, and hypertension. Often, seizures manifest with rhythmic motor movements and are associated with altered state of consciousness. Persistent loss of consciousness is worrying and should be aggressively evaluated for non-convulsive status epilepticus or raised ICP. We have frequently encountered patients with persistent alterations of consciousness who were reported to have had recurring "seizure-like" events after SAH that were non-epileptic on the electroencephalogram (EEG) and persisted despite adequate anticonvulsant medication. It appears that some of these events may be manifestations of cerebral posturing due to a sudden sustained rise in ICP, known as plateau waves. However, since seizures have been associated with intracranial injury, it is important that they be aggressively treated especially in cases of status epilepticus. The initial management involves the use of benzodiazepine (e.g., lorazepam and diazepam) and an anticonvulsant such as phenytoin or valproic acid. The use of new intravenous agents such as levetiracetam and lacosamide remain adjunct options. When there is no improvement in the level of consciousness or seizures persist, continuous EEG monitoring is a helpful tool for differentiating epileptiform from non-epileptiform events but it should not deter continuing management of status epilepticus. The presence of status epilepticus typically warrants long-term anticonvulsant treatment with outpatient follow up.

In seizure prophylaxis, there have been very few reports suggesting its benefit especially in the long term. There is some concern about worse cognitive outcome at 3 months with phenytoin reported in a few series. The major argument for seizure prophylaxis is that it decreases the risk of rebleeding from an unsecured aneurysm due to a seizure event. This theoretical benefit should be weighed along with the potential long-term effects by selecting patients with the above mentioned risk factors for seizures. When seizure prophylaxis has been instituted, limiting it to a duration of 7-14 day appears reasonable. We have occasionally continued prophylaxis for a longer period in patients with epileptiform discharges on EEG but without seizures and temporal hematoma associated with an middle cerebral artery aneurysm.

Nimodipine. Nimodipine has been demonstrated to improve functional outcome after aneurysmal SAH. It is typically given at doses of 60 mg every 4 h. It can cause hypotension and headache; the hypotensive effects are beneficial in the initial stages when blood pressure control is important. Subsequently, as one nears the vasospasm period when hypotension needs to be avoided, its use becomes challenging. Its benefit appears to be related to cerebral neuroprotection since its effect on vasospasm is minimal. This is further discussed in the section "Vasospasm" below.

Fever. See below.

51.3.1 Surgical and Endovascular Management

Patients with aneurysmal SAH are at an increased risk of re-rupture of the patent aneurysm (3-4% in first 24 h and 1-2% daily for 30 days) with a mortality rate >55%. The definitive approach to preventing further clinical deterioration from re-rupture involves securing the aneurysm via endovascular coiling or surgical clipping. Several studies have suggested that an increased time to securing a ruptured aneurysm increases the risk of rebleeding. However, in the International Cooperative Study on the Timing of Aneurysm Surgery, the overall outcome was not significant. Our approach is to secure the aneurysm as soon as possible with either surgical or endovascular techniques. In our opinion, this allows for easier management of vasospasm, a known and common complication of aneurysmal SAH.

The advent of endovascular treatment of intracerebral aneurysms with detachable coils has complemented and in some situations replaced surgical clipping in securing a ruptured aneurysm. The decision on which method of securing the aneurysm depends on several factors such as patient age, clinical grade, location (anterior vs. posterior circulation), aneurysm size and morphology, presence of other vascular injuries (e.g., intracerebral or subdural hematoma), procedural efficacy and facility-specific characteristics (availability of technical and infrastructure support).

Endovascular Management

This treatment technique involves deploying platinum coils through microcatheters into an aneurysm with the goal of achieving complete obliteration and prevent future rebleeding. This relatively minor invasive approach to treatment has made coiling a more attractive technique in securing aneurysms. The effectiveness of the procedure in the treatment of ruptured aneurysm can be measured by the procedural efficacy (rebleed rate and angiographic recurrence rate of a treated aneurysm). Comparison with surgical clipping in the International Subarachnoid Aneurysm Trial (ISAT) found a relative risk reduction of death or dependency by 23.9% at 1 year in the endovascular group. However, the rebleed rate at 1 year in the endovascular group was 2.9% vs. 0.9% in the surgical clipping group. The long-term outcome in this study, (mean follow-up, 9 years), suggest-

ed a non-significant increase in rebleed rate in the endovascular group. Murayama et al., in a series with a follow-up of over 11 years, reported that 55% of aneurysms treated with endovascular coiling could be completely occluded. The factors affecting incomplete occlusion and recurrence were aneurysm size and shape. It is important to note that aneurysm size and shape were also identified as predictors of rebleeding.

An anticipatory approach to the care of patients prior to an endovascular procedure is critical. Attention should be paid to adequate airway and ventilation management, blood pressure control, avoiding anesthetic agents (e.g., ketamine) and hypercapnia that may increase intracranial pressure. If an ICP monitor is already in place, close monitoring of ICP changes and especially the ICP waveform as a predictor of intracranial compliance and peri-procedural complication is informative. In the absence of an ICP monitor, sudden blood pressure spikes or evidence of procedural aneurysmal rupture may present an emergent need for placement of an ICP monitor with external CSF diversion. Other medical measures in treating raised ICP with hyperosmolar agents (mannitol, hypertonic saline), sedative anesthetic (benzodiazepine, barbiturates) may be considered in refractory elevated ICP. In some cases, the need for stent placement in an attempt at vascular reconstruction while securing an aneurysm may arise. In this circumstance, the subsequent need for antiplatelet therapy makes this an important determining factor in the timing of invasive procedures such as placement of external ventricular drains (EVD). Also of interest is the development of intra-arterial thromboembolism during endovascular coiling. Several case series have reported treatment of this complication with a glycoprotein IIb-IIIa antagonist such as abciximab with relative good outcomes. The frequency of aneurysmal rebleed and primary intracerebral hemorrhage in these series has been low, though hemorrhagic conversion of a cerebral ischemic lesion has been described. These patients should be monitored closely for neurological deterioration.

The selection of patients for endovascular coiling is therefore important so as to optimize benefit and reduce the above mentioned risk following treatment. In the ISAT study, the mean age was 52 years with older patients (>70 years) preferably undergoing endovascular coiling due to the higher surgical risk. For the same reason, we typically will consider endovascular treatment for patients older than 50 years, especially in

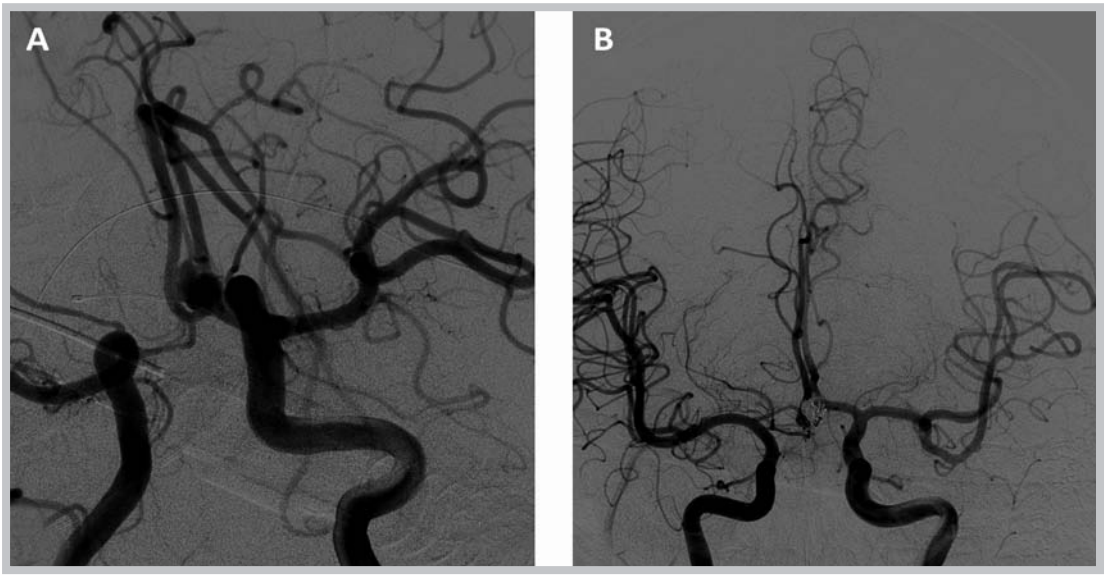

Figure 51.8. Cerebral DSA showing an aneurysm of the anterior communicating artery (A). Cerebral DSA immediately after endovascular occlusion of the aneurysm with platinum coils (B).

a setting of multiple medical conditions that preclude surgical clipping. Other features that are optimal for endovascular coiling include: aneurysms in the cavernous segment of the internal carotid artery aneurysm, internal carotid artery and posterior circulation (e.g., basilar tip), aneurysm neck diameter <5 mm, and a neck diameter to largest aneurysm dimension ratio <0.5.

In recent years, following the publication of the ISAT study, endovascular treatment of intracranial aneurysms has gained wider acceptance. Techniques and materials have improved significantly, so that wide-necked aneurysms which were once impossible to embolise can today be occluded with the help of balloons or stents (balloon-assisted coiling, stent-assisted coiling). However, the largest concern is the fact that on subsequent follow-up angiography some of the endovascular-treated aneurysms have grown due to initial incomplete filling of the aneurysm sac or have compacted coils in the dome of the aneurysm as a result of the water hammer effect generated by pulsatile blood flow allowing the neck to eventually grow and increase the risk of a re-rupture. This means that a significant proportion of these aneurysms require retreatment by adding more coils (with the risk associated with this new procedure). A slightly increased risk of re-rupture of coiled aneurysms when compared with surgically clipped ones has also been reported.

Surgical Management

Cerebrospinal fluid diversion and aneurysmal clipping are the main surgical treatments of intracranial aneurysms. The use of CSF diversion techniques is important at different stages in the treatment of aneurysmal SAH. At initial presentation, poor-grade SAH may be secondary to acute hydrocephalus requiring emergent ventriculostomy. Other CSF diversion techniques are typically reserved for late complications of SAH (discussed below). Though surgical clipping is a more invasive procedure, it accomplishes complete obliteration of the aneurysm in 91.8% of cases.

Ventriculostomy. This procedure involves the placement of a soft catheter into the ventricle to allow ICP measurement and CSF drainage. This can be done at the bedside or in the operating room during surgical clipping of the aneurysm. The benefit of an external ventricular drain stems from the experience that not all poor-grade SAH are immediately catastrophic due to complete cerebral circulatory arrest. Some 20-30% of patients with aneurysmal SAH have acute hydrocephalus and may manifest as poor-grade SAH. We emergently place an EVD in all our poor-grade patients to measure and relieve the intracranial pressure via cautious CSF drainage. This improves the clinical grade of some patients and thus decreases mortality. Acute deterioration from a good grade SAH may also result from acute hydrocephalus and is clinically suggested by worsening mental status, upgaze palsy, slow pupillary response, bilateral 6th cranial nerve palsy and bilateral lower extremity spasticity. Hence, the indications for an EVD in aneurysmal SAH are hydrocephalus, intraventricular hemorrhage, and poor-grade SAH. A theoretical advantage has been suggested in placing an EVD in patients with large amounts of SAH. Clearing of the bloody CSF may decrease the severity of vasospasm, but this remains to be proven clinically. When we use this approach, it is not done at the expense of increasing the risk of infection due to prolonged EVD use. Opponents to this theory suggest that the CSF drained is primarily from the ventricles where it is produced, thereby discouraging drainage of subarachnoid blood in the cisterns via their natural pathways.

As with every procedure in the intensive care unit, EVD insertion carries risks – aneurysmal rebleeding, infection (ventriculitis), and intracerebral hemorrhage. Theoretically, the concern about aneurysmal rebleeding is due to relieving the tamponade effect of elevated ICP on the transmural wall pressure of the aneurysm. Our practice has been to set a high pressure CSF drainage level (e.g., 20-25 mmHg) to avoid this complication in

patients with unsecured aneurysms while preserving cerebral perfusion pressure. Placing an EVD under strict sterile technique, maintaining a closed system, and timely decision on removing the EVD are important factors that help in minimizing infection. Other preventive measures include the use of antibiotic-coated catheters or antibiotic prophylaxis (e.g., cefazolin 1 g/8 h or clindamycin in patients with penicillin allergy) which are continued for the duration of the EVD. This, however, is a controversial issue: it decreases the rate of ventriculostomy-associated infections but increases the incidence of methicillin-resistant Staphylococcus aureus (MRSA) and Gram-negative infections. However, we have found daily CSF surveillance for glucose, protein, cell count, gram stain and culture to be helpful. A low glucose level with or without CSF positive cultures is highly suspicious of CSF bacterial infection. Prompt removal of the EVD and broad-spectrum antibiotics are our initial aggressive approach. Intracerebral hemorrhage complicating EVD insertion is commonly seen in the setting of an underlying coagulopathy, rupture of a bridging vein or cortical vessel and multiple passes or attempts to drain the ventricles. In non-emergent circumstances, we aim to correct the underlying coagulopathy or thrombocytopenia (INR <1.4 and platelet >100,000/µl) prior to inserting an EVD. In the case of an emergency EVD, we have found transfusing with fresh frozen plasma and/or platelets, as required before, during and after the procedure, to be helpful in reducing these complications. Factor VII could also be an option in these settings, but the cost limits its availability in some centres.

Surgical clipping. This surgical procedure accomplishes a higher rate of aneurysm obliteration as compared to endovascular repair and hence less need for re-exploration of the aneurysm. In the ISAT study, surgical clipping demonstrated a lower rebleed rate compared to aneurysm coiling. Also, the study showed that the need for retreatment of the aneurysm persisted in the long term after coiling as opposed to surgical clipping. It appears that surgical clipping was more beneficial in younger patients and larger lumen aneurysms. Among these features, other patient or aneurysm characteristics that favour surgical clipping include middle cerebral artery aneurysm, very small or large to giant aneurysms, wide neck aneurysm, associated intracerebral hemorrhage or parenchymal hematoma, and failed endovascular coiling. Despite the apparent advantage in securing a ruptured aneurysm, not all patients are eligible for surgical treatment. Relative exclusion criteria include poor clinical grade or complicated medical history, severe diffuse brain swelling that limits retraction during surgery, posterior circulation aneurysms due to their technically difficult access.

Another advantage of surgical clipping is the ability to create an internal CSF diversion by fenestration of the lamina terminalis during the surgical procedure. Some case series have suggested a decrease in the incidence of chronic hydrocephalus requiring a CSF shunt after this procedure. Uncommonly, decompressive craniectomy may be offered in the setting of severe diffuse cerebra edema, especially when there is associated intracerebral hemorrhage.

Post-operative care is geared towards:

- Detection of intracranial bleeding after surgery (intra-or extra-axial).
- Monitoring of specific complications of aneurysms, such as the development of diabetes insipidus after surgical clipping of anterior communicating artery aneurysms secondary to occlusion of hypothalamic perforating arteries or the detection of lower cranial nerve palsy associated with surgery for aneurysms of the posterior circulation.
- Early detection of brain, cerebellar or brainstem infarctions associated with the surgical procedure (particularly associated with the clipping of aneurysms of the middle cerebral artery, anterior cerebral, posterior inferior cerebellar and basilar artery aneurysms).

- Occurrence of seizures in the postoperative period and disturbances in the level of consciousness secondary to non-convulsive epilepsy.
- Development of cerebral edema or venous infarction associated with handling and surgical retraction.

Our practice is to control blood pressure with intravenous antihypertensives for the next 24-36 hours after the exclusion of the aneurysm. Subsequently, tight blood pressure control is relaxed as part of the preventive measures of vasospasm associated with aneurysmal SAH. Intubated patients are left on mechanical ventilation with short-acting sedatives for 24 hours; the ventilator is turned off for intermittent neurological evaluation.

51.3.2 Medical Management After Initial Aneurysm Treatment

Once a ruptured aneurysm is secured, the focus on medical management holds significant importance. The incidence of medical complications of aneurysmal SAH (23%) equals the rebleeding and vasospasm rates (23% and 22%, respectively). Our approach in this setting is guided by the principles of anticipating and preventing delayed cerebral ischemia due to vasospasm, with the management of medical complications peculiar to specific aneurysms (e.g., diabetes insipidus in anterior communicating artery aneurysm) and distinguishing neurological deterioration as a primary event or as a secondary manifestation (e.g., encephalopathy due to fever, hyponatremia, hypo- or hyperglycemia).

Fluid management. An important aspect of aneurysmal SAH management involves close attention to intravascular volume status. Following invasive procedures, especially with endovascular coiling, significant diuresis has been observed due to injection of contrast dye, with the concern that vasospasm may be worsened in the dehydrated state. Thus, close attention to periprocedural fluid balance is helpful in maintaining and responding to changes in intravascular volume. Ideally, strict intake-output monitoring should be instituted at admission. We have also found daily weight measurement to be helpful especially in some settings, as this also accounts for insensible losses over time. The goal is to maintain a slightly positive balance (500 ml) and if a central venous line is available, a central venous pressure (CVP) of 4-8 mmHg. Obviously, this approach should be adjusted in patients with cardiopulmonary dysfunction. We have found that placing a CVP monitor in this subgroup of patient is helpful, however, the timing should be such that it coincides with the period of vasospasm. Our choice of intravenous fluid is normal saline used at a standard infusion dose of 100-125 ml/h, suited to the conditions and requirements of a particular patient. This is also reasonable in patients with cerebral edema, as the main objective in these cases is to try to maintain a normal serum sodium level, while avoiding hyponatremia. We avoid the use of any hypotonic solution, except for enteral feeding usually supplemented with doses of saline (100-200 ml bolus every 4-6 h via gastric tube) or salt tablets (NaCl) by the same route.

Maintaining a “slightly wet state” has been routine practice in the management of SAH in recent years. We recognize that in patients with poor or borderline cardiorespiratory status this approach may increase the rate of complications such as pulmonary edema or difficulty in weaning off mechanical ventilation. Obviously, this policy must be tailored to this group of patients.

Electrolyte abnormalities. Electrolyte abnormalities are common in several clinical series. They may result in encephalopathy, or even cerebral edema in the case of hyponatremia. Hyponatremia is seen in 20-40% of patients and may result from the syndrome of inappropriate ADH secretion (SIADH) or cerebral salt wasting (CSW). Although

CSW and SIADH are viewed as distinct syndromes, it is our opinion that the two lie on a spectrum of sodium metabolism abnormalities in SAH. The presence of hyponatremia, increased urine sodium and hypovolemia usually suggests CSW. It appears that an increase in atrial and brain naturietic peptide after SAH may play a pathophysiological role in CSW. We have found CSW to be more common in SAH and that it heralds vasospasm; very rarely do we encounter isolated SIADH in our patient population. Some series have reported an early dilutional hyponatremia due to an observed surge in arginine vasopressin resulting in retention of free water. The hyponatremia of CSW can be treated with hypertonic saline infusions, fludrocortisone or oral salt tablets. Importantly, the associated diuresis should be replaced as it may lead to dehydration which is associated with cerebral hypoperfusion in cases of severe vasospasm. In a setting of SIADH, the challenge is to avert intravascular volume contraction. Hypomagnesemia is frequently seen, and aggressive correction has been investigated in several studies in an attempt to prevent vasospasm and delayed cerebral ischemia. The results have been conflicting. The rationale for this approach is the experimental demonstration of increased intracellular calcium associated with neurotoxicity ischemia and cell death; magnesium, a natural calcium antagonist, is thought to inhibit these cellular mechanisms. In a recent serie, a decrease in vasospasm was observed but no significant benefit with aggressive supplementation. Our approach continues to be to normalize the levels to the upper limit of the normal reference range (>2.0 mg/dl).

Hypernatremia occurs in such settings as: iatrogenic effect of hypertonic saline solution for managing intracranial hypertension and diabetes insipidus associated with severe diffuse brain damage (usually in the context of a very poor-grade SAH) or immediately after treatment of an anterior communicating artery aneurysm with compromise of the perforating vessels that supply the hypothalamus. Judicious use of hypotonic solutions, strict monitoring of serum sodium values, and potential use of desmopressin (DDAVP) needs to be evaluated in each case. In cases of diabetes insipidus, because severe dehydration can happen in some patients, it needs to be recognized immediately and treated aggressively with appropriate fluid replacement.

Fever. In most circumstances, the definition of fever as a temperature >38.5°C is reasonable but should not lead to complacency in aggressive management of low-grade fever which may manifest as encephalopathy or progressive neurological worsening. Evaluating for infectious and non-infectious causes allows for thorough assessment and appropriate intervention. Non-infectious causes to be considered include vasospasm, atelectasis, venous thromboembolism and transfusion-related reactions. The importance of prompt identification and treatment stems from the impact of fever on acute brain injury which includes altered mental status (encephalopathy), increased oxygen consumption causing an increased metabolic strain on injured neuronal and glial tissue, ischemic injury and worsening of cerebral edema leading to increased intracranial pressure. We have employed common physical (e.g., cooling blankets and Bair hugger cooling system) means and pharmacological agents (acetaminophen) with a goal temperature of <37.5°C. Of concern is the role of shivering in patients at risk of elevated intracranial pressure. Low doses of fentanyl have been helpful in our patient population. In cases were sedation is employed, propofol has been a helpful option. Rarely if ever should muscle relaxant be considered due to the increased incidence of critical illness neuropathy and myopathy.

In recent years the use of more sophisticated cooling methods such as intravascular catheters and contact cooling systems has increased and has proved to be a more effective and easy way to maintain temperature within the desired range and also allow optimization of gradual warming in cases where hypothermia is applied. In summary, strict temperature control and manipulation within the normal or desired range is one of the

current key interventions (and not so hard to achieve) that could prevent or ameliorate ischemic damage and progression of cerebral edema.

The diagnosis of fever of central origin is one of exclusion and can be established only when all other causes have been excluded. It is relatively common, usually overdiagnosed, and the danger is to by-pass treatable causes of fever. It is generally associated with severe brain damage or hypothalamic lesions.

Infections. Apart from being an important cause of fever, infections are a potential cause of increased length of ICU stay, morbidity and mortality in SAH. Common infections seen in SAH patients include pneumonia, urinary tract infections, bloodstream infections, meningitis and ventriculitis (see above). It appears that infections in SAH patients are more common in those with a central venous catheter, under mechanical ventilation or with a ventricular drain for intraventricular hemorrhage. It is believed that the heightened inflammatory response that follows infections also worsens the inflammatory component of cerebral vasospasm after aneurysmal SAH. Except for patients with EVD where we employ CSF surveillance, we do not conduct routine surveillance for other infections, relying more on the clinical picture of fever, increased sputum production or discoloration in ventilated patients, elevated white blood cell count and infiltrates on chest X-ray. Initial broad-spectrum antibiotic therapy is reasonable when subsequently narrowed to microbiological sensitivity results.

Anemia. It seems that there is a direct effect of SAH on red blood cell production, possibly related to increased cytokine production. Other possible factors include frequent phlebotomies, complications of invasive procedures and hemodilution from intravenous fluid infusions. The definition of anemia requiring transfusion has varied in different series and is controversial due to reports of poor outcome in SAH patients receiving transfusion and an increased risk of vasospasm. The reason for a poor outcome is unclear, though it is possible that patients who received blood transfusion were severely ill patients. Another consideration is the depleted nitric oxide (NO) content of packed red blood cells (PRBC). Nitric oxide is a potent vasodilator and may have a significant role in reversing vasospasm hence PRBC transfusion may decrease circulating NO concentration, with decreased end-organ perfusion by the microcirculation. Also, older PRBCs have proinflammatory properties and so may exacerbate the inflammatory component of vasospasm.

Despite these proposed drawbacks of blood transfusion in SAH patients, reports from recent studies suggest that low brain tissue oxygen and cellular energy dysfunction (lactate/pyruvate ratio >40) has been correlated with hemoglobin (Hb) <9 g/dl; however, the effects on functional outcome are unknown. Transfusion of PRBC in patients with Hb <7 g/dl has been our practice. In the 7-10 g/dl population, our decisions are driven by factors such as cardiac disease with evidence of dysfunction or impending failure, need for volume expansion with an added effect of increasing tissue oxygen delivery and the presence of vasospasm or risk of cerebral ischemia.

Hyperglycemia. The adverse effect of hyperglycemia on neuronal function in the clinical setting of acute brain injury is known, as has been observed in acute ischemic stroke, traumatic brain injury and in several series of aneurysmal SAH. In one series, blood glucose >200 mg/dl was a significant predictor of poor functional outcome in acute ischemic stroke and SAH. Other smaller series have shown hyperglycemia to be associated with an increased risk of symptomatic vasospasm and rebleeding in SAH patients. What constitutes an acceptable range for blood glucose has been the subject of debate based on studies on intensive insulin therapy due to concerns of severe hypoglycemia. The relationship between hyperglycemia and poor functional outcome appears to be independent of a history of diabetes mellitus in brain-injured patients in some series. In acute ischemic stroke studies, a worse functional outcome was observed in hyperglyce-

mic non-diabetic patients compared to diabetic patients. Also, in series involving SAH populations, the correlation of hyperglycemia and poor functional outcome was independent of factors that predicted hyperglycemia, such as diabetes mellitus. Hyperglycemia in these circumstances may be one part of a general stress response to the primary brain injury. The effects of the stress response leading to an increased sympathetic nervous system response as well as increases in stress hormones such as corticosteroids, glucagon and somatotropin may play an additional role in stress-induced hyperglycemia. However, despite the benefit of tight glycemic control, a common complication, hypoglycemia is likely to lead to significant neuronal dysfunction and may result in seizures and ischemia. This is based on observations using microdialysis techniques demonstrating critical decreases in cerebral glucose, an elevated lactate/pyruvate ratio, and cerebral glycerol (a marker of tissue damage or cellular distress) levels with normalization of hyperglycemia to a target of 140 mg/dl. Clinical studies have also identified hypoglycemia <60 mg/dl as an independent predictor of mortality at discharge. So far, all these point to a possible and significant detrimental effect of aggressive and tight glucose control in a subpopulation of patients with acute brain injury who may actually tolerate and benefit from a higher serum glucose level as compared to non-brain injured patients. Our approach is to institute aggressive treatment of blood glucose >180 mg/dl, starting at a low titration regimen. Where needed, conversion to a longer-acting insulin regimen is considered once clinical stability has improved and before discharge from the ICU.

Deep venous thrombosis. In the presence of focal weakness due to neurological injury, the incidence of deep venous thrombosis (DVT) appears to be higher in neurocritically ill patients. The use of prophylactic antithrombotic agents is complicated by the relatively increased risk of intracranial hemorrhage. Clearly, all antithrombotics should be avoided in the setting of acute SAH until the aneurysm is secured. This also applies to postsurgical patients for the first 24 hours, after which the decision to reinstate antithrombotic agents should be entertained. Heparin given at a dose of 5000 units twice a day has been our initial approach for the first few days, which is then advanced to an 8-hourly regimen as stability in hemorrhage is demonstrated. In addition, weekly venous duplex surveillance of the lower extremities is part of our routine practice. In our opinion, this offers an opportunity for aggressive treatment of progressive distal or proximal DVT. If proximal DVT is documented in the lower extremities and the patient has a contraindication to systemic anticoagulation (such as very recent bleeding, presence of intracerebral or extra-axial hemorrhage, presence of a fresh ventriculostomy, severe hypertension induced as part of vasospasm treatment), we proceed to the placement of a retrievable inferior vena cava filter with the idea that it will probably be safe to start anticoagulation later on and eventually remove the filter. In patients with distal DVTs of the lower extremities (below the popliteal vein), the treatment possibilities include systemic anticoagulation, inferior vena cava filter placement or venous duplex follow-up every 3 or 4 days (without treatment) to exclude the spread to more proximal veins. If this occurs, it should be treated like any proximal DVT.

Pulmonary complications. This represents a common complication in up to 80% of SAH patients and correlates with an increased ICU length of stay and poor functional outcome (impact on functional outcome varies in different series depending on whether neurological outcome was a main measure or not). Frequently encountered pulmonary complications include pneumonia, pulmonary edema, pneumothorax, transfusion-induced acute lung injury and pulmonary embolism. Pneumonia is observed more in aspiration due to poor airway control due to encephalopathy, ventilated patients or lung seeding from bacteremia. Pulmonary edema is commonly a result of fluid overload. Occasionally, one may come across patients who develop tachypnoea, hypoxia and bilateral pulmonary infiltrates, which raise the suspicion of neurogenic pulmonary edema. This

usually follows an acute neurological insult such as SAH, head injury, intracerebral hemorrhage, and seizures with or without status epilepticus. There may be pulmonary shunting, however, the electrocardiogram, echocardiogram and central venous pressures may be normal. Two possible theories have been linked to this phenomenon. One states that there is a sudden increase in sympathetic tone following an acute neurologic insult inducing pulmonary vasoconstriction due to massive catecholamine release with subsequent alteration of the Starling forces in the lungs with a resultant shift of fluid into the pulmonary alveoli. The second theory suggests an increase in inflammatory mediators that damage the endothelium, leading to abnormal capillary permeability. Fluid overload may also lead to pulmonary edema, which commonly occurs in patients with poor cardiac function and or overzealous fluid resuscitation during treatment for vasospasm. Management in both circumstances requires close attention to maintaining adequate ventilation with invasive or non-invasive methods depending on the severity of the respiratory insufficiency, avoiding manoeuvres that decrease cerebral perfusion pressures such as high positive end-expiratory pressures. Administration of intravenous fluids or several doses of volume expanders (e.g., albumin) for a few hours with cautious diuresis using low doses of diuretics have been helpful in our experience. It is important to note that dehydration worsens ischemia due to vasospasm so that in this setting maintaining an adequate intravascular volume is highly important. Hence, small doses of diuretics (e.g., furosemide 10 mg intravenously) given ever so often, while carefully monitoring the input-output balance has been our approach. The use of central venous pressure monitoring is helpful in directing diagnosis and treatment in these dicey situations.

The frequency of pulmonary embolism in neurologically ill patients is relatively low (0.3%) but can be devastating, nonetheless.

The treatment of pulmonary embolism often becomes a complex decision, particularly in the presence of a fresh external ventricular drainage, very recent bleeding, intracerebral or extra-axial hemorrhage or patients with vasospasm and severe induced hypertension, since the risks of bleeding in the context of systemic anticoagulation are quite high. Our practice in such circumstances has been to place an inferior vena cava filter until it is safe to start anticoagulation. In some cases, we have started continuous intravenous anticoagulation with heparin at low doses in order to obtain an activated partial thromboplastin time (aPTT) 1½ times above the patient's baseline aPTT (we don't use a bolus dose of heparin) for the following 36-48 hours. If the patient is neurologically stable, we repeat a head CT without contrast material to monitor the presence of asymptomatic intracranial bleeding. If there is not new bleeding, we then slowly increase the heparin dose to achieve the ideal aPTT in the following 24-36 hours. A new head CT is performed to rule out bleeding and if the patient remains stable, we start a low-dose oral anticoagulant, trying not to exceed the ideal prothrombin time for that patient. Of course, if the patient develops a new bleeding, heparin is stopped immediately, and emergent reversal with protamine is considered.

Cardiac complications. The effect of acute intracranial insults on cardiac function appear to be multifactorial, with instability of the autonomic function a proposed mechanism. Several reports in the epilepsy literature have described cardiac arrhythmia following discharge from epileptic foci in the brain. The same has been observed in acute ischemic and hemorrhagic strokes and commonly reported to involve the insula and parieto-temporal cortex. Similar observations have been made with a vast array of electrocardiographic abnormalities observed in up to 92% of SAH patients. These include ST segment alterations (15-67%), T wave changes (12-92%), prominent U waves (4-52%), QT prolongation (11-66%), conduction abnormalities (7.5%), sinus bradycardia (16%) and sinus tachycardia (8.5%). Life-threatening arrhythmias are less common and are mostly supraventricular tachyarrhythmias associated with older age, prior history of an ar-

rhythmia, hyperglycemia, brainstem herniation and myocardial infarction. Management of arrhythmias should follow typical measures with caution in the setting of cerebral edema and vasospasm to avoid hypotensive events that would compromise cerebral perfusion or lead to delayed cerebral ischemia (DCI). Following acute aneurysmal SAH, there has been reports of a marked elevation of endogenous catecholamines from the cardiac sympathetic nerves leading to a syndrome described as neurogenic stunned myocardium. The clinical syndrome is characterized by tachycardia, elevated troponin I, transient lactic acidosis, diffuse T-wave inversions, prolonged QT interval, reversible left ventricular wall abnormalities, pulmonary edema and cardiogenic shock. This neurogenic stunned myocardium is associated with a wide spectrum of reversible left ventricular wall motion abnormalities and includes a subset of patients with a typical pattern of apical akinesia and concomitant sparing of basal segments called "tako-tsubo cardiomyopathy". It is important to emphasize that most of these stress-related scenarios are eventually reversibly. Poor clinical grade, advanced age, prior use of cocaine and amphetamines have been described as risk factors for neurogenic stunned myocardium. We have consistently observed tachycardia and elevated troponin levels with this syndrome. Though elevated cardiac enzymes is a common finding in SAH, occurring in 68% of patients in one series, it appears that these findings, along with abnormalities on electrocardiography and echocardiography, were associated with delayed cerebral ischemia, poor outcome and death at 6 months. The interplay between acute brain injury and secondary cardiac injury such as neurogenic stunned myocardium becomes complicated in attempts at decreasing the effects of vasospasm after SAH. In cases where there is a need to augment intravascular volume and cerebral perfusion, we have typically leaned towards preserving brain function while closely monitoring cardiac functions with serial cardiac enzymes, electrocardiogram and echocardiograms. We have also found measuring central venous pressures and non-invasive cardiac index monitoring a reasonable and reliable substitute to placing pulmonary artery catheters. It is our routine practice to obtain a baseline transthoracic echocardiogram within 48 hours of admission to assess the patient's cardiac anatomy and function, as probably a third or more of patients with SAH may need adjustment of the hemodynamic status at some point in their course. Early knowledge of situations such as low baseline ejection fraction, severe left ventricular hypertrophy or hypertrophic stenosis of the outflow tract of the left ventricle is essential when selecting the drugs to be used for manipulation of the hemodynamics in these patients.

Hydrocephalus and the need for long-term CSF shunt. The management of acute hydrocephalus has been discussed earlier. This section addresses the 18-26% of patients who will ultimately require permanent CSF shunting due to subacute or chronic hydrocephalus (3-7 days and >1 week, respectively). Predicting these patients may sometimes be difficult, with some series suggesting advanced age, ventriculomegaly, intraventricular hemorrhage, poor clinical grade and female sex as possible associated factors. It seems reasonable to assume that the development of hydrocephalus after SAH is related to the presence of blood. Studies on animal models of hydrocephalus show an increase in intracranial pressure following the injection of blood into the subarachnoid space as opposed to saline. However, chronic hydrocephalus has also been associated with decreased CSF outflow from the fourth ventricle and/or compromised resorption of CSF through the arachnoid villi from fibrin deposition in these structures, since instillation of heparinised blood only results in a transient rise in intracranial pressure. However, the subsequent development of chronic hydrocephalus may be a result of an interplay between these two processes. SAH from posterior circulation aneurysms is associated with a higher incidence of hydrocephalus than anterior circulation aneurysmal rupture, possibly due to fibrin deposition in the fourth ventricular outflow and it may be the primary factor in chronic hydrocephalus. The diagnosis of chronic hydrocephalus

is based on clinical and radiological grounds. Clinical features include worsening mental status, which may be slow and progressive, bilateral sixth cranial nerve palsy and upgaze restriction. The presence of progressive ventriculomegaly on imaging studies supports the diagnosis. If an EVD was inserted during admission, a diagnosis of hydrocephalus is also possible during the weaning process of the EVD. This is evidenced by monitoring the CSF volume and ICP as the "pop-off" pressure is increased, rising CSF drainage volume output and ICP, with each increase in pop-off predicting a need for internalization of CSF drainage. Another tool is measuring the bicaudate index – a ratio of the width of the frontal horns at the level of caudate nuclei and the diameter of the brain at the same level. Reference ranges vary by age but are usually between 0.16-0.21

When we consider that the patient can begin weaning off the ventriculostomy, we do it gradually by increasing the opening pressure at a rate of about 5 mmHg per day (for example, if the ventriculostomy was opened at 10 mmHg, now we increase it to 15 mmHg and 24 hours later to 20 mmHg, etc.). During this dynamic process, we carefully watch for the presence of:

- Signs of neurological impairment (usually manifesting as impaired consciousness, sometimes subtle upward vertical gaze impairment and/or increased extensor tone of the lower limbs).
- Headache as a new manifestation or a significant increase in its intensity.
- Increased intracranial pressure.
- Ventricular enlargement on head CT as measured by the bicaudate index (a ratio of the width of the frontal horns of the lateral ventricles at the level of the caudate and the diameter of the brain at the same level). The ranges vary according to age.

If none of the above occurs, then we close the ventriculostomy and observe the patient; a new head CT is performed 24-48 hours later, and then we decide whether the ventriculostomy can be discontinued. Some other schools have a more aggressive policy for ventriculostomy weaning, placing many more permanent CSF shunts (a ventriculoperitoneal shunt in general). We prefer a slower weaning that allows us to drastically reduce the need for permanent CSF diversion, with a consequent decrease in long-term complications associated with this procedure. Long-term follow-up head CT is important because some patients may develop hydrocephalus with a delay of several weeks or possibly months. Some studies have proposed intraoperative fenestration of the lamina terminalis as a preventive measure, although other studies have shown no difference in the rate of development of chronic hydrocephalus.

51.3.3 Vasospasm

Following aneurysmal SAH, cerebral vasospasm remains a significant cause of mortality and morbidity in 50% of cases. Cerebral vasospasm refers to the narrowing of arterial blood vessels, leading to a decrease in brain perfusion, and has been linked to delayed cerebral ischemia (DCI). In this circumstance, vasospasm is termed symptomatic vasospasm. Cerebral vasospasm in general occurs in 30-70% of cases of SAH, afflicting the younger population (<35 years of age) more frequently, hence causing a greater impact on lost productive years. The relatively lower prevalence of cerebral vasospasm in the elderly has been attributed to stiffening of the vascular wall by atherosclerosis. The onset of vasospasm is typically 3-5 days after aneurysm rupture and peaks at about 7-10 days and subsequently resolves over a period of 2-3 weeks.

Vasospasm can be classified on clinical grounds based on the presence or absence of clinical neurological deficits: symptomatic or asymptomatic vasospasm; by sonography (transcranial Doppler) based on mean flow velocity in the cerebral vessels; radiological-

ly based on the presence of stenosis across a specific cerebral vessel. The presence of symptomatic vasospasm or DCI correlates with a poor outcome; therefore, preventive measures and therapeutic manoeuvres in this circumstance become important.

Our understanding of the pathophysiology of cerebral vasospasm in aneurysmal SAH is incomplete; however, the presence of oxyhemoglobin within the subarachnoid space and cisterns appears to instigate smooth muscle spasm and impaired autoregulation. This is supported by the relationship of clot thickness to the development of vasospasm and it may be that cisternal blood depletes vasodilatory or activates vasoconstrictor mediators. Also, pathological sections of arterial walls in cerebral vasospasm show an infiltration of the arterial wall by inflammatory cells which may perpetuate smooth muscle vasospasm and vessel wall stiffening. The significance of these pathophysiological mechanisms has been recently called into question as not all patients with vasospasm are symptomatic, i.e., DCI. In fact reversing vasospasm has not resulted in a reduction in DCI, as suggested in the CONSCIOUS study, raising the hypothesis that vasospasm may be an epiphenomenon or play a limited role in the ultimate development of DCI. Several other mechanisms that lead to DCI have been proposed, such as microcirculatory dysfunction, microthromboembolism, imbalance of endogenous vasodilators (nitric oxide) and vasoconstrictors (endothelin-1), and cortical spreading depression. Though several questions remain about the role of vasospasm in DCI, it constitutes an important aspect of SAH since there is a strong correlation between vasospasm and DCI. Hence, diagnosis, monitoring and treatment of vasospasm remain very important.

Clinical Features

In most cases, especially in the early phase, vasospasm is predominantly asymptomatic. Subsequently, headache, slow mentation, mild disorientation may be initial manifestations in these tenuous states. This should prompt detailed neurological examination focusing especially on the territory supplied by the vessel at risk, with a low threshold for calling abnormal changes. It is helpful to document a change in serial clinical examination (especially if performed by the same examiner) or to demonstrate sonographic evidence of a serial rise in mean flow velocity in the vessel in question. It cannot be overemphasized that attention to detail during the neurological examination in detecting subtle neurological changes is key to identifying DCI, as it helps direct the next diagnostic and or therapeutic intervention.

Also, it is important to remember that in most cases the installation of vasospasm is progressive as well as the decreased cerebral blood flow in the affected territory. This means that the ischemic areas commonly affected are initially the ones with higher metabolic consumption, such as the cerebral cortex; therefore, the typical initial signs of brain dysfunction associated with vasospasm may include the appearance of minimal encephalopathy, subtle disturbances in understanding and/or language expression, presence of inattention or neglect of one side of space, appearance of some apraxia, difficulty recognizing objects, the appearance of defects in the visual field or the presence of hemiparesis. Such abnormalities on the neurological examination are sometimes missed by the inexperienced observer, so it is important to perform a routine and repeated comprehensive neurological examination in patients with aneurysmal SAH at risk of developing vasospasm. In poor-grade or sedated and ventilated SAH patients, identifying subtle neurological changes by clinical examination is a challenge. In this circumstance, the use of short-acting sedatives to enable neurological examination while the sedatives are turned off becomes paramount. Some other clues in the diagnosis of vasospasm include an unexplained sustained rise in blood pressure and or ICP, if an ICP monitor is in place, the development of fever without a clear infectious source, and the appearance of hyponatremia generally secondary to a cerebral salt wasting syndrome.

Transcranial Doppler Ultrasound

This non-invasive method of measuring blood flow within a vessel by Doppler sonogram is based on the principle that the velocity of blood flow in an artery is inversely proportional to the ratio or luminal diameter of the vessel. The reflection of the ultrasound waves bouncing back from the red blood cells is used to measure the velocity during systole and diastole, from which mean flow velocity (MFV) and pulsatility index (PI) are calculated. These two parameters have been used as an index of severity of vasospasm. Cerebral vasospasm is suggested by a rising MFV and falling PI. Despite its non-invasiveness, ease of use and availability, transcranial Doppler (TCD) is plagued by significant limitations. The sensitivity of TCD is 67%, specificity 99%, with a positive predictive value of 97% and a negative predictive value of 78%. This holds for assessing the middle cerebral artery but may become highly unreliable in other vessels. In certain circumstances such as a hyperdynamic state, the absolute values of the MFV may be misleading; instead, using the Lindergaard ratio (ratio of velocity in the target intracranial vessel to the velocity in the ipsilateral extracranial carotid artery) is helpful for tracking trends. Monitoring with TCD is operator-dependent, showing wide variations according to operator experience and technique. Our approach has been to perform daily TCDs, typically by the same operator and following the trend of MFV and PI with frequent detailed neurological examination which guides our decision for further diagnostic options or treatment modification. In our opinion, TCD is a very useful daily screening tool for vasospasm in patients with aneurysmal SAH.

Radiological Studies

The significance of imaging studies in cerebral vasospasm hinges on the demonstration of vessel narrowing with or without cerebral ischemia. The role of non-contrast CT study of the head relies on the appearance of hypodensities in vascular territories suggesting cerebral ischemia. The obvious limitations of a delayed diagnosis and a low specificity and sensitivity are driving the search for more reliable CT studies. Contrast-enhanced CT angiograms demonstrate vessel narrowing up to the second order intracranial vessels suggesting vasospasm in SAH and is usually combined with CT perfusion studies. There has been a trend towards the use of perfusion CT studies to measure the mean transit time (MTT), cerebral blood volume (CBV), and cerebral blood flow (CBF) to predict cerebral ischemia. It appears that prolonged MTT may be an early predictor of DCI and angiographic vasospasm. The usefulness of these modalities is evident in patients with symptomatic vasospasm, especially in settings of nonspecific changes on the neurological exam or in the sedated and ventilated difficult to examine patient. Frequently we have encountered patients who develop high MFV, suggesting severe vasospasm with a normal or unchanged neurological exam. We typically have performed a CT perfusion study at day 7-9 from aneurysm rupture to assess for radiological evidence of cerebral ischemia.

Conventional cerebral angiography remains the gold standard for diagnosing vasospasm up to third and fourth order vessels. It has the advantage of prompt diagnosis and treatment with either balloon angioplasty or intra-arterial vasodilators. There is no consensus on the timing of the angiogram, with some authorities opting for a routine angiogram in all patients during the peak vasospasm period, with the intent to offer endovascular treatment following the diagnostic angiogram. Our experience has been that symptomatic vasospasm may be reversible with medical treatment alone, thus avoiding the added risk of the angiogram. Therefore, we reserve a diagnostic cerebral angiography for cases of unexplained neurological deterioration or for patients sedated and ventilated where it is very difficult to see changes in the neurological examination established after

aggressive medical treatment, as well as in cases where the artifacts produced by clips or coils prevent the correct interpretation of angio-tomographic images (CTA) or in patients in whom cerebral ischemic symptoms persist despite medical treatment. In these latter cases, we proceed immediately (after about 1 hour of aggressive medical treatment) to angiography to confirm the diagnosis of vasospasm and to perform mechanical or pharmacological angioplasty.

Medical Treatment

The aim of medical management of cerebral vasospasm is to decrease the risk of ischemia by improving cerebral blood flow, decreasing ICP, and decreasing metabolic oxygen demand. Historically, the triple 'H' therapy (hypertension, hypervolemia and hemodilution) has been the mainstay in the management of cerebral vasospasm although more recently the focus from triple-H therapy has shifted to the maintenance of euvolemia and induced hypertension. This represents a hyperdynamic state to increase cerebral perfusion pressure and cerebral blood flow. Despite its wide application, there is no strong evidence to support its use. It is important to note that the approach to management should be divided into prevention and treatment of vasospasm. The preventive measures include avoiding medical complications such as hyperglycemia, acidosis, electrolyte abnormalities, hypoxia, fever, and seizures as discussed earlier. Also, maintaining euvolemia may be guided by a slight positive fluid balance to accommodate for insensible losses. Two small randomized trials comparing prophylactic hypervolemia and euvolemia showed no difference in symptomatic vasospasm, cerebral blood flow or outcome. The development of CSW, which is common with cerebral vasospasm, adds a bit of a challenge to the care of these patients, as there is inappropriate diuresis and hyponatremia. Hypertonic saline infusion is commonly used but may in itself be an iatrogenic cause of diuresis. Hyponatremia and diuresis should be monitored closely and replaced, as they has been associated with the development of DCI. Prophylactic nimodipine should be started at the initial contact with the patient, as it has been shown to improve outcome by decreasing the relative risk of DCI by 18%; however, it has minimal or no effect on the incidence of vasospasm. Quite frequently, when a hyperdynamic state is needed, the hypotensive effect of nimodipine may pose a challenge. In this circumstance, splitting the dose (from 60 mg q4/h to 30 mg q2/h) may be helpful. Discontinuing the administration of nimodipine may occasionally be required in patients where higher arterial pressures have demonstrated neurological improvement. In recent studies, statins, HMG-CoA inhibitors, have had mixed reports on their effect on vasospasm and DCI. Reports have suggested that the anti-inflammatory properties and upregulation of endothelial nitric oxide synthetase plays a role in decreasing vasospasm and DCI. The results of the ongoing large randomized controlled trial (STASH) will hopefully shed more light on this.

As vasospasm progresses, the development of a neurological deficit should prompt an adjustment in treatment goals. The decreased cerebral blood flow associated with DCI has been reported to reverse with increased blood flow from volume expansion equalling non-ischemic brain on PET scans. Also, the use of vasopressors has been reported to increase cerebral blood flow in ischemic brain tissue. Despite the absence of randomized studies, it seems that initiating a hyperdynamic state in high-risk patients is reasonable, though it must be added that this comes at a price of potentially significant complications such as cardiac failure, pulmonary edema, cerebral edema, electrolyte derangements, bleeding diasthesis from the dilution of clotting factors and renal injury. We find that TCD monitoring is helpful as one trends the MFV and PI especially in patients with thick perisylvian clot. The presence of a MFV >200 cm/s and a PI <0.6 suggests sonographic vasospasm in high-risk patients, so that inducing a hyperdynamic state seems reasonable. There are several ways to accomplish the hyperdynam-

ic state and it should be tailored according to each specific patient. Aiming for a central venous pressure goal of 12-14mmHg, or in cases of baseline cardiac dysfunction, a non-invasive cardiac output/index monitoring goal of 3-4 l/min/m^2 has been helpful to guide therapy. Our fluid of choice in the absence of hyponatremia or cerebral salt wasting is 0.9% saline. We have used 250 ml of 5% albumin given 3-4 times a day in this setting as a volume expander. Reports suggest that it may be effective in the setting of cerebral salt wasting to help maintaining an adequate intravascular volume. Fludrocortisone promotes sodium and fluid retention and can be effective when given in anticipation of symptomatic vasospasm as it requires 48 hours to take effect. We have usually reserved it for high-risk symptomatic vasospasm patients and/or patients with CSW. The use of vasopressors is common; however, we restrict its use to high-risk patients with poor response to fluid therapy in the setting of symptomatic vasospasm. Studies comparing vasopressor agents are lacking and the choice of agent is tailored to the patient's underlying co-morbidities. In the presence of preserved cardiac function, phenylephrine or norepinephrine has been our first choice agent, reserving dopamine for the setting of bradycardia. If there is evidence of cardiac dysfunction, a combination of phenylephrine or norepinephrine with dobutamine or milrinone is a viable option. Vasopressors are titrated with the aim of obtaining a systolic blood pressure necessary to achieve the reversal of neurological deficits (we usually try to achieve a systolic blood pressure of around 200 mmHg or up to 220 mmHg in selected cases). If pure ionotropic agents are used, we aim for a cardiac index of above 3 l/min/m^2 that could result in the reversal of the neurological deficits. While the patient is on vasopressors, daily monitoring of electrocardiogram, cardiac enzymes, lactic acid and chest X-ray are implemented to assess for evidence of end-organ damage. In neurogenic stunned cardiomyopathy, the use of ionotropic agents such as dobutamine or milrinone might be preferred, with an intra-aortic balloon pump being a last resort. Several recent reports have suggested that cardiac output goal-directed therapy appears safe and effective in reversing neurological deficits in patients with no known cardiac dysfunction, the advantage being the prevention of complications of hypertension.

Endovascular Treatment

The modalities employed in treating vasospasm include balloon angioplasty and intra-arterial infusion of vasodilating agents. In most cases, endovascular treatment is reserved for symptomatic vasospasm recalcitrant to optimum hyperdynamic medical treatment. Balloon angioplasty involves the dilatation of focal spastic vessels by balloon inflation and it is reserved for segmental narrowing of proximal vessels due to increased complications which include arterial dissection, rupture, thrombosis and reperfusion injury causing hemorrhage and cerebral edema. Balloon angioplasty is very effective in reversing spastic vessels and improving clinical outcome; however, direct comparison with medical treatment is lacking. We have reserved it as a second line treatment option for symptomatic vasospasm due to the magnitude of its complications. Intra-arterial agents used in the treatment of symptomatic vasospasm include papaverine, verapamil, nicardipine and nimodipine. Indications for intra-arterial vasodilators are similar to balloon angioplasty, except that it is reserved for distal vessel spasm or diffuse vasospasm where balloon angioplasty is technically not feasible or associated with high risk. Intra-arterial vasodilators are effective but unfortunately of transient effect; in addition, the use of papaverine may lead to toxic effects on the brain, causing seizures, blindness, coma and direct cortical injury. Ideally, an ICP monitor is beneficial when papaverine is used since it can cause a sudden rise in ICP due to its vasodilatory effect and increase cerebral blood volume. This is more likely in the setting of a deranged autoregulatory mechanism common in SAH.

51.4 Rehabilitation

The finding of neglect, poor judgment, poor recent memory recall, and several other findings on neurological examination are often overlooked during the bedside clinical examination. Its importance hinges on the design of rehabilitation methods and programs to optimize functional recovery. This is even more pressing as SAH afflicts the relatively young people in their most productive years. The return to a full productive life is the goal. However, the spectrum of the impact of aneurysmal SAH in patients who survive this brain insult spans from no discernible neurological deficits to severe disability. It is well known that the absence of lesions on imaging studies does not equate to an absence of neurological injury. A wide range of cognitive impairments is quite frequently observed on neuropyschometric testing. Physical and occupational therapy should be initiated as early as possible, with subsequent transfer to a rehabilitation centre familiar with brain injury. This aggressive approach to rehabilitation helps to address social adjustment, emotional and cognitive dysfunction.

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52 Neurocritical Care of Patients With Arteriovenous Malformations

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52.1 Introduction

Arteriovenous malformations (AVM) are vascular anomalies in which there is a group of dilated and conglomerated blood vessels allowing bloodflow from the afferent artery to the efferent veins without a capillary bed in between. The direct connection between arteries and veins through multiple fistulas allows the formation of a circuit of high flow and low resistance that exposes the nidus and the draining veins to high pressure.
AVMs may affect brain parenchyma (90%), brainstem, cerebellum or spinal cord. In this chapter we will emphasize the management of AV malformation in the brain, brainstem and cerebellum.

52.2 Anatomy and Physiology

The architecture of AV malformations consists of one or more arteries that supply blood flow to the malformation, the presence of a cluster of blood vessels that are fragile due to their thin walls and small size and the veins that drain blood. AV malformations are congenital lesions usually manifest clinically in the second decade of life suggesting that changes in hemodynamic characteristics that occur over time may increase the likelihood of rupture and hemorrhage. These hemodynamic changes appear to be caused by structural abnormalities observed in the wall of cerebral arteries; arteries deficient in the middle muscular layer [1] result in lack of flexibility of the vessel wall that impairs the ability of the artery to constrict when exposed to high pressure resulting in transmission of blood flow and pressure to the nidus and the draining veins. Consequently, the veins become “arterialized” due to exposure to high pressure. The resulting fibromuscular layer thickening, and the structural lack of the elastic lamina in the veins result in decreased flexibility and increased venous resistance which is transmitted to the small fragile blood vessels that make up the nidus increasing the risk of bleeding [2]. Additionally, it has been well documented that the presence of thrombosis and stenoses in the draining veins increases the risk of bleeding likely due to development of backpressure that increases the risk of bleeding into the nidus.

52.3 Epidemiology

The prevalence of AVMs in the general population is 0.01%. The risk of hemorrhage is 2% to 4% each year [3]. The occurrence of cerebral hemorrhage is associated with a risk of death of 5-10% [3] of patients. The possibility of permanent neurological deficits can be as high as 30-50%. Most cases are sporadic but familial predisposition has been ob-

served in case reports. It is believed that the predisposition to AVMs is congenital but that the pressure and volume changes over time result in the development of the actual AVM. They may be occasionally associated with other syndromes such as Osler-Weber-Rendu or Sturge-Weber syndrome [4,5].

52.4 Clinical Presentation

Intracranial hemorrhage is the most common clinical presentation and occurs in 42-72% of symptomatic patients. The risk of bleeding does not vary with sex of the patient and the first episode usually occurs between 20 and 40 years of age. The bleeding is usually associated with the presence of aneurysms in the feeding arteries or nidus. It is estimated that these are present in at least 7% of AV malformations. Another common cause of bleeding is the obstruction of the draining veins causing increased pressure in the nidus. In the neurocritical care unit, the patient presents in one of the following ways: 1) spontaneous rupture during an endovascular procedure to occlude the AVM causing intracerebral, intraventricular, or subarachnoid hemorrhage or any combination; 2) progressive neurological deficits simulating a stroke due to compression of adjacent tissue by edema from venous hypertension or ischemia caused by the diversion of blood to the AVM; 3) focal or secondarily generalized epilepsy caused by irritation of the cerebral cortex; or 4) headache even in the absence of bleeding. Additionally, many patients are admitted to a Neurointensive care unit for close monitoring and blood pressure control after an embolization, radiation or surgical procedure.

52.5 Classification

The classification scheme by Spetzler and Martin (the Spetzler-Martin scale) provides information about the complexity of the AVM and risk of surgical excision. The classification has been validated in a prospective study [6] and takes into account three characteristics: diameter, whether the AVM is in an eloquent brain area, and the presence or absence of deep drainage (Table 52.1). The extent of the AV malformation is obtained by adding the values. Surgery is possible with grade 1, 2, 3 lesions (grade 3 lesions usually only after embolization). The incidence of minor and major neurological deficits after surgery is significant (18% and 12% respectively) for grade 5 lesions [6].

Categories	Value
Maximum diameter	
Small <3 cm	1
Medium 3-6 cm	2
Large >6 cm	3
Localization	
Non-eloquent brain	0
In or adjacent to eloquent brain	1
Venous drainage	
Only superficial	0
Deep	1

Table 52.1. **Spetzler-Martin Classification of AV malformations. Points are awarded in each category and added up. Higher scores signify higher morbidity with surgical resection.**

52.6 Evaluation

Different imaging modalities can be used in the evaluation and diagnosis of AV malformation and their complications. Computed tomography (CT) provides high sensitivity for

detecting intracranial hemorrhage. Sometimes the presence of an AVM may be suspected if one or more dilated draining veins can be seen, but in general other imaging studies are needed to accurately make the diagnosis.
Computed tomography angiography (CTA) shows the blood vessels with more detail than time of flight imaging by magnetic resonance angiography (MRA), while magnetic resonance imaging (MRI) provides better visualization of the AV malformation and its relationship to surrounding structures. However, conventional angiography is the most sensitive test to determine the details of the architecture of the malformation. Angiography provides details regarding the presence of aneurysms in the feeding arteries or the nidus and analysis of the venous drainage pattern as well as giving indirect information about venous hypertension and thrombosis.

52.7 Specific Treatment

It is important for the neurointensivist to familiarize himself with the different modalities of treatment of AVMs as well as possible complications. The combination of different treatment modalities such as microsurgery, stereotactic radiosurgery and endovascular embolization is often used to treat these lesions which adds to the complexity of the case in the intensive case unit.
Fractionated stereotactic radiosurgery directs high-dose radiation to a specific target with less toxicity to adjacent tissues and has the advantage of not being invasive, but has the disadvantage that it can only be applied to lesions less than 3 cm in diameter. The damage caused by radiation to the area of the AVM produces occlusion of blood vessels but the occlusion occurs slowly over 1 to 3 years after dosing. Some authors report rates in 81-90% of patients treated [7,8]. Some experts comment that the lesions that can be treated with radiosurgery are the same that are easily removed with surgery in non-eloquent brain. The main disadvantage of radiosurgery is that the patient remains exposed to the risk of bleeding for a period of up to 3 years.
Endovascular embolization using various compounds (glue or particles) is one of the most widely used techniques in the treatment of AVMs. These techniques have been used primarily as adjuvant therapy prior to surgery because resolution of the AV malformation is only obtained in 13% of patients [9] when embolization is not followed by another procedure. However its value as an adjuvant therapy is important because it reduces the size of the AVM making conventional surgery or stereotactic radiosurgery more effective and less dangerous.
The aim of embolization is to remove the feeding arteries thereby reducing blood flow through the nidus and consequently decreasing the size of the malformation. Commonly, multiple staged embolization procedures are needed to gradually occlude the malformation without causing sudden hemodynamic changes that may result in bleeding or other complications.

52.8 Complications and Treatment

All three procedures, radiosurgery, embolization and conventional microsurgery have the potential for complications. The main complication of stereotactic radiosurgery is radiation damage to tissues adjacent to the AVM which occurs in 6.4% of cases [10]. Other complications include damage to the cranial nerves (1%) and an increased frequency

of epilepsy (0.7%) [10]. Endovascular embolization can lead to intracranial bleeding as a result of the rapid changes in blood flow and pressure in the nidus of the AV malformation. Another feared complication that increases the chance of rupture is thrombosis of the draining veins that can occur as a result of embolic material migrating through the AV malformation to the draining veins. In addition, even successful suppression of blood flow through the malformation can cause slow flow and thrombosis of the draining veins leading to congestion and bleeding. Occlusion of the draining veins may result in venous infarction and/or hemorrhage complicating the postoperative period. Surgery has a similar complication profile as endovascular embolization with two caveats: 1) surgery has a higher infection rate, and 2) there is a greater chance of damage to adjacent tissues.

Intracerebral hemorrhage may result from hyperemia to tissue adjacent to the AVM due to redistribution of arterial blood from the now-embolized or ligated artery to adjacent arteries. Even in tissue experiencing normal flow, congestion and hemorrhages may occur. The reason for this is that tissue surrounding the malformation that has been chronically exposed to a low flow state because of a “steal” phenomenon (the low resistance AV malformation steals blood from the higher resistance normal vessels) may respond poorly to rapid correction of blood flow due to occlusion of arteries feeding the malformation and may expose tissue that is not used to “normal” perfusion to react as though it were hyperemic.

Endovascular embolization with particles or glue carries a risk of stroke due to inadvertent embolization of arteries that feed eloquent brain. Administration of a short-acting barbiturate (methohexital) followed by a neurological examination before and after can help identify whether any of the feeding arteries supply normal tissue adjacent to the malformation. Additionally, hemodynamic changes that occur during embolization of an AVM can lead to glue embolization to tissues other than brain such as lung and heart leading to pulmonary emboli or myocardial infarctions. All patients should be carefully examined after an endovascular procedure to detect the presence of new neurological deficits or systemic embolization. The diagnosis of ischemic stroke can be accomplished using magnetic resonance imaging (MRI).

The best way to avoid the above complications is to perform gradual, staged embolization of the AV malformation avoiding sudden changes in pressure and blood flow. Additionally, strict control of blood pressure during and after the procedure is thought to be vital in preventing reperfusion injury. Data regarding the management of blood pressure in patients with AV malformations are limited and no prospective studies support a specific strategy. The management proposed in this chapter is based on physiological principles of blood flow and is the strategy used in our practice. In patients who have undergone embolization or surgery, systolic pressure is maintained below 100 mmHg for the first 24 hours to prevent reperfusion injury. The liberalization of arterial pressure requirements is then done gradually over the next few days allowing the tissue to adapt to new local blood flow. Systolic pressures of less than 110 mmHg and 120 mmHg, respectively, are preferred on days 2 and 3 after the procedure.

The use of invasive blood pressure monitoring with an arterial catheter is recommended. The agents that control blood pressure without decreasing blood flow to the brain such as the balanced vasodilators and the arterial dilator nicardipine are preferred in patients in whom the AV malformation is completely occluded. In our practice a continuous infusion of nicardipine is the first option, especially when the systolic pressure must be kept below 100 mmHg. Maintaining blood flow while limiting blood pressure ensures adequate perfusion to non-AVM areas of the brain. Nitroprusside (which decreases cardiac preload and afterload) in conjunction with labetalol can be used in cases where the AV malformation is only partially occluded because the remaining abnormal blood vessels in the nidus must acclimate to the increased blood flow shunted to

them from the embolization. In these cases, decreased blood pressure and blood flow are desirable to avoid a disproportionate increase in blood flow through residual vessels of the malformation. Other agents such as angiotensin-converting enzyme and hydralazine can be administered when the blood pressure requirements have been liberalized. It is equally important to keep the patient well-hydrated with adequate analgesia to avoid sympathetic overdrive.

The management of blood pressure is just as important in patients presenting with spontaneous rupture of an AV malformation. Always assume the presence of an aneurysm until it can be ruled out angiographically. The systolic pressure should be maintained below 140 mmHg with the aim to prevent the spread of the hemorrhage and compression of adjacent structures due to increased intracranial pressure. Usually the definitive treatment of AVM is postponed until the patient is in stable condition and intracranial pressure is normalized. In patients at risk for elevated intracranial pressure (major bleeding, Glasgow Coma Scale Score (GCS) <8, and so on). Intracranial pressure monitoring is recommended and blood pressure should be adjusted to maintain cerebral perfusion pressure >60 mmHg.

Focal or secondarily generalized epilepsy as a result of AVM is a common form of presentation and its treatment does not differ from other forms of symptomatic focal epilepsy. A minority of patients present with focal neurological deficits resulting from compression of adjacent structures by an AVM. Historically, steroids have been used as an adjunct measure until definitive treatment can be instituted, but there are no studies that support their use.

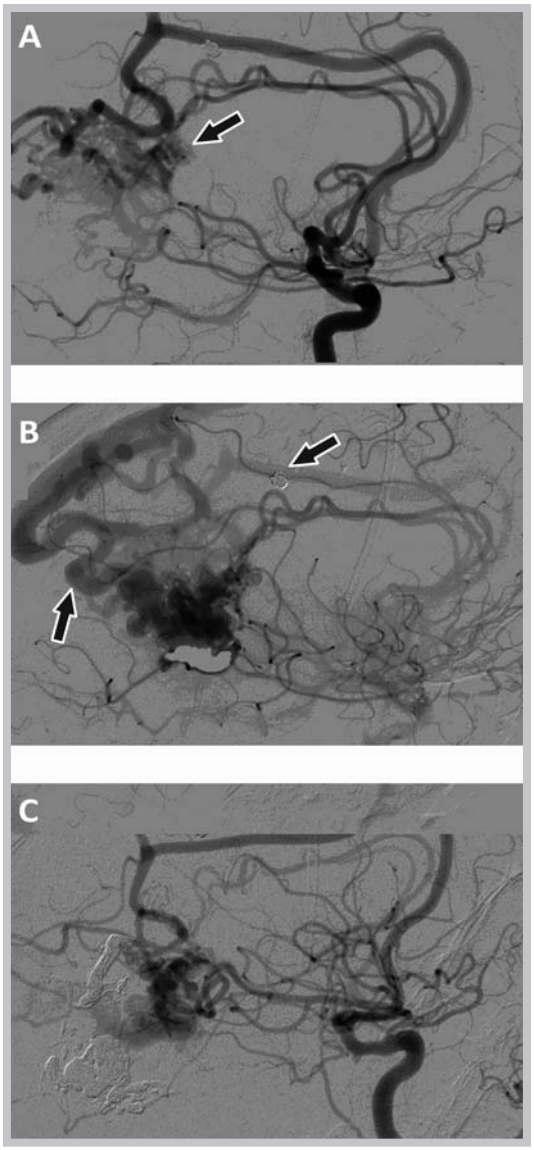

Figure 52.1. Example of MAV 1.

52.9 Conclusions and Key Points

- Intracranial hemorrhage is the most common form of presentation of AVMs.
- The presence of aneurysms in the feeding arteries or the nidus and the blockage of drainage increases the likelihood of rupture and hemorrhage.
- The Martin-Spetzler classification provides information on the risk of surgery but does not predict the risk of rupture or bleeding.

- AVMs are complex lesions and are commonly treated with a combination of embolization, microsurgery or stereotactic radiosurgery.
- Occlusion of the malformation (microsurgery or embolization) can result in bleeding due to rupture or damage to adjacent tissue reperfusion.
- The gradual embolization of the malformation and the strict control of blood pressure are the best way to avoid complications.
- Vasodilator agents such as nicardipine may be used during the early hours to control blood pressure.

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53 Intraventricular Hemorrhage

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53.1 Introduction

Intraventricular hemorrhage (IVH), defined as extravasation of blood into the brain ventricular system, is a condition with high morbidity and mortality. Fortunately, early diagnosis and prompt intervention due to advances in neuro-imaging and neuro-critical care has made it possible for many patients to survive and fully recover from this event.

Spontaneous intracerebral hemorrhage (ICH), which is bleeding into the brain parenchyma, has an estimated mortality of 30% as well as a high rate of morbidity among survivors [1]. Isolated IVH is quite uncommon, but IVH commonly occurs in up to 45% of all cases of ICH [1]. In patients with acute ICH, there is a strong body of evidence supporting the fact that extension into the ventricular system increases the overall mortality and is associated with poor outcomes [2-4]. The mechanism that holds IVH directly responsible for the dire neurological causata are not completely understood, but the results of recent and ongoing animal and human investigations are expanding our insight [5].

53.2 Etiology

Direct hemorrhage into the ventricles from a source or lesion that is in contact with, or part of a ventricular wall, is classified as primary IVH. Secondary IVH originates as an extension of an intraparenchymal or subarachnoid hemorrhage (SAH) into the ventricular system. About 30% of IVHs are primary and 70% are secondary. Isolated IVH is a relatively rare event, accounting only for 3% of all cases of intracranial hemorrhage [6].

Frequent causes of primary IVH include head trauma, insertion or removal of a ventricular catheter, intraventricular vascular malformations, tumors, and bleeding diathesis (Table 53.1.) Secondary IVH has some overlap but most commonly is a result of hypertensive intra-parenchymal hemorrhage into the basal ganglia and thalamus.

Primary IVH	Secondary IVH
• Germinal matrix hemorrhage in the premature newborn • Intraventricular/ periventricular vascular malformation or tumor • Coagulation or platelet disorder • Trauma • Insertion or removal of ventricular catheter • Drugs (cocaine, amphetamines) • Cerebral vein thrombosis • Idiopathic	• Hypertensive/ hemorrhagic stroke • Trauma • Vascular malformation, aneurysms, tumor • Pituitary apoplexy • Coagulation or platelet disorder • Drugs (cocaine/ amphetamines) • Vasculitis

Table 53.1. Causes of intraventricular hemorrhage.

Graeb		
Lateral ventricles	1	Trace of blood or mild bleeding
	2	Less than half of the ventricle filled with blood
	3	More than half of the ventricle filled with blood
	4	Ventricle filled with blood and expanded
3rd and 4th ventricles	1	Blood present, ventricle size normal
	2	Ventricle filled with blood and expanded
LeRoux		
1	Trace of blood	
2	Less than half of the ventricle filled with blood	
3	More than half of the ventricle filled with blood	
4	Ventricle filled with blood and expanded	
IVH score		
Lateral ventricles	1	Trace of blood or mild bleeding
	2	Less than 1/3 of the ventricle filled with blood
	3	Between 1/3 and 2/3 of the ventricle filled with blood
	4	Ventricle filled with blood and expanded
3rd and 4th ventricles	0	No blood
	1	Any blood
HCP	0	No
	1	Yes

Table 53.2 **Grading systems for IVH severity [7,8,9]. In the Graeb and LeRoux systems, each lateral ventricle is scored separately. For third and fourth ventricles, each one is scored separately, then added together. In the IVH score, each ventricle is scored separately for the mere presence of blood and each given a score 1 for the presence of hydrocephalus (HCP). Score ranges for the Graeb system is 0-12, for the LeRoux system is 0-16, and 0-23 for the IVH score. In all three systems, the higher the final score, the higher the prospect of poor outcome.**

Several grading systems have been described to classify the severity of IVH and are worth being familiar with for academic purposes [7-9] (Table 53.2).

53.3 Clinical Features and Diagnosis

The symptoms that can be directly attributed to blood within the ventricular system are indistinguishable from subarachnoid hemorrhage, with sudden onset of severe headache, nausea, vomiting, and meningismus (neck stiffness). There is typically minimal or no focal neurologic deficit, unless there is an intra-parenchymal component. With more extensive hemorrhage, consciousness progressively declines. In massive IVH, sudden loss of consciousness is the rule and generalized seizures are not uncommon [9].

The diagnosis of IVH is easily made via a non-contrasted head computer tomography (CT) scan. CT provides useful information regarding the extent of the hemorrhage and the presence or absence of hydrocephalus. It may also provide clues with regard to the etiology of IVH, based on the distribution pattern of blood within the ventricles (Figure 53.1).

Predominance of blood in the fourth ventricle with associated subarachnoid hemorrhage in the basal cisterns is typical for ruptured aneurysms of the posterior inferior

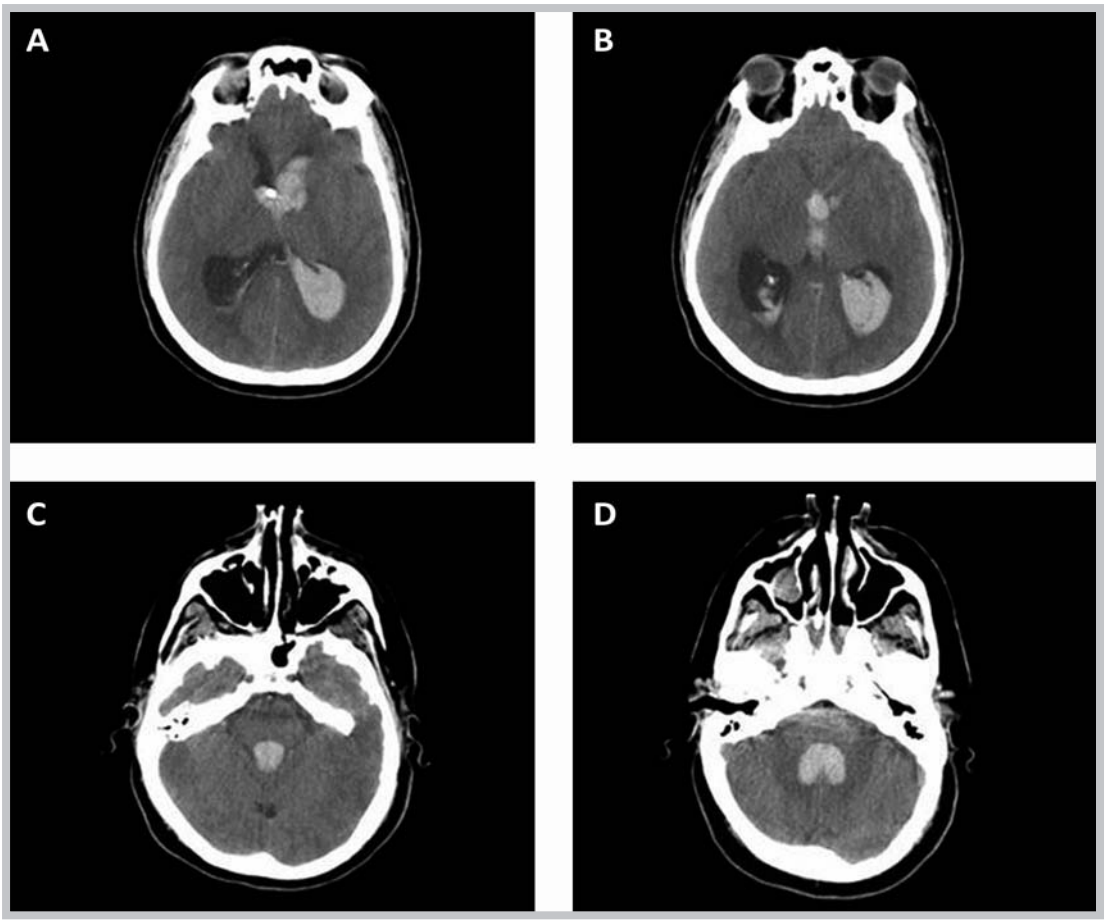

Figure 53.1. **Intraventricular hemorrhage in a 45-year-old man due to a left caudate hemorrhage extending caudally to the fourth ventricle.**

cerebellar artery. Isolated IVH in young adults should raise the suspicion for an arteriovenous malformation (AVM). IVH in association with medial thalamic or caudate intraparenchymal hemorrhage is common for patients with hypertensive ICH. In cases where

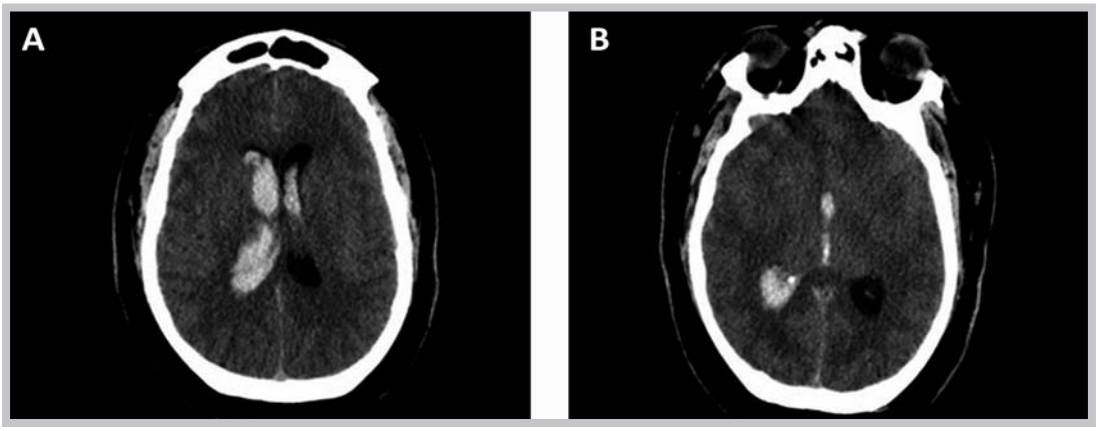

Figure 53.2. **Intraventricular hemorrhage in a 34-year-old man without evidence of a pre-existing ICH and a normal cerebral angiogram.**

the etiology cannot be delineated from CT scan alone, a gadolinium enhanced magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain is indicated to further explore and seek the etiology (Figure 53.2).
Angiography is reserved for cases with a high suspicion for AVM or aneurysms.

53.4 Pathophysiology of IVH

Acute IVH leads to acute intracranial hypertension and obstructive hydrocephalus, which then exerts pressure onto the ascending reticular activating system (ARAS) resulting in a depressed level of arousal. The presence of blood inside the ventricles may lead to obstructive hydrocephalus and subsequently to elevated intracranial pressure (ICP). Elevated ICP may significantly lower cerebral perfusion pressure (CPP) leading to cerebral ischemia, further augmenting brain injury [10].
Some studies support the theory that the blood itself causes damage to the ependymal and subependymal layers of the brain [11]. Neuropsychological data has shown that patients with IVH suffer from significant cognitive deficits even after the blood has completely disappeared, suggesting that the harmful effects of intraventricular blood may not only be due to the mere presence of blood in the ventricles, but a more complex neuro-hormonal mechanism [12]. It is likely that subarachnoid fibrosis, extensive ependymal cell loss, and subependymal glial proliferation on the walls of the ventricles is produced by blood in the cerebrospinal fluid, most likely as an inflammatory response [11,13-15].
There is very little known about the fibrinolytic system in the cerebrospinal fluid and brain tissue. Activity is localized in the vascular endothelial cells, meninges and choroid plexus, with minimal amounts of tissue-type plasminogen activator (t-PA) in the CSF of adults with no neurologic disease. In the event of ICH, increased levels of t-PA have been observed in the CSF. It is not known whether the increased levels result from an enhancement of local production or from leakage across a damaged blood-brain barrier [16,17]. Interestingly, this increase in fibrinolytic activity after an intracranial hemorrhage does not result in a rapid resolution of intraventricular blood [16-18]. Studies of serial CT scans performed on patients with IVH have seemed to suggest that the intraventricular blood gradually disappears over a period of 2 to 3 weeks after the hemorrhage [19,20]. In contrast, post-mortem studies have revealed the persistence of intraventricular blood for months after a hemorrhage [21].

53.5 Clinical Management of IVH

Treatment of IVH begins with stabilization of the patient followed by admission to an intensive care unit (ICU) where airway, neurological and hemodynamic surveillance and support are more meticulously possible. An official consensus or guideline on all aspects of IVH management - blood pressure control, indications for placing a ventricular drain, and administration of fibrinolytics – does not exist. However, lower mortality rates have been consistently observed when the treatment policy involves: 1) the use of an intraventricular drainage catheter (ventriculostomy drain) to maintain ICP within the normal range (usually less than 15-20 mmHg), and 2) Optimal management of blood pressure [5]. Management of IVH is multi-faceted and solely maintaining ICP within a normal range is insufficient to impact mortality or morbidity [22].

In our practice, all patients with IVH are admitted to the ICU for close monitoring of neurological status and hemodynamics. An intraventricular catheter is placed for emergent ICP control in patients with poor neurologic status (usually with Glasgow Coma Scale of 8 or less, signs of impending herniation) and/or radiographic evidence of ventriculomegaly secondary to the IVH. This catheter is typically kept open for continuous cerebrospinal fluid (CSF) drainage. It is crucial to correct any coagulopathies that may have contributed to the initial hemorrhage and prior to placement of this catheter. For control of elevated blood pressure, we follow the most recent American Stroke Association guidelines for management of spontaneous ICH and aneurysmal SAH: a target systolic value of 160 mmHg or less [23,24]. Anticonvulsant medications are not routinely used for isolated IVH, unless seizures were a part of the initial clinical presentation. Administration of intravenous recombinant activated factor VIIa (rFVIIa) has been shown to reduce the expansion of ICH volume when administered within 4 hours of symptom onset, but without a significant impact on survival or functional outcome [25]. There is some evidence that in patients with IVH, rFVIIa treatment may contribute to development of hydrocephalus, perhaps due to its pro-coagulant effect leading to delayed resolution of intraventricular blood [26].

A theory exists that accelerated clearance of the intraventricular clot using direct injection of thrombolytics such as recombinant tissue-type plasminogen activator (rt-PA) into the ventricles may have a positive impact on clinical outcome. The safety and efficacy of this treatment in increasing the rate of clot lysis has been demonstrated [27]. Intraventricular thrombolysis does appear to reduce mortality rate and accelerate blood clot resolution in patients with moderate to severe IVH [28,29]. Furthermore, functional outcome measures (Glasgow outcome scale, modified Rankin scale and National Institutes of Health Stroke Scale) seem to be improved in patients treated with rt-PA despite a trend toward more bleeding complications. Questions remain as to whether rt-PA is the right thrombolytic agent and what the appropriate dose is. This treatment is currently being studied in a phase III clinical (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage Phase III: CLEAR III). In some centers, intraventricular rt-PA is used in an “off label” fashion. We have successfully used small intraventricular doses of 1 to 2 mg rt-PA to re-establish the patency of a ventricular drain that has been obstructed by blood. For intraventricular fibrinolytic therapy, doses ranging from 2 to 4 mg of rt-PA at 12 to 24 hour intervals can be safely administered with minimal risk of bleeding complications. The injection of the fibrinolytic agent should be preceded by withdrawal of a volume of CSF equivalent to the drug volume being injected, to avoid a sudden increase in intracranial pressure. Injection is followed by a preservative free normal saline flush of 1 to 2 ml and clamping of the ventricular drain for 30 minutes to an hour. The ICP is closely monitored during this time period and if the pressures rise above 20 mmHg sustained over 5 minutes the ventricular drain is reopened, allowed to drain 5 to 10 ml and then closed again. If ICP continues to be elevated the drain is just left open and t-PA injected again in 12 to 24 hours if necessary. The decision to treat again is based on clinical status and residual intraventricular blood on follow up imaging studies

Prior to even considering fibrinolytics for the treatment of IVH the physician must be certain that the acute episode of bleeding has subsided and that any underlying condition contributing to the hemorrhage (hypertension, coagulopathy, aneurysm) has been corrected. This is critical in the management, as the administration of intraventricular fibrinolytics to a patient with vascular pathology (unsecured aneurysm) could be fatal. A repeat CT scan of the brain is performed within 12-24 hours of the onset of bleeding to assess stability of the hemorrhage.

Many practical issues concerning intraventricular fibrinolytic therapy still need to be addressed. The criteria for patient selection and the determination of an appropriate dose, timing, and protocol for administration are all the focus of CLEAR III.

53.6 Prognosis

The morbidity and mortality of patients with IVH largely depends on the extent and the volume of blood in the ventricular system [4,7,30,31]. Patients with secondary IVH fare more poorly than those with primary IVH [31,32]. If an ICH ruptures into the ventricular system, the mortality increases from 30% to 44% and if it involves all four ventricles, it can be as high as 60 to 91% [31,32]. As for the location, thalamic ICH patients with intraventricular extension seem to have the worst prognosis. Additional predictors of outcome include initial Glasgow Coma Scale and age greater than 80 years [4,31,32]. Long term consequence of IVH may involve a severe, persisting amnesic state [33].

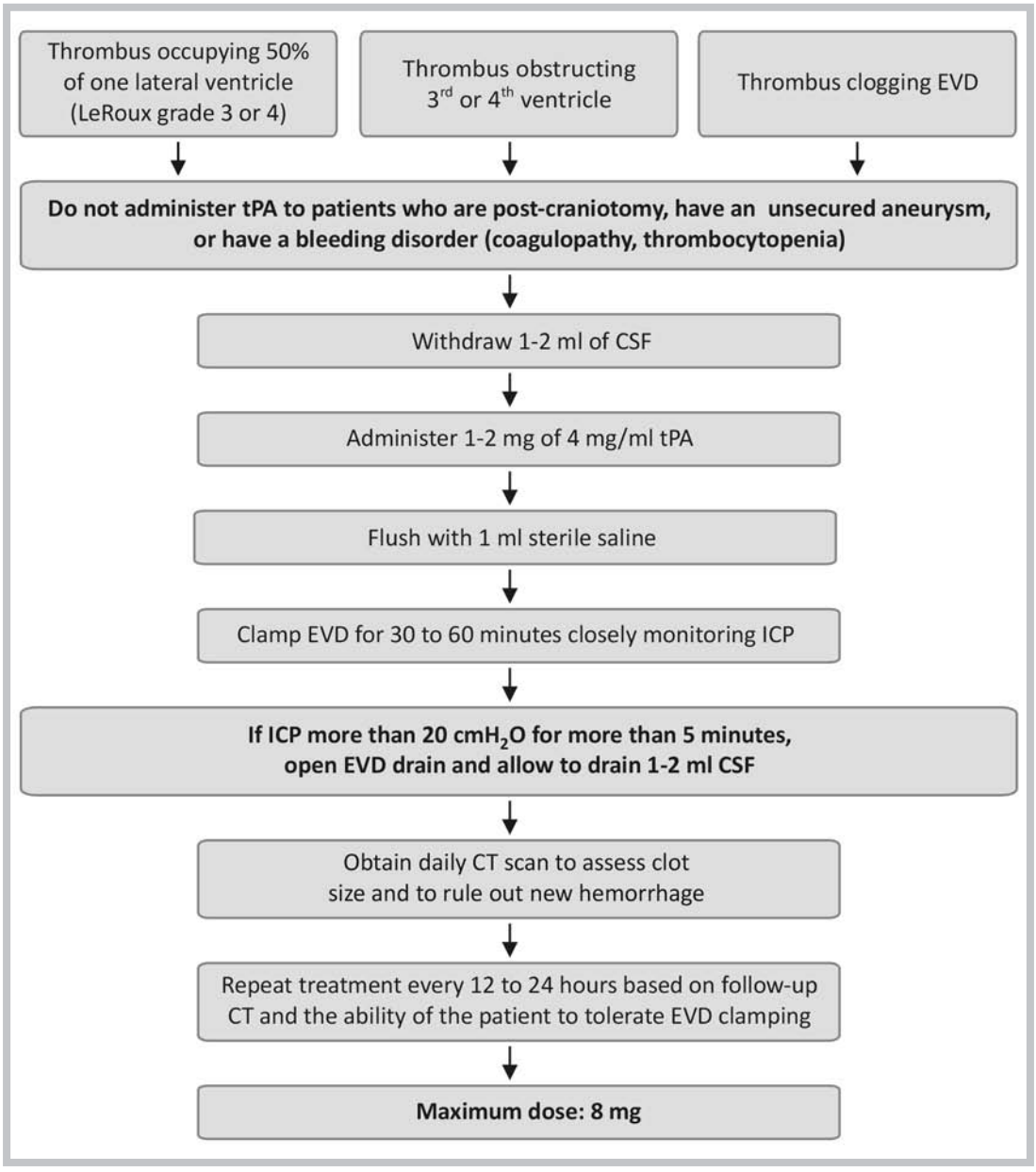

Figure 53.3. Example protocol for intraventricular thrombolysis.

53.7 Conclusions

IVH is an entity that can be associated with a large number of causes. The clinical picture depends on the severity of the hemorrhage and management consists of identifying the underlying etiology and placing an external ventricular drain to control and monitor intracranial pressure. Although reduced mortality rates have been reported with intraventricular fibrinolytic therapy, it is not clearly known if it improves neurologic outcomes.

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Section 7.
Infections in NICU

54 Control and Management of Nosocomial Infections in Neurocritical Care Units

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54.1 Objectives

This chapter describes the impact of nosocomial (healthcare-acquired) infections (HAI), risk factors, modes of prevention and treatment and organizational concepts such as surveillance and quality management in neurocritical care units. We will focus on nosocomial infections after dealing with general recommendations for infection control practices and surveillance and the differential diagnosis of fever:

- Ventilator-associated pneumonia (VAP).
- Central line-associated bloodstream infections (CLABSI).
- Catheter-associated urinary tract infections (CAUTI).
- Infections associated with extraventricular and lumbar drains.
- Surgical site infections after craniotomy/craniectomy.
- *Clostridium difficile*-associated diarrhea (CDAD) and nosocomial diarrhea.

54.2 Background and Basic Aspects of Infection Control

Nosocomial infections put a significant additional burden on intensive care patients, care givers and public health, yet many are preventable. Specific surveillance data on HAIs in neurosurgical and neurology intensive care units (ICUs) have been published by Dettenkofer and colleagues, but oftentimes only pooled data from general ICUs are available.
Neurocritical care patients carry an increased risk for infections secondary to suppression of cell-mediated immunity in general and T-lymphocyte function in particular. This can be aggravated by transfusion requirements.
A specific additional risk factor for VAP is the higher likelihood of microaspiration secondary to the underlying neurologic dysfunction.
Therefore, a comprehensive preventive approach is needed, and the so-called standard precautions (Centers for Disease Control and Prevention [CDC], Atlanta, USA) apply to all medical settings (CDC Isolation Precautions 2007; www.cdc.gov).
The most important factor is proper **hand hygiene**. This is achieved by performing an **alcoholic hand rub** before and after each patient contact. It should be practiced by all healthcare workers (HCWs) in the neurocritical ICU, including physicians, nurses, physiotherapists, technicians and other paramedical personnel, as well as visitors with direct patient contact (http://www.who.int/patientsafety/en).
Unfortunately, compliance with this simple and highly effective technique is poor. Observational studies in ICUs report compliance rates of around 40%, which could be en-

hanced to over 65% through educational campaigns. Such awareness programs need to be repeated at least once a year to achieve a more sustained effect.

The alcoholic hand rub should be well tolerated by the HCW's skin and should contain a moisturizing agent and be devoid of colorants or perfumes. A protective skin ointment or lotion should be used at least at the beginning and at the end of the workday.

Single-use gloves should be worn each time contact with body fluids and secretions is likely and used for procedures on one patient only. After glove removal, the hands need to be disinfected with an alcoholic hand rub.

Sterile gloves are required for sterile procedures (Table 54.1). In patients with known blood-borne diseases like hepatitis B (HBV) and C virus (HCV) infection and infection with the human immunodeficiency virus (HIV), double gloving can be used for increased protection.

Vaccination of all staff members against HBV should be enforced. A written policy for the management of exposure to HIV and post-exposure prophylaxis should be in place. The logistics to provide antiviral drugs within the recommended timeframe of 2 hours after exposure need to be determined to achieve best results.

Unsterile gowns and fluid impermeable aprons are worn when contamination with body fluids is possible.

Masks and face shields will protect staff from droplets, and special masks with higher protection grades (e.g., N95 or FFP2 respirator) need to be worn if airborne precautions are necessary, as in patients with open lung tuberculosis or SARS.

All personal protective equipment should be stored close to the point of care but protected from contamination and dust.

Dispensers for alcoholic hand rub should be easily accessible at the bedside and when entering and leaving a room. Personalized bottles carried by the team members can be an alternative.

Tap water may carry high-risk micro-organisms and should be accordingly tested for *Legionella* or *Pseudomonas aeruginosa* contamination (and treated accordingly). It should

Precaution	Peripheral IV	Arterial line**	CVC	Bedside tracheostomy	Bedside ventriculostomy/ lumbar drain	Bronchoscopy/ bronchoaveolar lavage
Skin-disinfection# (e.g., chlorhexidine/ alcohol, octenidine/ alcohol)	X	X	X	X	X	NA
Sterile gloves	-	X	X	X	X	X
Sterile gown	-	-	X	X	X	(X)
Sterile drape	-	Small*	Large*	Large	Large	Small
Hair cover	-	-	X	X	X	-
Face mask	-	-	X		X	X + goggles or face shield

Table 54.1. **Precautions for invasive procedures.**

X = recommended; (X) = useful in some cases, not required; CVC = central venous catheter (includes Swan-Ganz catheters)

Contact time according to manufacturer's recommendation, e.g., 60 seconds

* Use sterile covers and sterile gel for ultrasound probes if used to guide the procedure

** For long arterial lines (e.g., PICCO® catheter), arterial sheaths for interventional radiology or intra-aortic balloon pumps or access lines for extracorporeal circulation (e.g., extracorporeal membrane oxygenation [ECMO], Novalung®) use maximal barrier precautions as with CVC insertion.

never be used for oral care, inhalation therapy or filling of humidifying devices in the breathing circuit (sterile water required).
Routine cleaning of the ICU by trained personnel is important. This should be done at least once a day and each time a visible contamination occurs. In addition, contaminated surfaces need to be disinfected with an approved surface disinfectant at the correct concentration (e.g., knobs and contact displays three times a day). All contact surfaces close to the patient need to be disinfected daily and immediately when visibly soiled.
Medical equipment and reusable products need to be cleaned and disinfected or sterilized after use according to the risk (Spaulding classification: critical, semi-critical, non-critical) and the manufacturer's recommendations by trained staff utilizing a validated process.
Surveillance of nosocomial infections according to standardized definitions (www.cdc.gov/nhsn; www.nrz-hygiene.de/surveillance/surveillance.htm) is a useful tool in quality management in the neurocritical care unit.
At least ventilator-associated pneumonia (VAP) and central line-associated bloodstream infections (CLABSI) should be monitored. Oftentimes a surveillance program will lower the rate of infectious complications simply by increasing awareness ("Hawthorne effect").
In order to prevent the development of multidrug-resistant organisms (MDRO), an antibiotic stewardship program should be established and guidelines for the empiric therapy of important infections (as outlined below) should be in place. An updated unit-specific antimicrobial resistance profile and treatment options should be available to clinicians prescribing antibiotics (e.g., pocketcard).
The differential diagnosis of fever is especially crucial in the neurocritical care unit because many patients have fever not related to an infectious cause. Examples are: intracranial bleed, stroke, drug fever (especially phenytoin-induced), blood product transfusion, adrenal insufficiency, fat emboli, cytokine-related fever, pancreatitis, acalculous cholecystitis, pneumonitis without infection, pulmonary emboli/infarction, venous thrombosis, acute myocardial infarction, dressler syndrome (pericardial injury syndrome), tumour lysis syndrome, gout, thyroid storm, malignant hyperthermia, malignant neuroleptic syndrome, serotonin syndrome, withdrawal of certain drugs (especially benzodiazepines, opioids).

54.3 Ventilator-associated Pneumonia (VAP)

Tables 54.2 and 54.3 show the data for ventilator-associated pneumonia (VAP) and central line-associated bloodstream infections (CLABSI) from the German National Surveillance System (Krankenhaus-Infektions-Surveillance-System: KISS; www.nrz-hygiene.de/surveillance/surveillance.htm).
The diagnosis of VAP in critically ill patients can be challenging because of unspecific clinical symptoms and problems with interpreting bedside chest films. Chest computed tomography (CT) can be helpful.
Ideally, a sample of lower respiratory tract secretions is obtained before empiric antibiotic treatment is started. Specimens obtained by bronchoscopy, bronchoaveolar lavage (BAL) or mini-BAL with special protected catheters might be preferable to tracheal aspirates.
Regardless of the origin, each respiratory specimen should be transported to the microbiology laboratory within 2 hours and evaluated by Gram staining and cultured for routine aerobic and facultative bacteria. Additional special stains, rapid tests, PCR tests, and special medium cultures should be performed as directed by the clinical suspicion or epidemiologic situation of the unit. Quantitative culture results can be helpful in experienced hands, and close collaboration with medical microbiology is essential.

Type of ICU	Mode of ventilation	Number		25% Quantile		Median		75% Quantile	
		Ventilator days	Number Pneumonia	UR	IR	UR	IR	UR	IR
All ICUs (n=374)	Invasive	569,511	3173	23.84	1.8	35.94	4.3	49.51	7.54
	Noninvasive	40,101	NA	0.03		1.25		3.69	
Interdisciplinary (n=176)	Invasive	231,565	1306	20.17	1.69	30.25	4.17	45.11	7.64
	Noninvasive	18,506	NA	0.04		1.60		3.84	
Internal Medicine (n=74)	Invasive	103,811	427	25.15	1.33	32.87	3.29	46.25	5.83
	Noninvasive	7133	NA	0.36		1.53		3.72	
Neurology (n=9)	Invasive	12,843	50	46.67	1.6	54.02	4.97	58.46	6.56
	Noninvasive	653	NA	0		0.25		0.85	
Surgical (n=81)	Invasive	163,065	1024	31.91	3.16	42.28	5.5	56.5	10.96
	Noninvasive	9322	NA	0		0.74		2.87	
Neurosurgical (n=13)	Invasive	23,964	201	42.98	3.81	51.86	8.03	55.86	12.55
	Noninvasive	2369	NA	0		2.26		4.13	
Paediatric (n=11)	Invasive	13,709	17	14.77	0	35.11	0.93	47.25	1.44
	Noninvasive	2014	NA	0.53		1.57		6.65	

Table 54.2. **Ventilator-associated pneumonia (VAP) surveillance data (KISS January 2005-June 2006).**

NA = no data available IR = Incidence ratio per 1000 ventilator days
UR = Utilization ratio per 100 patients

Biomarkers such as C reactive protein (CRP), procalcitonin and interleukin 1 can be helpful, as well as soluble triggering receptors expressed on myeloid cells (sTREM) from BAL fluid to facilitate the differential diagnosis of pneumonia versus atelectasis.

A parallel obtained blood culture and fluid from diagnostic and/or therapeutic punctures of pleural effusions can yield additional microbiological culture results. Three consecutive urine specimens should be examined for legionella antigen in case of clinical suspicion or known water contamination.

The repertoire of preventive measures is quite long, and available studies have often shown their effectiveness in so-called bundles only:

- Aseptic/sterile handling of respirator equipment.
- Noninvasive ventilation (NIV) when possible.
- 30-45° elevated head position.
- Regular oral care and removal of dental plaques.
- Oral decontamination with chlorhexidine.
- Oral intubation preferred (also less sinusitis).
- Adequate cuff pressure (regular monitoring).
- Subglottic suctioning (special endotracheal tube required).
- Endotracheal tube with polyurethane high-volume-low pressure cuff.
- Heat and moisture exchange (HME) filter (needs to be changed according to manufacturer's recommendations).
- Closed suctioning (no superiority to open suctioning but reduced loss of PEEP).
- Positive end-expiratory pressure (PEEP) of at least 5 cmH_2O.
- Daily interruption of sedation (cave: ICP increase).
- Stress ulcer prophylaxis with sucralfate versus H_2-blockers and proton pump inhibitors (weak effect).
- Selective decontamination of the gut (SDD; under intense debate; for high-risk patients only).

The expected pathogens vary with the onset time of VAP. Early onset VAP (<4 days ventilatory support) is characterized by infections with *Streptococcus pneumoniae*, *Haemophilus influenzae* (and *Staphylococcus aureus*). Late onset VAP (>4 days ventilatory support) is characterized by infections with *Pseudomonas aeruginosa*, extended-spectrum beta-lactamase (ESBL), methicillin-resistant *Staphylococcus aureus* (MRSA), Enterobacteriaceae, *Acinetobacter* spp., *Enterobacter* spp., and *Candida* spp.
The empiric treatment options for severe cases should therefore include:

- A third generation cephalosporin or piperacillin/tazobactam or carbapeneme.
- In combination with an aminoglycoside (single-dose regimen, blood level monitoring) or fluoroquinolone (high dose).
- Plus linezolid or vancomycin in case of risk factors for MRSA.
- Plus high-dose fluconazole in case of risk factors for *Candida albicans* or caspofungin in case of risk factors for non-albicans Candida species.

Treatment should begin immediately after clinical diagnosis and deterioration of clinical status and be narrowed according to the microbiological results as soon as possible. For guidance on specific diagnostic procedures and appropriate antimicrobial therapy, consultation with an infectious diseases specialist (this also applies to all treatment information below) is strongly advised.

54.4 Central Line-associated Bloodstream Infections (CLABSI)

While the risk of peripheral venous catheter-related bloodstream infections appears to be low, standard precautions are necessary because of the severe nature of bloodstream infection. Skin disinfection should be performed for 30 seconds with an approved disinfectant like octenidine/alcohol or chlorhexidine/alcohol (60 seconds in case of central lines). After the skin is disinfected, it should not be palpated again with unsterile gloves or bare hands. There is no maximal duration a peripheral IV line can be kept in place, but the indication should be checked critically every day. However, IV lines placed under emergency conditions in the field or emergency room should be removed as soon as possible.

Type of ICU	Number		25% Quantile		Median		75% Quantile	
	Catheter days	CA sepsis	UR	IR	UR	IR	UR	IR
All (n=374)	2,502,548	4323	50.21	0.46	69	1.23	83.45	2.24
Interdisciplinary (n=176)	1,085,418	1478	46.82	0.25	64.07	0.83	75.15	1.65
Internal Medicine (n=74)	400,657	743	44.59	0.48	55.36	1.62	68.67	2.30
Neurology (n=9)	31,052	90	56.26	1.19	60.46	2.55	76.15	4.85
Surgical (n=81)	757,590	1453	74.65	0.83	83.82	1.62	93.68	2.51
Neurosurgical (n=13)	92,810	165	73.96	0.83	78.29	1.27	80.82	2.5
Paediatric (n=11)	45,293	141	28.48	1.52	48.32	2.7	57.71	6.31

Table 54.3. **Central line-associated bloodstream infections (CLABSI) surveillance data (KISS January 2005-June 2006).**

UR = Utilization ratio per 100 patients
IR = Incidence ratio per 1000 ventilator days

Arterial lines pose a slightly higher risk of catheter-related bloodstream infection and are nowadays more frequently used for hemodynamic monitoring with pulse contour devices like PICCO®, LidCO® or Flowtrac®.

Some require frequent additional blood draws and calibration (e.g., LidCO). A strictly aseptic technique should be used for all blood draws. Three-way stopcocks should be disinfected with alcohol before manipulation. The insertion of large bore arterial lines (sheaths) for access for interventional radiology procedures, intra-aortic balloon pumps or extracorporeal circulation devices (e.g., ECMO, Novalung®) require maximal barrier precautions as recommended for CVC insertion (Table 54.1).

Central venous catheters (CVCs) are frequently used for the administration of medications, volume infusion, parenteral nutrition and blood draws. Some special lines have probes for continuous central venous saturation monitoring, thus reducing the need for blood draws. Other lines are especially designed for intravascular cooling and are connected to a thermoregulation device. Special care is required not to dislodge the lines and to keep the connections clean. CVCs have the highest risk of catheter-associated bloodstream infection (Table 54.3).

Maximal barrier precautions are required for all central venous access procedures. Special carts with all necessary equipment and regular training of physicians and nurses facilitate this practice.

The indication for continuous use needs to be evaluated daily with clinical check of the insertion site, but a routine exchange of central lines is not recommended.

The best insertion site from an infection control point of view is the subclavian vein. However, for dialysis access and venous extracorporeal circulation devices, the jugular vein is preferred to prevent catheter kinking.

Peripherally inserted central catheters (PICC-lines) are sometimes used for long-term access (several weeks), as well as tunnelled CVCs or implanted port-devices (months).

If use for more than one week is anticipated, catheters coated antimicrobially may be considered.

The femoral vein seems to have the highest risk of infections and poses a special risk for colonization by faecal organisms and *Candida* spp., which should be taken into account for empiric treatment regimens of catheter-related sepsis.

If ultrasound is used to facilitate the venous puncture, the ultrasound probe should be protected with a sterile sheath and only sterile ultrasound gel should be used.

Catheter exchange over a wire can only be recommended if infection is clinically unlikely and the exchange procedure is performed for technical reasons (e.g., larger access required, leakage, etc.). However, if a catheter-related infection is suspected, the line should be removed and the tip should be cut under sterile conditions and sent to the lab for culture. Routine cultures of catheter tips are not necessary. Parallel blood cultures through the line and from peripheral veins can facilitate the diagnosis of catheter-related bloodstream infections.

If an exchange of the catheter is not feasible (e.g., implanted port, difficult access, dialysis access which cannot be replaced), antibiotic lock treatment as described by Mermel can be employed. Each catheter lumen is filled with a volume of 5 mg/ml gentamicin solution for 8 hours, which allows a rotating schedule. Treatment duration depends on how long the catheter needs to be saved. It should be continued for a week after clinical symptoms have improved.

Infusion systems should be changed every 96 hours. Those containing parenteral nutrition fluids need to be changed after 24 hours and those containing concentrated lipids (including propofol) should be changed every 12 hours. Special care to maintain aseptic conditions should be taken when drawing up propofol or other lipid formulations into syringe pumps.

Multidose vials should be avoided whenever possible. If they are used, they should be used for one patient only and always accessed with a sterile syringe and needle after careful disinfection of the rubber membrane with sterile alcohol.
Empiric treatment for catheter-related severe sepsis and septic shock should be effective against all common Gram-positive (especially coagulase-negative staphylococci) and Gram-negative organisms (especially *Pseudomonas* spp.) and, based on the individual epidemiological situation of the unit, sometimes MRSA and *Candida* spp. as well. Combination therapy includes:

- A third generation cephalosporin or piperacillin/tazobactam.
- In combination with either an aminoglyoside or fluoroquinolone and vancomycin.
- High-dose fluconazole can be added if needed.

Multiresistant organisms such as ESBL and vancomycin-resistant enterococci (VRE) require empiric coverage in outbreak situations or if the patient is already colonized or was infected with one of those organisms.

54.5 Catheter-associated Urinary Tract Infections (CAUTI)

The best preventive strategy for catheter-related urinary tract infection is to not continuously use catheters in the first place. Especially in patients with spinal cord injury, intermittent straight catheterization should be employed as soon as possible when strict fluid balance is no longer required.
If the need for long-term urinary catheterization is anticipated, a suprapubic catheter should be considered early on (e.g., patients with severe traumatic brain injury [TBI], large hemispheric stroke, subarachnoid hemorrhage [SAH] grades 4 and 5, minimal conscious or vegetative state, etc.).
Bladder irrigations or so-called bladder training should not be performed. If fluid instillation is needed for measuring bladder pressure (e.g., monitoring for abdominal compartment syndrome), a sterile transducer system should be used and a volume of 50-100 ml sterile fluid is injected. Special catheter sets with monitoring capabilities are available to reduce the need for manipulation.
When handling the Foley bag, retrograde flow must be avoided (e.g., during transport or diagnostic procedures in the radiology suite, etc.).
Empiric treatment for complicated catheter-related urinary tract infections utilizes:

- Piperacillin/tazobactam.
- Or a carbapenem.
- Or a fluoroquinolone.

and should be adjusted to culture results as soon as possible. The differential diagnosis between colonization and infection in critically ill patients can be difficult.

54.6 Infections Associated With Extraventricular (EVD) and Lumbar Drains

A special problem in the neurocritical care unit is the prevention and treatment of device-associated meningitis and/or ventriculitis. The insertion of extraventricular (EVD) and lumbar drains or monitoring bolts for intracranial pressure (ICP), microdialysis or brain tissue oxygenation may be performed as a bedside procedure in the unit under

maximal barrier precautions and aseptic conditions. Single-dose perioperative antibiotic prophylaxis can be considered, but the value of long-term antibiotic prophylaxis is highly questionable and very likely leads to the development of resistance and selection advantages for fungi.

There are several different monitoring devices and drainage systems on the market. They should all be handled in an aseptic fashion. Manipulation and disconnection should be strictly limited. Daily draws of cerebrospinal fluid (CSF) for glucose and cell count can be helpful in detecting an infectious process early but are of limited value if large amounts of blood are present (e.g., SAH).

If a nosocomial infection occurs, the most frequent organisms are:

- Coagulase-negative staphylococci (30%).
- Gram-negative rods (25%).
- Streptococci (20%).
- *Staph. aureus* (10%).

Antibiotic treatment is started with:

- High-dose vancomycin with blood level monitoring.
- In combination with a fourth generation cephalosporin (cefepime or ceftazidime) or meropenem.
- An additional combination with systemic or intrathecal gentamicin is used routinely by some centres.

Blood levels should be monitored when systemic gentamicin is given. The same empiric treatment scheme is used for ventriculoperitoneal shunt infections.

54.6.1 Surgical Site Infections After Craniotomy/Craniectomy

Surgical site infections can complicate the course of neurocritical care patients. CSF leakage and early deep tissue infection after decompressive craniectomy are among the most severe complications. The incidence of infectious complications is about 7% for delayed cranioplasties after decompressive craniectomy.

In order to detect such events early, surgical dressings should be inspected daily. Suspicious clear drainage can be checked for glucose content at the bedside to identify CSF.

Perioperative antibiotic prophylaxis should be limited to “single-shot” dosing.

Drains (e.g., subdural drains, subgaleal drains, subcutaneous drains, etc.) need to be handled with care under aseptic conditions and inspected daily.

For general aspects for prevention of surgical site infections see: http://www.who.int/patientsafety/safesurgery/en.

54.6.2 *Clostridium difficile*-associated Diarrhea (CDAD) and Nosocomial Diarrhea

Diarrhea in the ICU can be a symptom of: drug side effects, malabsorption, enteral nutrition formula, endocrinological diseases, cholestasis, inflammation, partial obstruction, infection.

All cases of diarrhea should be evaluated for *Clostridium difficile*. Outbreak situations with noro- or rotavirus are usually diagnosed by involvement of personnel and the high rate of attack. A positive toxin screen for *Clostridium difficile* is sufficient for the diagnosis in combination with the clinical picture. However, culture and typing are important for epidemiological reasons and especially in case of outbreak situations. Special infec-

tion control measures should be followed as outlined recently by the European Centre for Disease Prevention and Control (ECDC: http://ecdc.europa.eu/en).
Once positive for *Clostridium difficile*, no further testing is required and it is worthless to evaluate treatment success or to "clear" the patient. Isolation precautions may be ceased after symptoms have cleared for more than 2 days.
The primary treatment option is IV or enteral metronidazole. In severe cases (e.g., toxic megacolon), combination with enteral vancomycin should be started immediately.

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55 Selective Decontamination of the Oropharynx and Gastrointestinal Tract in Neurocritical Care Unit: A Useful Tool?

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55.1 Introduction

Selective decontamination of the digestive tract (SDD) is an antibiotic prophylactic strategy to control serious infections of lower airways and blood, and to reduce mortality. The full protocol of SDD includes four elements: a parenteral antimicrobial to control primary endogenous infections, enteral antimicrobials to control secondary endogenous infections, hygiene and topical antimicrobials to control exogenous infections, and surveillance cultures of throat and rectum to monitor SDD prophylaxis [1,2]. The aim of this chapter is to review the philosophy of SDD, its effectiveness and safety. A section is dedicated to the impact of SDD in critically ill neurological and neurosurgical patients.

55.2 Rationale

The key to infection control in the intensive care unit (ICU) is to appreciate that the three different types of infection, primary endogenous, secondary endogenous and exogenous, are due to a limited range of potentially pathogenic microorganisms (PPMs), six "normal" and nine "abnormal", and each require a different prophylactic approach [3-6]. Table 55.1 describes the three types of ICU infections and the preventative manoeuvres. The majority of infections in ICU are primary endogenous (about 55%), i.e. caused by

Infection	PPMs	Timing	Frequency	Manoeuvre
Primary endogenous	6 "normal" 9 "abnormal"	<1 week	55%	Parenteral antimicrobials
Secondary endogenous	9 "abnormal"	>1 week	30%	Enteral antimicrobials
Exogenous	9 "abnormal"	Any time during ICU stay	15%	Hygiene combined with topical antimicrobials

Table 55.1. **Classification of infections occurring in intensive care unit. "Normal" PPMs (potentially pathogenic micro-organisms) are *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Candida albicans, Staphylococcus aureus, Escherichia coli*. "Abnormal" PPMs are *Klebsiella, Proteus, Morganella, Enterobacter, Citrobacter, Serratia, Acinetobacter, Pseudomonas* species and methicillin-resistant *Staphylococcus aureus*.**

PPMs carried in the patient's digestive tract on admission to the ICU. These infections generally develop early during ICU stay (e.g., within the first week) and are caused by 6 "normal" PPMs such as *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Escherichia coli* and *Candida albicans*, and 9 "abnormal" PPMs such as *Klebsiella, Proteus, Morganella, Enterobacter, Citrobacter, Serratia, Acinetobacter, Pseudomonas* species and methicillin-resistant *Staphylococcus aureus*

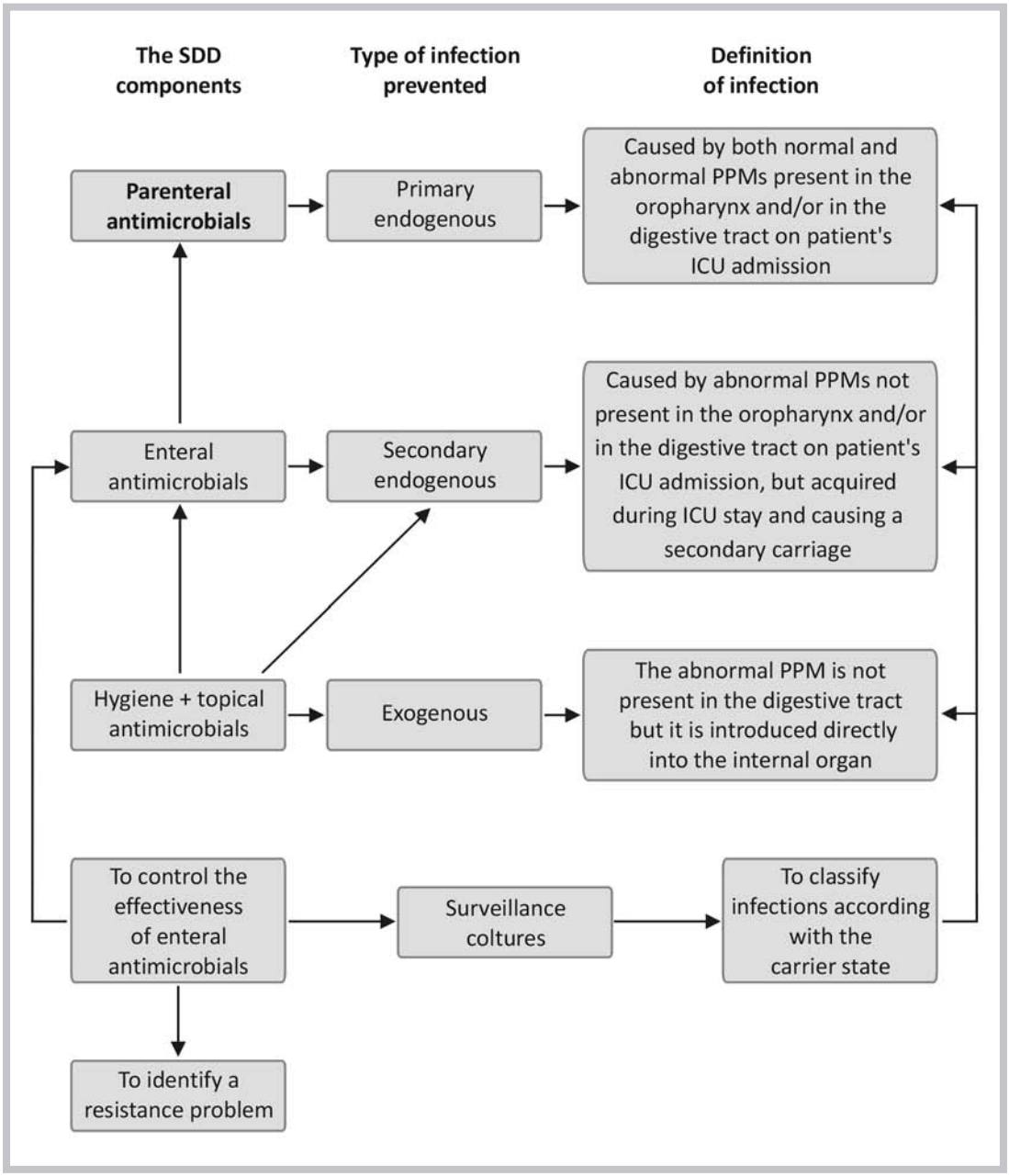

Figure 55.1. **The four components of the full protocol of SDD, and the type of infection controlled by each component.**

PPM = potentially pathogenic microorganism

ICU = intensive care unit

(MRSA). Primary endogenous infections can be controlled by the administration of parenteral antibiotics on admission to the ICU.

One third of ICU infections are secondary endogenous. They are invariably caused by 9 abnormal PPMs and develop late during ICU treatment (>1 week). These PPMs are not present in the patient's admission flora but are acquired during treatment on the ICU, followed by carriage and overgrowth, and, subsequently by colonization and infection of internal organs. Enteral administration of non-absorbable antimicrobials may control acquisition, carriage and overgrowth of these abnormal PPMs, preventing secondary endogenous infection.

Exogenous infections are caused by abnormal PPMs introduced directly into the internal organ, bypassing the carrier state. These infections may occur at any time during ICU stay. A high level of hygiene combined with topical antimicrobials is required to control exogenous infections. They occur less frequently (about 15%).

Secondary endogenous and exogenous infections are the "true" ICU-acquired infections.

55.3 The Four-component Protocol of SDD

The full SDD protocol is based on four components (Figure 55.1) [1]:

- Parenteral antimicrobials (e.g. cefotaxime 80 mg/kg/day or ceftazidime 80 mg/kg/day if the patient is suspected to carry a pseudomonal strain) for the first four days after ICU admission to control primary endogenous infections.
- Enteral administration, both oropharyngeal and intestinal, of non-absorbable antimicrobials to control secondary endogenous infections. The original protocol includes the combination of polymyxin E, tobramycin and amphoterincin B (PTA). In case of MRSA endemicity or carrier state of MRSA vancomycin can be added to classical mixture of PTA.

Author	Number of RCTs	Sample size	Lower airway infection OR (95%CI)	Bloodstream infection OR (95%CI)	Mortality OR (95%CI)
Vandenbroucke-Grauls [8]	6	491	0.12 (0.08-0.19)	NR	0.92 (0.45-1.84)
D'Amico [9]	33	5727	0.35 (0.29-0.41	NR	0.80 (0.69-0.93)
Liberati [10]	36	6922	0.35 (0.29-0.41)	NR	0.78 (0.68-0.89)
Safdar [11]	4	259	NR	NR	0.82 (0.22-2.45)
Silvestri [12]	42	6075			
• Yeasts			NR	0.89 (0.16-4.95)	NR
Silvestri [13]	51	8065	NR	0.63 (0.46-0.87)	0.74 (0.61-0.91)
Silvestri [14]	54	9473			
• Gram negative			0.07 (0.04-0.13)	0.36 (0.22-0.60)	NR
• Gram positive			0.52 (0.34-0.78)	1.03 (0.75-1.41)	NR
Silvestri [15]	21	4902	NR	NR	0.71 (0.61-0.82)

Table 55.2. **Efficacy of selective decontamination of the digestive tract assessed in eight meta-analyses of only randomized controlled trials.**

CI = confidence interval
NR = not reported
OR = odds ratio
RCTs = randomized controlled trials

- High levels of hygiene combined with topical antimicrobials to control exogenous infections.
- Surveillance cultures of throat and rectum taken on admission and then twice weekly (e.g. Monday and Thursday), to evaluate the efficacy of the manoeuvre and the development of resistance at an early stage.

55.4 Efficacy of SDD

SDD has been assessed in 59 randomised controlled trials (RCTs) [7], and 8 meta-analyses of only RCTs [8-15] (Table 55.2).

55.4.1 Carrier State

SDD significantly reduced oropharyngeal carriage by 87% (OR 0.13, 95% CI 0.07-0.2), and rectal carriage by 85% (OR 0.15, 95% CI 0.07-0.31) due to Gram-negative PPMs [14]. Gram-positive carriage was also reduced, but not significantly [14]. Additionally, fungal carriage was significantly reduced by 68% (OR 0.32, 95% CI 0.19-0.53) [12].

55.4.2 Lower Airway Infection

All meta-analyses showed a reduction of lower respiratory tract infection. The most robust meta-analysis by the Italian Cochrane Collaboration showed that the full protocol of SDD significantly reduced lower airway infection by 65% (OR 0.35, 95% CI 0.29-0.41) [10]. Five patients needed to be treated with SDD to prevent one episode of lower airway infection. Moreover, lower airway infection due to Gram-negatives was reduced by 89% (OR 0.11, 95% CI (0.05-0.20) and that due to Gram-positives by 48% (OR 0.52 95% CI 0.34-0.78) [14].

55.4.3 Bloodstream Infection

A recent meta-analysis including 51 randomized controlled studies comprising of 8065 patients demonstrated a significant reduction in bloodstream infections of 27% (OR 0.73, 95% CI 0.59-0.90) compared to control patients [13]. In particular, bloodstream infections due to Gram-negative PPMs were significantly reduced (OR 0.39; 95 % CI 0.24-0.63).

55.4.4 Fungal Infection

A recent meta-analysis evaluated the impact of SDD on fungal infections and demonstrated a significant reduction of fungal infections by 70% (OR 0.30, 95% CI 0.17-0.53), and a non significant reduction of fungemia due to a small sample size (OR 0.89, 95% CI 0.16-4.95) [12].

55.4.5 Mortality

Three large studies of 527 [16], 934 [17] and 6000 [18] patients have shown a mortality reduction of 30% (RR 0.70, 95% CI 0.51-0.95), 40% (OR 0.60, 95% CI 0.42-0.82), and

Author	Patients enrolled		Patient with neurological disorders at study entry (%)	
	SDD	C	SDD	C
Abele-Horn [21]	58	30	30 (51.7)	15 (50)
Aerdts [22]	17	49	9 (52.9)	15 (30.6)
Bergmans [23]	87	139	20 (22.9)	22 (15.8)
Camus [24]	130	126	26 (20)	36 (28.6)
de Smet [18]	2045	1990	231 (11.3)	273 (13.7)
Gastinne [25]	220	225	3 (1.4)	9 (4)
Georges [26]	31	33	27 (87)	25 (75.7)
Gosney [20]	103	100	103 (100)	100 (100)
Hammond [27]*	114	125	13 (11.4)	20 (16)
Jacobs [28]	36	43	21 (58)	27 (47)
Korinek [19]	96	95	96 (100)	95 (100)
Krueger [16]	265	262	76 (28.7)	73 (27.8)
Laggner [29]	33	34	2 (6.1)	3 (8.8)
Lingnau [30]	80	148	58 (72.5)	88 (59.5)
Pugin [31]	25	27	2 (8)	4 (14.8)
Quinio [32]	76	72	71 (93.4)	68 (94.4)
Rocha [33]	47	54	37 (78.7)	43 (79.6)
Sanchez Garcia [34]	131	140	55 (42)	45 (32)
Ulrich [35]	48	52	11 (22.9)	11 (21.2)
Unertl [36]	19	20	14 (73.7)	13 (65)
Wiener [37]	30	31	5 (16.7)	7 (22.5)
Winter [38]	91	92	17 (18.7)	16 (17.4)
Total	3782	3887	851 (22.5)	935 (24)

Outcome	Nr. RCTs	Nr. patients		Events		OR (95% CI)	p
		SDD	C	SDD	C		
Overall infection	8	628	694	251	388	0.44 (0.28-0.69)	<0.001
LRTI	19	1476	1631	190	446	0.29 (0.19-0.44)	<0.001
BSI	13	2941	2940	158	310	0.60 (0.43-0.84)	=0.0027
UTI	10	820	875	96	182	0.52 (0.36-0.74)	<0.001
Mortality	22	3782	3887	1023	1144	0.81 (0.68-0.96)	=0.013

Table 55.3 **Summary of randomized controlled trials of SDD including patients with neurological disorders at study entry and meta-analysis of the impact of SDD on infections and mortality. Data are retrieved after reviewing 59 published randomized controlled trials of selective decontamination of the digestive tract. Patients with neurological disorders included head trauma, brain bleeding, patients with Glasgow coma scale <8, impaired consciousness, neurological disease.**

* data were found in a separate publication (Hammond JMJ, Potgieter PD, Chest 1993;104:547-51) of a subgroup of only neurological patients included in the main publication [27]. Results of meta-analysis are presented as Odds Ratios with 95% confidence interval using the random effects model. Heterogeneity was assessed by the Cochran Q statistic and the I2 measure of inconsistency. No heterogeneity was found in all comparisons with the Cochran Q statistic; I2 values of 15.6% (overall infection) and 6.5% (UTIs) were found, indicating a non significant level of heterogeneity

SDD = selective digestive decontamination
C = control
RCT = randomized controlled trial
OR = Odds ratio
LRTI = lower respiratory tract infection
SDD = selective digestive decontamination
C = control
RCT = randomized controlled trial
OR = Odds ratio
LRTI = lower respiratory tract infection
BSI = bloodstream infection
UTI = urinary tract infection

16% (OR 0.835, 95%CI 0.720-0.968), respectively. All meta-analyses, producing a large sample size, have shown a significant reduction in mortality. The Italian Cochrane group showed a significant mortality reduction of 22% (OR 0.78, 95% CI 0.68-0.96); twenty-one patients should be treated to save one life [10]. Similarly, the only meta-analysis with the endpoint of mortality and including randomized studies in which the full SDD protocol was used showed a mortality reduction of 29% (OR 0.71, 95% CI 0.61-0.82) [15]. This effect achieved a 42% mortality reduction in studies where SDD eradicated the carrier state (OR 0.58, 95% CI 0.45-0.77). In summary, all large randomized studies and robust meta-analyses demonstrated a significant reduction in mortality when the full SDD protocol of parenteral and enteral antimicrobials was used.

55.5 Efficacy of SDD in Patients With Neurological Disorders

Two RCTs of SDD were undertaken in subjects with neurological disorders [19,20]. Korinek et al. assessed the effect of SDD (PTA protocol including a 4% vancomycin paste) on carriage and infection in 123 neurosurgical patients: 63 received SDD and 60 placebo [19]. SDD significantly reduced Gram-negative bacilli carriage and significantly reduced the number of infected patients (29 SDD vs. 49 control, p<0.001), infection episodes (36 SDD vs. 71 control, p<0.01), bronchopneumonia (15 SDD vs. 25 control, p<0.04), urinary tract infection (12 SDD vs. 24 control, p<0.01). The authors concluded that SDD was an effective technique in reducing infectious morbidity in comatose neurosurgical patients. Gosney et al. performed a prospective, randomized, placebo-controlled, double blind study in patients with acute stroke: 103 patients received SDD and 100 received placebo [20]. There were significantly less patients with pneumonia in SDD group compared with placebo (p=0.029).

There are 22 RCTs of SDD which reported data on patients with neurological disorders at study entry (Table 55.3). Apart from the two above mentioned studies [19,20], in the other 20 RCTs [16,18,21-38], mainly in trauma patients, the number of patients with neurological disorders on admission was specified; this percentage ranged from 1.4% to 94% of the study population. In those 22 studies, including a total of 7669 patients (3782 SDD, 3887 controls), there were 851 (22.5%) and 935 (24%) patients with neurological disorders in the SDD and control groups, respectively. Remarkably, a meta-analysis of these 22 RCTs including neurological/neurosurgery patients showed that SDD signif-

Outcome	Nr. RCTs	Nr. patients		Events		OR (95% CI)	P
		SDD	C	SDD	C		
Overall infection	3	219	221	83	149	0.22 (0.10-0.48)	<0.001
LRTI	6	349	422	87	181	0.35 (0.17-0.70)	=0.0032
Mortality	6	349	422	52	68	0.82 (0.39-1.73)	ns

Table 55.4. **Meta-analysis of six randomized controlled trials of SDD including a high percentage of patients with head trauma. All RCTs including a percentage of patients with head trauma >70% of the enrolled patients were included in the analysis. Results are presented as Odds Ratios with 95% confidence interval using the random effects model. Heterogeneity was assessed by the Cochran Q statistic and the I^2 measure of inconsistency. No heterogeneity was found in all comparisons.**

C = control
CI = confidence interval
LRTI = lower respiratory tract infection
OR = Odds Ratio
RCT = randomized controlled trial
SDD = selective digestive decontamination

icantly reduced all important infectious endpoints, such as overall infection, lower airway infection, bloodstream infection, urinary tract infection, and mortality (Table 55.3). Additionally, six out of those 22 RCTs included an important percentage (>70%) of patients with head trauma on admission [19,26,30,32,33,36]. Table 55.4 shows the meta-analysis of these 6 RCTs: both overall infections and lower respiratory tract infections were significantly reduced by SDD, whilst the reduction in mortality was not significant due to the small sample size.

Therefore, these results support the use of SDD in neurocritically ill patients, including those with head trauma and severe coma, as morbidity and mortality are reduced by the prophylactic manoeuvre of SDD.

55.6 Safety of SDD

The 25 year research on SDD demonstrated that SDD does not increase the resistance problem, but rather reduces it [39]. Two of the 59 RCTs [33,40] report an increase in resistance. Interestingly, the endpoint was the number of resistant isolates rather than the number of patients with resistant isolates in these two RCTs. Three RCTs evaluated the impact of SDD on the number of patients who carried antibiotic resistant aerobic Gram-negative bacilli (AGNB) [17,18,41]. A *Klebsiella pneumoniae* producing extended spectrum beta-lactamase was endemic in a Parisian hospital [41]: carriage and infection rates were 19.6% and 9%, respectively. Once enteral antimicrobials were added to the parenteral there was significant reduction in both carriage and infection (19.6% versus 1%; 9% versus 0%). A Dutch RCT including about 1000 patients reports that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin and polymyxins occurred in 16% of patients receiving parenteral and enteral antimicrobials, compared to 26% of control patients receiving only parenteral antibiotics with a relative risk of 0.6 (95% confidence interval 0.5-0.8) [17]. The largest multi-centre RCT to date [18] includes 6000 patients, and the proportion of patients with aerobic Gram-negative bacilli in rectal swabs that were not susceptible to the marker antibiotics was lower with SDD than with standard care or selective oropharyngeal decontamination (SOD), a modified SDD protocol without the gut component. For example, carriage of multi-resistant *P. aeruginosa* was 0.4% in SDD versus 0.8% in SOD and 1.3 in the group receiving standard care ($p<0.05$).

There are four long-term studies (≥2 years) evaluating the impact of polymyxin/tobramycin on resistance amongst AGNB [42-45]. The resistance data of the long-term studies confirm the RCT findings that rates of carriage and infection due to resistant AGNB in patients receiving enteral and parenteral antimicrobials are not increased but are actually lower compared with patients receiving solely parenteral antimicrobials. Most patients who require long term treatment on ICU have overgrowth of abnormal flora, defined as 10^5 AGNB per ml of saliva and/or g of faeces. Gut overgrowth guarantees increased spontaneous mutation, leading to polyclonality and antimicrobial resistance [46]. As the parenteral antimicrobials generally fail to eradicate the abnormal carrier state in overgrowth concentrations, the enteral antimicrobials polymyxin/tobramycin aiming at converting the abnormal carrier state into normal carriage, are the essential component of SDD because they eradicate carriage and overgrowth of AGNB including resistant mutants, maintaining the usefulness of parenteral antimicrobials.

Vancomycin-resistant enterococci (VRE) and MRSA are intrinsically resistant to the parenteral and enteral antimicrobials of the SDD protocol. VRE carriage and infection were the primary endpoints of SDD RCTs in two American ICUs with endemic VRE [47,48].

Author	Study		Patients		% patients with carriage (surv) and/or infection (diagn) due to VISA and/or VRE
	Type	Period	Type	Number	
de la Cal [55]	Prospective observational	4 years	Medical/ surgical >3 days of mechanical ventilation	799	13/799 (5%) carried VRE
Cerda [56]	Prospective observational	4 years	Burns	375	No emergence of VRE or VISA in either surv or diagn
Viviani [57]	Prospective observational	2 years	Mechanical ventilation >3days	265	No emergence of VRE or VISA in either surv or diagn
Silvestri*	Prospective observational	3 years	Mechanical ventilation >4 days	193	No emergence of VRE or VISA in either surv or diagn

Table 55.5. **Long-term studies (≥2 years) of enteral vancomycin on resistance amongst *Staphylococcus aureus* and enterococci: *Staphylococcus aureus* with intermediate sensitivity to vancomycin and vancomycin-resistant enterococci.**

* L. Silvestri, personal communication
Surv = surveillance samples
Diagn = diagnostic samples
VISA = vancomycin-intermediate *Staphylococcus aureus*
VRE = vancomycin-resistant enterococci

There was no difference between test and control groups. There are seven RCTs conducted in ICUs where MRSA was endemic at the time of the trial [25,27,30,37,40,49,50], they report a trend towards higher MRSA carriage and infection rates in patients receiving SDD. The addition of enteral vancomycin to the classical SDD is required to control MRSA in ICUs with endemic MRSA [51]. Neither *Staphylococcus aureus* with intermediate sensitivity to vancomycin (VISA) nor VRE emerged in any of the six RCTs using enteral vancomycin [19,23,16,31,52,53]. Four studies using long term SDD with vancomycin (≥2 years) failed to report the emergence of VISA or VRE ([54-56], L. Silvestri, personal communication) (Table 55.5).

55.7 Conclusions

SDD has been assessed in 59 randomised controlled trials and 8 meta-analyses of only randomised controlled trials. SDD using parenteral and enteral antimicrobials consistently demonstrated a significant reduction in lower respiratory tract infection, bloodstream infection, fungal infection and mortality.

Twenty five years of clinical SDD research showed that SDD does not increase the resistance problem but rather reduces it. Two RCTs of SDD were undertaken in patients with neurological disorders, both neurosurgical patients and patients with acute stroke, and confirmed the previous results in mixed (e.g., medical/surgical) ICU population. Moreover, the majority of trauma RCTs of SDD comprised of different percentages of patients with head trauma or other neurological disorders, such as an impairment of consciousness. These studies showed a significant impact on infectious morbidity and mortality.

A meta-analysis of a subgroup of RCTs including a high percentage of neurological patients confirmed these results. For these reasons we advocate the use of SDD in critically ill neurological and neurosurgical patients.

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56 Strategies for the Prevention and Management of Ventilator-associated Pneumonia in a Neurocritical Unit

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56.1 Introduction

One of the main causes of morbidity and mortality in the industrialized countries is trauma and traumatic brain injury (TBI). In recent decades its incidence has increased constantly. Severe multiple trauma patients usually require admission to intensive care units (ICU) and most require ventilatory support.

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in the ICU, with an incidence of 10-30% [1]. In addition, VAP prolongs hospital stay and days on mechanical ventilation and contributes to an increase in mortality. Although mortality attributable to VAP in critically ill patients is still debated, the association between VAP and late mortality has been demonstrated in cohort studies, particularly in patients in whom VAP is caused by virulent pathogens such as *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). In patients with VAP, there is an association between increased mortality and morbidity and inappropriate initial antibiotic treatment and delays in initiation of treatment. Early initiation and appropriate antibiotic treatment are important in the management of these patients.

In trauma patients on mechanical ventilation, VAP is a major complication, with an incidence of approximately 40 to 50%. This high incidence may be explained by the decreased level of consciousness, immunosuppression, and the need for emergency tracheal intubation. Although several recent studies have shown that VAP-related mortality in trauma patients is 8-59%, other studies found that VAP did not seem to increase mortality in severe trauma patients.

VAP in trauma patients differs from that in nontrauma patients due to characteristic risk factors and it is frequently associated with specific pathogens in the first week such as methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Haemophilus influenzae*. Trauma patients have a different distribution in the incidence of VAP because, unlike nontrauma patients, the incidence of early VAP is 30-40%. According to the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia, early VAP is defined as occurring within the first four days in the ICU and late VAP when it occurs after five days of admission to the ICU [2].

Brochard et al. recently showed that the beginning of VAP was associated with a higher probability of secondary brain injury, increased intracranial pressure, hypotension, fever and hypoxemia that all lead to a worse outcome [3].

The main objectives of this chapter are to review the risk factors, etiology, antibiotic treatment and prevention of VAP in trauma patients and to determine whether a different approach to such patients is needed.

56.2 Early Ventilatior-associated Pneumonia in Trauma Patients

Trauma patients can aspirate oropharyngeal secretions after brain injury, during resuscitation, and as a result of intubation. Endotracheal intubation is a major risk factor for developing VAP because it increases the risk of aspiration and weakens the bronchial clearance mechanism. The intubation procedure itself significantly increases the risk, as has been demonstrated in patients requiring reintubation [4]. Moreover, a majority of trauma patients require emergency tracheal intubation due to a decreased level of consciousness, cardiorespiratory arrest, psychomotor agitation and for air transport in some cases. Sloane et al. showed that 28% of patients who required prehospital rapid sequence intubation developed VAP and that this incidence was significantly higher than in patients intubated in the emergency department [5]. The cumulative risk of developing VAP is 3% per day of mechanical ventilation primarily within the first week of intubation.

Trauma patients often have a decreased level of consciousness that affects the swallowing reflex. Several studies have shown that the level of consciousness is also an important risk factor that increases the incidence of VAP [6,7]. Our group showed that the incidence of VAP was significantly higher among comatose patients (Glasgow Coma Score [GCS] <9) and the predominant pathogen isolated was MSSA, followed by *H. influenzae*. These data are consistent with other studies. In another study evaluating the risk factors for developing VAP within the first 48 hours of endotracheal intubation in nontrauma patients, the univariate analysis showed that high-volume aspiration of secretions, sedation, intubation for cardiorespiratory arrest or a decreased level of consciousness, emergency procedure, cardiorespiratory resuscitation, and a GSC <9 were statistically significant factors associated with VAP. But on the multivariate analysis, cardiorespiratory arrest and continuous sedation significantly increased the risk of VAP with an odds ratio (OR) of 5.13 and 4.4, respectively. Calvalcanti et al. showed in a case-control study that severe head and neck trauma, as measured by the Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS), were the only independent risk factors for VAP development [8]. Moreover, they suggested that the need for supine position in patients with cervical fracture could influence this association. An interesting finding was that a GSC <8 was not associated with the development of VAP. Over 60% of patients developed early VAP and the main pathogens were MSSA and *H. influenzae*.

Due to the high incidence of early VAP caused by MSSA, several studies assessed the relationship between respiratory tract colonization and VAP. Ewig et al. performed an observational study where they analyzed the patterns of bacterial colonization in mechanically ventilated patients with severe head injury [9]. They noted that the initial colonization of the upper and lower airway was mainly by MSSA, *H. influenzae* and *Streptoccocus pneumoniae*. This colonization pattern was an independent risk predictor of subsequent colonization of the tracheobronchial tree. Although initial colonization of the tracheobronchial tree by MSSA, *H. influenzae* and *S. pneumoniae* was associated with a higher probability of early VAP, they found no independent risk factor for it. They also showed prior antibiotic use had a protective effect against these patho-

gens. Subsequently, Sirvent et al. demonstrated that tracheal colonization by MSSA, *H. influenzae* or *S. pneumoniae* within the first 24 hours of intubation was an independent risk factor for the development of early VAP in patients with TBI [10]. Bronchard et al. in a prospective observational study in TBI patients showed that nasal bacterial load of MSSA, aspiration before intubation, and use of barbiturates were independent risk factors for early VAP [3]. Recently, Agbaht et al. conducted a retrospective observational study to assess whether trauma influenced the epidemiology of VAP [11]. They found that among patients with early VAP, MSSA was the pathogen most frequently isolated in trauma patients. But in nontrauma patients *Streptococcus* spp. were the most frequent and significantly associated with early VAP. Moreover, in early VAP with prior antibiotic use, MSSA was significantly more frequent in trauma patients than in nontrauma patients. MRSA was not responsible for early episodes of VAP in trauma patients. Cases of MRSA-related VAP in trauma patients occurred in those with more than 10 days of ICU stay, when the patients had been subjected to the effect of risk factors similar to the other patients.

Other risk factors have been analyzed. Tejada et al. in a prospective cohort study found that continuous enteral feeding, craniotomy, mechanical ventilation for more than 24 hours and the use of positive end-expiratory pressure (PEEP) were independent risk factors for developing VAP in trauma patients [12]. The relationship between continuous enteral feeding and VAP has been documented in other studies. The administration of enteral nutrition with high pH via a nasogastric tube could increase gastric bacterial colonization, as well as volume, pressure and reflux. They suggested that the relationship between the use of PEEP and the development of VAP was due to the use of PEEP among patients with the acute respiratory distress syndrome (ARDS) which predisposes to the development of VAP.

56.3 Late Ventilatior-associated Pneumonia in Trauma Patients

As mentioned, in the study by Rello et al. the risk of developing VAP increased with days of intubation [7]. While cardiorespiratory arrest and continuous sedation were associated with the development of VAP in patients intubated for 48 hours, no association was found in patients intubated for more than 48 hours. In contrast, prior antibiotic use was associated with an increased risk of VAP and the main pathogen associated was *P. aeruginosa*. Ewig et al. observed that the increase in the colonization of ventilated patients during their stay in the ICU was primarily due to *P. aeruginosa* and *Acinetobacter* spp. Multivariate analysis showed that prior antibiotic use was the only risk factor for late VAP [9].

Early ventilator-associated pneumonia	Late ventilator-associated pneumonia
• Reason for intubation* • High bronchoaspiration • Emergent intubation • Cardiopulmonary resuscitation • Glasgow Coma Score <9 • Sedation	• Prior antibiotic use

Table 56.1. **Risk factors for the development of early and late ventilator-associated pneumonia.**
* Cardiopulmonary arrest or decreased level of consciousness

Agbaht et al. in a medical-surgical ICU showed that the pathogens responsible for late VAP were MSSA and nonfermentative Gram-negative bacilli (GNB) [11]. The nonfermentative GNB were significantly more frequent in late VAP than in early VAP. These pathogens were isolated from patients with risk factors such as late VAP and prior antibiotic use. They also observed that late VAP had a different distribution of pathogens in trauma patients where *Acinetobacter baumannii* was the most frequently isolated compared with nontrauma patients in whom *P. aeruginosa* was the most common pathogen isolated. MRSA was isolated from patients with more than 10 days of mechanical ventilation. This pathogen was significantly associated with the absence of trauma, late VAP, and prior antibiotic use. The main risk factors for early and late VAP in trauma patients are summarized in Table 56.1 [21].

56.4 Prevention of Ventilator-associated Pneumonia

There are several different strategies for preventing VAP. These are generally classified into nonpharmacological (Table 56.2) and pharmacological (Table 56.3) strategies. The

Strategy	Effectiveness
General measures	
Use of a formal infection-control programme	Yes
Adequate hand hygiene before and after contact with the patient)	Yes
Use of protective gloves and gowns	Undetermined
Provision of adequate nutritional support	Yes
Specific measures	
Early removal of nasogastric and endotracheal tubes	Yes
Avoidance of gastric overdistension	Yes
Oral rather than nasal intubation	Yes
Continuous subglottic suctioning	Yes
Maintenance of adequate endotracheal tube cuff pressure	Yes
Routine change of ventilator circuit	Yes
Use of noninvasive mechanical ventilation	Yes
Routine change of line-suction catheter	Not
Chest physiotherapy	Not
Humidification with heat and moisture exchangers	Undetermined
Postural changes	Undetermined

Table 56.2. **Nonpharmacological strategies for the prevention of ventilator-associated pneumonia.**

Strategy	Effectiveness
Selective digestive decontamination	Undetermined
Prior antibiotic use	Yes (intubation)
Oral hygiene with chlorhexidine	Yes
Stress ulcer prophylaxis, sucralfate vs. ranitidine	Yes
Avoid deep sedation and muscle relaxants	Yes

Table 56.3. **Pharmacologic strategies for the prevention of ventilator-associated pneumonia.**

strategies do not differ according to the type of patient since they should be applied to all patients with endotracheal intubation. Recently, the verification of compliance with a series of measures and the implementation of "care bundles" have emerged as useful integrative strategies to reduce VAP incidence.

56.4.1 Nonpharmacological Strategies for Preventing Ventilator-associated Pneumonia

Nonpharmacological strategies aim to reduce the amount of secretions that reach the lower respiratory tract and include:

- Hand washing by healthcare workers is considered the main tool for controlling and decreasing cross-transmission of nosocomial infections. Alcoholic solutions have several advantages over washing with antiseptic soap: the application requires less time for staff, their effect is more durable, and the antimicrobial spectrum is greater than that of antiseptic soap, comprising Gram-positive and Gram-negative pathogens, mycobacteria, wrap viruses and fungi. But they are not active against spore forms. Also, the supply can be adapted to any area of the room, providing greater accessibility.
- Early removal of nasogastric and endotracheal tubes. As mentioned, the cumulative risk of developing VAP is 1% per day of mechanical ventilation and early removal of the endotracheal tube is necessary. The role of nasogastric tubes is more controversial because the tubes prevent the complete closure of the lower oesophageal sphincter and could promote the conveyance of pathogens from the stomach. But it presence is essential.
- Semirecumbent patient positioning. There is unanimous agreement that patients with endotracheal intubation remain positioned at 45 degrees to reduce the ocurrence of aspiration, however, this is difficult in clinical practice.
- Continuous subglottic suctioning. Randomized studies showed a reduction in episodes of VAP. This is especially useful in patients not receiving antibiotics and during the first week of mechanical ventilation. Its effectiveness in reducing VAP by *P. aeruginosa* has not been proved.
- Maintenance of adequate of endotracheal tube cuff pressure. The recommended pressure is from 25 to 30 cmH_2O, which should be repeatedly checked daily. Pressures <20 cmH_2O allow the passage of secretions in the lower airway and pressures >30 cmH_2O could damage the tracheal mucosa.
- Routine change of the ventilator circuit. The latest studies showed no difference in the incidence of VAP with changing ventilator-circuit tubing every 48 hours, every week or if they are used throughout the patient's ICU stay, as opposed to changing every 8 or 24 hours as previously done. The tubing should be changed if there is an accumulation of secretions in it or if the tubing falls to the ground or is damaged.
- Use of humidification systems, cascade humidifier or heat and moisture exchanger. Initial studies showed that patients with heat and moisture exchangers had a lower incidence of VAP than patients with cascade humidifiers. This was because the heat and moisture exchangers had an antibacterial filter and cascade systems humidified at a temperature that did not prevent bacterial growth. But this problem has now disappeared with the new systems, so it is recommended as clinically indicated and preferably by heat and moisture exchangers.

56.4.2 Pharmacological Strategies for Preventing Ventilator-associated Pneumonia

Pharmacological strategies aim to reduce the bacterial inoculum or amount of secretions and include [13]:

- Selective digestive decontamination. This measure is not highly recommended due to the conflicting results of studies and the risk of emergence of resistant pathogens.
- Use of preventive antibiotics. As described, a decreased level of consciousness is a risk factor for the development of early VAP in trauma patients. Antibiotic administration during intubation has shown a protective effect for early VAP in a randomized and at least one observational study. In other studies, however, prolonged administration of antibiotics has been associated with an increased risk of late VAP.
- Chlorhexidine oral rinse. This practice is part of general ICU patient care. A recent meta-analysis of oral hygiene with chlorhexidine showed that it is beneficial for the prevention of VAP and this benefit is more marked in patients after cardiac surgery.
- Prophylaxis of stress ulcers with sucralfate or ranitidine. Patients on mechanical ventilation are at increased risk of gastrointestinal bleeding and therefore receive stress ulcer prophylaxis with sucralfate or ranitidine. Although the latter increases the gastric pH and may promote bacterial overgrowth, a meta-analysis found no difference in the incidence of VAP between the two treatments.
- Avoiding the use of deep sedation and muscle relaxation. As mentioned above, deep sedation is an independent risk factor for developing VAP. Current recommendations advise minimizing the use of neuromuscular relaxation and have replaced the use of sedation guidelines with fixed patterns guided by the changing state of the patient. With this approach, the daily withdrawal of sedation or a “sedation vacation” is used to assess whether the patient can start weaning. This has led to a reduction in days on mechanical ventilation and a parallel reduction in the incidence of VAP.

56.4.3 Application of “Care Bundles”

The rationale for the use of “care bundles” is that the benefit obtained from the application of a group of three to five measures intended to reduce VAP is greater than the isolated use of a single measure. The choice of a measure is supported by published evidence that i can reduce the rate of VAP. Also, it assesses the implementation of these measures and compliance with them. Our group evaluated the results of a multicenter study after the implementation of five preventive measures, including hand hygiene with alcohol solutions, shortening the duration of mechanical ventilation by adjusting sedation, chlorhexidine oral rinse, avoiding change of tubing, and ensuring correct endotracheal tube cuff pressure. This project permitted standardization of the application of preventive measures, reducing the duration of mechanical ventilation and the overall rate of VAP.

56.5 The PIRO Score

The PIRO concept derived from an attempt to classify serious infectious diseases in a way similar to TNM staging of tumours [14]. Stratification is based on the PIRO classification of sepsis episodes as a predisposing condition of the patient, the nature and extent of insult or injury, the nature and magnitude of host response, and the degree

of concomitant organ dysfunction. The concept of the VAP PIRO score was developed by our group according to this concept and adapting it to VAP for the variables that were significantly associated with mortality in a multivariate analysis of a VAP database. These parameters were selected according to previous evidence for the association with poor prognosis of VAP and good agreement with the definitions of the PIRO concept. The VAP PIRO score identifies four independent variables associated with mortality, allowing the assessment of severity in each episode. These variables are: the presence of comorbidities (chronic obstructive pulmonary disease [COPD], immunocompromised state, chronic heart failure, chronic liver disease or chronic renal failure); bacteraemia; shock; and the acute respiratory distress syndrome (ARDS) (Table 56.4). To calculate the score, each present variable is given one point. The VAP PIRO score is the sum of these four variables.

PIRO	Variables	Score
Predisposition	Co-morbidities*	1
Injury	Bacteraemia	1
Response	Systolic blood pressure <90 mmHg#	1
Organ dysfunction	ARDS **	1

Table 56.4. Variables included in the VAP PIRO score.
* Chronic obstructive pulmonary disease, immunocompromised state, chronic heart failure, chronic liver disease or chronic renal failure. One point is given for each condition present.
# Or need of vasopressor agents to maintain this blood pressure
** Acute respiratory distress syndrome

The score is simple tool for daily clinical practice that helps us to assess severity and predict mortality in patients with VAP. The score was associated with an increased risk of death in the Cox regression of high-risk patients (VAP PIRO score of 2 points; HR 2.14, 95% CI 1.19-3.86) and patients at very high risk (VAP PIRO score of 3 to 4 points; HR 4.63; 95% CI 2.68-7.99).

The main advantages of this scoring system are its simplicity, the short time needed to calculate it, and its validity for all subgroups of patients admitted to the ICU, including trauma patients, because it discriminates properly and no differences were found when comparing nontrauma patients with trauma patients, early or late VAP, and episodes with or without undetermined etiology.

56.6 Treatment

The selection of optimal antibiotic therapy should take into account the risk factors that influence the epidemiology of VAP, days of intubation, and prior antibiotic use.

In trauma patients who develop VAP within the first four days on intubation and have not received previous antibiotic treatment, the main pathogen is MSSA. Therefore, antibiotic coverage for this pathogen is required. The ATS/IDSA guidelines recommend treating early VAP with a third-generation cephalosporin (no activity against *P. aeruginosa*) fluoroquinolone or ampicillin/sulbactam. Coverage is guaranteed with any of these antibiotics. Following the survey data, Agbaht et al. reported that antibiotic treatment against MRSA is not necessary because MRSA is rare in this subset of patients [11].

Risk factors for developing late VAP are similar to nontrauma patients, which mainly include days on mechanical ventilation and prior antibiotic use. Although the proportions of pathogens in late VAP differ between trauma patients and nontrauma patients, this does not affect the antibiotic treatment since it must cover the same pathogens. Moreover, these factors should take into account each ICU epidemiology and patients' comorbidities. Therefore the general guidelines need to be adapted to local sensitivity patterns and specific characteristics of the patient's co-morbidities. Following these rules, The

Tarragona Strategy was developed for the treatment of VAP (Table 56.5) which includes ten statements based on four key points [15]: 1) immediate start of antibiotic treatment; 2) broad-spectrum antibiotic coverage followed by de-escalation based on the results of microbiology; 3) administration of antibiotics in high doses and individualized doses depending on the pharmacodynamic properties of antibiotics; and 4) choice of antibiotic penetration based on lung function of the minimum inhibitory concentration (MIC) in vitro or plasma levels. The initial use of combination therapy to treat *P. aeruginosa* significantly reduces the possibility of incorrect antibiotic treatment, which is associated with a higher risk of death [16]. However, the administration of an effective single antibiotic or combination therapy provides similar results, suggesting that switching to monotherapy is feasible and safe once the pathogen sensitivity has been determined. In patients with suspected VAP caused by MRSA, linezolid appears to be the best option. Finally, it must be borne in mind that trauma patients on mechanical ventilation and with a high creatinine clearance have an increased volume of distribution requiring higher doses of antibiotic therapy to achieve normal appropriate MIC.

1. Antibiotic therapy should be started immediately.
2. Antibiotic choice can be targeted, and in some cases based on direct staining.
3. The prescription should be modified in light of microbiologic findings.
4. Prolonging antibiotic treatment does not prevent recurrences.
5. Patients with chronic obstructive pulmonary disease or 1 week on intubation should receive combination therapy because of the risk of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*.
6. Methicillin-resistant *Staphylococcus aureus* is not expected in the absence of antibiotic exposure, whereas methicillin-sensitive *S. aureus* should be strongly suspected in comatose patients.
7. Therapy against yeast is not required, even when colonization with *Candida* spp. is present.
8. Vancomycin administration for Gram-positive pneumonia is associated with a very poor outcome.
9. The choice of a specific agent should avoid any regimen to which a patient was previously exposed.
10. Guidelines should be regularly updated and adapted to local patterns.

Table 56.5. **Tarragona strategy for therapy of ventilator-associated pneumonia.**

56.7 Conclusion

Trauma patients have a higher incidence of early VAP risk factors than nontrauma patients and MSSA is the main etiology. In this scenario, the antibiotic coverage of this pathogen is required. In trauma patients who develop late VAP, risk factors such as days on mechanical ventilation and prior antibiotic use increase the risk of developing VAP secondary to *P. aeruginosa, A. baumanni* and MSSA. In such patients the susceptibility patterns of each unit need to be taken into account. The VAP PIRO score is a useful and simple tool to assess severity and predict mortality. The implementation of "care bundles" is a step forward in the prevention of VAP.

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57 The Diagnosis and Management of Central Nervous System Infections in the Neurocritical Care Unit

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57.1 Introduction

Central nervous system (CNS) infections requiring admission to a neurocritical care unit include meningitis, encephalitis, brain and spinal epidural abscess, subdural empyema, and ventriculitis. These conditions are also complications of patients with neurologic injury and contribute significantly to morbidity and mortality. Nosocomial CNS infections may complicate neurosurgical interventions (craniotomy or ventriculostomy placement), craniocerebral trauma, and invasive neuromonitoring devices. CNS infections have acute and chronic neurologic sequelae, including seizures, hydrocephalus, focal neurologic deficits, sensorineural hearing loss, cognitive deficits, and personality change [1]. Reducing morbidity and mortality is critically dependent on rapid diagnosis and on timely initiation of appropriate antimicrobial therapy. The challenges to these goals include logistical limitations to providing immediate antibiotic therapy, pharmacokinetic barriers to achieving effective concentrations of antimicrobials at the site of infection, and changing trends in microbial resistance. Understanding the role of inflammation and the immune response in CNS infections has contributed to development of new diagnostic strategies using markers of inflammation, direct installation of antibiotics into the CNS and to the study of agents with focused immunomodulatory activity. In the Neurointensive care unit, attention should be focused on maintaining adequate cerebral blood flow, avoiding secondary complications of CNS infections, and treating the whole patient with a systems approach in order to reduce the significant non-neurologic morbidity and mortality that accompanies these diseases.

57.2 Anatomy and Inflammation of the Central Nervous System

In contrast to invertebrates in whom the brain relies on “professional” macrophages and maintains robust regenerative capacity, the vertebrate brain largely excludes hematogenous cells (lymphocytes, antibodies, neutrophils) [2]. Instead, pathogen infiltration and clearance of toxic cell debris is performed by resident “amateur” macrophages: the microglia, astrocytes, and ependymal cells which are activated to express a wide range of pattern recognition receptors (PRRs) for bacterial cell wall glycoproteins and express anti-microbial peptides.

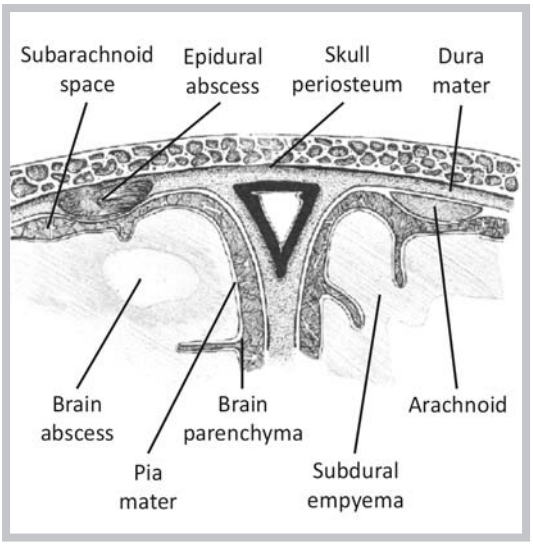

Figure 57.1. **Coronal view illustrating meningeal layers and common sites of central nervous system infections [3].**

Bacteria enter the CNS between the pia and arachnoid membranes (the subarachnoid space), a multistep process requiring evasion of host defenses (Figure 57.1). Bacteria responsible for meningitis attach to the nasopharyngeal epithelium, and are nearly all capable of secreting IgA proteases which prevent their destruction and allow them to cross the epithelium and invade the intravascular space [4,5]. Interactions between the bacterial capsular polysaccharide coat and complement regulatory proteins protect pathogenic bacteria from the complement system, increasing their ability to cross the blood-brain barrier (BBB) and enter the cerebrospinal fluid (CSF) [6].

The BBB is a highly specialized structural and biochemical barrier that regulates the entry of molecules into the brain and maintains ionic homeostasis [7,8]. The BBB is composed of nonfenestrated capillaries whose endothelial cells form continuous tight junctions that seal the paracellular cleft between adjacent endothelial membranes and prevent passive diffusion from the intravascular space to the brain parenchyma [7]. Within the CNS, a relatively low concentration of immunoglobulin and weak complement-mediated host defenses enable bacterial replication.

57.3 Pathogenesis of Bacterial CNS Infections

Clinical complications of bacterial CNS infections are largely mediated by host immune responses and leukocytes. An estimated 50% of neuronal cell loss occurring in the context of *Streptococcus pneumoniae* meningitis is the result of bacterial toxins (pore-forming pneumolysin, hydrogen peroxide); the other half is mediated by the inflammatory process [9-11]. Endogenous inflammatory mediators, such as interleukin IL-1, IL-6, and tumor necrosis factor TNF-α, which are part of the host immune response, contribute to neurologic injury by stimulating migration of neutrophils into the CSF. Proinflammatory cytokines (IL-1a, IL-1b, TNF-α, IL-6, granulocyte-macrophage colony-stimulating factor), produced by these invading leukocytes, activated endothelial cells, astrocytes, and perivascular macrophages, regulate brain inflammation by altering brain endothelial cell junction complexes, which disrupts the BBB and results in the development of vasogenic brain edema, increased intracranial pressure, and disruptions in cerebral blood flow [12-15]. Intercellular adhesion molecules, vascular cellular adhesion molecules, and selectins alter tight junction complexes by regulating leukocyte and endothelial cell interactions, and leukocytes themselves increase vascular permeability through interactions with endothelial cells and release of proinflammatory mediators [15-17]. Finally, chemokines and chemoattractant cytokines such as IL-8, monocyte chemoattractic protein-1, and chemokine ligand (CCL2) are proinflammatory mediators that selectively drive leukocytes into brain parenchyma and can regulate BBB permeability by expressing specific receptors on brain endothelial cells and by producing other proinflammatory agents [18].

Stimulation of the host immune response depends on components of the bacterial cell wall and lipopolysaccharide surface proteins [19]. Because levels of complements, immunoglobulins, and polymorphonuclear leukocytes are lower in the CSF than the serum, opsonic activity is inferior, and therefore bactericidal as opposed to bacteriostatic agents must be used to control infection [20,21].

There are also factors limiting excessive host immune responses. The TNF-related apoptosis-inducing ligand (TRAIL) appears to modify the inflammatory response and reduce neuronal cell death. Soluble TRAIL levels are elevated in the CSF of patients with bacterial meningitis [22]. In experimental meningitis, using intrathecal administration of pneumococcal cell wall (a TRAIL receptor ligand), TRAIL deficient mice had protracted inflammation, clinical impairment and increased apoptosis in the hippocampus. These changes were reversed by administration of recombinant TRAIL (rTRAIL) into the subarachnoid space of $TRAIL^{-/-}$ mice or by transplanting TRAIL-expressing bone-marrow cells into a chimeric mouse model. Therefore, TRAIL is an anti-inflammatory cytokine that limits the lifespan of activated leukocytes, mediates neuronal injury in meningitis, and may be useful as a therapeutic agent to reduce the acute inflammatory response and improve outcomes in invasive CNS infections [23].

Removing cytokine and chemokine activity with neutralizing antibodies to cytokines and chemokine receptor antagonists, respectively, has been shown experimentally to reduce brain edema formation. This may represent a new strategy for treating vasogenic brain edema, which causes significant morbidity in CNS infections [18,23,24]. Blockade of TNF-α, which contributes to cochlear injury, reduced postmeningitic hearing loss, and cochlear injury after *Streptococcus pneumoniae* meningitis [25]. Brain-derived neurotrophic factor, which has marked antiapoptotic effects in hypoxic ischemic injury, significantly reduced the extent of brain cell injury in experimental meningitis [26]. These therapies may become useful as adjunctive treatments for bacterial meningitis.

Also of importance is the blood-CSF barrier. The choroid plexi in the ventricles are perfused by unique fenestrated capillaries. The barrier function is produced by tight junctions between ependymal cells separating these capillaries from the ventricular cavity. The BBB and blood-CSF barrier have different physiology, but they both restrain CNS drug distribution [27-29]. Altered permeability of these barriers during meningeal inflammation can significantly increase drug penetration into the brain parenchyma and CSF, especially those that are poorly lipid-soluble [30].

57.4 Pathogenesis of Encephalitis

Encephalitis is an acute inflammation of the brain parenchyma. The most common causative agents are viruses including mumps, herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV), enteroviruses, togaviruses (eastern and western equine viruses), and lymphocytic choriomeningitis virus. Recently West Nile virus (WNV) and monkeypox in North America, and Chandipura viruses in the developed world have emerged as important causes of viral encephalitis [31]. Also, encephalitis caused by CMV, Epstein-Barr virus (EBV) and human herpes virus (HHV)-6 has increased with increasing populations with immunocompromised states, including HIV, organ transplantation, and cancer chemotherapy [32]. Immune-mediated conditions associated with encephalitis include acute disseminated encephalomyelitis, paraneoplastic limbic encephalitis, and voltage gated potassium channel limbic encephalitis [32]. Other microorganisms that can cause encephalitis include protozoa, such as *Toxoplasma gondii*, and bacteria, such as *Listeria monocytogenes* and *Mycobacterium tuberculosis*.

Viruses enter the CNS via reactivation of latent virus within the CNS or by viremia, followed by migration across the blood-brain barrier. Blood transfusions and donated organs are also increasingly recognized as sources of transmission [31]. Virus enters brain cells by adhesion to specific cell surface receptors on glia and neurons. Once inside the cell, the virus expresses proteins which inhibit apoptosis and complement opsonization which allows the virus to prevent detection by glia. Pathology occurs due to viral destruction of cells, para- or post-infectious inflammation, and by immune mediated responses [32]. Although neurons are primarily affected, blood vessels may be involved, causing vasculitis. Other associated features include meningitis, myelitis, radiculitis, and demyelination. Cerebral edema and raised intracranial pressure can result due to induction of perivascular lymphocytic inflammation, primarily in the gray matter and at the gray-white matter junction [33].

57.5 Clinical Evaluation of Patients With Suspected Central Nervous System Infection

Critical information leading to etiologic diagnosis can be obtained from a thorough examination of clinical features [34]. Identification of infectious agents in CNS is highly dependent on the CSF analysis, and occasionally serum or biopsy data. Neuroimaging also plays an important role in diagnosis and therapeutic decision-making.

57.5.1 Clinical Presentation

Acute Septic Meningitis

Acute bacterial meningitis is a neurologic emergency, with mortality and morbidity rates as high as 25% and 60% respectively, despite improvements in critical care [35,36]. In adults, the classic triad of fever, neck stiffness, and altered mental status has a low sensitivity for diagnosis of bacterial meningitis. A Dutch study of 696 episodes of adult community-acquired acute bacterial meningitis confirmed by CSF cultures reported the full triad in only 44% [37]. More sensitive was the finding of at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status which occurred in 95% of episodes. On admission, 14% of patients were comatose, and 33% had focal neurologic deficits. A retrospective French study investigated factors distinguishing between bacterial and viral meningitis in 90 patients with confirmed bacterial meningitis and 54 patients with untreated viral meningitis [34]. The presence of one of four findings at admission, among altered consciousness, seizures, focal neurologic findings or shock, and CSF absolute neutrophil count above 1,000/mm^3 was predictive of bacterial meningitis. CSF glucose less than 2 mmol/l and CSF protein above 2 g/l did not distinguish between bacterial and viral meningitis.

It is important to remember that patients who are elderly, immunocompromised, or previously treated with antibiotics may not manifest a febrile response. The combination of altered mentation and fever should alert the clinician to the possibility of meningitis in any elderly patient [38]. Other common findings are nuchal rigidity (30%) and focal cranial nerve palsies, including gaze paresis caused by hydrocephalus [39]. Seizures are reported to occur in 5% to 28% of meningitis cases and are a sign of cortical irritation, possibly due to a cortically based complication such as empyema, stroke, or venous thrombosis [40-42]. Seizure activity is an independent predictor of mortality [42].

In a review of 103 episodes of acute bacterial meningitis in adults, 34% of patients who had seizures died compared with 7% without seizures. Decreased level of consciousness on presentation is also predictive of mortality (26% versus 2%). Altered mental status is common in bacterial meningitis. The average Glasgow Coma Scale (GCS) score on admission is 10-11, of which 10-20% of patients are comatose [37]. It should be remembered that recovery is possible after prolonged deep coma, depending on the degree of structural brain pathology. Coma caused by diffuse cerebral edema can lead to cerebral herniation. Coma may also be caused by hydrocephalus and by multiple cerebral infarcts secondary to vasculitis [43].

Raised intracranial pressure is likely common in bacterial meningitis, but not frequently monitored. Intracranial hypertension in meningitis can occur due to cytotoxic edema, vasogenic edema and communicating hydrocephalus [44]. From van de Beek et al., mean opening pressure at time of diagnostic lumbar puncture was significantly elevated at 37 mmHg and was greater than 40 mmHg in 39% of patients, many of whom were comatose [37]. From a small Swedish study of patients with bacterial meningitis and GCS <8, 60% had raised intracranial pressure (ICP) on admission and 14/15 developed intracranial hypertension [45]. The mean initial ICP was higher in non-survivors (46 mmHg) compared to survivors (20 mmHg). No randomized controlled trials have investigated the potential benefit of ICP monitoring in comatose patients with CNS infeciton. Elevated ICP induces secondary brain injury by reducing cerebral perfusion pressure (CPP) leading to ischemia and by causing brain shifts leading to herniation syndromes.

Abnormal cerebral blood flow (CBF) autoregulation is common in patients with bacterial meningitis [46]. This implies that the cerebral circulation is directly dependent on blood pressure and therefore vulnerable to ischemia under conditions of low systemic blood pressure. Cerebral vasculopathy has also been documented in patients with bacterial meningitis which increases risk of ischemic stroke [47]. Other vascular complications of meningitis are cerebral venous thrombosis, venous infarction and intracerebral hemorrhage. Arterial or venous vascular complications are reported in up to 20-30% of patients [48].

A few rare manifestations of meningitis may provide clues to the causative organism: petechial or purpural rash in meningococcal meningitis, ataxia and labyrinthitis in *Haemophilus influenzae* meningitis, and cough, weight loss, night sweats, and cranial nerve deficits in tuberculosis meningitis (TBM). Systemic complications in bacterial meningitis include septic shock in 12%, pneumonia in 8%, and disseminated intravascular coagulation in 8% of cases [41]. Mortality is often related to systemic complications rather than neurologic causes, especially in the elderly, emphasizing the importance of critical care management of these patients. Risk factors for unfavorable outcome from 696 episodes of adult bacterial meningitis in the Netherlands treated between 1998 and 2002 included the following [37]:

- Advanced age.
- Presence of osteitis or sinusitis.
- Absence of rash.
- Low admission Glasgow Coma Score.
- Tachycardia.
- Positive blood culture.
- Elevated erythrocyte sedimentation rate.
- Thrombocytopenia.
- Low CSF white cell count.

The major risk factors for mortality are: seizure activity, decreased level of consciousness (LOC), Inadequate antibiotic therapy and gram-negative meningitis.

Encephalitis

The clinical scenario of encephalitis is a febrile patient who presents with altered mental status or other signs of diffuse cerebral dysfunction. A prodrome with fever, headache, myalgia, and mild respiratory infection is often present. Changes in level of consciousness with focal neurologic deficits may follow. Seizures are common, both focal and generalized; occurrence depends on the etiological agent [49,50]. Some characteristic presentations are parotitis associated with mumps and herpetic rash with *Herpes simplex* encephalitis (HSE) although the latter is rare. Immunocompromised patients with brainstem HSE may present with cranial nerve palsies such as diplopia, dysarthria, and ataxia [51,52].

HSE is the most important form of treatable encephalitis. The clinical picture is altered consciousness, memory loss, personality change, and confusion or olfactory hallucinations, following a prodrome of headache and fever [53]. About two thirds of patients have seizures, often focal motor seizures affecting the face and upper extremities due to frontal and temporal lobe involvement. Focal neurologic signs like hemiparesis and aphasia are more common with HSE than other encephalitides. HSE is a medical emergency, and it is associated with a high mortality rate and numerous sequelae. Over 20% of survivors have severe disability which includes cognitive and behavioral disorders, seizures, and postinfectious encephalomyelitis [54,55].

Most cases of adult HSE appear to be caused by reactivation of HSV-1, either in the trigeminal ganglion or latent virus in the brain itself [56] although more recently it is unclear if HSE represents primary or recurrent infection and strains of HSE and cutaneous herpes simplex may be different. HSE has no identified triggering factors and although immunosuppression is associated with more aggressive disease and worse outcome, it does not predispose patients to the disease [57]. HSV-2, which causes genital herpes in adults, accounts for approximately 10% of HSE, mostly in neonates and the immunocompromised. Most cases of recurrent meningitis (previously called Mollaret's meningitis) are thought to be caused by HSV-2 [50].

West Nile virus encephalitis (WNVE), caused by a single-stranded RNA virus of the *Flavivirus* family appears to only cause severe human disease in the United States and Israel [58]. The disease usually affects persons over age 55, and has a 15% mortality rate [59,60]. Neuroinvasive WNV only occurs in an estimated 1% to 2% of infections, but the risk of encephalitis increases with age and in immunocompromised states [49]. Without encephalitis, WNV represents a flu-like illness. Signs of encephalitis are typical: fever, fatigue, nausea/vomiting, headache and altered mental status. WNVE presents with delirium in 38%, stupor in 27% and coma in 22% [61]. Other neurologic features include movement disorders, sometimes with Parkinsonian features, postural tremor, and myoclonus and cerebellar signs [61-63]. Seizures are infrequent. WNV can cause an acute flaccid limb paralysis in 10% of neuroinvasive cases, caused by infection of the anterior horn cells of the spinal cord, causing profound weakness and respiratory failure [64]. This poliomyelitis-like illness also occurs in other *flavivirus* encephalitides (*Japanese encephalitis virus* and *St. Louis encephalitis virus*) and *enteroviruses* [61-65]. The mortality in WNV is caused by respiratory failure in half of such cases. Morbidity is high, due to long-term limb weakness and functional disability [64]. Ophthalmologic disease, such as chorioretinitis and vitritis, and rhabdomyolysis are associated findings [66,67]. Pediatric WNV has similar manifestations and infection rates to adults and accounted for 12% of all neuroinvasive cases in the United States in 2004 [68,69].

Brain Abscess

Brain abscesses are focal, purulent infections of brain parenchyma. Site-specific focal neurologic deficits, such as aphasia and weakness are common although signs of in-

creased intracranial pressure may be the only presenting feature [70]. Fever is less common than in meningitis and when neck rigidity is present (25% of cases) it may indicate associated meningitis [38]. Seizures occur in up to 40% of cases and are often generalized tonic-clonic [71]. The route of transmission is usually contiguous spread from a local primary focus (paranasal sinusitis, otitis media, mastoiditis, penetrating head trauma (10%)). Twenty percent of cases spread hematogenously from either a pulmonary source (bronchiectasis, lung abscess), cardiac source (heart valve – infective endocarditis), or conditions with right to left shunt. The mouth, skin, and gastrointestinal tract may also be sources. In cases of hematogenous seeding, multiple abscesses are seen in 20%. Polymicrobial infections are not uncommon. *Staphylococcus pyogenes* is common in penetrating skull injuries. Organisms to consider in immunocompromised patients are *Listeria*, mycobacteria, fungi, and parasites. The important complications from abscess to watch for include strokes caused by cortical thrombophlebitis, rupture of abscess into ventricle or subarachnoid space causing meningitis or ventriculitis and increased intracranial pressure. The mortality from brain abscess is 10% overall.

Cranial Epidural Abscess

Cranial epidural abscess is an extra-axial infection occurring in the virtual space between the dura mater and the skull. It is most often located in the frontal region, and presents with headache, fever, and nausea, but rarely focal neurologic signs. Spread of infection is limited by tight adherence of dura to the overlying skull. These infections are usually related to trauma and neurosurgery, but can occur secondary to meningitis, sinusitis, and other extra-cranial sources. The most common infectious etiologies are streptococci, staphylococci, and anaerobes, with many infections being polymicrobial [72,73].

Subdural Empyema

Subdural empyema occurs in the potential space between the dura mater and the arachnoid, most commonly over the cerebral convexity. Unlike epidural infections, subdural empyema can spread more diffusely and cause inflammation of the brain parenchyma, edema, mass effect, elevated intracranial pressure, septic thrombophlebitis, and venous infarction [72,74]. Findings are therefore more severe including altered level of consciousness, focal neurologic deficits, and seizures. The sources of infection are the para-nasal sinuses, hematogenous spread via emissary veins in the subdural space, and extension of an epidural abscess into the subdural space [72,75].

Infratentorial empyema is a rare complication of bacterial meningitis. It presents as subacute meningitis with neck stiffness and decreased consciousness and should be suspected in a patient with recent history of otitis, sinusitis, or mastoiditis (especially after surgery) and findings suggesting meningitis and a posterior fossa lesion [76]. The preferred method of diagnosis is MRI with diffusion-weighted imaging (DWI) based on several reported cases of delayed diagnosis with CT which failed to visualize the lesions. DWI can distinguish subdural empyema from reactive subdural effusion [77]. The high mortality rate of this condition (34%) is due to its subdural location, hydrocephalus, and delayed detection. The management is antimicrobial therapy and a low threshold for neurosurgical exploration.

Ventriculitis

Ventriculitis is an infection of the ventricular system of the brain. The ventricles act as a reservoir of infection and inflammation, which causes blockage of CSF outflow tracts and hydrocephalus [78]. Ventriculitis complicates meningitis in 30% of adult cases, and up to 90% of neonatal cases [74]. It is clinically important when inflammation and bac-

terial load in the ventricles exceed those in the paraspinal space [78]. It is often a late complication of meningitis, when patients fail to improve with conventional therapy, but it can occur as a primary process [79,80]. Ventriculitis is frequently associated with intracranial devices, namely a CSF shunt or external ventricular drain (EVD). The risk of ventriculitis or meningitis with an EVD in place is most commonly reported in the 10% to 15% range, and depends on the type of EVD, insertion technique, management, and duration [81-84]. Blood in the CSF is a significant risk factor for ventriculostomy-related infections, and contributes to the high incidence of these infections in aneurysmal subarachnoid hemorrhage patients (10%) and patients with intraventricular hemorrhage (IVH) (13.7%) who have EVDs [83-85]. Other significant risk factors for infection are protocol violations in EVD care and CSF leaks [86]. Infection is reported to occur in 8% to 40% of patients receiving a CSF shunt, most within the first month after implantation [72]. Common pathogens causing EVD and CSF shunt infections are gram-positive organisms, such as *Staphylococcus epidermidis* and *Staphylococcus aureus*. Up to 25% of infections, however, are caused by gram-negative organisms, such as *Escherichia coli*, *Klebsiella* species, *Acinetobacter*, and *Pseudomonas* species [72].

57.5.2 Cerebrospinal Fluid Analysis

Diagnosis and management of CNS infection largely relies on CSF analysis. It is important to obtain CSF access as soon as it is safe. Concerns about uncal or cerebellar tonsillar herniation and the need to initiate empiric antibiotics emergently are often competing demands. The literature supporting necessity of doing a head CT scan prior to lumbar puncture (LP) is minimal while the evidence in favor of not delaying antibiotics in suspected meningitis is significant. Unfortunately the availability of CT frequently delays starting antimicrobial therapy [87]. In van de Beek's study of 696 episodes of community-acquired acute bacterial meningitis [37], CT was performed before LP in 48%, and in 63% of subjects presenting with impaired consciousness or neurologic deficits. In two thirds of subjects who had a CT scan, antimicrobial therapy was not started until after CT results were obtained. In many countries it is common practice to perform a head CT before performing LP in patients with suspected meningitis, due to a perception that this is a standard of care or because of fear of litigation [88]. In fact, only 1-2% of patients with meningitis herniated, and a much smaller percentage do so within hours of LP [44]. A normal CT does not eliminate risk for herniation. Criteria for performing head CT to assess risk for cerebral herniation prior to CSF access are the following [89,90]:

- Immunosuppression (to rule out *Toxoplasma encephalitis* or lymphoma).
- Significant alteration in mentation or comatose patient.
- Focal neurologic deficits.
- Seizures.
- Papilledema, poorly reactive pupils, or ocular palsies.
- Bradycardia or irregular respirations.
- Sedation or muscle paralysis.

In a prospective study of 301 adults with clinically suspected meningitis, 78% of subjects underwent CT before LP [88]. Of these, 24% had an abnormal finding and 5% had mass effect. Abnormal findings on CT were associated with the following clinical features at baseline:

- Age greater than 60 years.
- Immunocompromised state.
- History of a CNS lesion.
- History of seizures within 1 week before presentation.

- Abnormal level of consciousness.
- Inability to answer two consecutive questions correctly or follow two consecutive commands.
- Focal neurologic deficits including gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language.

Of the 96 subjects who had none of these findings, only three had abnormal findings on CT and underwent LP without subsequent herniation (negative predictive value of 97%). The delay from admission to time of lumbar puncture in patients who first underwent CT resulted in a greater delay in administering empiric antibiotic therapy in this group [88]. It is well-described that the diagnostic sensitivity of CSF is not decreased by delaying LP by 1 or 2 hours after starting antibiotics [91]. If available, CSF counterimmunoelectrophoresis, CSF latex agglutination and coagulation tests detect common bacterial antigens in 70-100% of cases [92].

It is recommended that in all patients with clinical signs suggestive of increased ICP, even without abnormalities on head CT, one must exercise caution in performing an LP, or use a small 22- or 25-gauge needle to remove the smallest amount of CSF possible and minimize CSF leakage [89]. In a review of lumbar puncture associated with brain herniation in acute bacterial meningitis, the incidence of cerebral edema with brain herniation was 5%, accounting for approximatetly 30% of the mortality [93]. Many such reports describe a temporal association between the LP and the herniation event although herniation may also occur gradually due to ongoing CSF leakage from the LP site or due to cerebral vascular engorgement. The best clinical indication to delay the LP are clinical signs of ''impending'' herniation rather than CT findings. Aggressive treatment of herniation has been reported to produce good outcomes. Therefore, a high-risk patient should have blood drawn for culture and empiric antibiotic therapy initiated prior to CT.

Typical CSF findings in various CNS infections are presented in Table 57.1. Gram's stain of CSF will show organisms in 60% to 90% of bacterial meningitis cases and cultures are positive in 80% [38]. Most patients will have a CSF white blood cell count greater than 100 WBC/mm^3 in 90% of cases and greater than 1,000 WBC/mm^3 in 60%.

CSF glucose levels are less than 40 mg/dl in 50% to 60% of patients. The CSF to serum glucose ratio of less than 0.4 is 80% sensitive and 98% specific for bacterial meningitis in children over 2 months of age [92]. Decreased CSF glucose is also seen in fungal, tuber-

Infection	Cell count (cells/mm^3)	Glucose	Protein
Bacterial meningitis	Elevated (100-5000) PMNs predominate	Decreased	Elevated
Viral meningitis	Elevated (10-500) Lymphocytes predominate	Normal	Elevated
Fungal meningitis	Normal to elevated (0-500) Lymphocytes predominate	Normal to decreased	Elevated
Tuberculous meningitis	Normal to elevated (0-1000) Lymphocytes predominate	Decreased	Elevated
Brain abscess	Normal to elevated (0-500) Mixed differential	Normal	Elevated
Ventriculitis	Elevated (100-5000)* PMNs predominate	Decreased	Elevated

Table 57.1. Cerebrospinal fluid findings in CNS infections.

* Note: in post-neurosurgical patients, or patients with a ventriculostomy, the CSF cell count may be elevated as a result of surgical manipulation and inflammation. Reduction in CSF glucose may be a more sensitive indicator of infection.

PMNs = Polymorphonuclear leukocytes

culous, or carcinomatous meningitis. The CSF protein level is the most resistant to rapid change after starting treatment; levels remain elevated for 10 days or longer [94]. The CSF findings in subdural empyema and epidural abscess typically show a polymorphonuclear pleocytosis (10-500 WBC/mm^3), normal glucose, increased protein, and often negative Gram's stain and culture [71]. Blood cultures are positive in up to 50% of cases of meningitis [72]. Hyponatremia is common in both meningitis and encephalitis and is caused by the syndrome of inappropriate antidiuretic hormone (SIADH). CSF lactate concentrations are non-specific for suspected community-acquired bacterial meningitis, but may be useful for diagnosis of post-neurosurgical meningitis where a CSF lactate concentration cut-off of 4 mmol/l was superior to the CSF:serum glucose ratio [92,95]. This cut-off had a sensitivity of 88%, specificity 98%, positive predictive value 96% and negative predictive value 94%. Routine use of latex agglutination tests for bacterial antigens is not in common use because it does not appear to modify the decision to administer antimicrobials. Additionally, false-positive results have been reported [92]. They may be useful for patients pretreated with antibiotics with negative Gram's stain and CSF cultures. Bacterial DNA detection by polymerase chain reaction (PCR) for common meningeal pathogens has relatively limited availability, but should increase with further refinements which improve sensitivity and specificity [92]. Broad-range real-time PCR and DNA sequencing for bacterial meningitis detects virtually all pathogenic bacteria and has a sensitivity between 86% to 100% and specificity of 98% when compared with culture [96,97].

Laboratory diagnosis of tuberculous meningitis (TBM) remains challenging. The typical CSF profile is a lymphocytic predominant pleocytosis with elevated protein and low glucose, but has many exceptions, especially in HIV-positive patients [98-100]. The acid-fast stain for tuberculosis (TB) has sensitivity as low as 30%, which can be improved to about 80% with repeat CSF sampling and meticulous examination [72]. Culture, the gold standard, is only positive in 40% to 70% of cases and, even with fully automated liquid culture systems, takes from 1 to 3 weeks to a positive result. Several mycobacterial antigen and antibody kits have been designed but lack adequate sensitivity and specificity to gain wide acceptance [98,101,102]. CSF adenosine deaminase activity (ADA), a biomarker, is elevated in TBM and in developing countries the CSF ADA activity at a cut-off value of 6.97 IU/l has a reported sensitivity and specificity of 85% and 88%, respectively, for distinguishing TBM from non-TBM or nonmeningitis [103]. CSF ADA levels are also elevated in conditions such as lymphoma and sarcoidosis. Molecular diagnosis with commercial nucleic acid amplification tests for diagnosis of TBM have a sensitivity of 60% to 83% and specificity of 98% to 100% [102,104]. Real-time PCR is fast and has greater sensitivity than conventional PCR, but still cannot be used reliably to rule out TBM [105]. Nucleic acid amplification tests, if available, should be the first-line test to rule in TBM due to their high specificity [105]. Radioimmunoassay detection of interferon-gamma release measures a major mediator of the immune response in TB, affecting macrophage stimulation and lymphocyte Th1 transformation [106]. Interferon-γ assays in CSF were compared with PCR for diagnosis of TBM and had a higher sensitivity (70% versus 65%) with a specificity of 94% [107]. Combination of PCR and interferon-γ improved sensitivity to 80% and the incremental value of test combinations such as these shows promise, although further prospective studies should be performed. Currently, careful bacteriology is as good as or better than molecular methods, although the latter are sensitive for longer when anti-TB drugs have been started [103,108].

Acute-phase reactants have been examined for their usefulness in diagnosing acute bacterial meningitis, but appear to have limited usefulness in the intensive care unit. Elevated procalcitonin (PCT) concentrations can differentiate between bacterial and viral meningitis in children (cut-off 0.5 mg/l; sensitivity 94%; specificity 100%) and adults (cut-off

0.2 ng/ml; sensitivity and specificity up to 100%) [109-111]. Of 48 adult patients with acute bacterial meningitis and a serum PCT level on admission above 0.5 ng/ml, serum PCT levels decreased rapidly (from 4.5 to 2 mg/ml) (within 24 hours) with appropriate antibiotic treatment, suggesting this test may replace repeat lumbar puncture at 48 to 72 hours to assess antibiotic therapy [112]. Alternatively, in patients with ventriculitis and a ventricular catheter, PCT levels usually remain within the normal range, even with positive bacterial cultures [113,114].

Nosocomial EVD-related infections are difficult to diagnose because of lower diagnostic value of CSF values, less specific clinical signs of infection, and slow-growing and fastidious organisms [115]. Broad-range real-time polymerase chain reaction (RT-PCR) may have a role in producing faster diagnosis (about 4 hours) with probable increased sensitivity over cultures after antibiotic treatment and ability to detect bacteria, especially gram-negatives that are difficult to isolate [96]. Disadvantages of PCR include inability to identify antibiotic sensitivities, false negative results, and contamination issues. The ratio of leukocytes:erythrocytes in CSF divided by leukocytes: erythrocytes in peripheral blood (called the cell index) has been used to detect EVD-related infection in patients with IVH [116]. At IVH onset, the CSF relationship of leukocytes to erythrocytes should be equal to that in peripheral blood; the cell index should be 1. In 7/13 patients with definitive ventriculitis, the cell index showed a significant rise 3 days before the conventional diagnosis of catheter-related ventriculitis. Antimicrobial therapy led to a rapid decrease of both the cell index and usual infection parameters [116].

Viral CNS infection is associated with normal-to-mild ICP elevation, CSF lymphocytosis (neutrophils if tested early), WBC counts of 50/mm^3 to 2000/mm^3, normal glucose, and elevated protein [71]. HSV-1 encephalitis is typically associated with hemorrhagic CSF and very high CSF red cell count. CSF culture and serologic testing of acute and convalescent serum may be beneficial. For HSE, the sensitivity and specificity of PCR in CSF are 98% and 94%, respectively. One third of cases remains PCR-positive long after starting acyclovir treatment [117]. It is recommended to repeat LP at 24-48 hours and continue treatment for 10 days, due to the possibility of false negative PCR for HSV with early testing if features are consistent with HSE [118,119]. PCR has good specificity for CMV (95%) and *Toxoplasma* (100%), but lower sensitivity (79% and 42%, respectively) [71]. In patients with suspected enteroviral meningitis, enteroviral RT-PCR is more sensitive than viral culture for detecting enteroviruses (sensitivity 86% to 100%; specificity 92% to 100%) [120]. The diagnosis of most important viruses, as well as *Mycoplasma pneumoniae* can be determined by detection of IgM (and IgG) antibodies in CSF (and relative to serum) by an enzyme-linked immunosorbent assay. Oligoclonal bands may distinguish inflammatory from noninflammatory causes of encephalopathy. Anti-HSV-1 antibody in CSF can be detected at 10 days, with 50% sensitivity [32]. Immunocompetent patients should be initially tested with PCR for HSV, VZV (both potentially treatable with antiviral therapy), and enterovirus [32]. For immunocompromised patients, EBV and CMV PCR should be added and HHV-6 and HHV-7 considered. Other PCRs to send depend on clinical indication. Quantitative PCR (comparing virus in CSF with that in blood) may be required to determine the significance of a positive PCR assay, especially in HIV patients who may carry infected lymphocytes without representing pathogenic infection.

Findings in viral CNS infection on peripheral blood count are leukocytosis or leukopenia, atypical lymphocytes (EBV), or eosinophilia (eosinophilic encephalitis) [32]. Serum amylase may be elevated in mumps; cold agglutinins occur in mycoplasma, upon which serologic investigations are indicated for mycoplasma and *Chlamydia*; infiltrates on chest X-ray in atypical pneumonia should be followed by investigation for *Mycoplasma*, *Legionella* or *Lymphocytic choriomeningitis virus*. HIV testing should be performed for uncertain causes of CNS infection [32].

In fungal meningitis, in immunosuppressed patients, CSF may appear normal, although opening pressure may be high. In cryptococcal meningitis in HIV-positive patients a predominantly lymphocytic pleocytosis with low CSF glucose and high protein levels is common [39]. The encapsulated fungus can be identified by India ink examination of CSF, and serologic detection of cryptococcal antigen is sensitive and relatively specific for CNS cryptococcal infection. Repeat LP and CSF analysis to document CSF sterilization is not indicated routinely [92].

A patient who does not respond clinically after 48 hours of appropriate antimicrobial therapy, especially in cases of penicillin- or cephalosporin-resistant pneumococcal meningitis, and adjunctive dexamethasone therapy, should undergo repeat CSF analysis [92,121].

57.6 Neuroimaging Findings in Central Nervous System Infections

In uncomplicated bacterial meningitis, CT scans are usually sufficient for clinical management to assess cerebral edema, hydrocephalus, and base of skull pathology such as fractures, inner ear infection, or mastoiditis. Other important findings include subdural effusions, brain stem encephalitis (rhombencephalitis) with *Listeria* infection, and cortical infarcts secondary to vasculitis (20% of cases) [122]. CT or MR venography should be used to diagnose cerebral venous sinus thrombosis. MR DWI shows parenchymal complications of meningitis, such as infarcts of septic vasculitis earlier than other sequences. Encephalitis, cerebritis, and TB are DWI-hyperintense; neurocysticercosis lesions are DWI-hypointense. Toxoplasmosis is variable, whereas lymphoma shows no restriction of water diffusion [122]. MR angiography can suggest vasculitis. Ventriculitis is detected best by T2 fluid-attenuated inversion recovery (FLAIR) images showing periventricular hyperintensity or ependymal enhancement and irregular intraventricular debris [122]. In TBM, basal meningeal enhancement, hydrocephalus, tuberculoma, and infarction are all more common than in bacterial meningitis, where subdural collections are more common [123]. Based on a CT study of 94 children with TBM [123] basal meningeal enhancement or tuberculoma was 89% sensitive and 100% specific for diagnosis of TB. Precontrast hyperdensity in the basal cisterns on cranial MRI may be the most specific radiologic sign of TBM in children [124]. In Lyme disease, multifocal nonenhancing patchy lesions on T2 weighted images (T2WI) can be seen [122]. In acute HSE, FLAIR or T2WI show asymmetrical changes of necrotizing encephalitis in the first 48 hours and may be diagnostic. Diffusion abnormalities disappear within 14 days after symptom onset, while T2 hyperintensities persist [122]. Single photon emission CT (SPECT) may indicate hyperperfusion suggesting inflammation and neuronal injury in the temporal and frontal lobes relatively early, although half of scans are normal in the acute stage, and hyperperfusion is a nonspecific finding [71].

Bacterial abscesses are hyperintense on DWI with reduced apparent diffusion coefficient (ADC) in contrast to nonpyogenic lesions, which are generally hypointense or mixed-signal. Proton MR spectroscopy shows lactate, cytosolic amino acids, and absence of choline [122]. Extra-axial bacterial empyemas appear slightly hyperintense relative to CSF and hypointense to white matter on T1WI and hyperintense on T2WI, distinguishing them from sterile effusions and chronic hematomas [122]. Epidural hematomas can be distinguished from subdural empyema by a hypointense rim representing displaced dura in the former. On DWI, subdural empyema is usually hyperintense, whereas epidural hematoma usually has a low or mixed-signal intensity [122].

57.7 Antimicrobial Therapy

57.7.1 Distribution of Drug Into the Central Nervous System

Antimicrobial distribution into the CNS is influenced by physical barriers, and physiochemical properties of the antimicrobial itself. The major physiochemical factors governing antimicrobial penetration into the CNS are listed in Table 57.2. Only the unbound concentration of drug is available to diffuse across the BBB and blood-CSF barrier. Therefore highly protein-bound agents have limited ability to penetrate the CNS [125].

The tight junctions within the BBB and blood-CSF barrier limit diffusion of large molecular weight substances (>500 daltons). Anti-infectives with larger molecular weights such as vancomycin or amphotericin B have limited ability to penetrate an intact barrier [27,125]. More lipophilic agents (defined by a high octanal-to-water partition coefficient) will penetrate the CNS more readily than hydrophilic compounds. Lipophilicity can also affect the distribution of drugs within the CNS. Highly lipophilic agents accumulate in the lipid-rich brain structures, with a resultant lower concentration in the CSF and extracellular fluid. CSF levels may therefore underestimate overall CNS penetration [125]. The degree of ionization at physiologic pH also affects penetration of the BBB. Most drugs are weak acids or weak bases, and therefore polarity can vary depending on the pH. The pH of blood, CSF, and extracellular fluid changes with infection, and this can influence the polarity and, therefore anti-infective penetration of the CNS [125].

The choroid plexus contains specialized active transcellular transport systems involved in the excretion of drugs across the cerebral vessel wall [27]. During active CNS infection, impaired CSF excretion systems may result in higher CSF concentrations of antibiotics. As inflammation diminishes, antibiotic concentrations may subsequently decrease [28]. Disruption of the BBB during inflammation also affects antibiotic penetration. Hydrophilic agents such as vancomycin rely on passive diffusion through opening of tight junctions in the BBB and therefore have increased penetration during meningeal inflammation [126]. Hydrophilic drugs which use active transport systems such as penicillin and ceftriaxone may have lower concentrations in brain tissue after BBB injury [127].

57.7.2 Timing and Appropriateness of Initial Antimicrobial Therapy

Mortality from delaying antibiotic treatment for CT and LP is estimated at 10 to 20 times the risk of complications associated with lumbar puncture. A prospective multicenter

Physiochemical property	Effect on CNS penetration
Lipophilicity	Highly lipophilic drugs more readily penetrate the CNS
Protein binding	Highly protein bound drugs have reduced CNS penetration
Molecular weight	Substances >500-800 daltons have reduced ability to penetrate the BBB
Ionization	Polar, ionized compounds are less likely to cross the BBB. Polarity can vary for many drugs with changes in physiologic pH
Active transport	Specialized active transport cells in the choroid plexus may excrete drugs across the vessel wall

Table 57.2. **Physiochemical properties influencing antimicrobial penetration into the CNS.**

observational study of 156 adults hospitalized for pneumococcal meningitis found three factors independently associated with 3-month mortality: simplified acute physiology score II, isolation of a nonsusceptible strain, and an interval of greater than 3 hours between hospital admission and administration of antibiotics [128]. A retrospective cohort study of 286 adults with community-acquired bacterial meningitis assessed causes of unfavorable outcomes [129]. The major finding was that time to starting appropriate antibiotic treatment relative to the onset of first symptoms and particularly to the onset of consciousness disturbance was significantly delayed in the poor outcome group. Practice guidelines for the management of bacterial meningitis recommend that patients with purulent meningitis receive the first dose of antibiotics as soon as possible, and that antibiotic administration not be delayed for an LP [92]. The appropriate selection of initial antibiotics is also crucial. In a retrospective review of 109 subjects with community-acquired meningitis, 22 subjects did not receive appropriate initial antibiotic coverage, of whom 100% died, as compared with 23% of patients receiving appropriate therapy [130].

57.7.3 Antimicrobial Selection and Dosing

Meningitis

Empiric therapy of meningitis must consider patient age, immune status, and whether the infection is acquired in the community or nosocomial setting. Recommendations for empiric therapy of meningitis are listed in Table 57.3. Organism-specific recommendations are provided in Table 57.4.

Before the availability and widespread use of the *H. influenzae* type B vaccine, *Haemophilus influenzae* accounted for nearly 50% of bacterial meningitis cases (most being in children) in the United States [1,132]. Now, *H. influenzae* causes only a small percentage of cases, with the median age of patients with bacterial meningitis shifting from 15 months to 25 years [133]. In the United States and many countries, most cases of community-acquired bacterial meningitis are caused by *Streptococcus pneumoniae* (47%), followed by *Neisseria meningitidis* (25%), group B *Streptococcus* (13%), *Listeria monocytogenes* (8%), and *H. influenzae* (7%) [133]. More recently traditionally nosocomial gram-negative organisms (e.g., *Klebsiella* species, *Serratia* species, *Pseudomonas* species, and *Acinetobacter* species) are becoming increasingly common [134]. Such trends reflect a shift in the epidemiology of meningitis from a disease of the young and otherwise healthy to a disease of the elderly and immunocompromised. The immunocompromised are especially susceptible to meningitis caused by *Listeria monocytogenes* and gram-negative bacilli.

Of even greater concern is the emergence of resistance of both gram-negative organisms to 3rd and 4th generation cephalosporins and to carbapenems [135-137] and of gram-positive organisms to methicillin (methicillin-resistant *Staphylococcus aureus* – MRSA) and vancomycin (vancomycin-resistant *Enterococcus* – VRE). Multidrug resistant (MDR) gram-negative bacteria, including *Acinetobacter* spp. and *Citrobacter* spp. [138,139], and gram-positives such as *Staphylococcus epidermidis* are becoming more common. Even *Streptococcus pneumoniae* is developing reduced sensitivity to cephalosporins and even carbapenems [140].

In the setting of neurosurgery, head trauma and CSF leak, and cerebrospinal shunts, the most common organisms are *S. aureus* and gram-negative bacilli. Effective source control is critical, which often necessitates surgical removal of foreign materials. In patients with CSF shunts who are shunt-dependent, removal of the shunt often necessi-

tates placement of a temporary EVD. For TBM, the Infectious Diseases Society of America and American Thoracic Society recommend a similar regimen as for pulmonary TB [141]. An intensive 2-month phase with four drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) is followed by a continuation phase for 6 to 9 months.

Patient-specific factor	Common pathogens	Preferred regimen	Alternative regimens
18-50 years	*S. pneumoniae, N. meningitidis, H. influenzae* (non-immunized patients)	Ceftriaxone[1] 2 g IV q 12 hrs ***or*** cefotaxime[2] 2 g IV q 6 hrs	Meropenem[2] 2 g IV q 8 hrs ***or*** chloramphenicol[3,4] 50 to 100 mg/kg/day in 4 divided doses ***or*** moxifloxacin[3] 400 mg IV daily
		plus vancomycin[2,5] 15 mg/kg IV q 8-12 hrs	***plus*** vancomycin[2,5] 15 mg/kg IV q 8-12 hrs
>50 years	*S. pneumoniae, N. meningitides, L. monocytogenes,* gram-negative bacilli	Ampicillin[2] 2 g IV q 4 hrs	Ampicillin[2] 2 g IV q 4 hrs ***or*** trimethoprim/sulfamethoxazole[2] 5 mg/kg (TMP-SMX) IV q 6 hrs
		plus vancomycin[2,5] 15 mg/kg IV q 8-12 hrs	***plus*** vancomycin[2,5] 15 mg/kg IV q 8-12 hrs
		plus ceftriaxone[1] 2 g IV q 12 hrs ***or*** cefotaxime[2] 2 g IV q 6 hrs	***plus*** meropenem[2] 2 g IV q 8 hrs ***or*** moxifloxacin[3] 400 mg IV daily
Impaired immunity	*L. monocytogenes*, gram negative bacilli, *S. pneumoniae, N. meningitidis*	Ampicillin[2] 2 g IV q 4 hrs	Ampicillin[2] 2 g IV q 4 hrs ***or*** trimethoprim/sulfamethoxazole[2] 5 mg/kg (TMP-SMX) IV q 6 hrs
		plus vancomycin[2,5] 15 mg/kg IV q 8-12 hrs	***plus*** vancomycin[2,5] 15 mg/kg IV q 8-12 hrs
		plus ceftazidime[2] 2 g IV q 8 hrs ***or*** cefepime[2] 2 g IV q 8 hrs	***plus*** meropenem[2] 2 g IV q 8 hrs ***or*** ciprofloxacin[2] 400 mg IV q 8 hrs
Neurosurgery, head trauma, cerebrospinal shunt	Staphylococci, gram-negative bacilli, *S. pneumoniae*	Vancomycin[2,5] 15 mg/kg IV q 8-12 hrs	Vancomycin[2,5] 15 mg/kg IV q 8-12 hrs
		plus cefepime[2] 2 g IV q 8 hrs ***or*** ceftazidime[2] 2 g IV q 8 hrs	***plus*** meropenem[2] 2 g IV q 8 hrs ***or*** ciprofloxacin[2] 400 mg IV q 8 hrs

Table 57.3. **Recommendations for empiric antimicrobial therapy for bacterial meningitis in adults [131].**

[1] Dose adjustments may be indicated in patients with combined hepatic and renal insufficiency

[2] Dose adjust for renal insufficiency

[3] Caution in patients with hepatic insufficiency, dose adjustment may be required

[4] Monitor for bone marrow suppression, including leukopenia, thrombocytopenia, and aplastic anemia

[5] Monitoring of serum drug levels is recommended to optimize dosing

Organism	Preferred regimen	Alternative regimen	Duration
S. pneumoniae (PCN MIC <0.1)	Penicillin G[1] 4 million units IV q 4 hrs ***or*** ceftriaxone[2] 2 g IV q 12 hrs ***or*** cefotaxime[1] 2 g IV q 6 hrs	Meropenem[1] 2 g IV q 8 hrs ***or*** chloramphenicol[3,4] 50 to 100 mg/kg/day in 4 divided doses ***or*** moxifloxacin[3] 400 mg IV daily	10-14 days
S. pneumoniae (PCN MIC ≥0.1) (CTX MIC ≤0.5)	Ceftriaxone[2] 2 g IV q 12 hrs ***or*** cefotaxime[1] 2 g IV q 6 hrs	Meropenem[1] 2 g IV q 8 hrs ***or*** moxifloxacin[3] 400 mg IV daily ***or*** vancomycin[1,5] 15 mg/kg IV q 8-12 hrs	10-14 days
S. pneumoniae (PCN MIC ≥0.1) (CTX MIC >0.5)	Vancomycin[1,5] 15 mg/kg IV q 8-12 hrs ***plus*** ceftriaxone[2] 2 g IV q 12 hrs ***or*** cefotaxime[1] 2 g IV q 6 hrs	Vancomycin[1,5] 15 mg/kg IV q 8-12 hours ***plus*** rifampin[3] 900-1200 mg IV/PO daily in 2-3 divided doses	10-14 days
N. meningitidis	Penicillin G[1] 4 million units IV q 4 hrs	Ampicillin[1] 2 g IV q 4 hrs ***or*** ceftriaxone[2] 2 g IV q 12 hrs ***or*** cefotaxime[1] 2 g IV q 6 hrs ***or*** chloramphenicol[3,4] 50 to 100 mg/kg/day in 4 divided doses	7-10 days
H. influenzae	Ceftriaxone[2] 2 g IV q 12 hrs ***or*** cefotaxime[1] 2 g IV q 6 hrs	Chloramphenicol[3,4] 50 to 100 mg/kg/day in 4 divided doses	7-10 days
L. monocytogenes	Ampicillin[1] 2 g IV q 4 hrs ***plus*** gentamicin[1,5,6] 3-5 mg/kg/day IV in 3 divided doses	Trimethoprim/sulfamethoxazole[1] 5 mg/kg (TMP) IV q 6 hrs	21 days
Group B *Streptococcus*	Penicillin G[1] 4 million units IV q 4 hrs ***or*** ampicillin[1] 2 g IV q 4 hrs	Vancomycin[1,5] 15 mg/kg IV q 8-12 hrs ***or*** ceftriaxone[2] 2 g IV q 12 hrs ***or*** cefotaxime[1] 2 g IV q 6 hrs	14-21 days
Enterobacteriaceae, Klebsiella species	Ceftriaxone[2] 2 grams IV q 12 hrs ***or*** cefotaxime[1] 2 g IV q 6 hrs	Meropenem[1] 2 grams IV q 8 hrs	14-21 days
	+/- gentamicin[1,5,6] 3-5 mg/kg/day IV in 3 divided doses ***or*** ciprofloxacin[1] 400 mg IV q 8 hrs	***+/-*** gentamicin[1,5,6] 3-5 mg/kg/day IV in 3 divided doses ***or*** ciprofloxacin[1] 400 mg IV q 8 hrs	

Organism	Preferred regimen	Alternative regimen	Duration
P. aeruginosa, *Acinetobacter* species	Cefepime[1] 2 g IV q 8 hrs ***or*** ceftazidime[1] 2 g IV q 8 hrs	Meropenem[1] 2 g IV q 8 hrs	14-21 days
	+/- gentamicin[1,5,6] 3-5 mg/kg/day IV in 3 divided doses ***or*** ciprofloxacin[1] 400 mg IV q 8 hrs	***+/-*** gentamicin[1,5,6] 3-5 mg/kg/day IV in 3 divided doses ***or*** ciprofloxacin[1] 400 mg IV q 8 hrs	
S. aureus, *S. epidermidis* (methicillin-sensitive)	Nafcillin[2] 2 g IV q 4 hrs ***or*** oxacillin[2] 2 g IV q 4 hrs	Vancomycin[1,5] 15 mg/kg IV q 8-12 hrs ***+/-*** rifampin[3] 900-1200 mg IV/PO daily in 2-3 divided doses	14-21 days
S. aureus, *S. epidermidis* (methicillin-resistant)	Vancomycin[1,5] 15 mg/kg IV q 8-12 hrs	Linezolid 600 mg IV/PO q 12 hrs	14-21 days
	+/- rifampin[3] 900-1200 mg IV/PO daily in 2-3 divided doses		

Table 57.4. **Pathogen-specific recommendations for antimicrobial therapy for bacterial meningitis in adults. Reproduced from [127] with permission.**

[1] Dose adjust for renal insufficiency
[2] Dose adjustments may be indicated in patients with combined hepatic and renal insufficiency
[3] Caution in patients with hepatic insufficiency, dose adjustment may be required
[4] Monitor for bone marrow suppression, including leukopenia, thrombocytopenia, and aplastic anemia
[5] Monitoring of serum drug levels is recommended to optimize dosing
[6] Once daily dosing of gentamicin has been evaluated in an animal model suggesting superior CNS penetration vs. conventional dosing
CTX = Cefotaxime
MIC = Minimum inhibitory concentration
PCN = Penicillin

Ventriculitis and Cerebrospinal Fluid Shunt Infections

Ventriculitis and EVD and CSF shunt infections frequently involve gram-positive organisms, such as *S. epidermidis* and *S. aureus* (including MRSA). Up to 25% are caused by gram-negative organisms. The enteric gram-negative bacilli are of concern in patients who have a ventriculoperitoneal shunt, due to the risk of contamination of the peritoneal end of the catheter [72,81]. Initial broad-spectrum antibiotic selection should include coverage for resistant gram-positive organisms (such as MRSA) and resistant gram-negative organisms (such as *Pseudomonas* and *Acinetobacter* species). Vancomycin combined with a cephalosporin with antipseudomonal activity (e.g., cefepime or ceftazidime) or vancomycin plus meropenem are recommended. Infected hardware should be removed, replaced, or externalized when appropriate.

For ventriculitis, there is scientific rationale for installation of antibiotics directly into the ventricles: meningeal inflammation, which enhances the ability of antimicrobials to penetrate the BBB is less pronounced in ventriculitis [142]; and the ventricles can act as a persistent reservoir of infection and inflammation, causing difficulty with eradication and potential blockade of CSF outflow tracts [143]. Under these conditions, the penetration of systemic β-lactams and glycopeptides into the CSF is poor and results in subtherapeutic concentrations in the CSF and high failure rates [144-146].

Intraventricular administration of antibiotics may be necessary in some circumstances in an effort to overcome these difficulties [147,148].

Brain Abscess

The type of pathogen associated with brain abscess depends on patient-specific risk factors. Immunocompromised patients and patients undergoing recent neurosurgery or head trauma (especially penetrating brain injury) are at higher risk [149,150]. Brain abscesses are often polymicrobial (up to 60% of cases), with anaerobic bacteria in up to 49% of cases [151,152]. Frequently isolated organisms include *Streptococcus milleri, Bacteroides* species, *Enterobacteriaceae,* and *S. aureus*. Immunocompromised individuals are at risk for brain abscess from fungi, *Nocardia*, and *Toxoplasma*. Optimal treatment involves a combination of antibiotics and surgical intervention to obtain source control. Surgical approaches include stereotactic aspiration or excision. Stereotactic aspiration may be preferred if the abscess is in eloquent brain or an area unsuitable for excision (e.g. brainstem or diencephalon) [153]. Broad spectrum empiric therapy is indicated, the choice of which depends on risk factors for selected organisms (i.e. history, immune status, primary infection site). In immunocompetent patients, initial coverage with vancomycin, ceftriaxone (or cefotaxime), and metronidazole is recommended [150]. Antibiotics should be tailored to the causative organism when microbiologic data become available. Metronidazole often is continued, even if an anaerobic source is not identified on culture because anaerobes are fastidious and have a low culture yield. Patients with recent neurosurgery or head trauma and a presumed nosocomial source of infection should be treated with a third- or fourth-generation cephalosporin with antipseudomonal activity (ceftazidime or cefepime), along with vancomycin (to cover MRSA or methicillin-resistant *S. epidermidis*) and metronidazole. In HIV-positive patients empiric therapy to cover *Toxoplasma* with sulfadiazine and pyrimethamine (along with folinic acid) should be considered. Addition of amphotericin B should be considered in neutropenic and post-transplant patients to cover fungal sources, such as *Aspergillus*, *Cryptococcus*, and *Mucoracae.* If *Nocardia* is suspected, trimethoprim/sulfamethoxazole should be added to the empiric regimen [150,154]. In most cases of brain abscess, 6 to 8 weeks of treatment is required, depending on the clinical and radiographic response.

Epidural Abscess

Empiric treatment of cranial epidural abscess consists of broad-spectrum antibiotics, usually in combination with surgical drainage to prevent progression to subdural empyema. The most common etiologies include *streptococci, staphylococci*, and anaerobes. Infections are often polymicrobial [72,73]. Initial treatment with vancomycin, ceftriaxone (or cefotaxime), and metronidazole is appropriate in most cases. Substitution of ceftriaxone with ceftazidime, cefepime, or meropenem is recommended where *Pseudomonas aeruginosa* or other resistant gram-negative nosocomial pathogens are suspected, such as after recent neurosurgery or trauma. Metronidazole is not necessary in regimens containing meropenem which has adequate anaerobic coverage.

Spinal epidural abscess is usually caused by hematogenous spread, with direct seeding of the epidural space. It may also be a complication of adjacent discitis or vertebral osteomyelitis. Other causes of spinal epidural abscess include surgery of the spine, neuraxial anesthesia/analgesia, and LP [72,73,155]. The most common organism involved is *S. aureus*, occurring in 60% to 90% of cases [155,156]. Other causative organisms include aerobic and anaerobic streptococcal species, and gram-negative organisms such as *E. coli* and *P. aeruginosa* [72,73]. Urgent surgical decompression is usually indicated to prevent neurologic deficits. Empiric antimicrobials should be started immediately. In most instances, vancomycin combined with a cephalosporin with antipseudomonal activity (ceftazidime or cefepime) or meropenem is indicated until culture results are available. In selected cases where there are no risk factors for nosocomial drug-resis-

tant organisms, empiric therapy with nafcillin (or oxacillin), combined with a third-generation cephalosporin (ceftriaxone or cefotaxime) may be appropriate. Antibiotic coverage should be narrowed once culture data are available, and treatment should continue for 3 to 4 weeks. In the case of vertebral osteomyelitis or discitis, treatment for 4 to 6 weeks is indicated [72].

Subdural Empyema

Early surgical evacuation in addition to appropriate antibiotic therapy is usually required for successful management. Empiric antibiotic selection for subdural empyema is the same as that for intracranial epidural abscess, as the bacteriology of these infections is identical [75].

Viral Encephalitis

Treatment of viral encephalitis is largely supportive and includes optimization of fluid balance and electrolytes; symptomatic treatment of fever, headache, and nausea; airway protection; management of ICP; and management of seizures. For HSE encephalitis, early treatment (within 2 days of onset) with acyclovir (10 mg/kg intravenously every 8 hours for 14 to 21 days) is associated with improved mortality (70% versus less than 20%) and morbidity [157]. Some other herpes viruses (VZV and herpes B virus) also respond to acyclovir. Therapy usually is started empirically if encephalitis is suspected until diagnostic confirmation is obtained (usually by CSF PCR) [157-159]. Dose adjustment is required in patients with renal insufficiency. Adequate hydration should be maintained during treatment, because acyclovir can cause a crystal nephropathy that is usually reversible. Some recommend repeat CSF examination at completion of treatment and to continue acyclovir if HSV PCR is still positive [32]. Prolonged high dose oral valacyclovir for 3 months after 3 weeks of treatment is also being studied. Oral valacyclovir does not achieve adequate CSF levels to be considered a primary treatment for HSE.

Corticosteroids and mannitol are usually reserved for patients with cerebral edema and intracranial hypertension. However, a nonrandomized retrospective study of 45 subjects with HSE treated with acyclovir found that combination treatment with corticosteroids and acyclovir was an independent predictor of good outcome at 3 months [160]. An experimental encephalitis study showed reduced MRI abnormalities months after infection in animals treated with corticosteroids [161]. Despite the immunosuppressive effects of steroids, they do not enhance viral replication in experimental HSE [162]. For VZV encephalitis, steroids are sometimes used to treat the vasculitic component [32].

CMV encephalitis is an opportunistic pathogen most commonly seen in transplant recipients and other immunosuppressed patients [163]. Current recommendations for both CMV and HHV-6 encephalitis are a combination of ganciclovir (5 mg/kg intravenously every 12 hours) and foscarnet (90 mg/kg intravenously every 12 hours, or 60 mg/kg intravenously every 8 hours) [163-165]. Ganciclovir and foscarnet are associated with severe adverse effects, including renal insufficiency, bone marrow suppression, encephalopathy, and seizures. Both ganciclovir and foscarnet require careful monitoring and dose adjustment in the setting of renal dysfunction [166].

Treatment for severe adenovirus infections have included cidofovir or ribavirin. Patients with life-threatening enterovirus infections have been treated successfully with pleconaril on a compassionate-use basis, and it is deserving of further study [167,168]. Pleconaril is a novel antiviral that inhibits enteroviral replication by integrating into the capsid of picornaviruses and preventing the virus from attaching to cellular receptors and uncoating to release RNA into the cell. Treatment of WNV and other flaviviruses with interferon alpha for 7 days was studied in a randomized, controlled trial of Japanese encephalitis in Vietnamese children, which did not improve outcomes at 3 months [32].

Fungal Central Nervous System Infection

Fungal infections of the CNS are encountered more commonly as opportunistic infections in the immunocompromised. Fungi may cause meningoencephalitis and brain abscess or granuloma. Causative organisms include *Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, Candida albicans, Sporothrix schenkii, Blastomyces dermatidis, Zygomycetes* species, and *Aspergillus* species, with the latter two more commonly causing brain abscess [169]. Optimal treatment of CNS fungal infections is ill defined. The incidence of invasive fungal infections is rising despite the emergence of newer antifungal agents, and outcomes in general are poor [170]. Most treatment regimens consist of an initial induction phase with an amphotericin-based regimen that lasts 2 to 6 weeks, depending on clinical response. This is followed by a chronic suppressive phase with a triazole antifungal with activity against the pathogen being treated (usually fluconazole or voriconazole) that can last from 6 weeks to lifelong suppression. Optimal treatment also should include management of risk factors for fungal disease, such as hyperglycemia, and minimizing immunosuppressant drugs where appropriate.

Although amphotericin B is considered the first-line agent for most CNS fungal infections, it has a large molecular weight and has poor penetration of the BBB. For this reason flucytosine is often added to amphotericin B in the treatment of cryptococcal, *Candida*, and *Aspergillus* CNS infections. The dose of amphotericin B deoxycholate (AmB) is 1 mg/kg intravenously daily, combined with flucytosine 25 mg/kg orally every 6 hours. Higher doses (1.5 mg/kg daily), however, are recommended in the setting of mucormycosis [171]. Flucytosine requires dose adjustment in the setting of renal insufficiency, and serum levels should be monitored. Levels greater than 100 mg/ml are associated with an increased risk of bone marrow depression, which can be irreversible and result in death [172,173]. The goal peak flucytosine level is 70 mg/ml to 80 mg/ml (drawn 4 hours after a dose at steady state), and the goal trough level is 30 mg/ml to 40 mg/ml.

In patients with renal insufficiency, a lipid-based amphotericin product is recommended. Both liposomal amphotericin B (L-amB) (5 mg/kg/d) and amphotericin B lipid complex (ABLC) (5 mg/kg/d) have been evaluated in a small number of patients, and they appear to have efficacy similar to conventional amphotericin B [174-176]. The amphotericin B products differ significantly with respect to particle size, electrical charge, and volume of distribution, all of which may influence CNS penetration and antifungal activity. Many animal studies show poor distribution of amphotericin products into the CSF; however, brain tissue concentrations appear to be adequate, and CSF concentrations do not appear to correlate with clinical efficacy [177]. An animal model of *C. albicans* CNS infection has demonstrated greater antifungal efficacy with AmB and L-AmB over ABLC and amphotericin B colloidal dispersion, but the clinical relevance of these findings has yet to be demonstrated [178].

Voriconazole is a promising therapy for susceptible CNS fungal infections, in particular invasive aspergillosis. Voriconazole penetrates the CSF well with a median CSF-to-plasma ratio of 0.5 [179]. Schwartz and colleagues [180] conducted a retrospective analysis of voriconazole in 81 subjects who had CNS aspergillosis; 35% had a complete or partial response. Thirty-one percent of subjects survived for a median of 390 days and 38% had neurosurgical intervention for the infection, which was associated with improved survival, making it difficult to clearly discern the impact of voriconazole on outcomes. Considering that reported mortality of CNS aspergillosis approaches 100% [181], this study suggests voriconazole is a reasonable option for CNS aspergillosis, and an alternative for other susceptible CNS fungal infections when an amphotericin-based regimen cannot be tolerated. Initial dosing of voriconazole is 6 mg/kg intravenously every 12 hours for two doses, followed by 4 mg/kg intravenously every 12 hours. Voriconazole is metabo-

lized by the hepatic CYP isoenzymes CYP2C9, CYP2C19, and CYP3A4 and is susceptible to numerous drug interactions, with many combinations being contraindicated.

Posaconazole is an extended spectrum triazole antifungal with in vitro activity against *Candida, Aspergillus, Zygomycosis,* and *Fusarium* species. In an open-label clinical trial in patients with refractory invasive fungal infection the subset of patients with CNS disease had mostly cryptococcal meningitis and were HIV-positive. Successful outcomes were observed in 14 of 29 (48%) of patients with cryptococcal disease, and 5 of 10 (50%) patients with other fungal infections [182]. Based on this report, and animal studies suggesting efficacy [183,184], posaconazole may be considered as salvage therapy in cryptococcal meningitis where other therapies have failed. Currently, posaconazole is only available as an oral medication (200 mg every 6 hours for 7 days, followed by 400 mg twice daily). It is highly lipophilic, with a very large volume of distribution (1,774 l), and is highly protein bound (>98%). It is an inhibitor of cytochrome P450 3A4, and is therefore subject to numerous clinically significant drug interactions.

Caspofungin and micafungin are the first of a new class of antifungals (echinocandins) that target the fungal cell wall through inhibition of β-1,3 glucan synthesis. Caspofungin is highly protein-bound and has a large molecular weight and a small volume of distribution, all of which indicate poor CNS penetration. From animal data the brain tissue-to-plasma ratio is approximately 0.1 [185]. Hsue and colleagues [186] reported a case of treatment failure associated with the use of caspofungin for meningeal coccidiomycosis. In this report, CSF concentrations were undetectable, despite adequate serum concentrations. In spite of sporadic reports of treatment successes [187,188], these agents cannot be recommended for CNS fungal disease at this time.

Given the poor CNS penetration of AmB and its significant systemic toxicities, there has been interest on the use of intrathecal AmB for treating invasive CNS fungal infections. It can be administered through a reservoir device or as an intraventricular injection, and is typically given in conjunction with systemic amphotericin and flucytosine. Dose ranges for intrathecal AmB range from 0.01 mg to 1.5 mg, and intervals range from daily to weekly [189,190]. Adverse effects associated with intrathecal AmB include arachnoiditis, paraplegia, paresthesias, nausea, vomiting, headache, and back pain. Hydrocortisone (15 mg to 25 mg) can be added to the intraventricular mixture to reduce toxicity. Prophylactic administration of antipyretics and antiemetics may also help alleviate some adverse effects. Although intraventricular AmB is usually reserved for patients who have not responded to systemic therapy, or have relapsed, limited evidence shows that early therapy with both systemic and intraventricular amphotericin B can lead to significant differences in survival, and CSF sterilization compared with systemic therapy alone [191,192].

57.8 Glucocorticoids for Bacterial Meningitis

Several meta-analyses regarding adjunctive corticosteroid therapy have been published, most of which include children as the majority of the studied population [193-200]. A Cochrane collaboration review including 18 clinical trials and 2750 people concluded that adjunctive steroid treatment is associated with a reduction in mortality and hearing loss in all patients (adults and children) with bacterial meningitis without major adverse events [193], a finding that concurs with the recommendations of the Infectious Diseases Society of America [92]. Subgroup analysis for causative organisms showed mortality benefit in patients with *S. pneumoniae*, and reduction in hearing loss in children with *H. influenzae*.Routine steroid therapy appears to be justified in most adults although

two more recent large randomized controlled clinical trials (RCTs) from Vietnam and Sub-Saharan Africa that evaluated the effectiveness of dexamethasone for adult bacterial meningitis concluded that adjunctive steroids were not associated with better survival or reduction in neurological deficits [201,202].

Despite relatively high dose, much of mortality benefit may be due to reduction in systemic rather than neurologic complications.

The rationale for use of steroids is based on experimental data showing that the inflammatory response in the subarachnoid space contributes significantly to the morbidity and mortality of bacterial meningitis [35]. De Gans and colleagues [203] demonstrated in a large prospective randomized, controlled trial that dexamethasone given before or with the first dose of antibiotic and then every 6 hours for 4 days improved the outcome in adults with acute bacterial meningitis, particularly pneumococcal meningitis, without serious adverse effects. Unfavorable outcomes were reduced from 25% to 15% and mortality from 15% to 7% in dexamethasone-treated subjects. On the basis of this study, the Infectious Diseases Society of America Practice Guideline recommends use of dexamethasone (0.15 mg/kg every 6 hours for 2 to 4 days) in patients with suspected meningitis [92]. Dexamethasone should be continued only in patients with gram-positive diplococci on Gram's stain or *S. pneumoniae* in CSF or blood cultures. It should not be given to patients with prior administration of antibiotics.

A major concern has been the rapidly rising incidence of highly resistant *S. pneumoniae* requiring combination therapy with vancomycin. Vancomycin penetration into the CNS is largely dependent upon meningeal inflammation, and some experimental studies show that dexamethasone significantly decreases the achievement of therapeutic vancomycin concentrations in the CSF [204,205], resulting in clinical treatment failure in adults [206]. In contrast, more recent data suggest this can be overcome by giving higher doses of vancomycin via continuous infusion (15-mg/kg loading dose followed by 60-mg/kg per day infusion) [207]. Expert opinion recommends adjuvant dexamethasone even in patients with highly resistant pneumococcal isolates [92,208]. There are no data to support adjunctive steroids in patients who have nosocomial and postneurosurgical meningitis, and meningitis related to CSF shunts.

In patients who have TBM, a randomized, double-blind, placebo-controlled study of 545 subjects conducted in Vietnam demonstrated that adjunctive treatment with dexamethasone reduces mortality (31.8% versus 41.3%), but probably does not prevent severe disability (18.2% versus 13.8%) [209]. The prespecified subgroup analysis of patients with HIV demonstrated a nonsignificant reduction in the risk of death, although none were treated with antiretroviral drugs, and the results may not be generalizable to populations with access to antiretroviral treatment. The results of this trial suggest that for non-HIV patients with TBM, 4 to 8 weeks of dexamethasone should be administered (2 to 4 weeks of tapering intravenous steroids followed by tapering oral therapy).

57.9 Management of Complications of Acute CNS Infection

57.9.1 Elevated Intracranial Pressure

The management of elevated ICP in conditions such as bacterial meningitis or encephalitis should follow the same principles as for other etiologies. Osmotic therapy with mannitol or hypertonic saline has not been adequately studied in CNS infections. Small doses of mannitol (0.25 to 0.5 mg/kg) appear to be equally effective to larger doses. If mannitol is used, the serum osmolar gap should be followed to ensure accumulation is not oc-

curring [210]. Hypertonic saline may be required to treat SIADH associated with bacterial meningitis given that low serum osmolarity can worsen cerebral edema. Fever may not only raise ICP but also worsen secondary brain injury and should always be aggressively managed [211]. It is recommended to use surface cooling or endovascular methods as antipyretics and cooling blankets have limited efficacy. Steroids may reduce inflammation in the subarachnoid space and lessen cerebral edema. Effect of steroids on ICP in this condition has not been studied. When patients arrive in the ICU having already received antibiotics, but not steroids, it is of questionable benefit to introduce steroids at this time because much of inflammation with meningitis occurs in response to destruction of bacteria by antibiotics [212]. Mechanical interventions to reduce ICP may be warranted provided that a mass lesion has been excluded and risk for cerebral herniation from CSF drainage is minimal. Options include repeat large volume lumbar puncture, lumbar drain placement, ventriculostomy and decompressive craniectomy. Clinicians should have a low threshold to re-image the brain to rule out hydrocephalus (occurs in 20% of acute bacterial meningitis).

57.9.2 Cerebrovascular Complications

Although the lower limit of safe cerebral perfusion pressure is unknown in CNS infections, CPP should be maintained >60 to 70 mmHg to avoid cerebral ischemia even in patients with intact autoregulation. Due to the high incidence of arterial or venous complications in acute bacterial meningitis, computed tomographic venography (CTV), magnetic resonance angiography (MRA), or magnetic resonance venography (MRV) should be considered in patients who deteriorate or fail to improve with antibiotic therapy. Careful anticoagulation appears safe in patients with cerebral venous sinus thrombosis in the setting of CNS infection [213].

57.9.3 Severe Sepsis and Septic Shock

In patients with severe sepsis or septic shock, early goal-directed therapy including aggressive fluid resuscitation reduces mortality and is not associated with worsened cerebral edema [214,215]. In experimental bacterial meningitis it was demonstrated that fluid restriction can decrease cerebral blood flow and worsen cerebral ischemia [216]. This suggests that hypovolemia and hypotension should be avoided in patients with CNS infection. Preference for systemic vasopressors in the setting of meningitis has not been studied. Norepinephrine appears to improve CBF more effectively than dopamine at least in head-injured patients [217]. Vasopressin has been studied in experimental traumatic brain injury and appears to be equally as effective as phenylephrine for maintaining cerebral perfusion pressure, improved intracranial pressure, and brain tissue oxygenation compared with phenylephrine [218]. Based on combined data from 4 clinical trials of drotrecogin alfa, which found that the median APACHE II score of enrolled patients with meningitis was 22, it appears unlikely that patients with meningitis and septic shock should be treated (scores >25 derive benefit). Furthermore, 5.7% of patients with bacterial meningitis had intracerebral hemorrhage as a complication of drotrecogin alfa compared with 1% control patients [219]. The role of systemic corticosteroids in CNS infection with septic shock is unclear at this time. In this regard it is noteworthy that in a post-hoc analysis of the European Dexamethasone in Adulthood Bacterial Meningitis Study [203], investigating only patients with pneumococcal meningitis who died within 14 days, mortality benefit from steroid therapy was attributable to a beneficial effect on systemic complications with no significant reduction in mortality due to neurologic causes [220].

57.9.4 Intraventricular and Intrathecal Antibiotics

The clinical situations in which intraventricular antibiotics have been studied include: 1) severe meningitis with associated ventriculitis; 2) intraventricular rupture of a purulent brain abscess; and 3) cerebrospinal fluid shunt infections. For the latter, there is reasonable evidence for the instillation of antimicrobial agents into the ventricles in difficult-to-eradicate shunt infections or in patients who cannot undergo surgical management [92]. Success rates of conservative management of patients with CSF shunt infections caused by coagulase-negative Staphylococci appears to be comparable to conventional management with shunt replacement [221].

Intraventricular instillation of most antimicrobials has been viewed as associated with significant toxicity, although most recent reports suggest that intraventricular/intrathecal administration with agents such as polymyxin B, colistin and vancomycin is not associated with severe or irreversible toxicity [222]. Toxicity appears to be dose-related and early reports may have been associated with inappropriate dosing. Moreover, systemic toxicity of the intravenous route of these same agents may be offset by using the CSF route. Exact therapeutic doses and the role of adjuvant systemic or local CSF therapy are not well understood at this time.

There is a positive publication bias in the literature as almost all reports are case reports or small case series and there are no randomized clinical trials of intraventricular antimicrobial use in adult CNS infection. The success rates of CSF sterilization suggest that therapy with intraventricular antimicrobials is a potentially effective treatment against both gram-negative and -positive MDR meningitis as well as fungal meningitis. In a review by Falagas et al. [223] of intraventricular/intrathecal use of polymyxins in 64 patients (31 case reports/series) with gram-negative meningitis, an overall cure rate of 80% was reported including 91% of CNS infections due to *Acinetobacter* spp. As mentioned earlier, therapy with both systemic and intraventricular amphotericin B in fungal CNS infection can improve survival, and CSF sterilization compared with systemic therapy alone [191,192]. For tuberculous meningitis the addition of intraventricular rifampin or isoniazid has anecdotal reports of efficacy [224,225], whereas multidrug resistant *Mycobacterium tuberculosis* appears to respond favorably to intraventricular amikacin and levofloxacin [226,227].

Although no antimicrobial agent is approved by the Food and Drug Administration for intraventricular use, commonly used agents (depending on the causative organism) include vancomycin, gentamicin, tobramycin, and polymyxins. The usual dose of intraventricular vancomycin is 10 mg to 20 mg per day, continued for 48-72 hours after CSF cultures become negative. Potential adverse effects of intraventricular vancomycin include ototoxicity, CSF eosinophilia, seizures, altered mental status, and local tissue irritation [147,228]. The usual daily dose of intraventricular gentamicin and tobramycin is 5 mg to 10 mg, and that of amikacin is 10 mg to 20 mg [229,230]. Toxicities for these aminoglycosides are similar to those of vancomycin.

Redosing is determined by calculation of the inhibitory quotient (trough CSF concentration divided by the minimum inhibitory concentration of the agent for the isolated pathogen). This number should exceed 10 to 20 for consistent CSF sterilization [231]. Polymyxins (polymyxin B and colistimethate) have been used in ventriculitis caused by multi-drug resistant *Acinetobacter* and *Pseudomonas* species, with the most common adverse effect of meningeal irritation being dose-dependent and reversible [232]. Dosing has varied substantially (5-20 mg of colistimethate daily), and as for all of the above regimens, the optimal duration is unknown. Preservative-free formulations should always be used for intraventricular administration.

57.10 Prophylactic and Periprocedural Antibiotics for Neurosurgical Procedures and External Ventricular Drains

Nosocomial meningitis accounted for 40% of acute adult bacterial meningitis in a review of 493 episodes, of which 81% occurred within 1 month of neurosurgery or head injury [40]. A retrospective study reported an overall meningitis rate of 1.52% [86] in 6243 subjects undergoing craniotomy, of whom 17% did not receive perioperative antibiotics. Independent risk factors for meningitis were CSF leakage, concomitant incision infection, male sex, and duration of surgery. Perioperative antibiotic prophylaxis reduced incidence of incision infections significantly from 8.8% to 4.6%, but did not prevent meningitis. In patients receiving antibiotics, organisms were mainly noncutaneous and tended to be less susceptible to the prescribed prophylactic antibiotics. Meningitis from noncutaneous organisms were associated with a higher mortality rate compared with cutaneous organisms. The investigators recommended use of narrow-spectrum antibiotics for prevention of surgical site infections without any effect on the risk of meningitis.

Ventriculostomy-related infection (VRI) rates are generally 5% to 10%, with a range of 0% to 22% [81]. Definition of CSF infections related to ventriculostomies is important. The following categories of VRI are potentially useful [85]:

- **Confirmed VRI:** positive CSF culture obtained from ventricular or lumbar catheter associated with CSF pleocytosis and clinical symptoms not related to other causes.
- **Suspected VRI:** positive CSF culture and CSF pleocytosis without clinical symptoms or with other likely source of infection.
- **Contaminant:** isolated positive CSF culture in conjunction with negative Gram's stain, normal CSF cell counts and absent clinical symptoms.

Some researchers accept CSF pleocytosis or low CSF glucose alone as evidence of CSF infection, although positive cultures are considered the gold standard. Others apply more stringent criteria, requiring an initial sterile CSF culture at time of EVD insertion, two separate CSF cultures on separate days, and assess the number of risk factors to determine whether infections are related to the catheter or not. Risk factors that predispose patients with ventriculostomies to ventriculitis or meningitis are intraventricular hemorrhage, subarachnoid hemorrhage, cranial fracture with CSF leak, craniotomy, systemic infection and catheter irrigation [81]. Because CSF surveillance may increase the risk of VRI, clinicians often collect CSF only at time of EVD insertion, removal, and when clinically indicated. The value of routine CSF surveillance has been questioned as it has not been shown to predict VRI before actual positive culture with clinical symptoms [232]. However, some studies suggest that accessory tests, including cell index, lactate level, and IL-1B may be helpful in diagnosing VRI before the onset of ventriculitis [116,233].

The data on duration of EVD as a risk factor for VRI is controversial. In Lozier's analysis [81], ten studies (2046 EVDs in 1698 subjects) reported a positive association, and seven studies (2199 EVDs in 2113 subjects) reported no association between duration of catheterization and CSF infection. There is a likely relationship between duration of EVD and infection, but it may not be a continuous rise. Holloway and colleagues [83] reported an increasing risk of infections during the first 10 days of EVD, followed by a significant decrease afterwards despite the population still being at risk. This has been the authors' experience as well. While EVD duration may not be easily modified, other potential prevention strategies are antibiotic prophylaxis and routine EVD change. The data on antibiotic prophylaxis (none versus periprocedural versus continuous) is conflicting. One randomized, controlled trial [234] randomized 228 subjects to either perioperative anti-

biotics only (ampicillin/sulbactam) or prolonged antibiotics for the duration of the ventricular catheter (ampicillin/sulbactam and aztreonam). Prolonged antibiotic prophylaxis significantly reduced the incidence of both CSF and extracranial infection, but selected resistant or opportunistic pathogens, such as *Candida* and MRSA. The mortality of patients with CSF infection in the continuous antibiotic group was significantly higher than in the perioperative antibiotic-only group. A retrospective study of 308 subjects compared prophylactic antibiotics administered for the duration of the EVDs with periprocedural antibiotics, and found no difference in the overall rate of ventriculitis [235]. The use of continuous prophylactic antibiotics is therefore discouraged based on the risk of selecting resistant organisms.

It has been argued based on retrospective data that EVDs should be changed around day 5, when the infection risk starts to go up. Based on the majority of retrospective evaluations, however, prophylactic catheter exchange has not been effective in preventing VRI, and has been associated with increased risks of ventriculostomy associated hemorrhage and poor catheter positioning [236].

Finally, a comment on the efficacy of antimicrobial-impregnated EVDs. A prospective randomized, controlled trial evaluated EVDs impregnated with minocycline and rifampin in 288 subjects (mainly subarachnoid hemorrhage and trauma) requiring EVDs [237]. The antibiotic-impregnated catheters were half as likely to become colonized as the control catheters (17.9% versus 36.7%) and seven times less likely to be associated with positive CSF cultures (1.3% versus 9.4%). Heparin-coated catheters, which have been shown to lower the incidence of bacterial colonization and septicemia in central venous catheters [238], have also been evaluated in a randomized, controlled study of 198 subjects requiring EVDs (mostly with subarachnoid hemorrhage and trauma), but demonstrated no benefit in catheter colonization when compared with non-heparin-coated EVDs. Finally, a hydrogel-coated EVD, which has a proposed advantage of reducing clot and bacterial adhesion, was evaluated in a prospective randomized trial [239]. This also failed to demonstrate reduction in bacterial colonization. At this time it appears that the antibiotic impregnated EVDs are effective in reducing the likelihood of VRI. A large bore antibiotic impregnated catheter for drainage of intraventricular hemorrhage is not available at present.

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58 Tuberculous Meningitis: The Critical Issues

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58.1 Introduction

The global burden of tuberculosis is still high, particularly in the developing world. Tuberculosis is a leading cause of death from infectious disease, second only to human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) [1]. Globally there were an estimated 9.27 million new cases (139 per 100,000 population) of tuberculosis in 2007 and the number of prevalent cases was 13.7 million (206 per 100,000 population). Some 22 high-burden countries, most of them in the developing world, collectively account for 80% of the global tuberculosis burden. An estimated 1.3 million deaths occurred among HIV-negative incident cases of tuberculosis (20 per 100,000 population) and an additional 456,000 deaths among incident cases of tuberculosis that were HIV-positive [2]. Human immunodeficiency virus infection increases the lifetime risk of developing clinical tuberculosis post-infection to 1 in 3 [3].
The incidence of central nervous system (CNS) tuberculosis is not well studied. The incidence of CNS tuberculosis generally reflects the incidence and prevalence of tuberculosis in the community. About 10% of patients who have tuberculosis develop CNS disease [4]. HIV infection predisposes to the development of extra-pulmonary tuberculosis, particularly tuberculous meningitis [5]. There were 206 per 100,000 prevalent cases of tuberculosis in 2007 [1] and the projected incidence cases of CNS tuberculosis would be 20.6 per 100,000 population in the year 2007, most of it would be in the high-burden countries. The incidence rates of tuberculous meningitis are age-specific and range from 31.5 per 100,000 (<1 year) to 0.7 per 100,000 (10-14 years) in the Western Cape Province, South Africa [6]. There are no community-based mortality studies in CNS tuberculosis. The estimated mortality due to tuberculous meningitis in India is 1.5 per 100,000 population [7]. HIV co-infection is associated with higher complication and case fatality rates [8,9].

58.2 Pathogenesis and Pathology

Lymphohematogenous spread of *M. tuberculosis* from a primary focus leads to the development of a Rich focus in the brain. Tuberculous meningitis results from the release of *M. tuberculosis* into the subarachnoid space from a meningeal or subcortical Rich focus. This results in a local T-lymphocyte-dependent response, caseating granulomatous inflammation [10,11]. The cytokine tumour necrosis factor alpha (TNF-α) is critical in the neuropathogenesis of *M. tuberculosis*. TNF-α plays a role in granuloma formation and also in host-mediated destruction of infected tissue [12,13]. However, TNF-α concentrations in the cerebrospinal fluid (CSF) have not correlated with disease severity and outcomes in humans [14,15]. Tuberculous meningitis is also characterized by an increased CSF expression of other pro-inflammatory cytokines such as interferon (INF)-γ, interleu-

kin (IL)-1β, IL-8, and the anti-inflammatory cytokine IL-10 [14,16]. There is evidence of significant blood-brain-barrier (BBB) breakdown in patients with tuberculous meningitis [14,17] and this has been attributed to matrix metalloproteinases (MPP) [18].

The pathological process of tuberculous meningitis includes basal exudate formation, an obliterative vasculitis, encephalitis and tuberculoma formation. The release of *M. tuberculosis* into the subarachnoid space results in the development of inflammatory exudate that affects mostly the sylvian fissures, basal cisterns, brainstem, and cerebellum. Blockage through adhesion formation of the basal subarachnoid cisterns can result in hydrocephalus. The adhesive exudate envelops the arteries and compromises the cranial nerves. The latter may explain the cranial nerve palsies seen in tuberculous meningitis. An obliterative vasculitis of both large and small vessels, perforating vessels, commonly results in infarction in the territory of the affected vessel [10,11]. In an autopsy study of 190 cases of neurotuberculosis, hydrocephalus was noted in 71% and it was severe in 36%. Vasculitis and infarcts were noted in 70% of cases, whereas large infarcts involving the middle cerebral artery territory were noted in only 3.2% of cases. Perforating vessels to the basal ganglia are most commonly occluded [11]. Tuberculomas often occur in the absence of tuberculous meningitis but may occur along with tuberculous meningitis. Tuberculomas are thought to arise when tubercles in the brain parenchyma enlarge without rupturing into the subarachnoid space [13]. The reported frequency of tuberculomas on the initial computed tomography (CT) scan in patients varies between 2 and 38% and they are often multiple [19].

58.3 Clinical Features

Tuberculous meningitis is difficult to diagnose as the clinical features are non-specific and vary widely and are often diagnosed when brain damage has already occurred [12,20,21]. The variables that may determine disease evolution and clinical presentation include age and HIV co-infection. Patients with HIV co-infection may less commonly have fever, headache, and meningismus and they are more likely to have an altered mental status [22,23].

Tuberculous meningitis often presents with meningitis symptoms of fever (60-95%), headache (50-80%), and signs of meningismus (40-80%), focal neurologic deficits (hemiplegia 10-20%, paraparesis 5-10%, any cranial palsy 30-50%), behavioural changes (10-30%) and altered mental status (30-60%). Seizures can complicate the disease: 50% in children and 5% in adults [12]. In a large cohort of children, the common clinical characteristics on admission were fever (67%), headache (25%). meningismus (98%), altered mental state (96%), motor deficit (63%), brainstem dysfunction (39%), cranial nerve palsies (27%), and elevated intracranial pressure (23%). Seizures were present on admission in 47% of children and 97% of the children presented with severe grade disease (stage II and III) [21]. A rare clinical syndrome, tuberculous encephalopathy has been described in children. The syndrome is characterized by coma, convulsions, involuntary movements, and pyramidal signs with normal CSF. Post-mortem pathology showed diffuse cerebral edema and demyelination and was presumed to be due to allergic encephalomyelitis [24]. Other unusual clinical features include movement disorders, tremor, chorea, ballismus, and myoclonus [25].

The severity of tuberculous meningitis at presentation is classified into three grades according to the patient's Glasgow Coma Scale (GCS) score and the presence or absence of focal neurological signs, the modified British Medical Research Council criteria [26]: Grade I. alert and orientated without focal neurological deficit; Grade II. GCS score 10-

14 with or without focal neurological deficit or GCS score 15 with focal neurological deficit; Grade III. GCS <10 with or without focal neurological deficit. Severe grade disease is associated with high mortality and morbidity [21].

Some clinical and CSF findings are predictive of a diagnosis of tuberculous meningitis. In children the clinical variables predictive of tuberculous meningitis include: symptoms lasting longer than 6 days, optic atrophy, focal neurologic deficits, abnormal movements, and a CSF leukocyte differential <50% neutrophils. The diagnostic sensitivity is 98%, the specificity is 44% when at least one feature is present, the sensitivity is 55% and the specificity is 98% if three or more features are present [27]. The adult study in Vietnam identified five clinical variables predictive of diagnosis of tuberculous meningitis: age (<36 years: 2, >36 years: 0); white cell count (>15000: 4, <15000: 0); history of illness (>6 days: -5, <6 days: 0); CSF leukocyte count (>750: 3, <750: 0), and percent of CSF neutrophils (>90: 4, <90: 9). A maximum score of four or more on admission was diagnostic of tuberculous meningitis. This diagnostic rule had a sensitivity of 86% and a specificity of 79% [28].

58.4 Laboratory Diagnosis

Tuberculous meningitis cannot be diagnosed clinically with certainity as the presenting features of the disease are often non-specific. Rapid diagnosis, particularly in grade II and III disease, is critical for instituting appropriate management interventions to prevent complications and reduce morbidity and mortality. Unfortunately, there is still no single diagnostic method that is both sufficiently rapid and sensitive.

CSF of untreated tuberculous meningitis typically shows moderate lymphocytic pleocytosis, moderately elevated protein concentration, and low glucose levels. The opening pressure, in the absence of spinal block, is usually moderately elevated (180-300 mm-H_2O). Acellular CSF has been reported in the elderly and in patients with HIV co-infection [12,13,21,29]. Adenosine deaminase (ADA) enzyme is primarily associated with T cells and monocytes and is elevated >15 IU/l in the CSF in tuberculous meningitis, (sensitivity 50-83% and specificity 95%). The test results can be obtained within a few hours [29]. Tuberculostearic acid, a fatty acid component of the *M. tuberculosis* cell wall, has been detected in the CSF of patients with tuberculous meningitis. Although the method has good sensitivity (95-100%) and specificity (91-99%), its limitations are that it requires expensive equipment and considerable expertise [13].

Bacteriological diagnosis, demonstration of acid-fast bacilli (AFB) of *M. tuberculosis* by Ziehl-Neelsen staining (sensitivity 25%) and culture (sensitivity 18-83%) is highly specific (100%) [21]. Multiple samples of CSF enhance the sensitivity up to 86% [30]. A study from Vietnam reported a bacteriological diagnosis of tuberculous meningitis in 81% of adults with the disease; acid-fast bacilli were seen in 58% patients and cultured from 71% patients. CSF volume, duration of symptoms, CSF neutrophil count, lactate, and glucose were all independently associated with bacteriological confirmation [31]. Semi-automated radiometric culture systems such as Bactec have reduced culture times.

Tests to detect *M. tuberculosis* specific antibodies and antigen in the CSF of patients with tuberculous meningitis are rapid and less expensive. But the techniques are limited by the inability to differentiate acute infections from previous infection and problems with cross-reactivity, in addition to variable and often poor sensitivity and specificity. For the antibody assays the reported sensitivity (52-93%) and specificity (58-199%) were quite variable Similarly for the antigen assays, the sensitivity and specificity were 38-94% and 95-100%, respectively [13].

Commercially available nucleic-acid amplification and other polymerase chain reaction (PCR) assays may provide a screening tool for the diagnosis of tuberculous meningitis. The value of these assays lies largely in the rapidity with which results can be obtained and the very good specificity of these tests [29]. A systematic review of the diagnostic sensitivity and specificity of commercially available nucleic-acid amplification assays for tuberculous meningitis estimated 56% sensitivity (95% confidential interval [CI], 46-66) and 98% specificity (95% CI, 97-99) and the negative predictive value and positive predictive value were 44% and 35.1%, respectively. The sensitivity of these assays is too low, and about half those testing negative will have the disease [32].

58.5 Neuroradiology

Neuroimaging, both contrast computer tomography (CT) and magnetic resonance imaging (MRI), reveals the pathology and the complications of tuberculous meningitis. Though the image characteristics are nonspecific, the findings when correlated with the given clinical features may give a clue for the diagnosis [33]. The imaging characteristics include basal meningeal enhancement (Figures 58.1a and 58.2), hydrocephalus (Figures 58.1a and b), tuberculoma(s), and infarcts (Figure 58.3). Hydrocephalus and basal meningeal enhancement are the most common findings [33-39]. In a large cohort of children (554 patients) from South Africa, the common features on CT were hydrocephalus (82%), basal meningeal enhancement (75%), infarctions (32%), and tuberculomas (13%) [21]. The data in a recent study by Thwaites et al. [38] suggest tuberculomas form in most patients during treatment, predominantly within the meninges (Figure 58.4). Certain neuroimaging findings seem to be specific for the diagnosis of tuberculous meningitis in children: basal meningeal enhancement, tuberculomas, or both on contrast CT (sensitivity 89% and specificity 100%) [34] and the presence of hyperdensity in the basal cisterns on non-contrast CT scans [35].

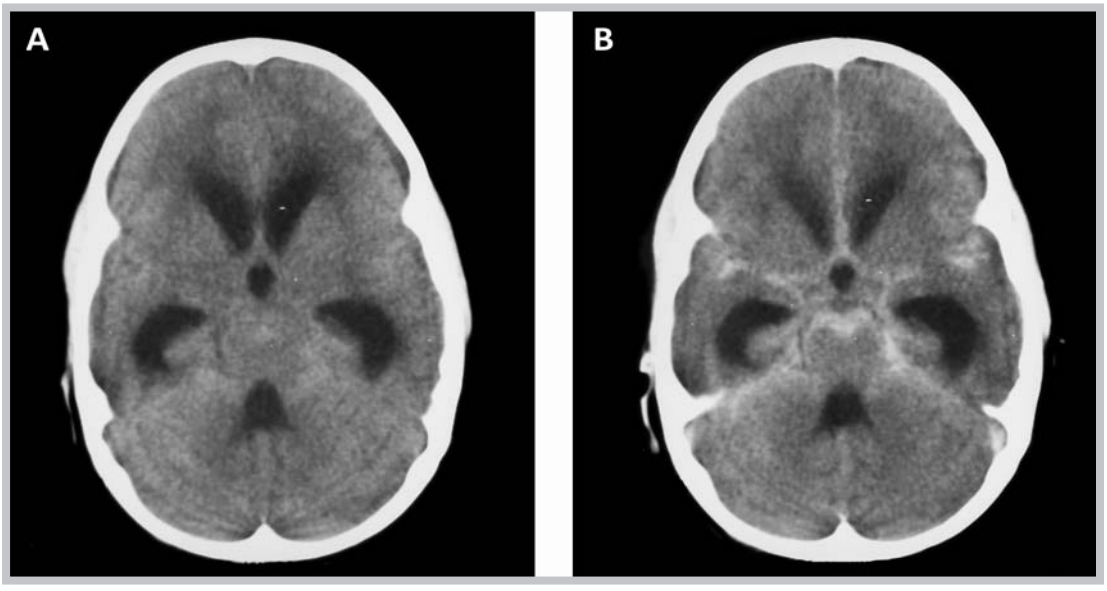

Figure 58.1. **Plain (A) and contrast (B) computed tomography (CT) showing hydrocephalus and basal meningeal enhancement.**

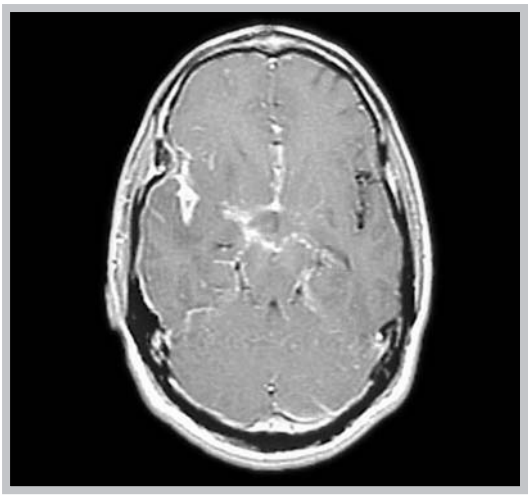

Figure 58.2. Contrast magnetic resonance imaging (MRI) showing basal meningeal enhancement.

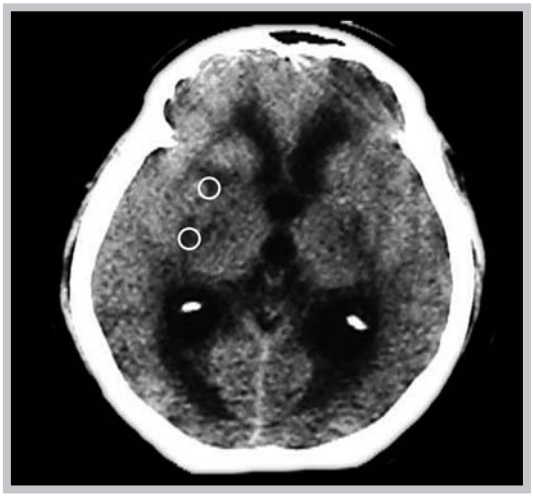

Figure 58.3. Plain CT showing mid hydrocephalus and multiple infarcts (dots).

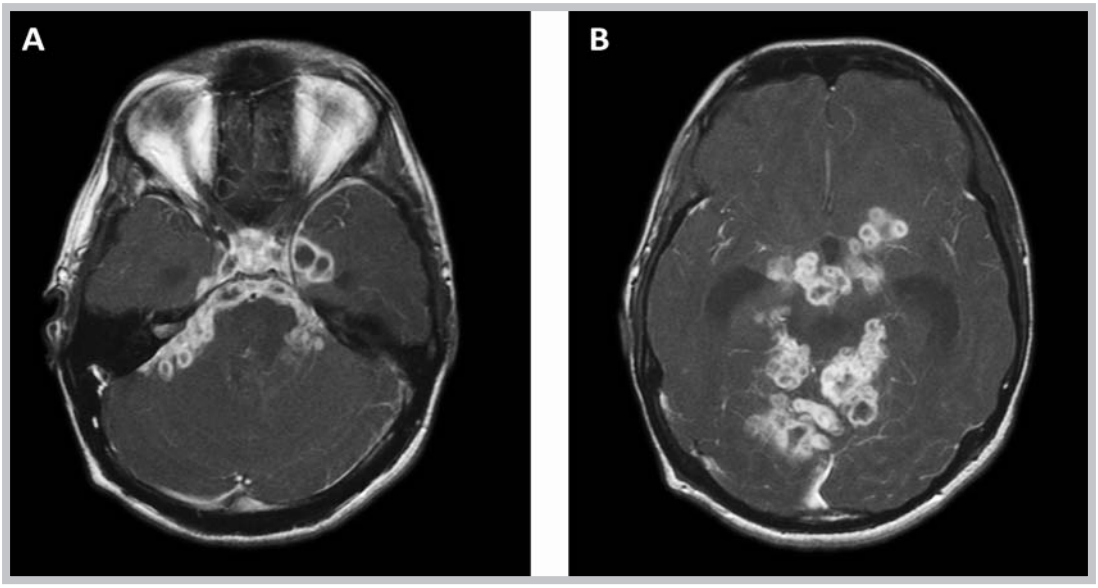

Figure 58.4. Contrast MRI showing basal meningeal enhancement and intra-meningeal and adjacent parenchymal tuberculomas.

58.6 Treatment of Tuberculous Meningitis

58.6.1 Antituberculous Drug Treatment

There is a scarcity of controlled trials of antituberculous drugs in CNS tuberculosis. Most of the guidelines follow the model of short-course chemotherapy of pulmonary tuberculosis: an "intensive phase" of treatment with four drugs, followed by treatment with two drugs during a prolonged "continuation phase" [12]. The Infectious Disease Society of America, the Center for Disease Control and Prevention, and the American Thoracic

Drug	Blood-brain Barrier Permeability	Mechanism	Dose Children	Adult
Isoniazi	Yes	Bactericidal (Intra-extracellular)	10-15 mg/kg	300 mg
Rifampin	Yes inflamed	Bactericidal (intra-extracellular)	10-20 mg/kg	600 mg
Pyrazinami	Yes	Bactericidal (intracellular)	15-30 mg/kg	2000 mg
Ethambutol	Yes inflamed	Bacteriostatic	15-20 mg/kg	1000 mg

Table 58.1. **First-line antituberculous drugs.**

Society guidelines recommend an initial 2-month induction therapy with isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 7 to 10 months of additional isoniazid and rifampin for an isolate that is sensitive to these drugs (Table 58.1). Recent a systemic review suggests that a 6-month regimen might be sufficient if the likelihood of drug resistance is low [40].

58.6.2 Multi-drug Resistant Tuberculosis

Multi-drug resistant (MDR) (resistant to both isoniazid and rifampin) tuberculosis is a concern in high-burden countries. There were an estimated 500,000 cases of MDR tuberculosis in 2007, mostly from high-burden countries: 131,000 in India, 112,000 in China, 16,000 in South Africa, and 15,000 in Bangladesh. Furthermore, 55 countries had reported cases of extensively drug resistant (EDR) tuberculosis defined as MDR tuberculosis plus resistance to a fluoroquinolone and injectable second-line drugs by the end of 2008 [2]. In high-burden countries, the proportion of tuberculosis cases that are MDR may range from 1 to 14% or more [41]. Thus the probability of a patient with tuberculous meningitis in high-burden countries having MDR tuberculosis would be 0.1 to 1.4%. It will be extremely difficult clinically to suspect MRD tuberculous meningitis. MDR tuberculous therapy should be considered if there is a history of prior exposure to antituberculous drugs, contact with a patient with MDR tuberculosis, or poor clinical response to first-line drugs [13]. Resistance to isoniazid was associated with significantly longer times to CSF bacterial clearance [42]. In a prospective study of Vietnamese adults with tuberculous meningitis, isoniazid and/or streptomycin resistance was associated with slower CSF bacterial clearance but not with any difference in clinical response or outcome. However, combined isoniazid and rifampicin resistance was strongly predictive of death (RR of death 11.63, 95% CI 5.21-26.320) [43]. MDR tuberculosis requires extended treatment with second-line drugs that are less effective and have more adverse effects than isoniazid-based and rifampin-based regimens [44]. With the emergence of EDR tuberculosis, even the second-line drugs will be ineffective. Ethinomide and cycloserine have good CNS penetration and may be used as part of an “intensive phase” treatment regimen in patients with suspected MDR tuberculous meningitis [13]. Therapeutic drug monitoring has been used to assist in the management of MDR tuberculosis [45,46].
TMC207, an investigational diarylquinoline compound, acts by specifically inhibiting mycobacterial ATP synthase. In vitro, it inhibits drug-sensitive and drug-resistant *M. tuberculosis* isolates and is also bactericidal against dormant tubercle bacilli [47-50]. In a two-stage, phase 2, randomized, placebo-controlled trial consisting of an exploratory stage (8 weeks) followed by a separate proof-of-efficacy stage (24 weeks) in patients with newly diagnosed, smear-positive pulmonary infection caused by MDR *M. tuberculosis*, the addition of TMC207 to standard therapy reduced the time to conversion to a negative sputum culture as compared with placebo and increased the proportion of patients with conversion of sputum culture. The drug was well tolerated except for significant nausea [51].

The in-hospital case-fatality rate was 57% in patients with MDR tuberculous meningitis, with significant functional impairment in most of the survivors (Patel 2004) [52]. The morality was near 90% in patients with HIV-associated MDR tuberculous meningitis [53].

58.6.3 Adjunctive Steroid Therapy

A Cochrane systematic review concluded that overall adjunctive therapy with corticosteroids reduces the risk of death (RR, 0.78, 95% CI, 0.67-0.91). Data on disabling residual neurological deficits from three trials showed that corticosteroids reduce the risk of death or disabling residual neurologic deficit (RR, 0.82, 95% CI, 0.70-0.97). The review recommends the routine use of corticosteroids in HIV-negative people with tuberculous meningitis to reduce death and disabling neurological deficits amongst survivors. Corticosteroids should be used irrespective of age and disease stage [54]. A recent Vietnam adult study of adjunctive dexamethasone therapy in tuberculous meningitis demonstrated a significant reduction in mortality but not in morbidity [55]. A further subgroup analysis revealed that this benefit occurred among all severe grades of CNS tuberculosis and that this benefit was not seen in patients with HIV co-infection. The study also found that treatment with dexamethasone was associated with less severe adverse events, particularly hepatitis. The mechanism by which dexamethasone exerts its survival benefit is uncertain. Two possible mechanisms have been proposed: 1) the effect of dexamehasone on the deleterious aspects of the immune response in the CNS; and 2) the ability of dexamehtasone to prevent hydrocephalus and/or infarction [13,38]. Dexamethasone does not seem to improve outcome by attenuating immunological mediators of inflammation in the subarachnoid space or by suppressing peripheral T-cell response to mycobacterial antigens [15]. There is some evidence to suggest that adjunctive dexamethasone may affect outcome from tuberculous meningitis by reducing hydrocephalus and preventing infarction [38].
The initial dose of dexamethasone is 8 mg/day for children weighing <25 kg and 12 mg/day for children weighing ≥25 kg and for adults for 3 weeks and then decreased gradually during the following 3 weeks [56]. In the trails by Thwaites et al. [55], the initial dose was 0.3 mg/kg/day for grade I and 0.4 mg/kg/day for grades II and III, followed by gradual tapering over 6 weeks.

58.7 Treatment of Complications

In patients with tuberculous meningitis, potential neurologic complications requiring careful attention include altered mental status, elevated intracranial pressure (eICP), hydrocephalus, vasculitis, and acute seizures. Critical care of these patients should focus not only on treatment of the underlying infection and its immediate complications but also on minimizing secondary brain injury. Aggressive and appropriate care within the intensive care unit setting can minimize these complications and improve the chance of a good outcome [19].

58.7.1 Fever

Fever is a common feature in patients with tuberculous meningitis and the reported frequency varies between 60 and 95% [12]. Fever is regarded as a fundamental component of the acute-phase response to infection. Despite considerable research, it remains un-

clear whether infection-related fever is globally beneficial or harmful [57]. No data exist to determine the effect of fever on the pathology and ICP in tuberculous meningitis.
Fever management has become a common practice in neurologic and neurosurgical ICUs in patients with acute brain insult [58]. Fever exacerbates the degree of resulting neuronal injury in the presence of acute brain insult [58-60] and it also raises ICP [61]. However, there are several uncertainties with regard to infection-related fever management. There are very few studies that have looked into the effect of infection-related fever in patients with acute brain insult. Retrospective data indicate that stroke patients with preceding bacterial infections have poorer neurological and behavioural outcomes than do their uninfected counterparts [62,63]. In one experiment in which rats were injected with *E. coli* lipopolysaccharide prior to the induction of global brain hypoxia, fever was associated with increased neural damage [64]. Thus, fever management to achieve normothermia might be warranted in patients with severe grade tuberculous meningitis. However, one has to exercise caution in patients with associated sepsis. Low or normal temperature during bacteraemia has been shown to be associated with poor outcome [65]. Standard fever management consists of antipyretic drug therapy and external/physical cooling. Newer methods with surface cooling and intravascular cooling devices are more effective in lowering fever than standard fever management protocols [58].

58.7.2 Fluid and Sodium Disturbances

Disturbances of sodium, intravascular volume, and water are common in tuberculous meningitis. The reported frequency of hyponatremia in patients with tuberculous meningitis varies between 35 and 65% [66-68]. Hypotonic hyponatremia causes the entry of water into the brain, resulting in cerebral edema [69]. Hyponatremia without eICP may be associated with altered mental status. In patients with tuberculous meningitis, both hyponatremia and altered mental status are independent predictors of death or severe disability [70].
In tuberculous meningitis it is often difficult to precisely determine the cause of hyponatremia. The differential diagnosis includes the central salt wasting syndrome (CSWS), the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and adrenal insufficiency. The CSWS is defined as renal loss of sodium during intracranial disease, leading to hyponatremia, excessive natriuresis, volume depletion and clinical response to volume and salt replacement [71]. The available evidence suggests that the cause of hyponatremia in tuberculous meningitis is due to CSWS [72-77]. The CSWS involves renal salt loss resulting in hyponatremia and hypovolaemia, whereas SIADH involves a physiologically inappropriate secretion of ADH or increased renal sensitivity to ADH, leading to renal conservation of water and euvolaemic or hypervolaemic hyponatremia [71].
At presentation, many patients with tuberculous meningitis have compromised volume status. The first step is to assess the volume status and replace the volume with normal saline and simultaneously investigate the patient for hyponatremia. The therapy in CSWS is volume and sodium replacement (0.9% sodium chloride or 3% if necessary). The rapidity of sodium replacement depends on the rate at which the hyponatremia developed. Treatment of hyponatremia developing at a rate of >0.5 mmol/l/h should be aggressive, as it is a life-threatening complication and may cause death from severe cerebral edema and herniation (Kroll 1992) [78]. Mineralocorticoid or fludrocortisone supplementation has also been shown to be effective in returning serum sodium levels to normal [79,80]. Volume restriction is the treatment of choice in SIADH and in pa-

tients with symptomatic hyponatremia; 3% sodium chloride is usually combined with frusemide to facilitate free water excretion and correct hyponatremia.

58.7.3 Acute Seizures

Acute seizures occur in about 50% of children with tuberculous meningitis and in 5% of adults [12]. New-onset acute symptomatic seizures are not uncommon in patients with HIV-associated tuberculous meningitis [81]. Rarely convulsive status epilepticus (CSE) [82] and non-convulsive (NCSE) [83] status epilepticus (SE) may complicate tuberculous meningitis. Patients with the first acute symptomatic seizure caused by CNS infection are at a higher risk for 30-day mortality [84].

In patients with CNS infections, recurrent seizures are common after the first acute seizure [85]. Probably, these patients will need AED prophylaxis to prevent seizure recurrence, at least for the period of resolution or stabilization of an acute CNS insult. The plan in such patients would be acute abortive treatment with benzodiazepines, followed by a loading dose of phenytoin/fosphenytoin and subsequent maintenance therapy. An alternative drug is levetericetam. Studies using levetericetam in SE and NCSE, both in children and adults, suggest the efficacy of the drug when administered early, and a dose of <3000 mg daily is likely to provide benefits [86-88]. AEDs may be continued if there is a high risk of recurrence for a period of 3 to 6 months [89].

While using AEDs, interactions with other co-medications, particularly anituberculous drugs, should be considered. Isoniazid inhibits phenytoin, carbamazepine and valproic acid, producing high serum levels of these AEDs and thus toxicity [90,91]. Rifampin lowers the concentration of valproic acid, phenytoin, carbamazepine, lamotrigine, making some of these drugs relatively ineffective [90]. When combined with isoniazid, rifampicin counters the former's inhibitory effect on the metabolism of phenytoin. Isoniazid, rifampin, pyrazinamide and valproic acid are all hepatotoxic drugs. When used together, they may potentiate hepatotoxicity. Preferably, valproic acid should be avoided; if given, liver function should be monitored at regular intervals.

58.7.4 Vasculitis

Vascular pathology associated with tuberculous meningitis, arteritis, arterial spasm, intraluminal thrombus, and external compression of proximal vessels by exudates in the basal cisterns, all compromise cerebral perfusion and oxygen delivery to the brain [10,11,92]. In an autopsy study, arteritis and infarcts were seen in 70% of brains. Arteritis mostly involved the perforating branches of the major arteries at the base of the brain [10,11].

It is not clear how to treat this serious complication of tuberculous meningitis or the compromised cerebral perfusion and infarction. Recently delayed abnormalities of cerebral oxygenation, despite ICP control and full conventional therapy, have been shown in two patients with tuberculous meningitis, confirming the progressive nature of the vascular insult [93]. Corticosteroids may be beneficial. How corticosteroids exert their beneficial effect in tuberculous meningitis is not clear. One of the mechanisms may be an anti-inflammatory effect. However, this effect is difficult to prove [94]. The Vietnam adult study suggests that dexamethasone might improve survival from tuberculous meningitis by reducing the incidence of infarction and speeding the resolution of hydrocephalus [38]. Corticosteroids might antagonize vascular endothelial growth factor (VEGF) β and thereby reduce vasogenic cerebral edema [95]. Gujjar et al. [96] studied the efficacy of triple-H therapy in patients with tuberculous arteritis and suggested that it is safe and may be beneficial in the management of patients with tuberculous arteritis.

58.7.5 Intracranial Pressure

In patients with tuberculous meningitis, elevated intracranial pressure (eICP) is one of the predictors of poor outcome. The relative risk of poor outcome in children with clinical features of eICP was 1.7 (95% CI, 1.7–2.2; p 0.002). In this study, the stage of the disease at admission was found to be an independent risk factor for poor outcome (odds ratio [OR], 4.8, 95% CI, 2.7-8.7; p <0.001) [21]. The presence of hydrocephalus usually signifies eICP; in patients with hydrocephalus, the stage of the disease at admission is a predictor of poor outcome [97-100].

Pathogenesis of ICP

Understanding the pathogenesis of eICP is essential for formulating appropriate therapeutic interventions. The pathological substrate of eICP includes: 1) diffuse edema consequent to encephalitic processes; 2) micro- and macroinfarcts secondary to vasculitis of both small and large vessels and the associated edema and space-occupying effect; 3) hydrocephalus due to CSF blockage by adhesion formation of the basal subarachnoid cisterns; 4) a space-occupying effect of associated tuberculoma(s) [10,11]. Rarely, mostly in children, tuberculous encephalopathy may contribute to eICP. Tuberculous encephalopathy is an immune-mediated allergic process with no appreciable inflammatory reaction; the pathology includes demyelination and edema [24].

In addition to the pathological substrate, other players in the pathogenesis of eICP in tuberculous meningitis include fever and hyponatremia. Hyponatremia is a common finding in such patients and results in osmotic water shifts, leading to an increase in intracellular fluid (ICF) volume, especially brain cell swelling or cerebral edema [69]. An increase in brain temperature in the presence of acute cerebral damage is associated with a significant raise in ICP [61].

Management

The clinical presence of papilledema may help to diagnose eICP. The GCS is a reliable scale to assess brain injury severity. A GCS <8 suggests serious pathology and possible eICP. In addition to clinical evaluation, neuroimaging is an essential component in the management of eICP in patients with tuberculous meningitis. It provides a good idea about the possible pathological substrate of eICP. The imaging evaluation usually begins with a contrast CT scan as an emergency procedure: 1) to identify intracranial lesions, tuberculomas and space-occupying infarcts that may need surgical correction; 2) to identify CSF obstruction, hydrocephalus; and 3) to appreciate the severity of cerebral edema or the presence of brain shift.

There are no established guidelines for when to institute ICP monitoring in patients with tuberculous meningitis and eICP. In one study in children with hydrocephalus and eICP, response to therapy was assessed by means of repeated lumbar CSF pressure monitoring and CT scanning. No correlation was observed between lumbar opening pressure and the degree of hydrocephalus as measured by CT [101]. Studies in children with other CNS infections, encephalitis and bacterial meningitis have shown the usefulness of ICP monitoring in the optimal management of ICP [102,103]. It will be appropriate to monitor ICP in patients with tuberculous meningitis with features of ICP and grade II and III disease.

Management of eICP should be carried out in a stepwise fashion as in any other clinical setting. The initial steps should include optimal head positioning to allow for venous drainage and adequate analgesia and sedation. Additional basic measures should focus on optimizing hemodynamic status and oxygenation (airway and ventilation control).

Osmotherapy

The administration of osmotic agents is one of the principal strategies to lower eICP. Commonly used agents are mannitol and hypertonic saline. Osmotic agents, most often mannitol, have been used in patients with CNS infections to treat eICP [104-106]. But none of the studies systematically evaluated the efficacy of the osmotic agents. Similarly, there are few studies in which eICP was treated with an ICP-targeted approach [107]. Hypertonic saline can be used as an alternative to mannitol. It may also be used in otherwise refractory intracranial hypertension to treat eICP. The safety and efficacy of hypertonic saline in the treatment of eICP in other clinical settings has been well established. However, caution is advised with high osmolar loads because they carry an increased risk for potentially deleterious consequences of hypernatremia or may induce osmotic blood-brain barrier opening, with possibly harmful extravasation of the hypertonic solution into the brain tissue [108].

Hyponatremia is a common complication of tuberculous meningitis, and hypovolaemia is often present early in the course of the disease. Fluid therapy should aim at avoiding hypovolaemia and hypo-osmolality. When such a clinical situation is associated with eICP, hypertonic saline may be an appropriate choice [19]. Hypertonic saline is devoid of the risks of dehydration and tubular damage as occur with mannitol.

Hydrocephalus

Hydrocephalus can be treated with diuretics, osmotic agents, serial lumbar puncture, external ventricular drainage or ventriculoperitoneal shunt. The addition of acetazolamide and furosemide was significantly more effective in achieving normal ICP than antituberculous drug treatment alone [109]. In a series of 217 children with tuberculous meningitis and hydrocephalus, medical treatment obviated the need for shunt surgery in over 70% of children [110]. However, patients on medical treatment should be closely monitored to detect worsening or lack of improvement, and shunt surgery should be considered if medical management fails. Ventriculoperitoneal shunt is associated with favourable outcome. The grade of the disease at presentation is a predictor of outcome after shunt surgery [97-100]. In mild and moderate hydrocephalus, early shunt surgery (2 days after diagnosis) was associated with better outcomes compared with delayed surgery (3 weeks after diagnosis [111].

Tuberculomas

The reported frequency of tuberculoma(s) on the initial CT scan varies between 2 and 38% [19]. A growing body of evidence suggests that most often tuberculomas resolve with antituberculous treatment [19].Surgical excision is indicated in: 1) tuberculomas causing obstructive hydrocephalus and significant eICP; 2) tubuerculomas causing obstructive hydrocephalus and not resolving on medical treatment; 3) large space-occupying tuberculomas with eICP; 4) tuberculomas with associated compartmental shifts and not resolving with medical treatment [19].

Prognosis

The reported mortality associated with treated tuberculous meningitis varies between 20 and 50% [13]. In a recent, large retrospective cohort study of all the children with tuberculous meningitis in the Western Cape of South Africa, the mortality was 13% [21]. This very low mortality has been explained by directly observed treatment, active treatment of hydrocephalus, and low rate of HIV co-infection and MDR tuberculosis in the study population. However, the morbidity was quite high, and only 16% of patients had a normal outcome. The morbidity reported in other series varied between 20 and 30%

[13]. A major prognostic indicator for mortality and morbidity was disease stage at presentation [21,112]. In the South African study in children, ethnicity, disease stage, headache, convulsions, motor function, brainstem dysfunction, and cerebral infarction were independently associated with poor outcome on multivariate logistic regression analysis. The area under curve (AUC) of the model was 0.84 (95% CI, 0.80-0.89) [21].

58.8 Conclusion

Tuberculous meningitis is a serious CNS infection with significant mortality and high morbidity among survivors. Most factors found to correlate with poor outcome can be directly traced to the degree of disease progression at the time of diagnosis. The only way to reduce mortality and morbidity is by early diagnosis and timely recognition of complications. Aggressive and appropriate care within the intensive care unit setting can minimize associate brain injury and improve the chance of a good outcome.

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59 *Acinetobacter* Infections: An Emerging Problem in the Neurosurgical Intensive Care Unit

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59.1 Introduction

Interest in *Acinetobacter* spp. has been growing for the past 30 years. One of the main reasons for the present increased interest in this genus is the emergence of multiresistant strains, several of which are pan-resistant to antibiotics and suddenly cause an outbreak of infection [1]. Some of these outbreaks of nosocomial infections have occurred in intensive care units (ICUs) where treatment and control are difficult.

Multidrug-resistant *Acinetobacter baumannii* is a rapidly emerging pathogen in the healthcare setting, where it causes infections including bacteraemia, pneumonia, meningitis, urinary tract infections, and wound infections. The associated mortality is high. The crude mortality rate associated with bacteraemia is approximately 52% and that associated with pneumonia ranges from 23 to 73% [2,3]. It is among the most difficult antimicrobial-resistant Gram-negative bacilli to control and treat due to its ability to survive under a wide range of environmental conditions and to persist for extended periods of time on surfaces, making it a frequent cause of outbreaks of infection and an endemic healthcare-associated pathogen.

Recently, an increased rate of infections caused by *A. baumanii* strains resistant to antibiotics traditionally used in therapy has been reported [3-5]. This is an especially severe event in such infections as post-surgical meningitis because the choice of an antibiotic depends not only on the sensitivity of *A. baumanii* but also on the antibiotic's penetrability through the blood-brain barrier. Multidrug-resistance complicates the treatment of infection, making the search of new agents imperative and the return to old drugs for optimal treatment of this multidrug-resistant organism.

The focus of this review is to summarize the current state of knowledge regarding *A. baumannii* in relation to its taxonomy, identification, microbiology, epidemiology, infections, resistance to antibiotics, and the potential therapeutic approaches to postsurgical meningitis in particular.

59.2 Microbiological Characteristics

The genus *Acinetobacter* comprises ubiquitous Gram-negative bacilli that were originally identified in the 1930s [3,6]. Subsequently, several changes were introduced into the taxonomic classification of *Acinetobacter* spp. The genus *Acinetobacter* initially en-

compassed a heterogeneous collection of non-pigmented, oxidase-positive and oxidase-negative Gram-negative rods [3,6-8]. The genus *Acinetobacter* is now defined as including Gram-negative (but sometimes difficult to stain) coccobacilli, with a DNA G1C content of 39 to 47 mol%, that are strictly aerobic, nonmotile, nonfermentative, catalase-positive and oxidase-negative. Good growth occurs at 40°C without the need for growth factors, while nitrates are reduced only rarely [3]. It appears as bacilli during the rapid growth phase and as cocobacilli in the stationary phase [9].

Over 20 species belonging to the genus *Acinetobacter* have been identified [10]. *A. baumannii* (two genomic species) is the species of greatest clinical relevance, and it is typically associated with outbreaks in the hospital setting [11]. Other species that have been associated with disease in humans belong to the *A. calcoaceticus-A. baumannii* complex that includes three *Acinetobacter* genomic species: *A. johnsonii, A. wolffii, and A. calcoaceticus* subsp*. anitratus* [9].

59.3 Epidemiology

Increasing isolation of multidrug-resistant (MDR) *A. baumannii* has been reported worldwide, and it is now one of the most difficult nosocomially acquired Gram-negative pathogens to control and treat [12]. *A. baumannii* has the ability to utilise various sources of nutrition, which accounts for its growth on routine laboratory media. This explains its survival as an environmental pathogen. Some strains can survive environmental desiccation for weeks, a characteristic that promotes transmission through fomite contamination in hospitals [13]. The capacity of *Acinetobacter* spp. to survive on most environmental surfaces for long periods of time suggests that all animate and inanimate entities should be considered reservoirs.

In healthcare settings, colonized and infected patients are often the sources of *A. baumannii* infections; however, the ability of the organism to survive for prolonged periods on environmental surfaces has also contributed to protracted outbreaks in these settings [12]. *Acinetobacter* has been isolated from pasteurized milk, frozen foods, chilled poultry, foundry, and hospital air, vaporizer mist, tap water faucets, peritoneal dyalisate baths, bedside urinals, washcloths, door handles, keyboards, angiography catheters, ventilators, contaminated gloves, duodenoscopes, laryngoscope blades, plasma protein fraction, and hospital pillows [14-16]. This ability to grow on medical equipment and throughout the hospital environmental emphasizes the need for special attention to disinfection [17-20].

Multidrug-resistant *Acinetobacter* spp. infections have been described in patients admitted to rehabilitation centres and long-term care facilities, as well as in patients hospitalized for acute illnesses [21-26]. The origin of a particular epidemic strain of *A. baumannii* in a hospital is often unknown [21]. There are several factors that maintain the presence of *Acinetobacter* spp. in the healthcare environment, including the presence of susceptible patients or health workers colonized or infected by the microorganism. *Acinetobacter* spp. can colonize the skin, wounds, and the respiratory and gastrointestinal tracts. Up to 25% of healthy ambulatory adults exhibit cutaneous colonization and 7% of adults and children have transient pharyngeal colonization. It is the most common Gram-negative organism persistently carried on the skin of hospital personnel and it has been found to colonize 45% of inpatient tracheostomy sites and 41% of faecal samples in ICUs [22-23]. Differentiating between colonization and infection has clinical and therapeutic relevance because the presence of colonized or infected patients is important in maintaining the organism in the hospital. According to Landman et al. [27], 31-50%

of patients admitted to ICUs have clinical samples testing positive for *A. baumannii* but only between 10-35% show clear signs of infection.

Acinetobacter baumannii can cause community-acquired infections although less frequently than nosocomial infections. Multidrug-resistant *Acinetobacter* infection has been reported among patients residing in rehabilitation and long-term care facilities, as well as in acute care hospitals [24-26]. Several factors maintain the presence of multidrug-resistant *Acinetobacter* spp. in the healthcare setting, including the presence of susceptible patients, the presence of patients already colonized or infected with the organism, selective pressure from antimicrobial use, and incomplete compliance with infection control procedures [28].

In addition to transmission, the emergence of resistance occurs in the context of selective pressure from broad-spectrum antimicrobial therapy with carbapenems or third-generation cephalosporins. The relative contribution of antimicrobial selective pressure and transmission between patients to the emergence of multidrug-resistant *Acinetobacter* spp. is not known [29-31].

59.4 Antimicrobial Resistance

Various terms have been used (sometimes interchangeably) to denote antimicrobial-resistant phenotypes of *Acinetobacter* spp. The most common definitions of multidrug resistance are carbapenem resistance or resistance to more than three classes of antimicrobials [32].

The emergence of multiresistance in *Acinetobacter* spp. complicates the choice of antibiotic treatment and is associated with significant morbidity (63.4%) and mortality (44.2%) [33]. The resistance rate varies between geographic areas, hospitals and even different hospital wards within the same hospital [34]. Some studies [35] found sensitivity rates of imipenem and amikacin of almost 74% in North America and Europe, 60% and 23%, respectively, in Latin America, and 69.2% and 59.6%, respectively, in the Asian region. According to the SENTRY study [36-38] involving 30 European centres from 2001 to 2004, the proportion of strains resistant to imipenem, meropenem, ampicillin-sulbactam and polymyxin B was 26.3%, 29.6%, 51.6%, and 2.7%, respectively. More recent data collected in the MYSTIC study (Meropenem Yearly Susceptibility Test Information Collection) involving 40 hospitals in 12 European countries showed higher rates of resistance to meropenen (43.4%) and imipenem (42.5%) [39]. These results may be even higher in ICUs where several studies have reported resistance to meropenem and imipenem of nearly 75-80% [40].

In several countries, the rate of resistance to colistin is now 2-3% in relation to previous use, and heteroresistant populations have emerged which can hinder its future use in monotherapy [41]. Although tigecycline once appeared to be a good alternative to conventional treatments, reports have increasingly described the emergence of resistant strains even during treatment with the drug, severely compromising its use in empirical therapy. A German study of 215 strains of *A. baumannii* found resistance rates to tigecycline of almost 6% compared to 2.8% for colistin [42]. Another recent study reported resistance rates of 25%, suggesting that the role of antibiotic therapy with these drugs should be carefully evaluated [40].

Several risk factors for the acquisition of multidrug-resistant strains have been identified. These include the previous use of antibiotic treatments, especially carbapenems and third-generation cephalosporins, followed by quinolones, aminoglycosides and metronidazole, and the number of previous antibiotics. The second most common risk

factor is the use of mechanical ventilation. Other factors include a stay in the ICU, duration of ICU stay and overall hospital stay, severity of the underlying disease, recent surgery and invasive techniques [43,44]. *Acinetobacter* spp. display mechanisms of resistance to all existing antibiotic classes, as well as a prodigious capacity to acquire new determinants of resistance [45]. The capacity of *Acinetobacter* spp. to develop extensive antimicrobial resistance may be due in part to the organism's relatively impermeable outer membrane and its environmental exposure to a large reservoir of genes.

59.4.1 Mechanisms of Resistance

Resistance mechanisms for *Acinetobacter* spp. generally fall into three categories: 1) antimicrobial-inactivating enzymes; 2) reduced access to bacterial targets; and 3) mutations that change targets or cellular functions. Because *Acinetobacter* spp. are Gram-negative organisms, they possess an additional outer membrane that acts as a permeation barrier [2,13,44].

59.4.2 Resistance to Beta-lactams

The mechanism of resistance to beta-lactams involves: 1) their hydrolysis by beta-lactamases; 2) changes in penicillin-binding proteins (PBPs) that inhibit their action; 3) alterations in the structure and number of porin proteins that result in decreased permeability to antibiotics through the outer membrane of the bacterial cell; and 4) the activity of efflux pumps that further decrease the concentration of an antibiotic within the bacterial cell [46,47].

The most important problem in multidrug-resistant *Acinetobacter* is its resistance to carbapenems. This resistance is mediated by various mechanisms:

- Metallo-β-lactamase (VIM, IMP).
- OXA carbapenemases (class D).
- Cell permeability changes.
- Target (PBPs) changes.

The metallo-β-lactamases and OXA carbapenemases are the most important mechanisms of resistance in *A. baumannii* because they confer resistance to carbapenems. These enzymes belong to either Ambler Class B (metallo-β-lactamases) or class D (oxacillinases) [48]. Metallo-β-lactamases are efficient carbapenemases. Three groups of this enzyme class have been found in *Acinetobacter* spp*:* IMP-like MBL, VIM-like MBL, and SIM-1. IMP and VIM confer high-level resistance to carbapenems and most other beta-lactams, with the exception of aztreonam. MBL are class-1 integrons and may be transferred and expressed along with resistance genes to other antimicrobials such as aminoglycosides [34,47,57-59].

The other group of enzymes (carbapenem-hydrolysing oxacillinases) consists of oxacillinases with intrinsic carbapenemase activity. The significant contribution of these enzymes to carbapenem resistance in *A. baumannii* has been emphasized, particularly when they are accompanied by IS*Aba1* and IS*Aba3* in the naturally occurring plasmid [60-62].

A third mechanism of carbapenem resistance involves porins, which are outer-membrane proteins that allow antimicrobials, such as beta-lactams, to permeate into the bacterial cell. Loss or modification of porin proteins has been shown to confer carbapenem resistance and high-level resistance is observed in the presence of both loss of porin function and expression and production of carbapenemases [47,63]. Another mechanism contributing to carbapenem resistance is the overexpression of bacterial efflux

pumps that decrease the concentration of beta-lactam antibiotics in the periplasmic space [64]. Efflux pumps cause clinical resistance in *Acinetobacter* spp. by acting in association with the overexpression of AmpC beta-lactamases or carbapenemases. With less beta-lactam entering the periplasmic space, the weak enzymatic activity of beta-lactamase is amplified. Besides removing beta-lactam antibiotics, efflux pumps can actively expel quinolones, tetracyclines, chloramphenicol, disinfectants, and tigecycline [66,62,47].

Various factors associated with the emergence of strains resistant to carbapenems and sensitive to colistin have been identified, including prior exposure to quinolones and antipseudomonal drugs and the number of antibiotics used previously [65].

59.4.3 Resistance to Aminoglycosides

Resistance to aminoglycosides is mediated by three mechanisms: alteration of the ribosomal target; reduction of uptake; and enzymatic modification of the drug. Alteration of the ribosomal target only affects streptomycin. The second mechanism is fairly common in *Acinetobacter* spp., but resistance to aminoglycosides in *A. baumannii* is mediated principally by aminoglycoside-modifying enzymes. These include aminoglycoside O-phosphotransferases, aminoglycoside N-acetyltransferases, and aminoglycoside O-nucleotidyltransferases. They are mediated primarily by plasmids or transposons that can play a role in the spread of resistance. These enzymes may also be chromosomally located [3,67,68].

59.4.4 Resistance to Quinolones

Resistance of *A. baumannii* to quinolones is often caused by modifications in the structure of DNA gyrase secondary to mutations in the quinolone resistance-determining regions of the *gyrA* and *parC* genes [69,70]. These changes result in a lower affinity for the binding of quinolone to the enzyme-DNA complex. As mentioned above, a second mechanism of resistance to the quinolones is mediated by efflux systems that decrease intracellular drug accumulation [48].

59.4.5 Resistance to Tetracyclines

Two different mechanisms of resistance to tetracyclines have been described in *A. baumannii*. TetA and TetB are specific transposon-mediated efflux pumps; TetB determines the efflux of both tetracycline and minocycline, whereas TetA drives only the efflux of tetracycline. The second mechanism is the ribosomal protection protein, which shields the ribosome from the action of tetracycline. The *tet*(M) gene encodes this protein, which serves to protect the ribosome from tetracycline, doxycycline, and minocycline [3,46].

Tigecycline is the first antibiotic of a new class called glycylcyclines that may be useful for multidrug-resistant *Acinetobacter* [71-73]. Tigecycline overcomes the two major mechanisms of resistance to tetracyclines (ribosomal protection and efflux), but tigecycline resistance emerging during therapy has been reported [72]. This resistance appears to be attributable to overexpression of the AdeABC multidrug efflux pump [73]. Probably this mechanism can be upregulated by the previous use of other antibiotics (e.g., fluoroquinolones, aminoglycosides) that are administered frequently in patients with serious infections [74].

59.4.6 Resistance to Polymyxins

There are several suggested mechanisms of resistance to colistin/polymyxin B in Gram-negative bacteria, most of which involve changes in the outer membrane. The mechanism of resistance to colistin likely resides in modifications in the lipopolysaccharide of *A. baumannii* (acidification, acylation, or presence of antigens that interfere with the binding of the antibiotic to the cell membrane) [3]. A strong association has been reported between the use of colistin and the development of resistance in clinical isolates of *A. baumannii* [75].

59.5 Virulence and Pathogenicity

A. baumannii is regarded as a low-grade pathogen with limited virulence. However, this microbe has certain features that allow it to increase the virulence of those strains implicated in infections. The bacteria's invasiveness may be related to substances that protect the surface of phagocytosis, i.e., the polysaccharide capsule. The presence of fimbriae allows adhesion to human epithelial cells. Studies have investigated the production of such enzymes as butyrate esterase, caprylate esterase, leucine and aryl amidase which may damage tissue lipids and the potentially toxic role of the lipopolysaccharide component of the cell wall and the presence of lipid A. Apart from sharing factors in common with other Gram-negative bacteria, *Acinetobacter* spp. produce a lipopolysaccharide that can exert an endotoxigenic effect through lipid A and that enhance the ability of these microorganisms to capture iron through the secretion of siderophores, which allows them to survive in the human body. Moreover, some strains of *Acinetobacter* spp. can produce slime which was considered to be the main factor responsible for the enhancement of virulence in mixed infections [1,3,76].

All these factors act together in the pathogenicity of *Acinetobacter* spp. The capsular polysaccharides and lipopolysaccharides (LPSs) act in synergy by blocking access of the human complement to the bacterial cell wall, thus preventing its lytic activity on bacterial membranes. Furthermore, the hydrophilicity conferred by the presence of capsular polysaccharides, together with other nonspecific adherence factors (i.e., fimbriae), prompts the colonization of human epithelial cells by pathogenic strains [77]. Enzymes able to damage tissue lipids are also produced during the infectious stages of colonization. Interestingly, the action of LPSs in the pathogenicity of *Acinetobacter* is not limited to the protection of bacterial cells from host defences; these molecules are, in fact, provided with a powerful endotoxic activity, and their production in vivo is thought to be related to *Acinetobacter* septicaemia symptoms [78,79].

59.6 Useful Antibiotics for *Acinetobacter* Infections

Distinct classes of antimicrobial agents considered potentially effective in the treatment of *A baumannii* infection include: sulbactam; antipseudomonal penicillins or cephalosporins; carbapenems; monobactams; aminoglycosides; fluoroquinolones; glycylcyclines; and colistin [80]. However, the emergence of strains with high resistance to carbapenems, aminoglycosides and fluoroquinolones [35,36,81] poses a challenge to the clinician; therefore, sulbactam, tigecycline and colistin represent the current therapeutic approaches associated with satisfactory efficacy.

59.6.1 Carbapenems

Imipenem and meropenem have been regarded as the treatment of choice for severe *A. baumannii* infections, although the increase in resistance rates of *A baumannii* isolates to carbapenems, especially in Europe and North America, have diminished their usefulness [35]. Furthermore, carbapenem-resistant *A. baumannii* strains might only rarely be susceptible to other antipseudomonal agents [80], making treatment very difficult.
As described above, carbapenem resistance in *A. baumannii* is mediated by several mechanisms, including plasmid or chromosomally encoded carbapenemases (mainly OXA-23-like, OXA-24-like, or OXA-58-like class D β-lactamases), as well as metallo-β-lactamases (class B β-lactamases), efflux pump mechanisms, penicillin-binding protein alterations, and modifications or loss of outer membrane proteins (porins) [48,80]. More than one of these resistance determinants could be present in the same strain, thus conferring it high-level resistance.
A recently developed carbapenem is Doripenem, a novel, forthcoming carbapenem that possesses a broad spectrum of activity against Gram-negative bacteria similar to that of meropenem, while retaining the spectrum of imipenem against Gram-positive pathogens [82]. It is approved for the treatment of complicated urinary tract and complicated intra-abdominal infections. An indication for hospital-acquired pneumonia including ventilator-associated pneumonia is pending. Its principal features are: 1) bactericidal action against most species; 2) β-lactamase stability to commonly occurring enzymes, including the emerging extended-spectrum β-lactamases (ESBLs); 3) pharmacokinetic and pharmacodynamic qualities similar to those of meropenem (half-life of 1 h) with minimal risk of convulsive adverse reactions; 4) postantibiotic effects of nearly 2 h in vitro for *Pseudomonas aeruginosa*; and 5) low serum protein binding (8.9%). Doripenem is stable enough in the presence of renal dehydropeptidase I that it need not be coadministered with a dehydropeptidase I inhibitor such as cilastatin. Pharmacokinetic studies have supported a 3-times-daily dosing schedule [83].
The most frequent adverse reactions are: nausea, diarrhoea, headache, phlebitis, hypersensitivity reaction, and *C. difficile*-associated colitis. In contrast to imipenem, doripenem did not cause electroencephalographic changes or seizures in animal studies [84-86]. Doripenem may be have a important role in the treatment of *Acinetobacter* infection because it has a lower minimum inhibitory concentration (MIC) than ertapenem or imipenem when tested against *Acinetobacter* spp. [85,86] and some isolates that are intermediate or resistant to other carbapenems may be susceptible to doripenem [85,86]. In a recent study 86 on 12,581 isolates collected between 2005 and 2006 and tested with doripenem, imipenem and meropenem, the MIC(90) of doripenem (0.12) was comparable to that of meropenem (0.12) and superior to that of imipenem (2), though the susceptibility of the isolates exceeded 99% for all evaluated carbapenems. Doripenem (MIC(90) = 2, 89.1%S) was twice as active at MIC(90) against imipenem-susceptible *Acinetobacter* spp. as imipenem or meropenem. However, none of the carbapenems was active against A*. baumannii* strains expressing plasmid-mediated carbapenemases [86,87].

59.6.2 Colistin

Colistin belongs to the Polymyxins group and is available in two forms, colistin sulphate and colistimethate sodium. Colistimethate sodium is a non-active prodrug that is hydrolyzed in vivo to the active form and used for parenteral administration due to its lower toxicity [89]. Polymyxins show bactericidal activity against A *baumannii* by interacting

with anionic lipopolysaccharides on the bacterial cell membrane, leading to an increase in membrane permeability [36,90]. Resistance rates against these agents have remained low despite their more frequent use and the presence of carbapenem-resistant strains [37,91,92].

The usual dose of colistin is 2.5-5 mg/kg/day in 2 to 4 divided doses. In persons weighing >60 kg, the most frequent dose is 80-160 mg/8 h. Dose adjustment is required in the presence of renal failure. Since the bactericidal activity of colistin is concentration-dependent, administering large doses over less frequent intervals may be a favourable approach [93-97]. Isolated case reports described the cure of A. baumannii bacteraemia with continuous intravenous colistin (2,000,000 IU/24 h) in patients with allergic reactions to other treatment [96]. However, the emergence of heteroresistant strains with increasing frequency, along with the pharmacodynamic characteristics of the drug, appear to discourage their use in 24-hour intervals. Owen et al. [97] showed a rapid bactericidal concentration-dependent effect, with regrowth at 3 hours after administration that was clearly significant at 24 hours, even at concentrations 32 and even 64 times above the MIC in some isolates, which advises against its use as monotherapy, and at 24-hour intervals in the presence of heteroresistant strains.

Colistin alone or in combination with other antimicrobials like rifampicin demonstrated its usefulness in several infections due to *A. baumannii* such as ventilator-associated pneumonia, meningitis, and bacteraemia, with rates of clinical and microbiological response close to 80% and 95%, respectively, depending on the type of infection [98-102] It has sometimes been used in nebulized form in variables doses, although the most common are 2-4 million IU with conventional intravenous treatment. The response rate was 85.7% after a single treatment. More studies are needed to clarify its role [103].

The most common toxic effects of colistin are nephrotoxicity and polyneuropathy. For this reason, the systemic administration of polymyxins was abandoned for about 20 years in most areas of the world. However, the problem of infections due to multidrug-resistant Gram-negative bacteria such as *P. aeruginosa* and *A. baumannii* has led to the re-use of polymyxins. Most non-comparative studies have reported an 8-21% rate of renal toxicity associated with polymyxin therapy which appears to be correlated with the cumulative dose, although recent studies using doses of 225 mg/8 h did not observe the occurrence of nephrotoxicity. Patients with pre-existing renal dysfunction in any stage including hemodiafiltration or hemodialysis seem to be more susceptible to the renal adverse effects of polymyxins [102,104-109]. However, a recent study by Hartzell et al. [110] reported a higher percentage of nephrotoxicity (45%), with interruption of therapy in 21% of patients. This study evaluated nephrotoxicity according to the RIFLE criteria (risk, damage, failure, loss and end stage renal disease), and the higher toxicity was possibly related to greater rigor in applying the criteria. Other side effects are neurotoxicity, bronchoconstriction, chest tightness or cough following administration via the respiratory tract. Chemical meningitis with intraventricular or intrathecal use has been infrequently reported [111-112].

Resistance to colistin is low but it has already been reported. The risk factors significantly associated with the isolation of colistin-resistant isolates were age, length of ICU stay, surgical procedures, use of colistin, use of monobactams, and duration of use of colistin. Although the use of colistin was identified as the only independent risk factor in the multivariable model [113]. To prevent this phenomenon, colistin should be used judiciously, given that treatment options for colistin-resistant Gram-negative bacteria are limited. However, in many occasions it must be used as empirical therapy. Falagas et al. [114] estimated that between 4 and 5 of 100 patients admitted to the ICU will die if colistin is not included in empirical antibiotic treatment. Colistin should probably be included as

empirical antibiotic therapy in those ICUs where the probability of contracting a microorganism sensitive only to colistin is close to 50%.

59.6.3 Ampicillin-sulbactam

Sulbactam was introduced in the 1980s as a beta-lactamase inhibitor in combination with beta-lactamic antibiotics [4,5]. Sulbactam exerts its bacteriostatic activity against *Acinetobacter* spp. by binding to PBP2. The most frequently used combination is ampicillin/sulbactam (ratio 2:1), although the two agents are not synergetic [115-117]. The combination of ampicillin-sulbactam has been used by some authors in doses of 2 g/6-8 h [34,115]. The use of ampicillin/sulbactam had been described in retrospective series. Combination therapy has shown effectiveness similar to imipenem therapy in *A baumannii* ventilator-associated pneumonia or bacteraemia caused by multidrug-resistant drugs [115-122]. Favourable clinical outcomes have also been reported with sulbactam or combination ampicillin/sulbactam therapy in patients with other types of nosocomial infections like meningitis [101,121]. Therefore, ampicillin-sulbactam is a sensible option for the treatment of life-threatening *Acinetobacter* infections. However, the role of sulbactam in the treatment of *Acinetobacter* infections is limited due to the development of multidrug-resistant strains.

59.6.4 Glycylcyclines

Glycylcyclines are a novel class of antimicrobial agents related to the tetracyclines. Tigecycline was the first commercially available agent in this class. Tigecycline is a semisynthetic derivative of minocycline that arises from the incorporation of the t-butyl glycylamide radical in position 9 of minocycline, a structural change that enhances its spectrum and provides a better resistance profile. Its mechanism of action is like that of tetracycline: it inhibits protein translation by binding reversibly to the 30S subunit of the bacterial ribosome. This binding blocks the entry of aminoacyl t-RNA to the site of the ribosome, thus preventing the incorporation of amino acids and the subsequent formation of long-chain peptides [123-125]. Glycylcycline binds five times more effectively than tetracycline, which may affect its ability to overcome resistance to tetracyclines from the protection of the ribosome. Moreover, it seems that the mode of interaction of tigecycline with the ribosome is different from that of tetracyclines. It shows bacteriostatic activity against *A baumannii* because it interferes with bacterial protein synthesis through ribosomal binding and thus exhibits its time-dependent bactericidal activity. Tigecycline is extensively distributed into many tissues, resulting in a prolonged half-life that justifies twice-daily dosing. Fifty-nine percent of a tigecycline dose is excreted through the liver, and 33% is excreted through the kidney. In patients with severe hepatic impairment (Child's class C), the normal dose of tigecycline (100 mg initial dose, then 50 mg twice daily) should be reduced to 25 mg twice daily after the normal loading dose. No adjustments are required for any level of renal impairment [124].

Tigecycline is able to evade the most common mechanisms of resistance to tetracyclines in *A baumannii*, including efflux pumps encoded by the *tet*(A) and *tet*(B) determinants, and ribosomal protection mechanisms. Nevertheless, several unique multidrug efflux pumps have been shown to reduce the organism's susceptibility to tigecycline and the rate of resistance is nearly 6% [126,127].

Clinical experience with the use of tigecycline for the treatment of patients with multidrug-resistant *A baumannii* infections is accumulating. Tigecycline has been used in a small number of critically ill patients – mainly as part of combination antibiotic regi-

mens—for the treatment of various types of infections, including ventilator-associated pneumonia and primary or secondary bacteraemia [128-132]. In early case series, most patients had a good clinical outcome. However, the failure of tigecycline to clear *A. baumannii* bacteraemia was reported in a few cases [132]. Furthermore, pharmacokinetic and pharmacodynamic data indicate that tigecycline blood concentrations seem to be suboptimal for maximal antibacterial activity to be exerted in this compartment. There are increasing reports indicating that resistance to tigecycline developed during treatment. In a recent review of retrospective data on 42 severely ill patients, 31 of which had a respiratory tract infection (in 4 cases with secondary bacteraemia) and 4 had bacteraemia, tigecycline therapy (in combination with other antibiotics in 28 patients) was effective in 32/42 cases, but resistance developed in 3 cases during the treatment [128].
Clinicians should be aware that tigecycline MICs for *A. baumannii* isolates may increase during therapy after brief exposure to the drug. Patients receiving tigecycline for *Acinetobacter* infection should be monitored for the development of clinical resistance, and isolates should be monitored for evidence of microbiologic resistance.

59.6.5 Aminoglycosides

Aminoglycosides have shown moderate rates of antimicrobial activity against *A baumannii.* In worldwide collections of *Acinetobacter* spp. isolates, susceptibility rates to amikacin were approximately 60% [36] and the activity of aminoglycosides is lower for multidrug-resistant isolates of *A baumannii* compared with non-multidrug-resistant ones [133]. Reports on the clinical use of aminoglycosides in human beings are scarce and refer to cases of bacteraemia [134] or meningitis [101] in which aminoglycosides have been used in combination with other classes of antimicrobial agents.

59.6.6 Fluoroquinolones

Fluoroquinolones have moderate antimicrobial activity against *A baumannii.* Although levofloxacin has been shown to yield a lower MIC compared with ciprofloxacin and ofloxacin against *Acinetobacter* spp., overall resistance rates to ciprofloxacin and levofloxacin in clinical isolates are around 50% [135]. Nonetheless, the activity of fluoroquinolones against recent multidrug-resistant or imipenem-resistant isolates has been reported to be low [36,133]. The clinical data are based on in vitro studies where levofloxacin showed effectiveness similar to imipenem in a mouse pneumonia model against a strain susceptible to both agents [135]. However, no comprehensive evidence exists for the effectiveness of fluoroquinolones in the treatment of human infections caused by *A baumannii.*

59.6.7 Combination Therapy

Several novel antibiotic combinations demonstrated increased activity in vitro compared with that of any single agent against multidrug-resistant *A. baumannii* isolates. Whether these combinations yield improved outcomes over those seen with a polymyxin or another agent alone remains to be determined. However, against infections with species resistant to all antibiotics, including polymyxins, novel combinations are the only remaining therapeutic option. Several drug combinations have been tested, mostly involving colisitin, carbapenems, rifampicin, fluoroquinolones and sulbactam [136].
Although most of the studies were done in vitro and in animal models of pneumonia, they show that combined therapy, especially the combination with rifampin, obtained

better results than monotherapy with carbapenems or colistin [137-141]. The colistin and rifampicin combination (colistin sulphomethate sodium (2 million IU 3 times a day and intravenous rifampicin 10 mg/kg every 12 h) in the treatment of ventilator-associated pneumonia or bacteraemia caused by carbapenem-resistant *A. baumannii* demonstrated a clinical response of 76% and mortality of 21% [139].

The combination of imipenem and ripampicin has been investigated in some clinical studies; however, the published data are contradictory. Although the combination is synergistic, in vitro studies indicate that because 70% of patients develop high rates of resistance to rifampicin, this combination cannot be recommended [142]. The combination of imipenem with sulbactam has demonstrated synergistic activity in vitro, although some work indicates that the association of carbapenem with ampicillin-sulbactam is associated with better outcomes than the combination of imipenem with amikacin or carbapenems alone. The clinical utility of this combination in patients infected with carbapenem-resistant *A. baumannii* is not well established [91,143].

The assessment of *in-vitro* synergy of the combination of imipenem with a polymyxin against carbapenem-resistant *A baumannii* strains has provided mixed findings. Among other polymyxin-based combination regimens for multidrug-resistant *A baumannii*, the combination of colistin with a carbapenem has shown in vitro either synergistic or indifferent activity [144,146] but clinical effectiveness has not been substantiated [145]. Tigecycline has demonstrated synergy with levofloxacin, amikacin, imipenem and colistin, but there are few data at present to recommend its systematic use [147].

59.7 Specific Infections Due to *A. Baumannii* in Neurosurgery Intensive Care Units

Acinetobacter baumannii is an important cause of nosocomial infections. Risk factors specific for nosocomial infection include length of hospital stay, surgery, wounds, severity of underlying diseases, previous infection, faecal colonization with *Acinetobacter*, treatment with broad-spectrum antibiotics, especially amikacin and imipenem, parenteral nutrition, indwelling central intravenous or urinary catheters or other invasive procedures, admission to a burn unit or ICU, and mechanical ventilation or tracheostomy [28,148].

In many cases, these infections have significant morbidity and mortality. Some studies report an overall mortality rate of 43.3%, a related mortality of 30%, and attributable mortality of 24.3%, with a worse prognosis for critical ICU patients infected by this bacterium compared to those infected by other microorganisms [149].

59.7.1 Postsurgery Nosocomial Meningitis. General Characteristics

A. baumannii meningitis is an infrequent infection mostly associated with intraventricular catheters, cerebrospinal fluid (CSF) fistula or head trauma [148,149]. It is a serious problem in the neurosurgical ICU, especially in patients with intraventricular catheters where the incidence of infection varies from 0 to 27% [150-152].

The risk of nosocomial meningitis in these patients is related to [155-157]:

- Type of neurosurgical procedure.
- Glasgow Coma Scale <10.
- Emergency surgical procedure.
- Presence of surgical wound infection.

- Presence of an external CSF drain.
- Duration of an intraventricular catheter >5 days.
- Absence of antibiotic prophylaxis.

The average incidence is around 2.3% (0.5-11%) and varies with the type of intervention [156]:

- Clean 0.8-5%.
- Clean with insertion of foreign material 6.9%.
- Clean-contaminated 6.8%.
- Contaminated 9.7%.
- Dirty-infected 9.1%.

The most frequent mode of acquisition of nosocomial meningitis is direct transmission during invasive neurosurgical procedures (80%). The extension from a contiguous focus (otitis, mastoiditis, sinusitis, subdural empyema and epidural abscess) and cases secondary to bacteraemia from a distant focus only account for 20% of nosocomial bacterial meningitis [156]. Some studies indicate that up to 40% of patients harbour colonization or infection by the microorganism in places other than the central nervous system (CNS) before the onset of meningitis [153]. Given that the main route of acquiring meningitis is through surgical wounds or intraventricular catheters, this situation is of great importance. Hence, these patients should be monitored systematically for colonizing flora and measures of asepsis applied in their care.

The clinical manifestations of postsurgical meningitis caused by *A. baumannii* are unremarkable, mostly fever and progressive loss of consciousness. Therefore, these manifestations are attributed to the underlying disease, subsequently delaying the final diagnosis of meningeal infection, and representing a prognostic factor of mortality [105,157]. CSF data are consistent with an increased leukocyte count (75-100% polymorphonuclear leukocytes) accompanied by elevated protein with normal or decreased blood glucose levels. Due to the poor specificity of clinical and laboratory data, routine Gram staining and culture are essential in patients with fever of unknown origin and intraventricular catheter.

Infection of CSF shunts carries high morbidity and, above all, taken together, high mortality, which has been estimated to be 15-20%, which may even be higher in certain risk groups, such as preterm infants. The average incidence is 2.6% (range, 4.5-14%) [157,158]. CSF shunts can be divided into two groups: internal referrals or referral shunts and external ventricular drain or external lumbar drain.

- The most commonly used internal shunts are ventriculoperitoneal devices which drain into the abdominal cavity. Ventriculoatrial shunts are used less frequently and tend to be placed in patients in whom the abdominal route is not feasible. The incidence of infection in CSF internal shunts is between 1.5 and 39% (mean, 10%) according to the series. The most important factor associated with infection is the technical expertise of the neurosurgeon. Arguably, following the largest series, overall infection rates >10-15% are hardly admissible and demand the implementation of preventive strategies. The organisms involved are usually skin flora. Coagulase-negative *Staphylococci* (mainly *S. epidermidis*) are the most common pathogens, followed by *S. aureus*
- External shunts are catheters that communicate the subarachnoid or ventricular space with the outside. The main therapeutic indications are: acute hydrocephalus, massive intraventricular hemorrhage, intracranial pressure measurement, closure of CSF leaks, and occasionally drug administration. The incidence of infection differs depending on the device: in the case of an external shunt or peripherally inserted central catheter (PICC) it ranges from 5 to 7% and 3-5% for the Ommaya reservoir. In this case, the causal organisms are almost always, *Staphylococci* and Gram-

Type of surgery	Type of complication	Risk factors
Ventriculostomy	Meningitis	Previous surgery Shunt >5 days ICP >20 mmHg Irrigations Extensive dural lesion
ICP catheter	Meningitis Supuration	Age Duration of ICP monitoring Steroid treatment
Ommaya reservoir	Meningitis	Aspiration of CSF

Table 59.1. **Risk factors associated with external shunts.**

negative pathogens. Patients with this type of drainage are frequently admitted to ICUs where the prevalence of nosocomial infection, especially from often multiresistant gram-negative bacilli, is high. Infection rarely occurs at the time of catheter insertion, but rather over subsequent days. External catheters remaining in place beyond 5-7 days are at highest risk.

Several risk factors associated with infection of internal shunts are: duration of surgery, vascular thrombosis, age, resurgery, ventriculoatrial > ventriculoperitoneal.

Risk factors associated with infection of external lines are shown in Table 59.1.

The most common clinic manifestation [155,156] is shunt malfunction syndrome, consisting of headache, nausea or vomiting, behavioural changes or gradual decrease in level of consciousness, with or without fever. These symptoms are attributable to intracranial hypertension and are suspicious of infection.

In peritoneal shunts, abdominal clinic is common (up to 40% of cases), often presenting as pain in the right lower quadrant, with or without signs of peritoneal irritation. Other complications include intestinal perforation or pseudo-obstruction symptoms. Any abdominal symptoms in a patient with a peritoneal shunt should suggest the possibility of infection. Abdominal ultrasound may reveal a cystic image or inflammatory liquid mass in the distal insertion of the catheter.

Ventriculoatrial shunt infection manifests mainly with fever, which can be elevated and accompanied by chills and even sepsis. Potential complications are severe, such as tricuspid endocarditis, septic pulmonary embolism, paradoxical cerebral embolism, mycotic aneurysm in the territory of the pulmonary artery, cardiac tamponade, myocardial perforation, pseudotumour right atrial thrombosis *in situ* or diffuse glomerulonephritis associated with hypocomplementemia and nephritic syndromes.

Contamination	Culture of CSF + normal CSF + no symptoms
Colonization ventriculostomy	• Positive cultures • Normal CSF • No symptoms. Possible fever
Possible infection Ventriculostomy	• Negative culture • CSF: ↓ glucose, ↑ proteins, ↑ leucocytes
Ventriculostomy infection	• CSF: ↓↓↓ glucose, ↑↑↑ proteins, ↑↑↑ leucocytes • Positive culture • Fever and other symptoms
Ventriculitis	• All the anterior • Fever and meningitis symptoms

Table 59.2. **Diagnostic criteria for external shunt infection.**

External shunt ventricular catheter infection manifests with the development of ventriculitis, fever and altered mental status. As in shunt infection, meningitis can occur if ventriculitis is severe. Sometimes, there are signs of infection at the catheter insertion point. Occasionally, an abscess may occur in the intracerebral route of the catheter. The infection of external lumbar drainage catheters may lead to predominantly purulent meningitis and spinal cord that, if severe or not treated promptly, will also cause ventriculitis.

Diagnostic criteria for postoperative meningitis secondary to external shunts have been developed [159].

The final diagnosis is based on clinical and CSF cytochemical findings of a microorganism isolated in the CSF culture. If necessary, the catheter is removed (all CSF shunts, internal or external, are removed, whatever the reason, and a culture from the catheter tip is obtained). In external lines, the fluid sample is obtained through a ventricular or lumbar catheter. In an internal line, CSF is usually obtained by puncturing the reservoir or valve, or sometimes through the exteriorized distal catheter. In patients with a permanent ventriculoperitoneal shunt, lumbar puncture is contraindicated, as there is danger of locking, and the CSF sample taken by lumbar puncture may differ biochemically and biologically from that taken from the reservoir (infection site).

CSF samples must be grown in aerobic and anaerobic conditions. In some slow-growing infections, the fluid characteristics may be normal and the cultures negative or take long to grow, so that infection is sometimes determined only when culture of the catheter, once removed, is positive (5-10% cases). Lumbar CSF culture offers maximum sensitivity in lumboperitoneal shunts (80-90%) but decreases significantly in ventriculoperitoneal shunts (50-60%) and even more in ventriculoatrial shunts (40%). Ventricular CSF generally shows an inflammatory response with pleocytosis of variable intensity, but in general an average of 100-150 cells. Glucose may be decreased and protein is usually elevated, although usually mild to moderate. The infection of a derivation can be mildly or asymptomatic and present with normal biochemical CSF characteristics, so that only microbiological study can document its existence. In such cases, the results of Gram staining and density of bacterial growth need to be assessed and doubtful cultures repeated, given that contamination may occasionally occur.

Blood cultures must be obtained if the patient is septic. The positivity of blood cultures is <20% in ventriculoperitoneal shunts but up to 95% in ventriculoatrial shunts. A surgical wound or decubitus skin ulcer in the path of the catheter must also be cultivated if it shows signs of infection. Characteristics of meningitis secondary to CSF leak are different from ventricular shunts [160]. The occurrence of CSF leaks is relatively common after traumatic brain injury and certain types of surgical procedures. The incidence of CSF leaks following head injury varies from 2.6 to 30% depending on the type and location of injury. The cumulative incidence at 10 years of meningitis in untreated CSF leakage ranges from 10 to 30% and mortality can be >10% [160]. The most common causative agent in meningitis associated with CSF fistulas is *S. pneumoniae* [161,162].

59.7.2 Postneurosurgery Meningitis Caused by *A. baumannii*

Nosocomial meningitis caused by *A. baumannii* is a major problem in the ICU, especially in patients with intraventricular catheters where the incidence of infection varies from 0 to 27% depending on the study [150-152]. Meningitis is more common in patients with intraventricular hemorrhage, head trauma, prolonged hospital stay and ICU stay [101,150-153]. Other risk factors are the presence of intraventricular catheters for more than 7 days in all postsurgical meningitis [154], and previous antibiotic therapy.

The incidence of nosocomial meningitis caused by *A. baumannii* varies across different series. In large series, it ranks as the fifth major cause of nosocomial meningitis and in recent series it is the second leading cause of infection in patients with ventricular shunts in some ICUs [163-165].

Nosocomial meningitis caused by *A. baumannii* often has a subacute onset with a longer course than community-acquired meningitis [166]. The clinical manifestations of postoperative meningitis caused by *A. baumannii* are mainly subacute fever and progressive loss of consciousness. In many cases these manifestations are attributed to the underlying disease, thus delaying the final diagnosis of meningeal infection, which is a predictor of mortality [101,153]. A small number of patients may show meningeal signs, neurological or seizure focus; however, since many cases occur in sedated patients under mechanical ventilation these data are difficult to assess. CSF data are consistent with increased leukocyte count in f late diagnosis with a 75-100% polymorphonuclear leukocyte count, accompanied by elevated protein with normal or decreased blood glucose levels. There are reports of contamination, so that in suspicious cases repeated lumbar puncture may be useful [167]. The nonspecific clinical and laboratory data make routine performance of Gram staining and culture essential in patients with fever of unknown origin, intraventricular catheter carriers or those admitted to a neurosurgical ICU.

The published mortality rate is 15-71% and 33% in our own experience [101,153]. In some reviews the patients who died had significantly increased pleocytosis and elevated protein, which would seem a worse prognostic sign although not statistically significant [153]. What is clearly established is that the main determinants of mortality are the absence of foreign material removal and the delay of appropriate treatment. Early intraventricular catheter removal with adequate empirical therapy are essential for the survival of patients.

59.7.3 Agents in the Treatment of Meningitis Caused by *A. baumannii*

Acinetobacter spp. quickly develop resistance to multiple antimicrobials. This complicates the treatment of these infections, making the search of new agents and the return to old drugs imperative.

Cephalosporins

The current Infectious Diseases Society of America (IDSA) guidelines recommend as empirical treatment of postsurgical meningitis a combination of vancomycin plus cefepime, ceftazidime or meropenem [168]. But current resistance rates of *Acinetobacter* spp. to both cefepime and ceftazidime are >50% and in some hospitals even approach 100% for strains resistant to carbapenems. These data currently discourage their use as empirical treatment. In the few cases where they may be used, the usual dose should be increased to supply 12 g/day of ceftazidime and 2 g/8 h of cefepime [163].

Carbapenems

Until the emergence of resistance, carbapenems alone or in combination with amikacin were the first-line treatment for this type of infection. However, resistance to the new antibiotics in recent years has led to the use of alternative agents such as ampicillin-sulbactam or colistin [152]. Meropenem is preferred over imipenem given the risk of imipemem-associated convulsions at doses necessary for treating meningitis [84,86,87]. It is sometimes difficult to distinguish drug-induced seizures from those produced by the disease causing meningitis. Given that many of these patients have potentially epileptogenic lesions, it seems recommendable to avoid the use of this drug. Doripenem has some epileptogenic activity in animals, so its use is discouraged in the absence of new

data. However, meropenem is associated with a very low risk of seizures even in the presence of meningitis, making it the carbapenem of choice in this infection [169].
Several studies have investigated the most effective meropenem dose in meningitis. The most commonly used dose is 2 g/8 h administered intravenously over 30 minutes and it has been compared against infusion of 2 g/8 h over 3-4 hours. One of the problems of treatment with carbapenems is not only the increasing emergence of resistant strains but also the emergence of resistance during treatment. What the scarce literature data seem to show is that 3-hour infusion is associated with less emergence of resistance during treatment, as this is the currently recommended route in this treatment.

Ampicillin-sulbactam

Sulbactam was introduced in the 1980s as a beta-lactamase inhibitor in combination with beta-lactamic antibiotics [5] with in vitro activity against *Acinetobacter* spp. enhanced by its affinity for penicillin-binding proteins. Intravenous sulbactam penetrates only 1% of the blood-brain barrier but increases up to 32% in meningeal inflammation [121,172]. The combination of ampicillin-sulbactam has been used in doses of 2 g for 6-8 hours, with a mortality rate of 20-25% [101,121].
In our experience, the mortality was 33% in about 4 cases treated with 3 g/8 h and it was significantly lower than with other treatments, except for a combination of intrathecal and intravenous colistin [101]. In a series of 8 cases published by Jimenez Mejias et al. [121], doses of 1 g/6-8 hours led to the death of patients receiving treatment every 8 hours. A dose of 2 g/6 h is now considered more suitable for the treatment of meningitis [163].

Fluoroquinolone

Quinolones, especially levofloxacin, exhibit in vitro activity against *Acinetobacter* spp. [173], but problems such as high resistance rates (over 60%), scarce clinical experience, and reduced penetration across the blood-brain barrier limit their role in the treatment of meningitis. Experience in the treatment of *A. baumannii* meningitis is limited to only four isolated cases but with therapeutic success [174,175]. Quinolones penetrated 6-37% of the blood-brain barrier [176], so that it may be necessary dose to 800 mg/8 h with ciprofloxacin. However, this higher dose in treating meningitis could be accompanied by a theoretical risk of seizure [177].
Current recommendations [163,168] advise quinolones only as an alternative treatment in the absence of other options. The recommended doses are 400 mg/8 h or more with ciprofloxacin and 750 mg/24 h or 500 mg/12 h for levofloxacin.

Aminoglycosides

Bacterial multiresistance and the poor penetration of many drugs across the blood-brain barrier have led to the use of intrathecal therapies initially with aminoglycosides and most recently with colistin. The use of intrathecal and intravenous amikacin has been reported in the treatment of meningitis refractory to standard therapy in a small number of cases with cure rates of 50-60% [171,178]; however, given the low penetration of aminoglycosides in the CSF, it must be administered only by intrathecal route. The exact dose of intrathecal amikacin has not been established and varies between 5 and 50 mg/24 h. The most frequent dose is 30 mg/24 h [163]. In recent study a 20 mg/day dose achieved cure rates of 83.4% without causing side effects [101].
Recent studies on 55 episodes of meningitis caused by *A. baumannii* found that patients who had received intravenous and intrathecal treatment had better outcomes than those receiving only parenteral treatment, although the small number of cases did not allow for statistically significant differences [101].

Study	Design	Patients	Treatment	Dosing	Cure
Levin et al., 1999 [182]	Prospective nonrandomized	5 CNS infections	Colistin	2.5-5 mg/kg/day iv divided in 3 doses	80%
Jiménez-Mejias et al., 2000 [180]	Case report	1 meningitis	Colistin	5 mg/kg/day iv in 3 doses	Yes
Jiménez-Mejias et al., 2002 [179]	Case report	1 meningitis	Colistin	5 mg/kg/day iv in 4 doses	Yes
Levin et al., 2003 [119]	Prospective nonrandomized	2 CNS infections	Ampicillin-sulbactam	6 g/day in 3 doses	None
Jimenez-Mejias et al., 1997 [121]	Retrospective	8 postsurgical meningitis	Ampicillin-sulbactam	2 g/iv/6-8 h	75%
Cawley et al., 2002 [172]	Case report	Meningitis	Ampicillin-sulbactam	2 g/iv/3 h	Yes
Siegman-Igra et al., 1993 [150]	Retrospective	25 nosocomial meningitis	Various	Not reported	3 deaths
Nguyen et al., 1994 [171]	Retrospective	7 postsurgical meningitis	2 imipenem + amikacin 3 imipenem + amikacin + intrathecal aminoglycosides 2 others treatments	Not reported	86%
Benifla et al., 2004 [185]	Case report	1 postsurgical meningitis	Intrathecal colistin Ampicillin-sulbactam	40,000 IU/day	Yes
Gleeson et al., 2005 [186]	Case report	Postsurgical meningitis	Rifampicin Meropenem	600 mg/24 h Dose not reported	Yes
Vasen et al., 2000 [189]	Case report	Postsurgical meningitis	Intrathecal colistin	10 mg/24 h for 21 days	Yes
Karakitsos et al., 2006 [190]	Retrospective	Postsurgical meningitis	Ripampicin Colistin	10 mg/kg/12 h 10-20 mg/day	Yes
Al Shirawi et al., 2006 [191]	Case report	Postsurgical meningitis	Intravenous colistin Intrathecal colistin	No 3 mg/24 h	Yes
Bukhary et al. (2005) [192]	Case report	Postsurgical meningitis	Intravenous colistin	160 mg/6 h	Cure
Charra et al., 2005 [193]	Case report	Brain injury, postsurgical meningitis Intraventricular catheter	Intravenous colistin Intrathecal colisitin	No 5-10 mg/24 for 21 days	Cure
Fernández-Viladrich et al., 1999 [5]	2 Case report	Postsurgical meningitis	Intrathecal colistin Intravenous tobramicin	5 mg/12 h	Cure
Ho et al., 2007 [194]	Case report	Postsurgical meningitis	Intravenous colistin Intrathecal colistin	160 mg/6 h 1.6-6.4 mg/24 h	Cure
Ng et al., 2007 [195]	4 cases	Postsurgical meningitis	Intravenous colistin Intrathecal colistin	No 5-10 mg/12 h	Cure
Lopez- Álvarez et al., 2009 [152]	3 cases	Meningitis	Intravenous colistin Intrathecal colisitin	160 mg/8 h 5 mg/12 h	Cure
Rodriguez-Guardado et al., 2008 [101]	51 cases	Intraventricular catheters	Carbapenem [21] Ampicillin-sulbactam [4] Intravenous and intrathecal colistin [8] Carbapenems plus aminoglycosides [9]	Various 3 g/8 h 160 mg/8 h+10 mg/12 h Various	Cure 12/21 Cure 3 /4 Cure8/8 Cure 7/9

Table 59.3. **Main clinical studies on *A. baumannii* meningitis treatment.**

Colistin

The role of colistin in the treatment of meningitis was initially limited due to its poor CSF penetration (25% of serum levels) without modifications in the presence of meningeal inflammation [179]. However, it has been administered in isolated clinical cases by intrathecal and intravenous routes with good results [101,180]. It is the first-line treatment in multidrug-resistant *A. baumannii* strains [184]. Recent series described the cure of 8 cases of nosocomial meningitis at a dose of 225 mg/8 h by the intravenous route. However, the use of high doses of colistin increases the risk of nephrotoxicity [179,180,182]. Due to the suboptimal penetration of colistin through the blood-brain barrier [179], the drug is administered by the intraventricular or intrathecal route [101,111,63,183,184] or in combination with other antibacterial agents such as aminoglycosides [11,16,101,184].The dose of intrathecal colistin is generally 5 mg/12 h. In recent study the dose was 10 mg/12 h without increasing side effects [101]. In this review, all patients treated with intravenous and intrathecal colistin survived without evidence of local toxicity. Although the small number of cases studied limits the statistical significance of the results, the present data show that combined colistin by either route can be both safe and effective for this infection [101]. These findings support evidence that intravenous treatment alone should not be recommended. Recently, some cases have been successfully treated with intrathecal colistin alone, although at present there are few data to support such therapy. Treatment regimens for nosocomial meningitis that don't include intravenous colistin with intrathecal colistin should be considered suboptimal [101,163].

The duration of treatment is controversial, but it should be continued for at least 3 weeks after the withdrawal of foreign bodies or after two consecutive negative cultures.

Rifampicin

Rifampicin may be useful in combination with various other drugs used in meningitis treatment like colistin, ampicillin-sulbactam or carbapenems. It has in vitro synergy with colistin and its use could be considered as adjuvant treatment. However, intravenous rifampicin alone without other treatment is discouraged.

Tigecycline

New antibiotics include tigecycline, a member of a new class of antibiotics, the glycines. In animal studies of meningitis, tigecycline at a single dose of 20 mg/kg/day showed CSF concentrations >1 µg/ml 3 h after infusion. The CSF penetration of tigecycline is minimal, with concentrations of 0-15 µg/ml at 90 minutes after the administration of a dose of 100 mg far under the required MIC, so its use cannot be recommended [187], although an isolated cases of cure of meningitis with tigecycline have been described [188].

59.7.4 Empiric Treatment of Nosocomial Meningitis Due to *A. baumannii*

Nosocomial meningitis is an important cause of morbidity and mortality; it requires urgent and effective treatment, including antibiotic therapy and general supportive measures of the critically ill patient. Delay in the diagnosis and inadequate treatment are the most important factors of mortality. For this reason, in the early diagnosis of meningitis it is very important to perform complementary techniques and quickly initiate appropriate antimicrobial therapy to prevent worsening of the patient's condition.

Kind of risk	Therapy
If risk factors of *Acinetobacter* spp. infection: • Previous colonization or infection • Previous use of carbapenems or cephalosporins	Meropenen 2 g/8 h IV plus intrathecal amikacin 30 mg/day
If risk factors of carbapenems resistance: • Previous use of antibiotics (quinolones, carbapenems) • Admission to ICU • Mechanical ventilation • Previous surgery	Colistin 2-5 mg/kg/8 h plus intrathecal colistin with or without rifampicin 600 mg/24 h orally

Table 59.4. **Empirical treatment of** *A. baumannii* **nosocomial meningitis. Modified from [163].**

It is therefore recommended that in patients with suspected meningitis (and before administering antibiotics, except in selected cases as detailed below), blood samples and lumbar puncture (unless contraindicated) should be taken and sent to the microbiology laboratory for culture. If a CT of the head is required prior to lumbar puncture, this should not delay the delivery of treatment, so that blood cultures will be done and the appropriate therapeutic regimen initiated. Once the CT is obtained, if there are no contraindications, a lumbar puncture will be carried out. We recommend Gram staining of the CSF sample in suspected cases of nosocomial meningitis.

The aim of antibiotic treatment should be to achieve rapid sterilization of the CSF. Antibiotics should have rapid bactericidal activity, as bacteriostatic action is not enough to clear the infection and delayed sterilization of CSF has been associated with an increased incidence of neurological sequelae. It is essential that the antibiotic concentration in the CSF is greater than the minimum bactericidal concentration (MBC), and that the ratio between both concentrations (the bactericidal index) exceeds 1. Bactericidal activity in the CSF is optimal if the bactericidal rate is about 10. When the antibiotic does not reach the necessary concentration in the CSF through systemic administration, direct administration by the intraventricular or intrathecal route is necessary. The initial antibiotic dose must be maintained throughout the entire course of therapy without reducing the dose when the patient improves, since the penetration of the antibiotic across the blood-brain barrier normalizes as the CSF decreases. In nosocomial meningitis, empiric therapy should cover *P. aeruginosa* and *A. baumannii* and *Staphylococcus* spp., especially if an intraventricular catheter is present. Empirical treatment for nosocomial meningitis due to *A. baumannii* is illustrated in Table 59.4.

59.7.5 Definitive Treatment

Medical treatment alone is not considered the most appropriate at this time. The cure (or at least a prolonged remission of infection) occurs in approximately 25-40% of cases and mortality is high (24-53%), so this treatment option is not recommended in all cases. The combination of systemic and intrathecal antibiotics produces more efficient results, with remission rates of 75%; however, given the significant morbidity and mortality associated with this infection, the level of recommendation remains low, unless accompanied by withdrawal of foreign material.

Medical and Surgical Treatment

The use of intravenous and intrathecal antibiotics has cure rates of 40%, which increases to 70% if accompanied by withdrawal of an intraventricular catheter. It has been shown that catheter-related meningitis caused by *A. baumannii* is related to biofilm formation

[196]. There is universal agreement that the removal of foreign devices is critical to healing and one of the main factors influencing mortality. Hence, unless absolutely contraindicated, the removal of all shunt components should be advised. Depending on whether or not maintaining continuous CSF drainage is essential, the type of hydrocephalus that led to shunt insertion, and preferences of the surgical team, there are different treatment options:

- If the patient's condition requires a permanent shunt and the cause that led to the shunt was obstructive hydrocephalus, the following options can be chosen:
  - Externalization of the distal catheter to reduce intracranial hypertension and to drain the infected CSF. After 3-5 days of appropriate antibiotic therapy for sterilization of the ventricles, the rest of the system is withdrawn and an external ventricular drain is placed in the contralateral ventricle while continuing antibiotic treatment.
  - Removal of the infected catheter and insertion during the same surgical procedure of an external ventricular catheter on the contralateral side.
- If the patient needs permanent derivation and the cause that led to the shunt was a communicating hydrocephalus, we recommend entirely removing the infected system and placing a lumbar catheter for external CSF drainage.
- If the patient can remain without CSF drainage, at least temporarily, we recommend early removal of the infected catheter and appropriate antibiotic treatment. Once the infection has been cleared, or at least controlled with antibiotic treatment, a new system can be placed on the contralateral side.

The appropriate time for the final relocation of the shunt depends on the etiological agent of infection, initial response to antibiotic treatment, and removal of the infected system. To this end, the patient's progress should be monitored every 3 days by cytological analysis, biochemical and CSF culture. In infections caused by Gram-negative or mixed flora, we recommend a period at least 14 days. In brief, the recommendation for medico-surgical treatment is based on:

- Removal of foreign material.
- Removal of all system components at the start of treatment.
- An external device must be placed elsewhere. The new system will be placed in a permanent place at a second time.

59.7.6 Duration of Antibiotic Treatment and Indications for Lumbar Puncture Control

The duration of antimicrobial therapy should be individualized and based on clinical response. Furthermore, the recommended duration of antimicrobial therapy in many cases is not based on controlled studies (which is very difficult in this type of illness) and recommendations are often taken from various different studies. The general recommendation is to continue treatment for 21 days according to the IDSA guidelines or to maintain therapy until microbiological cultures test negative.

The optimal number of negative cultures to ensure clearance of infection is unknown, but treatment must usually continue until three consecutive negative cultures have been obtained. Intravenous therapy should be maintained until after completing intraventricular culture [197]. In noncarriers of intraventricular catheters a lumbar puncture should be done within 4 days of starting treatment and the treatment changed if cultures remain positive. A control culture should be obtained if there is no evidence of improvement at 72 hours of starting treatment.

59.7.7 Indications and Dosing Schedules of Intrathecal Antimicrobial Therapy

As previously discussed, intrathecal therapy seems essential in infections with *A. baumannii*. The usual dosage of the drugs most commonly used intraventricularly is shown in Table 59.5.

Antibiotic	mg/day
Gentamycin	5-10
Tobramicin	5-10
Amikacin	10-50
Colistin	10-20

Table 59.5. **Recommended daily intraventricular drug dose.**

Steroid Treatment

The benefit of adjunctive therapy with dexamethasone has been well established in meningitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* [198,199], although its role in Gram-negative meningitis is more controversial. However, many of these patients may require steroids for their underlying disease, and it should be borne in mind that whenever indicated the drug should be administered concomitantly or 15-20 minutes before antibiotic treatment.

59.7.8 Hospital-acquired/Ventilator-associated Pneumonia (VAP)

Pneumonia is the most common infection in ICUs, accounting for 31-47% of nosomial infections. Pneumonia develops in 8-28% of patients on mechanical ventilation and is responsible for more than 50% of antibiotic use in ICUs. Mortality rates vary from 20 to 70%, with a worse prognosis after inappropriate empirical therapy. It can also prolong the hospital stay from 6 to 30 days and represents a significant increase in hospital costs [200].

Acinetobacter spp. are a major cause of VAP and are associated with mortality rates of 50-70% [201] in some cases associated with inappropriate initial antibiotic therapy [202]. The incidence of the microorganism varies, but it is the second commonest etiological agent among the Gram-negative bacteria. Longer periods of hospitalization, longer time on mechanical ventilation, and prior use of antibiotics are the major factors that increase the risk of VAP due to *Acinetobacter* spp [203].

The occurrence of VAP due to *A. baumannii* sensitive only to colistin is associated with previous treatment with carbapenems [204], previous episodes of VAP, and prior antimicrobial therapy for >10 days [205,206]. It is necessary to differentiate between true infection and colonization to avoid introducing unnecessary treatments.

The agents with the greatest antimicrobial activity are imipenem/cilastatin, amikacin, colistin, ampicillin/sulbactam and tigecycline. Treatment with imipenem is considered the treatment of choice in carbapenem-susceptible strains. However, the increase of strains resistant to carbapenems has promoted the use of alternative antibiotic treatments. As in the case of meningitis, prolonged infusion of meropenem 2 g/8 h for at least 3 hours seems to be associated with lower rates of resistance. An experimental study investigating the utility of combination treatment with amikacin showed that the combination of imipenem plus amikacin was inferior to imipenem alone with the imipenem-susceptible strain, despite their in-vitro synergy, and was inferior to amikacin alone with the imipenem-resistant strain. The combined use of imipenem with amikacin was less efficacious than monotherapy, probably because of a drug-drug interaction that resulted in decreased pharmacokinetic and pharmacodynamic parameters for both antimicrobial agents. Further studies assessed prospectively or retrospectively treatment

with colistin in patients with VAP caused by *A baumannii* [94,98,100]. Specifically, no difference in clinical response was reported between patients treated with intravenous colistin for infections caused by organisms susceptible only to polymyxins and those treated with other agents, mainly carbapenems, for infections caused by carbapenem-susceptible organisms.

Colistin may also be administered by inhalation. The dose of aerosolized colistin may range between 500,000 IU every 12 h and 2,000,000 IU every 8 h. Several studies have reported favourable clinical outcomes with the use of aerosolized colistin along with intravenous colistin or other parenteral antimicrobial agents for nosocomial pneumonia caused by multidrug-resistant *A baumannii* [100,204]. In a recent study involving 60 critically ill patients who received aerosolized colistin (2,000,000 IU) over 16 days in concomitant intravenous treatment with colistin or other antimicrobial agents, bacteriological and clinical response of VAP was observed in 83.3% patients. No adverse effects related to inhaled colistin were recorded. Aerosolized colistin may be considered as an adjunct to intravenous treatment in patients with VAP due to multidrug resistant, Gram-negative bacteria susceptible to colistin in critically ill patients [205,206]. Data on patients treated with inhaled colistin are scarce. In a recent study by Falagas et al., 4 of 5 patients treated with inhaled colistin showed healing and one died. Although the results are promising, a greater number of cases are needed to assess its future role [207].

The efficacy and safety of ampicillin-sulbactam for VAP caused by multidrug resistant *A. baumannii* have been evaluated in a few reports, with a clinical improvement of 67% [120]. High-dose ampicillin/sulbactam was comparably safe and effective with respect to colistin in critically ill patients with multidrug resistant *A. baumannii* VAP [208].

The role of tigecycline alone or in combination with other antimicrobials for the treatment of VAP showed best clinical response (84%) in a small retrospective case series. However, 4 patients had clinical failure: 3 with VAP and 1 with VAP plus bacteraemia that developed resistance to tigecycline during therapy, and 3 patients with VAP had a recurrence of infection Tigecycline may be effective when used alone or in combination with other antimicrobials for VAP caused by multidrug resistant *A. baumannii*. However, the emergence of a resistant strain while one patient was receiving therapy raises concern [126,209].

The treatment of VAP caused by *A. baumannii* should be based on microbiological results; however, until these are obtained, appropriate empirical therapy should include two intravenous agents active against the most common local flora or an intravenous agent and one inhaled. The presence of *A. baumannii* susceptible only to colistin should be suspected in patients with VAP, previous antibiotic treatment in the 10 days preceding the new episode [210] and in this case the best option would probably be the use of systemic and inhaled colistin combined.

A very important issue in hospital-associated pneumonia (HAP) is its prevention. There is convincing evidence that specific interventions can be employed to prevent HAP/VAP. Evidence-based interventions focus on the prevention of aerodigestive tract colonization (avoidance of unnecessary antibiotics and stress ulcer prophylaxis, use of sucralfate for stress ulcer prophylaxis, chlorhexidine oral rinse, selective digestive decontamination, short-course parenteral prophylactic antibiotics in high-risk patients) and the prevention of aspiration of contaminated secretions (preferred oral intubation, appropriate ICU staffing, avoidance of tracheal intubation with the use of mask ventilation, application of weaning protocols, and optimal use of sedation to shorten the duration of mechanical ventilation, semirecumbent positioning, minimization of gastric distension, subglottic suctioning, avoidance of ventilator circuit changes/manipulation, routine drainage of ventilator circuit condensate) [211].

59.7.9 Bloodstream Infections

Bacteraemia, followed by respiratory tract and surgical wound infections, is the most significant infection caused by *A. baumannii* [212]. The known risk factors for *A. baumannii* bacteraemia are previous colonization with *A. baumannii*, invasive procedures, and the use of broad-spectrum antimicrobials. Other risk factors are immunosuppression and mechanical ventilation [213,214]. Consequently, episodes of bacteraemia due to *A. baumannii* occur most frequently in critically ill patients admitted to an ICU [201]. The clinical manifestations of bacteraemia caused by *A. baumannii* are not specific. The most common sources of bacteraemia are intravascular catheters and the respiratory tract [215-217]. *A. baumannii* bacteraemia is associated with a high crude mortality rate, but it is difficult to distinguish morbidity and mortality attributable to *A. baumannii* from that attributable to the common and severe co-morbidity in these patients. The risk factors associated with higher mortality are: presence of inappropriate antimicrobial treatment, age >65 years, development of septic shock, and severity of the underlying disease [218-221].
Generally, imipenem is the most active agent against *A. baumannii*. However, the description of imipenem-resistant *A. baumannii* strains is becoming increasingly common. Among the different antimicrobial regimens prescribed, the combination of a carbapenem and ampicillin-sulbactam was associated with a better outcome than the combination of a carbapenem and amikacin, or a carbapenem alone. Colistin has shown efficacy in bacteraemia, unlike the resistance to tigecycline described during treatment [222-225].

59.8 Infection Control and Prevention

Several studies have indicated that colonization with multidrug-resistant Gram-negative bacilli is a frequent precursor of true infection. Specific sites of colonization may be amenable to eradication strategies. Hand colonization contributes significantly to *Acinetobacter* transmission and can be controlled by proper handwashing, glove use, and use of antiseptic- or alcohol-based soaps [226]. The duration of colonization is controversial but important because it is crucial to decide the time of isolation of patients, the potential transmission time, and other steps to follow. The duration of colonization is unknown but it should be considered that isolation is no longer necessary after three consecutive negative cultures obtained 1 week apart. It is also important to consider the number of patients colonized at any given time. The greater the number of patients colonized, the greater the risk of transmission between patients, increasing both environmental pollution and health personnel [226].
The digestive tract has only rarely been implicated as a major site for *Acinetobacter* colonization [227,228]. If this is documented during an outbreak, selective decolonization with polymyxin B or aminoglycosides could be attempted [229].
The strategies for infection control and prevention of outbreaks caused by multiresistant *A. baumanii* need to be simultaneous and multiple to be useful. Identification of colonized and infected patients, combined with implementation of infection control measures such as hand hygiene and contact isolation precautions might help prevent transmission of this organism within medical facilities. These strategies have included [230-234]:

- Institute active surveillance of groin, axillary, and/or wound cultures for *A. baumannii* in all patients.
- Use contact precautions for colonized or infected patients.

- Increase the availability and use of alcohol-based hand rubs, with daily review of antibiotic susceptibility of all clinical isolates.
- Select cefepime or carbapenem-resistant isolates.
- Review patient records prospectively to determine geographic location, nosocomial acquisition, and presence of clinical infection.
- Emphasize contact precautions to prevent transmission of isolates.
- Assign a dedicated infection-control nurse to affected area or areas.
- Use polymyxin B to selectively decontaminate colonized wounds.
- Consider inhaled polymyxin B for pulmonary colonization or infection (to supplement parenteral therapy).
- Use surveillance techniques to monitor personnel, equipment, and environmental contamination.
- Instruct housekeeping staff to decontaminate the inanimate environment on a regular schedule.
- Close the contaminated unit if necessary.
- Use molecular epidemiologic techniques to determine clonality of isolates.

59.9 Conclusion

- *A. baumannii* is an increasingly important emerging pathogen associated with significant morbidity and mortality. The increasing rate of resistance has made its treatment difficult, especially in neurosurgical infections.
- *A. baumannii* infections are of growing importance in neurosurgical ICUs not only because of the occurrence of nosocomial meningitis but also because of other infections such as ventilator-associated pneumonia or bacteraemia.
- There are several factors that maintain the presence of *Acinetobacter* spp. in the healthcare environment, including the presence of susceptible patients or health workers colonized or infected by the organism. *Acinetobacter* spp. can colonize the skin, wounds, and the respiratory and gastrointestinal tracts. Over 25% of healthy adults have cutaneous colonization and 7% of adults and children have transient bacterial colonization. Gram-negative bacillus is most frequently isolated from the skin of healthcare workers and colonizes 45% of tracheotomised patients and 41% of stool samples from ICU patients. Differentiating between colonization and infection is of particular clinical and therapeutic relevance in view of the multidrug resistance of this organism and the limited therapeutic options available.
- Both imipenem and meropenem have been considered as the treatment of choice for serious infections due to *A. baumannii*. Doripenem is a new carbapenem which may have an important role in the treatment of *Acinetobacter* infection, and its MIC is lower than that of ertapenem or imipenem against *Acinetobacter* spp. However, meropenem is the only suitable drug for the treatment of meningitis.
- Colistin is a polymyxin and is available in two forms, colistin sulphate and sodium colistimethate. The usual dose is 2.5-5 mg/kg/day divided into 2 to 4 doses. In patients with >60 kg body weight, the most commonly used dose is 80-160 mg/8 h, taking into account that dose adjustment in renal insufficiency is required.
- Colistin is useful alone or in combination with other antibiotics such as rifampicin in ventilator-associated pneumonia, meningitis, bacteraemia, and so on. The most common side effects are nephrotoxicity and polyneuropathy.
- Tigecycline may be useful in ventilator-associated pneumonia but currently cannot be recommended as empirical or direct treatment or in bacteraemia and postsurgi-

cal meningitis, given the low levels reached in the blood and CSF. Patients receiving tigecycline as treatment for *A. baumannii* should be monitored for the clinical development of resistance and isolates should be checked by testing for microbiological resistance.

- Nosocomial meningitis caused by *A. baumannii* is associated with the presence of intraventricular catheters, CSF fistula or head injury. It is a serious problem in the neurosurgical ICU, especially in patients with intraventricular catheters.
- Nonspecific clinical and laboratory data should be integrated with Gram stain and culture in patients with fever of unknown origin, intraventricular catheter carriers, or those admitted to the neurosurgical ICU.
- Mortality is associated with the absence of foreign material removal and delays in the institution of proper treatment; therefore, early removal of intraventricular catheters with adequate empirical therapy are essential for the survival of patients.
- The duration of treatment should be at least 3 weeks after the removal of foreign material or after two consecutive negative cultures.
- The recommended treatment is medico-surgical and is based on the use of meropenem 2 g/8 h by infusion for least 3 h in strains sensitive to carbapenems or intravenous and intrathecal colistin or strains with suspected resistance to carbapenems. Antibiotic treatment should always be accompanied by the removal of foreign material. If required, an external device should be placed elsewhere. A new system should be placed at a later time.

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60 Multiple Organ Dysfunction in Patients With Brain Injury

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60.1 Introduction

Like any other critically patient in intensive care, patients with severe head trauma are at risk of developing multiple organ dysfunctions. Despite being common, the interactions between neurological disorders and non-organic neurological disorders are not completely certain. It is known, however, that the development of non-neurological organ dysfunction appears to be associated with adverse functional outcomes and higher mortality in both traumatic neurological injury and non-traumatic injury.

In a recent observational study, respiratory dysfunction was the most common dysfunction, occurring in 23% of patients with severe traumatic brain injuries (TBI), followed by cardiovascular dysfunction in 18%, and coagulation disorder in 4%. The development of a non-neurological organ dysfunction was independently associated with increased hospital mortality and worse functional outcome as assessed by the Glasgow Outcome Scale (GCS). Other studies found that the mortality of TBI patients appears to increase significantly when there is another associated organ dysfunction (65% vs. 17%).

In addition, extra-cerebral organ dysfunctions have been reported in severely ill neurological patients in the absence of other commonly associated risk factors such as systemic trauma, shock or infection. This indicates that the severe neurological injury can itself be a risk factor for the development of multiple organ dysfunctions.

Morevoer, several studies indicate that the inflammatory brain response can produce systemic immune and inflammatory changes and that this pro-inflammatory state characterizing TBI can have a significant role in the development of other organ dysfunctions.

Among the various organic dysfunctions that can occur in patients with severe TBI, we will discuss in more detail the pulmonary, cardiovascular and changes in coagulation because they are more directly related to the neurological event itself by how often that happens and the impact that they may have on the outcome of these patients.

60.2 Changes in Pulmonary Function

Among the various organic dysfunctions that can occur in a TBI patient, pulmonary complications are the most frequent, especially pulmonary infections and pulmonary edema. It is also unclear whether the pulmonary abnormalities are directly or indirectly caused by neurological damage and if the mechanisms involved change according to the neurological pathology. The clinical relevance of these complications was evaluated in a study which estimated that pulmonary changes are responsible for up to 50% of deaths after TBI.

- Bronchial aspiration
- Pulmonary infection
- Atelectasis
- Pulmonary edema (neurogenic, cardiogenic or inflammatory)
- Inflammatory mediators released by the brain (?)
- Massive release of catecholamines (sympathetic "storm")
- Pulmonary thromboembolism
- Central alteration of respiratory pattern
- Adverse effects of treatment for "neuroprotection"
- Adverse effects of treatments for control of intracranial hypertension

Table 60.1. **Possible mechanisms involved in pulmonary alterations in neurological patients.**

Several mechanisms are involved in the respiratory failure of patients with TBI (Table 60.1). Brain damage may also increase pulmonary vulnerability to mechanical ventilation injury or to ischemia and reperfusion. These mechanisms, associated or not, usually culminate in changes in ventilation-perfusion and consequent hypoxia.

The development of neurogenic pulmonary edema is a recognized complication and probably frequent among severe acute brain injuries, but underdiagnosed. Its pathophysiology is unknown but believed to involve a massive discharge of catecholamines, leading to a consequent hypertensive crisis and increased inflammatory response and resulting in increased pulmonary capillary permeability. Experimental and clinical studies have observed that the mere elevation of intracranial pressure (ICP), even without significant hemodynamic changes, increases the protein content in the lung's lymph. Experimentally, neurogenic pulmonary edema can be prevented with prior use of alpha-adrenergic blockers, which favours this hypothesis. Neurogenic pulmonary edema usually appears suddenly and very quickly (minutes or hours) after injury of the central nervous system, although there are reports of later onset. Another clinically relevant aspect is that neurogenic pulmonary edema is often confused with pulmonary edema caused by fluid overload, acute respiratory distress syndrome or aspiration pneumonia. It is likely that non-serious forms with fewer manifestations ("subclinical") are very common, while severe neurogenic pulmonary edema is rarer. The diagnosis should be made by history and exclusion of other causes since there are no specific tests for it.

The real impact of neurogenic pulmonary edema on the morbidity and mortality in severe neurological patients is unknown. The fact that this complication usually occurs in severe cases makes it difficult to evaluate their influence on the final results. It is known, however, that hypotension, low cardiac output and hypoxemia are determinants of secondary brain injury, with consequent worsening of morbidity and mortality. Treatment is supportive, with mechanical ventilation in severe cases. The use of positive end-expiratory pressure (PEEP) may be beneficial, but ICP must be monitored. The use of vasodilators, inotropes and diuretics is controversial.

Table 60.2 lists the risk factors of ventilator-associated pneumonia (VAP) in severe neurological patients. In TBI patients the incidence of VAP is estimated to be 30-50% and most of these infections are not serious. However, it is important to note that some studies have shown that the early development of pneumonia in neurological patients significantly increases mortality even after adjusting for the severity of neurological pathologies and co-morbidities.

- Altered level of consciousness
- Bronchial aspiration
- Emergency tracheal Intubation
- Deep and prolonged sedation
- Prolonged mechanical ventilation
- Re-intubation
- Previous use of antibiotics (?)
- Immunosuppression (?)

Table 60.2. **Risk factors of ventilator-associated pneumonia in TBI patients.**

The most commonly isolated agent in VAP during the first week (early onset) is *Staphylococcus aureus*. In such cases, the

upper airways seem to be subject for tracheobronchial colonization and therefore VAP. In cases of late-onset VAP, Gram-negative bacteria predominate and the possible sources of colonization would be not only the upper airways but also the stomach.

Although most available studies have been in stroke patients, the prevention of respiratory infections in neurological patients in general has been underscored as a strategy to improve prognosis. In TBI patients, measures are applied to prevent VAP used for all critical patients, especially protocols to reduce the time on mechanical ventilation, reduction of atelectasis and lung collapse. The use of early tracheotomy in the prevention of VAP is controversial, but it seems to favour a more rapid weaning from mechanical ventilation. It is important to note that the parameters commonly used for weaning from mechanical ventilation generally do not apply to TBI patients.

The use of prophylactic antibiotic therapy or selective decontamination to reduce the incidence of VAP in severe neurological patients is controversial. Although some studies have shown benefit, others did not show any effect or even a worsening in outcome with the use of these preventive strategies.

Development of the acute respiratory distress syndrome (ARDS) in TBI patients poses a major challenge because the hypoxemia resulting from the manoeuvres intended to improve it (e.g., increase in PEEP, alveolar recruitment or permissive hypercapnia) may aggravate brain injury.

The impact of PEEP on ICP is not linear and is often unpredictable. There are evidences that the impact of PEEP on ICP is related more to variations in $PaCO_2$ and pulmonary compliance than with the PEEP value itself. Several studies have shown that values of up to 15 cmH_2O of PEEP do not cause significant changes in ICP or cerebral perfusion pressure (CPP). Lung recruitment manoeuvres using pressures up to 60 cmH_2O were associated with worsening hemodynamics and cerebral oxygenation. Also during bronchoscopy in patients with severe TBI it has been shown that major changes occur in ICP and CPP, although transitory, and that the use of intra-tracheal lidocaine did not abolish these effects.

Thus, there is a linear correlation between PEEP and ICP. ICP monitoring in all patients with severe TBI and respiratory failure is recommended, which may be necessary in the use of PEEP >8-10 cmH_2O. Special care should be taken with the use of alveolar recruitment manoeuvres or bronchoscopy.

Furthermore, there is evidence that patients ventilated without PEEP show progressive deterioration of lung compliance. Thus, we have routinely used PEEP of around 8-10 cmH_2O for all serious neurological patients. This strategy seems to be beneficial for preventing progressive lung collapse without causing significant negative effects on cerebral hemodynamics. Although it is essential to avoid hypovolemia and hypotension in severe neurological patients, it is also essential to avoid fluid overload, especially in patients with ARDS. In cases where there is a deterioration in lung function, one should not delay the use of measures to reduce the total volume of fluid infused or the use of diuretics in patients who are hemodynamically stable.

However, not only does brain injury impact on the lungs, but also severe lung injury has an impact on the brain. Recent studies have shown that patients who were on mechanical ventilation, especially those with ARDS, were noted to have cognitive dysfunction that resembles cases of mild dementia and that persist for several years after discharge. The pathophysiology of these cognitive changes is unclear but probably has multiple etiologies such as hypoxemia, hypotension, delirium and sepsis, among other factors.

The incidence of deep vein thrombosis (DVT) in trauma patients varies from 6 to 58% and several studies have identified severe TBI as an independent risk factor for DVT. A recent study evaluating 2000 TBI patients showed that they are 3 to 4 times more likely to develop DVT. However, there is no consensus on strategies for DVT prophylaxis in head-

injured patients nor has its impact on the outcome of these patients been determined. The possible mechanisms involved in an increased risk for DVT include: immobilization, activation of the extrinsic coagulation pathway, elevated levels of circulating tissue factor, and high levels of von Willebrand factor.

60.3 Cardiovascular Dysfunction

Serious injury of the central nervous system can trigger important cardiocirculatory changes, even in patients without previous heart disease. Such changes may increase cardiac morbidity and mortality not only by damaging the heart itself but also by secondary brain damage that may occur as a result of reduced cerebral perfusion. Although the true incidence of these complications is not known, it is known that they can hap-

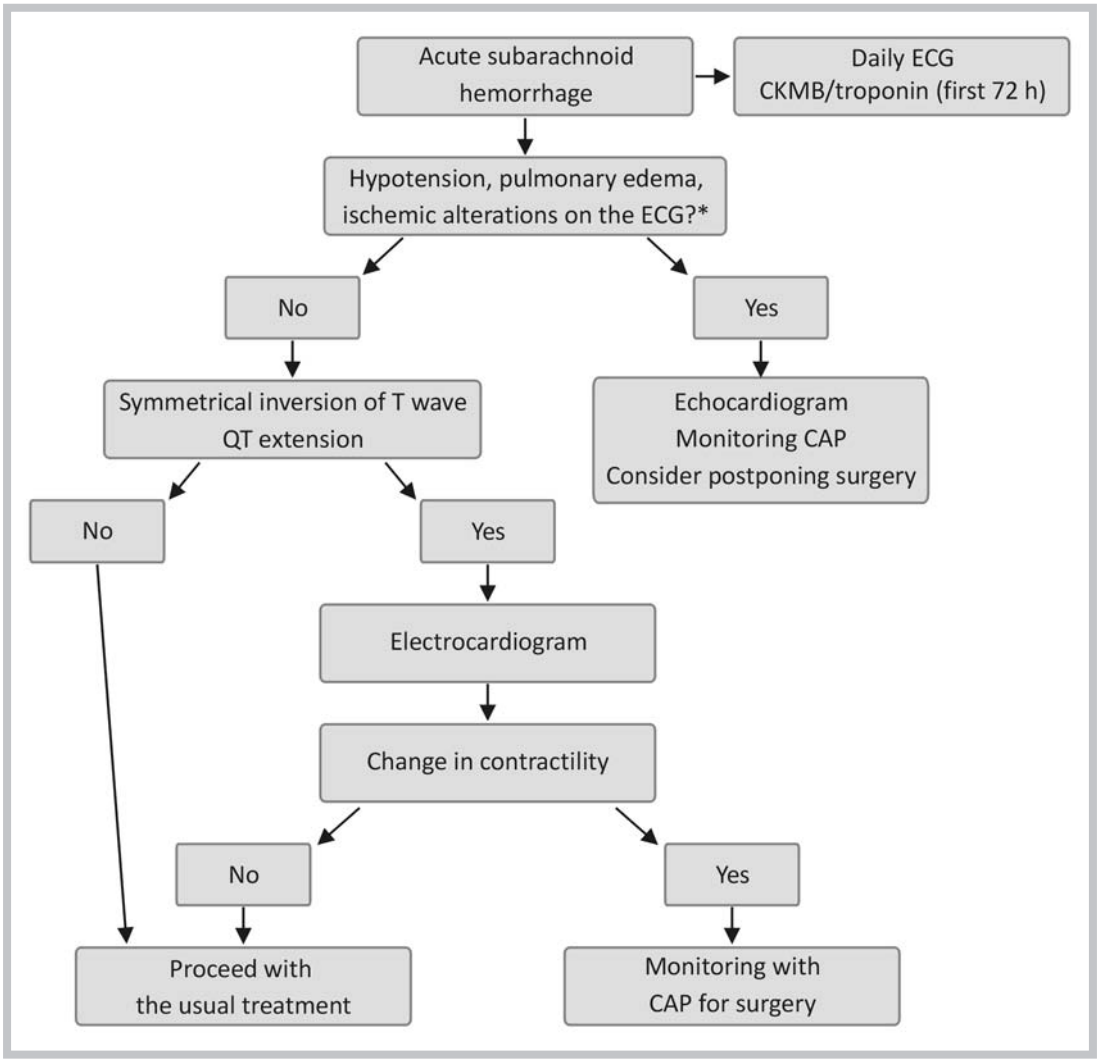

Figure 60.1 **Algorithm for the diagnosis of left ventricular dysfunction in severe neurological patients. Modified from [Mayer, 1995].**

*Q waves, ST elevation or other changes diagnostic of acute ischemia

pen in any severe acute neurological condition, especially in cases of subarachnoid hemorrhage. Cardiovascular complications secondary to neurological events are usually divided into cardiac arrhythmias, myocardial ischemia, neurogenic pulmonary edema and hypertension.

Cardiac arrhythmias are the most frequent. However, these rhythm changes are not always purely electrical phenomena and many patients have evidence of myocardial damage and structural enzyme elevation (4-25% of cases), changes in global and segmental myocardial contractility on the echocardiogram ("stunned myocardium") and myocardial necrosis in clinical pathology. Echocardiographic studies in patients with subarachnoid hemorrhage have demonstrated reversible changes in myocardial contractility and in almost all of them no pathology was detected on either coronary angiography or at autopsy studies. Myocardial lesions described in anatomopathological examination include: subendocardial and intramyocardial hemorrhage, myocardial necrosis, and myofibrillar degeneration. These changes were given different names such as myocytolysis, myofibrillar necrosis, myofibrillar degeneration, and necrosis in bands. They are distributed throughout the myocardium, more concentrated in the subendocardial region and often involve the conduction system.

A suggested algorithm for diagnosing changes in ventricular function in patients with subarachnoid hemorrhage can be used in other neurological patients who have severe hemodynamic instability or suspected cardiac dysfunction (Figure 60.1). Clinically, patients with alterations of myocardial contractility will also frequent present hemodynamic instability and pulmonary edema, supporting the concept that these lesions contribute to increased morbidity and mortality. Treatment is supportive only, with emphasis on the maintenance of cardiac debt and adequate pressure levels. In the presence of significant hemodynamic instability, one should consider the early use of invasive hemodynamic monitoring.

60.4 Coagulopathy

It is known that coagulopathy is associated with severe TBI, particularly penetrating injuries. It is also believed that the presence of coagulopathy worsens the prognosis of these patients, being an unfavourable outcome. However, the features, the pathophysiology, and the real incidence of coagulopathy associated with severe TBI are not fully understood. Some studies showed an initial state of hypercoagulability, followed by a state of increased fibrinolysis or disseminated intravascular coagulation. This last possibility could predispose or aggravate a multiple organ failure.

A recent study evaluating 436 patients with severe TBI noted coagulopathy associated in 36% of cases, being more frequent in the more severe cases and penetrating injuries. This study also showed that this combination significantly increases mortality. What complicates the analysis of studies on coagulopathy associated with severe TBI is the lack of consistency in diagnostic criteria for coagulopathy, whether they are clinical, laboratory, or temporal. Besides, it is unclear whether correction of coagulation abnormalities improves the outcome of these patients.

60.5 Key Concepts

Non-neurological organ dysfunction is common in patients with severe TBI and is independently associated with worse functional outcome and higher mortality.

Pulmonary dysfunctions are more common in TBI patients, occurring in 25-50% of patients. The etiology of these changes is multifactorial, which complicates specific preventive strategies.

The impact of PEEP on ICP is not linear and is unpredictable. Generally, PEEP up to 15 cmH_2O does not cause significant changes in ICP. However, ICP monitoring is recommended in all cases of severe TBI in which PEEP >8-10 cmH_2O may be necessary.

Cardiovascular disorders are also frequent and, especially when triggered states of low cardiac output have a significant impact on morbidity and mortality.

Although the pathophysiology of coagulation disorders associated with TBI is not fully understood, it is well recognized that these changes are indicators of an unfavourable outcome.

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61 Tetanus and Botulism: Intensive Care Management

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61.1 Introduction

Tetanus and botulism are infectious, non-contagious diseases caused by neurotoxins produced by anaerobic bacteria *Clostridium tetani* and *Clostridium botulinum*. These neurotoxins are highly neurotropic and are among the most violent and powerful toxins known. Tetanus is characterized by spastic paralysis due to blockage of inhibitory circuits in the spinal cord, while botulism is characterized by flaccid paralysis due to inhibition of the release of acetylcholine at the neuromuscular junction. Both conditions are associated with high mortality and rapid progression to severe forms, and should therefore be treated in intensive care units (ICUs), preferably in reference services.

61.2 Development

Tetanus results from contamination of a wound by *Clostridium tetani* spores that, under anaerobic conditions, convert to the vegetative form and thus can multiply, producing tetanospasmin. The toxin initially circulates through the bloodstream before migrating over hours or days by motor nerve fibres to the central nervous system (motor neurons of the spinal or cranial nerve nuclei), blocking the inhibitory interneurons of Rushaw and allowing stimulation of the lower motor neurons by impulses coming from the brain and sensory regions. The result is spasticity and muscle spasms. Manifestations of hyperexcitability are due to the action of tetanospasmin which increases acetylcholine release and decreases the levels of glycine.

In botulism the toxin absorbed in the gastrointestinal tract or in a wound spreads via hematogenous route to the nerve endings, more specifically the presynaptic membrane of the neuromuscular junction, blocking the release of acetylcholine, resulting in flaccid paralysis. Botulinum toxin most often it is ingested in food contaminated by *Clostridium botulinum*, although in special situations, the toxin can be produced after the ingestion of spores that germinate in the faeces or the contaminated wound under anaerobic conditions.

With tetanus the diagnosis is based exclusively on the clinical picture and history of injury and requires a high index of suspicion to identify the early signs and symptoms and disease progression. The diagnosis of botulism is based on the history and clinical picture and specific laboratory tests, although the early recognition of initial clinical manifestations, enabling immediate therapeutic intervention, is critical in the prognosis of the disease, especially when it is the index case of a foodborne outbreak.

Tetanus is characterized by the prolonged contraction and spasms of skeletal muscles. The generalized form of tetanus is the most common. Usually, the first clinical manifestation of tetanus is contracture of the muscles of mastication, which progresses to trismus (lockjaw). Dysphagia may also appear at the initial stage and is characterized by "choking" when the patient tries to swallow. Stiffness of the facial muscles causes accentuation of the natural creases of the face, twitching of the nostrils and lips (sardonic smile), wrinkled forehead, arching eyebrows, and closed eyelids, giving a characteristic expression known as *tetanic facies*. In this descending pattern of manifestations, the neck muscles are the next involved, with stiff neck, then the paravertebral muscles, the chest and the intercostal muscles, which can make breathing difficult. In this phase the most frequent complaint is neck and back pain. Stiffness may also involve the abdominal muscles and limbs. As the condition progresses, spasms can increase in intensity and duration and may be triggered by various stimuli (light, noise, urination, defecation, accumulation of bronchial secretions, etc.) or arise spontaneously. Paraspinal muscle spasm may cause crushing and fracture of vertebrae. The most serious signs of progress are dysfunctions of the autonomic nervous system: profuse sweating; fluctuations in blood pressure that can be rapidly followed by cardiovascular collapse, instability of the heart; ileus; and fluctuations in blood glucose levels. The patient remains lucid throughout the course of the illness. Fever is uncommon and usually occurs when there is secondary infection in the "gateway" or, more frequently in the respiratory tract. The incubation period (time between injury and appearance of the first symptom) is ≤10 days and the period of progression (time between the first symptom and the first spasm) ≤48 hours, the time elapsed between the occurrence of the first tetanus symptom and admission ≤36 hours and the occurrence of spasms in the first 24 hours of hospitalization are indicators of poor prognosis and may be useful to guide treatment choice. Before intensive care became available, mortality due to tetanus was caused by spasms of the glottis, aspiration and respiratory infection. Since the wider availability of intensive care, complications associated with disruption in the autonomous nervous system have become the leading causes of death. The course of the illness begins to decline 2 to 4 weeks after onset, initially with improved autonomic nervous system function, followed by cessation of spasms, and slow and gradual reduction of muscle contracture. Remission usually occurs within days or weeks.

The hallmark of botulism is descending flaccid paralysis that usually begins in the territory of cranial nerves and manifesting as blurred vision, unilateral or bilateral palpebral ptosis, difficulty converging the eyes, double vision and ophthalmoplegia, weakness of the mastication muscles, swallowing and speech, with consequent dysarthria and dysphasia. Muscle weakness may progress symmetrically to neck muscles, trunk and limbs, causing difficulty sustaining the neck, dyspnea, respiratory failure and flaccid quadriplegia. Autonomic nervous system dysfunction is characterized by dilated pupils and absence of photoreactivity, dry mouth, ileus, fluctuations in blood pressure and heart rate, sweating and urinary retention. As with tetanus, the patient with botulism retains clear senses and mental status during the course of the disease. In foodborne botulism, the most common form in adults, the intoxication results from the ingestion of botulinum toxin and can start with nausea, vomiting, diarrhoea and abdominal pain, with or without concomitant neurological symptoms. In wound botulism, as the toxin is produced and absorbed at the wound site, there is no gastrointestinal symptoms, but fever may occur. Intestinal botulism is more common in children and occurs after the ingestion of *Clostridium botulinum* that start toxin production. The initial symptoms are constipation and irritability, followed by neurological symptoms. In untreated cases, death can result from airway obstruction or respiratory failure. The disease can progress over 1-2 weeks and stabilize for more than 2 or 3 weeks. The recovery phase can be very slow in severe cases and last for several months.

Although the diagnosis of tetanus is exclusively clinical and epidemiological, with botulism the laboratory may have fundamental importance in confirmation of diagnosis, identify the type of toxin, and in some cases, isolate *Clostridium botulinum*, although the presence of the bacterium is not conclusive for diagnosis. The detection of toxin in serum or in the content of vomiting, gastric lavage and/or intestinal tract and faeces remains the standard method for diagnosis. Considering that this is a life-threatening intoxication and that early treatment can define therapeutic success, collecting and sending biological material for laboratory examination should be done as soon as possible, preferably within the first 7 days of illness and before the administration of antibotulinic serum. The most widely used diagnostic test is still the mouse bioassay, although a more rapid immunoassay for the detection of botulinum neurotoxin has recently been developed. Electromyography may be useful in identifying the location of involvement, the characteristic lesion being at the neuromuscular junction. Repetitive nerve stimulation shows an increase in the amplitude of the motor potential, and these changes disappear after clinical recovery.

The differential diagnosis for tetanus should include strychnine poisoning; bacterial meningitis; tetany due to hypocalcemia; rabies; hysteria; intoxication from metoclopramide and neuroleptics; inflammation of the mouth and pharynx that can be accompanied by trismus; peritonitis; neck stiffness due to acute cervical osteoarthritis; neck stiffness; septicaemic spondylitis; and seizures.

The differential diagnosis for botulism is with the Guillain-Barré and Müller Fisher syndromes, myasthenia gravis, stroke, central nervous system tumours and alcoholic coma.

Any case of botulism should be reported immediately to health authorities so that measures of investigation and containment of outbreaks can be promptly adopted. Even small outbreaks of foodborne botulism can precipitate a national emergency and overload the ICU.

61.3 Treatment

Because both are potentially life-threatening conditions with an unpredictable evolution, tetanus and botulism should be treated at an ICU, preferably with trained and qualified medical and nursing staff. In Pernambuco, Brazil, the centralization of care in the ICU with an experienced team specializing in the treatment of tetanus has resulted in a significant reduction in mortality.

The treatment of tetanus has the following objectives: neutralization of the toxin, elimination of focus, and symptomatic treatment.

61.3.1 Neutralization of the Toxin

Human anti-tetanus immunoglobulin (HTIG) is given intramuscularly (IM) at a dose of 1000 IU to 3000 IU, although Blake and Feldman (1976), in a retrospective study, found the same efficacy with 500 IU. HTIG should not be administered intravenously (IV). The anti-tetanus serum (ATS) can be used as a second choice at a dose from 10,000 to 20,000 IU IM or IV at any age. The administration of the ATS should be preceded by a skin sensitivity test. If the patient tests negative, promethazine is administered IM 15 minutes before injecting the serum. If the test is positive, ATS cannot be administered and HTIG is given.

A randomized clinical trial conducted by the authors of this chapter compared patients who received HTIG by intrathecal and intramuscular routes with a group treated with

HTIG intramuscularly. The group that received HTIG via intrathecal and IM benefited from a better response in relation to various criteria: better clinical outcome; shorter hospitalization time and fewer spasms; lower proportion of overall complications such as respiratory infection and need for artificial ventilation; shorter time on ventilation and lower mortality rate, although for this last variable the difference was not statistically significant. The HTIG was preservative-free, at a dose of 1000 IU, injected into the subarachnoid space by suboccipital or lumbar puncture. In a recent meta-analysis, Kabura et al. (2007) found the intrathecal administration of antitoxin was more beneficial than IM administration for the treatment of tetanus.

61.3.2 Elimination of Focus

The suspicious focus should be widely debrided to remove foreign bodies and necrotic tissue. Prior systemic administration of tetanus antitoxin is recommended. The wound should be cleaned with oxidant liquids such as hydrogen peroxide, potassium permanganate 1: 5000 or aqueous solution of iodine.
Antibiotic treatment can be done with metronidazole at a dose of 1-1.5 g day (15-30 mg/kg/day) divided into 3 parts (8/8 hours) or even a single dose/day for 7-10 days or crystalline G penicillin at a dose of 12-15 million IU/day (200,000 IU/kg/day) in equal fractions of 4/4 hours for 7-10 days. Other alternatives are clindamycin, ampicillin-sulbactam and erythromycin.

61.3.3 Symptomatic Treatment

Among muscle relaxants and sedatives, benzodiazepines, barbiturates and phenothiazines have been used more frequently. The diazepines are considered by most authors as the drug of choice as they have a sedative and relaxant action and are inexpensive. The initial dose is 10 mg IV at intervals ranging from 12/12 hours to 1/1 hour. Attention should be paid to the level of consciousness and respiratory depression, especially among the elderly. Doses should be adjusted according to the patient's response and severity of the case. The observed side effects are: behaviour disorders, diplopia, dizziness and ataxia. Cases of prolonged coma due to residual effect have been observed in tetanus treated with diazepines, especially among elderly patients. Chlorpromazine also has a sedative and relaxant action and can be combined with diazepines in severe cases (dose of 25 mg IV with a minimum interval of 6 hours). The most frequent side effects include tachycardia, pallor, hypotension, glucosuria, jaundice and sweating.
In cases of serious illness in which muscle spasms do not remit with high-dose muscle relaxants, pancuronium or vecuronium can be used. The use of neuromuscular blocking requires that the patient is mechanically ventilated and sedated. Pancuronium is most widely used because of its low cost and long half-life, at a dose of 0.1 mg/kg, which may be repeated up to 1/1 hour. In cases of severe cardiovascular instability, vecuronium is preferred due to its lack of cardiovascular side effects. Atracurium can also be an alternative, although it is more expensive and can cause cardiovascular instability.
There is no consensus on the most appropriate way to treat autonomic nervous system dysfunctions and most publications are based on case reports or small series. It is expected that an ideal treatment regimen will be effective in stabilizing the cardiovascular system, while preserving compensatory functions to prevent sudden death. In cases of severe, prolonged tachycardia, associated with consistently elevated blood pressure or blood pressure instability, morphine can be used at an initial dose of 5-10 mg 8/8 or even 4/4 hours, SC or IV. In more severe cases, the dose can vary from 240 to 2500 mg/

day or 0.01 to 0.1 mg/kg/minute with continuous infusion. However, when very high doses are needed, its use should be limited to short periods of time.

Thwaites et al. (2006), in a randomized and double-blind study testing the effect of magnesium sulphate in an IV solution for the control of spasms and autonomic nervous system dysfunction, observed a reduction in the need for verapamil to control the tachycardia associated with autonomic nervous system dysfunction.

A number of patients with tetanus will require tracheostomy during its clinical course, even though some may not require mechanical ventilation. Tracheostomy should preferably be performed before intubation, although orotracheal intubation is rarely used in patients with tetanus. The most frequent indications for tracheostomy include:

- Apnea attack.
- Dysphagia preventing the patient from swallowing saliva and/or expel secretions.
- Marked trismus obstructing the ability to swallowing saliva.
- Frequent and intense muscle spasms (neuromuscular blocking + mechanical ventilation).
- Signs of bronchoaspiration or “choking”.
- Lower respiratory tract infection/secretion in the lower airways.
- Pulmonary atelectasis.

Attention should be paid to the need for early tracheostomy in patients with clinically rapid progression or more indicators of severity: period of onset 48 hours; incubation period ≤10 days; time between symptom onset and hospital admission ≤36 hours; presence of spasms on admission or within 24 hours; and in the elderly. The early indication for tracheostomy may reduce the occurrence of aspiration and apnea and avoid the need for mechanical ventilation. The early indication also prevents an emergency procedure with a higher risk of complications.

Outcomes after botulism treatment are directly related to early diagnosis and site conditions. Treatment should be performed in a hospital with an ICU and supported by two sets of actions: supportive care and specific treatment.

The general measures of cardiorespiratory support and monitoring are the mainstays in the treatment of botulism. Respiratory care is essential and respiratory failure may occur early, owing to impairment of swallowing, obstruction by viscous mucus or the progression of muscle paralysis. Also, cardiac monitoring is essential, since in severe forms of the disease autonomic nervous system dysfunction is frequent. Critically sick patients may need a neurologist, infectivologist, cardiologist, pulmonologist and intensivist, as well as rehabilitation specialists.

Specific treatment relies on heterologous antitoxin to neutralize the circulating toxin that has not yet reached the nerve endings. The decision to administer antitoxin must be based on clinical findings, history and physical examination but should not be delayed while awaiting laboratory tests results, as this is the only specific treatment and its early use is essential. On the other hand, its indication should be carefully weighed because it is not devoid of risk, as some patients are hypersensitive to the serum of other animals. The serum may be specific to the toxin subtype or polyvalent (combination of 2-4 antitoxins A, B, E and F). Each country has its own system of distribution of botulinum antitoxin to reference units. The dose is one ampoule intravenously diluted in 0.9% saline at a ratio of 1:10 and infused approximately over 1 hour. All biological material for testing should be collected before administrating the antitoxin. In a large outbreak of foodborne botulism in Thailand, botulinum antitoxin was given to some patients on the fourth day of illness and to others on the sixth day, with an inadvertent 2-day delay due to a temporary unavailability of the serum in the country. There was a statistically significant difference between the two groups in the duration of mechanical ventilation and time to extubation, favouring the group that had received the antitoxin earlier.

In cases of foodborne and intestinal botulism, there is no indication for antibiotic treatment because its use can increase the release of toxins into the intestinal lumen. In wound botulism, antibiotic therapy can be given with crystalline penicillin (10-20 million IU/day IV in divided doses of 4/4 hours) or metronidazole (2 g/day IV, 6/6 hours for 7-10 days). Antibiotic therapy for other infections that may occur during the course of the disease should be selected cautiously when using aminoglycosides and tetracyclines, because they can potentiate the neuromuscular blockade by reducing the entry of calcium into the neuron.

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62 Neurological Complications of HIV

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62.1 Introduction

HIV and AIDS cause significant morbidity and mortality worldwide, including Latin America. In 2007, estimates of adult HIV prevalence rates in Latin American ranged from 0.2 in Bolivia to 2.5 in Guyana. While the incidence of many neurological complications of HIV has decreased with potent antiviral therapy (ART), central nervous system (CNS) complications remain a significant burden. This is due to poor compliance, lack of access to medications, viral resistance, immune dysregulation despite viral control, and changing patterns of illness. The neurological intensivist must be able to diagnose and manage the varied CNS manifestations of HIV.

The first step is to consider the possibility of or recognize the existence of underlying HIV as a factor in the patient's presentation. Because the differential is so broad in someone with advanced HIV, the neurological ICU patient's HIV status should be routinely assessed. Once a patient tests positive for HIV, the level of immunosuppression should be quantified with viral load and T cell subsets. Those patients with CD4 counts >500 cells/µl for the most part carry the same risks as non-HIV infected patients. Those with mild reductions in CD4 counts to 200-500 cells/µl have an increased risk for tuberculosis, syphilis, varicella zoster, and cognitive impairment.

Most of the severe neurological complications of HIV occur at CD4 counts <200 cells/µl. In patients with a marked virologic and/or immunologic response to ART (precipitous drop in HIV viral load or in-

Focal brain lesions	With mass effect: • Toxoplasma • Primary CNS lymphoma • PML immune reconstitution inflammatory syndrome • Tuberculoma • Fungal abscess • Neurocysticercosis • Pyogenic abscess
	Without mass effect: • PML • HIV-associated stroke • HIV-associated dementia
Diffuse brain lesions	• HIV meningoencephalitis • Post-infectious encephalomyelitis • CMV encephalitis • VZV encephalitis • Neurosyphilis • Neurodegenerative diseases
Meningitis	• Cryptococcal • HIV • Coccidioidal • Tuberculous • Neurosyphilis • HSV-2 • VZV • Pyogenic • Neoplastic
Myeloradiculitis	• HIV vacuolar myelopathy • CMV myeloradiculitis • HTLV-1 myelopathy • Neurosyphilis myelitis • Tuberculous myelitis • VZV myelitis • HSV-2 myeloradiculitis • Toxoplasma myelitis • Epidural lymphoma • Subac. combined degeneration (B12 defic.)

Table 62.1. Central nervous system complications of HIV.

crease in CD4 cell counts), previously asymptomatic or successfully treated neurological infections may worsen due to an exuberant immune response to residual infectious antigens. This immune reconstitution inflammatory syndrome (IRIS) can cause atypical presentations of neurologic disease.

As with any neurological disease process, the initial step is to localize the disease within the nervous system. HIV and the opportunistic infections associated with it can affect virtually any part of the central (Table 62.1) or peripheral nervous system (Table 62.2). Furthermore, more than one process may be active simultaneously, which can be challenging for localization. For the purposes of this chapter, the most important complications will be reviewed with a view to the neuro-ICU practitioner.

Neuropathy	• HIV distal symmetric polyneuropathy • Antiretroviral drug toxic polyneuropathy • Acute inflammatory demyelinating polyneuropathy • Chronic inflammatory demyelinating polyneuropathy • Mononeuritis multiplex (HIV, CMV, VZV, HBV, HCV) • Diffuse infiltrative lymphocytosis syndrome
Myopathy	• HIV myopathy (polymyositis) • Zidovudine myopathy • Pyogenic myositis • Toxoplasma myositis
Other	• HIV-associated neuromuscular weakness syndrome (lactic acidosis)

Table 62.2. **Peripheral nervous system complications of HIV.**

62.2 Focal Brain Lesions

The most common causes of focal brain lesions specific to HIV+ patients are toxoplasma encephalitis (TE), primary CNS lymphoma (PCNSL), and progressive multifocal encephalopathy (PML). In two large series from the United States and Italy, among those HIV patients in whom diagnosis was confirmed, approximately 45% were due to TE, 30% to PCNSL, 20% to PML, and the remainder to other causes, including tuberculous and fungal infection. In certain parts of the world including Latin America, tuberculoma is not an infrequent cause, with an increased incidence of tuberculosis co-infection with HIV. In one study from South Africa, tuberculosis was the most common cause of focal brain lesion in patients with HIV. Patients who are also intravenous (IV) drug users are also at higher risk of pyogenic abscess with typical organisms, as well as mycotic abscess. While the incidence is not increased in HIV patients, neurocysticercosis (NCC) remains an important infectious cause of focal brain lesions in Latin America and should be considered in all patients with cystic brain lesions regardless of their HIV status. HIV may be associated with stroke, either directly (through a large vessel vasculopathy) or due to opportunistic organisms causing infectious vasculitis. Hence, HIV should be considered in the differential diagnosis of stroke in young patients. The clinical syndrome, radiographic appearance, serological and DNA studies, and – in the case of TE – response to treatment, can help to distinguish the three most common HIV-specific causes of focal brain lesions.

TE is caused by the intracellular protozoan parasite *Toxoplasma gondii* which may be transmitted by ingestion of food or water contaminated with the faeces of infected cats or by ingestion of infested undercooked pork and lamb. Once infected, humans carry the parasite in cyst form for life, with reactivation occurring in the setting of immunosuppression, usually with CD4 counts <100 cells/µl. Toxoplasma is found worldwide but certain areas, including Latin America, have increased seroprevalence. In certain parts of Brazil, antibodies to *T. gondii* are found in up to 80% of adults. TE tends to present acute-

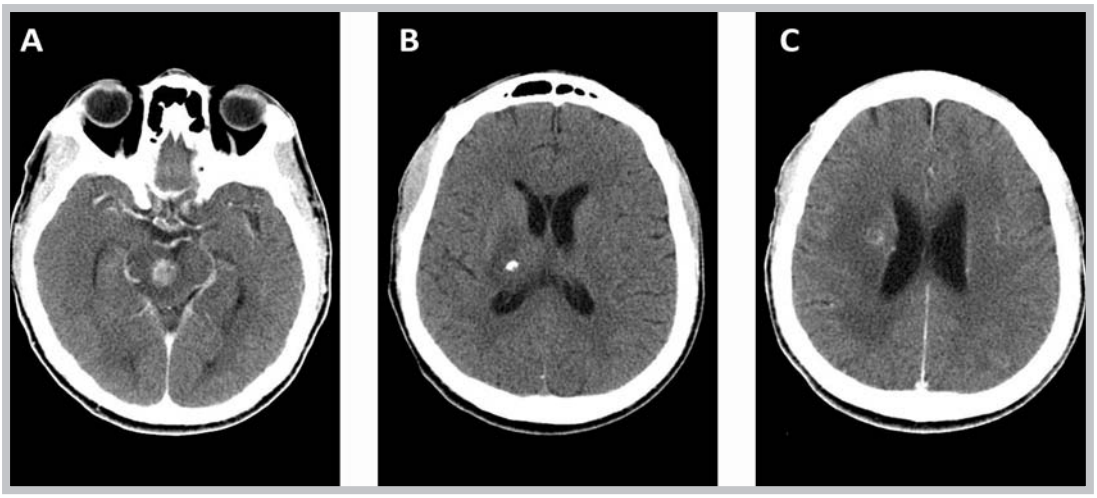

Figure 62.1. CT with contrast, showing hypodensity in the right cerebral peduncle and periventricular corona radiata with mild mass effect and patchy rim enhancement (A, C), as well as a hyperdense calcification in the right thalamus (B).

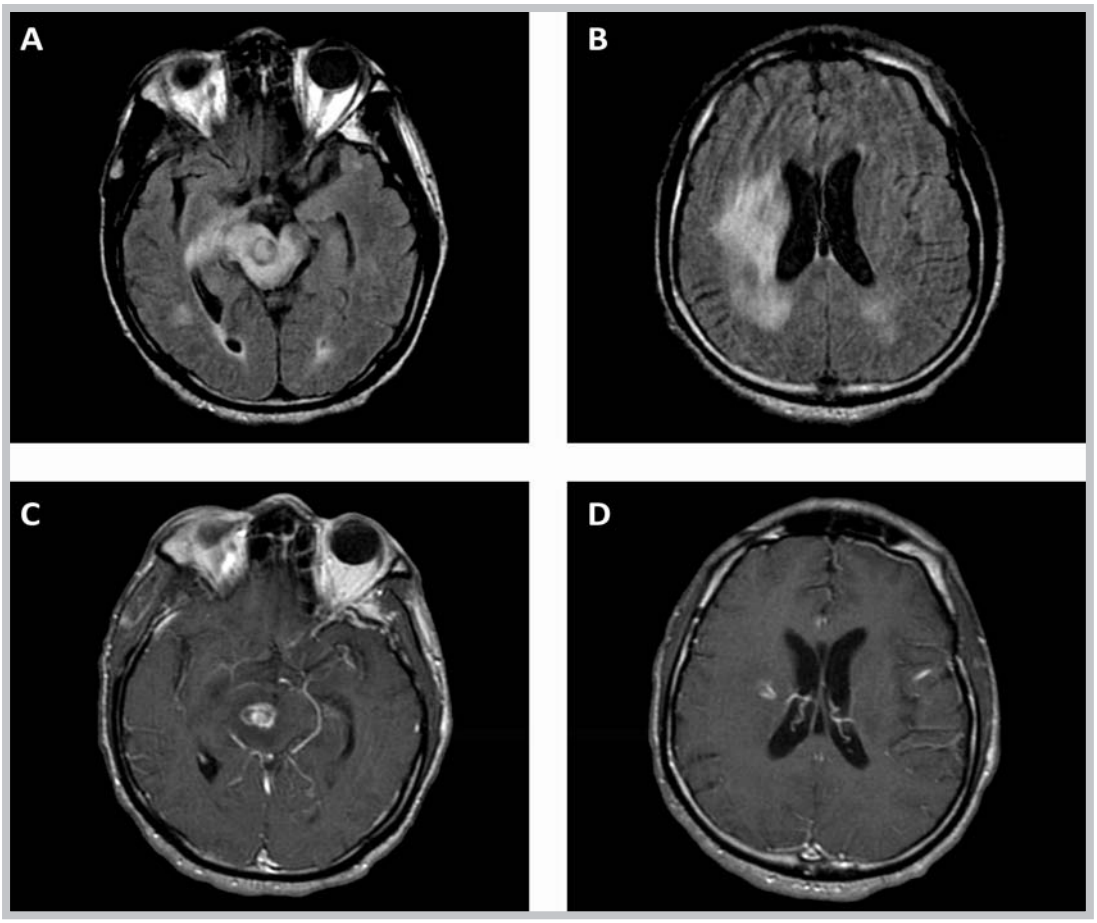

Figure 62.2. CT with contrast, showing hypodensity in the right cerebral peduncle and periventricular corona radiata with mild mass effect and patchy rim enhancement (A, C), as well as a hyperdense calcification in the right thalamus (B).

ly over a period of days. The most common presenting symptoms and signs include headache, confusion, fever, and focal deficits including hemiparesis, ataxia, and psychomotor retardation. Seizures are also a frequent complication. Untreated, the infection is uniformly fatal. The classic appearance on imaging with computed tomography (CT) and magnetic resonance imaging (MRI) is that of multiple ring-enhancing lesions with surrounding edema, although solitary lesions may rarely occur (Figures 62.1 and 62.2). It most commonly affects the hemispheres and basal ganglia. Serologic testing for antibodies to toxoplasmosis is highly sensitive, with only rare false negative results in the setting of profound immunosuppression (CD4 count <50 cells/µl). Hence, negative toxoplasma serology should suggest an alternative diagnosis in most cases. Many patients with CD4 counts <100 cells/µl are placed on trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis of *Pneumocystis* pneumonia and TE, so the current use of TMP-SMX reduces the probability of a focal brain lesion being due to TE. The recommended primary treatment of TE includes oral pyrimethamine (200 mg loading dose, then 75mg/day) plus folinic acid and either sulfadiazine (6-8 g/day orally in 4 divided doses) or clindamycin (600-1200 mg IV or 450 mg orally 4 times daily) for six weeks. Combination anti-retroviral therapy should be initiated after clinical and radiographic response. Maintenance dosing of pyrimethamine 25-50mg daily and sulfadiazine (2-4 g daily in 4 divided doses)

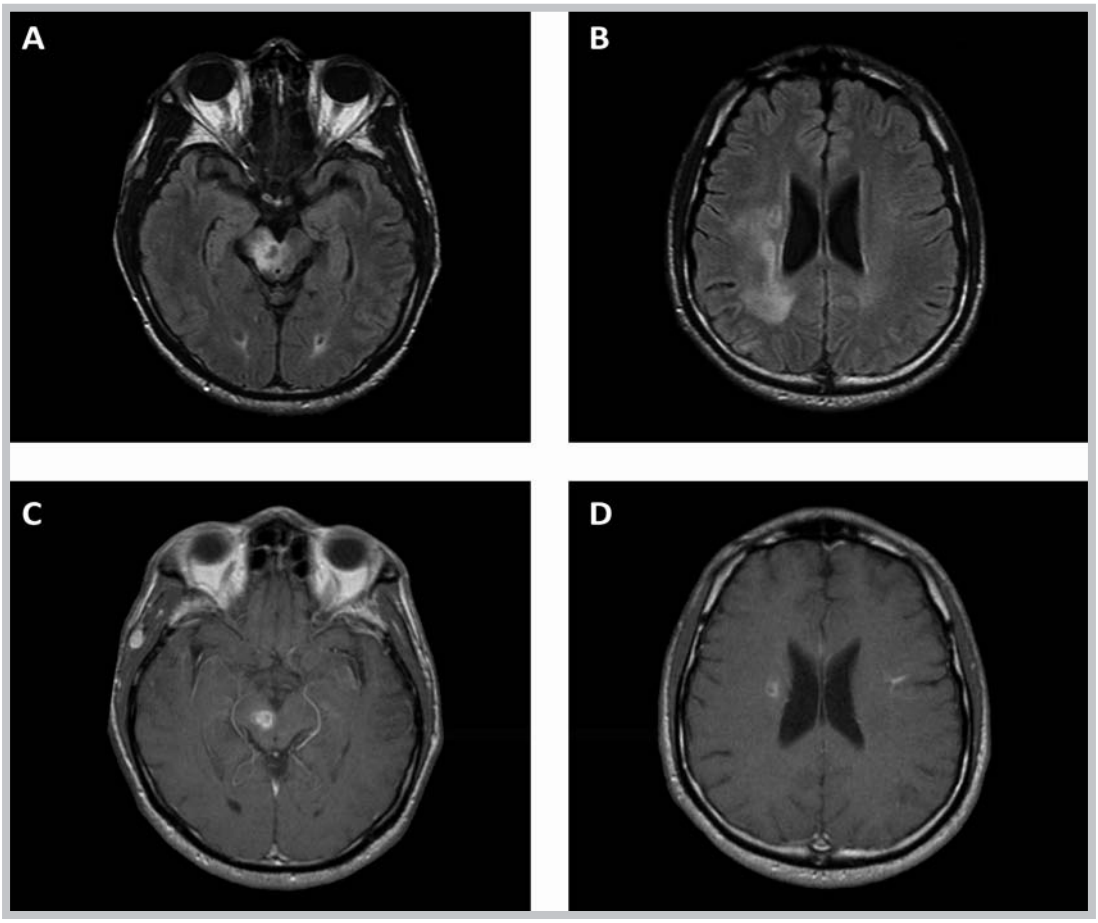

Figure 62.3. **Toxoplasmosis. Fluid attenuated inversion recovery (A, B) and T1 post contrast (C, D) MRI showing improvement in T2 hyperintensity in the right cerebral peduncle and periventricular corona radiata with mild mass effect and patchy rim enhancement 4 weeks after starting treatment.**

is continued until at least 6 months after CD4 counts rise above 200 cells/µl. Steroids (dexamethasone 4 mg every 6 hours) may be used in extreme cases associated with significant midline shift or signs of herniation but it should be avoided in most cases to prevent confusion regarding the specificity of response to TE treatment.

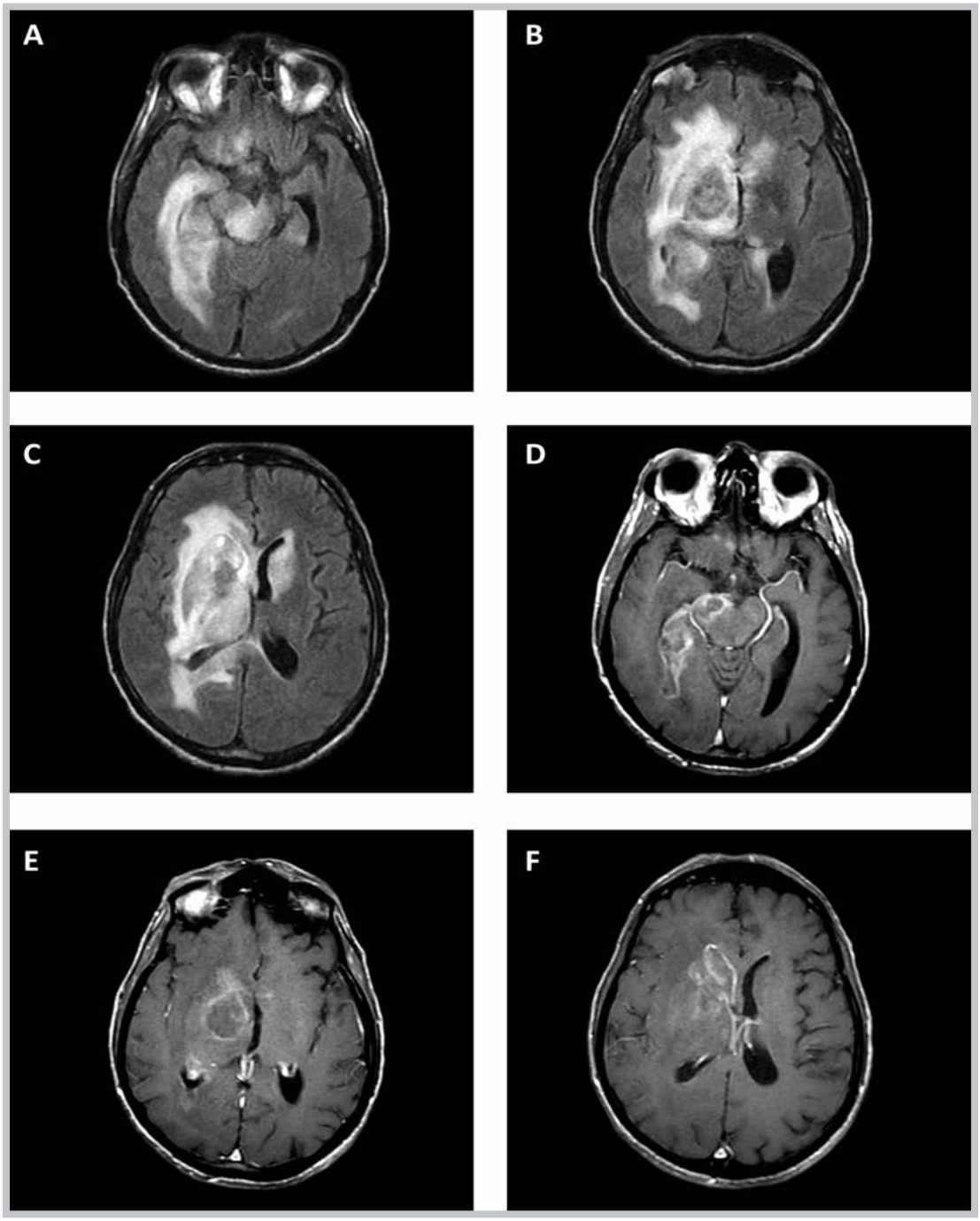

Figure 62.4. **Primary central nervous system lymphoma. FLAIR (A, B, C) and T1 post-contrast (D, E, F) MRI showing T2 hyperintense lesion with patchy rim enhancement and surrounding edema in the right midbrain and basal ganglia with extension across the genu and splenium of the corpus callosum.**

Antiepileptic drugs (AEDs) may be used for secondary prophylaxis but they are not routinely used for primary prophylaxis. Given the hepatic metabolism and toxicity of the TE antimicrobials, AEDs with lower hepatic toxicity and enzyme induction should be preferred (i.e., levetiracetam). The vast majority of patients will show significant improvement clinically and radiographically within 2-3 weeks (Figure 62.3). Failure to do so should strongly suggests an alternative diagnosis.

Primary CNS lymphoma is the second most common cause of focal brain lesions in HIV. In patients with HIV, PCNSL is associated with Epstein-Barr virus (EBV) infection, as opposed to PCNSL in non-immunocompromised patients. Histopathology typically reveals a large B-cell lymphoma. Presenting symptoms are nonspecific; a majority of patients present with mental status changes such as lethargy, confusion, memory loss, and behavioural changes. Furthermore, up to 80% of patients have a history of constitutional symptoms, including fever, night sweats, weight loss, and fatigue (which are common in advanced HIV as well). Focal symptoms, including hemiparesis, aphasia, ataxia, and cranial nerve deficits are also common, but patients may lack clear localizing symptoms and signs. Symptoms are typically present for days to weeks before diagnosis. Patients are profoundly immunosuppressed with CD4 usually <50 cells/μl. CT and MRI reveal a wide spectrum of findings, including solitary or multifocal lesions; ring, patchy, or homogenous enhancement; and cortical or subcortical location (Figure 62.4).

Compared to non-immunocompromised patients, PCNSL in HIV is more likely to be multifocal, found in cortical as well as deep locations, and with less homogenous enhancement (due to central necrosis from rapid growth). Radiographic appearance is not reliable in terms of differentiating PCNSL from TE or other infections, but in general PCNSL is more likely to involve periventricular and corpus callosum white matter and less likely to involve the posterior fossa than TE. Metabolic imaging including single-photon emission computed tomography (SPECT) has been used in some studies to differentiate PCNSL from other causes of mass lesions, but these technologies are not widely available or validated. Given the strict association with EBV, the presence of EBV DNA on PCR assay of cerebrospinal fluid (CSF) lends strong supportive evidence for PCNSL. CSF cytology may be diagnostic, but its sensitivity is poor as only a minority of PCNSL have leptomeningeal involvement. While up to 25% of non-HIV-associated PCNSL may include ocular involvement, ocular spread is not well established in HIV so that the yield of ophthalmological examination is low. Some clues in favour of PCNSL over TE include negative toxoplasma serology, adherence to prophylactic TMP-SMX, and lack of response to specific treatment for TE. The combination of negative toxoplasma serology and positive CSF EBV DNA PCR should strongly support the diagnosis of PCNSL in these patients. In many cases, however, biopsy is necessary to confirm the diagnosis prior to initiating potentially toxic therapies. It is important to note that the administration of corticosteroids prior to biopsy to reduce mass effect may compromise the diagnostic yield as PCNSL may rapidly but temporarily shrink in response to corticosteroids. HIV-related PCNSL has traditionally been treated with whole brain radiation combined with corticosteroids with modest benefit and significant neurotoxicity in the few who survive long enough. The median survival in untreated PCNSL is 1 month, and with radiation this is extended to 2-5 months (often due to other opportunistic infections). Chemotherapy has been avoided due to the already profound immunocompromised state of these patients. However, with the advent of effective combination antiretroviral therapy (cART), survival in PCNSL has improved. Furthermore, high-dose methotrexate, which has become standard therapy in non-HIV PCNSL, has also been shown to improve survival with fewer neurotoxic effects compared to radiation. In practice, some combination of cART, methotrexate, and radiation is often used, depending on patient characteristics.

The third most frequent cause of focal brain lesions in HIV is PML. The JC virus (or John Cunningham virus) is a polyomavirus typically acquired in childhood and which remains latent in the kidneys, blood, and lymphoid organs. Up to 86% of normal subjects in Europe had antibodies to JCV. In the setting of immunocompromisation from HIV (also in hematologic malignancy or treatment with immunosuppressive medications), JCV may reactivate with a tropism for the cerebral white matter. This usually occurs with CD4 counts <200 cells/µl. It infects the oligodendrocytes, causing lysis and demyelination. Compared to TE and PCNSL, PML presents more insidiously over weeks to months. Patients present with focal deficits, including hemiparesis, ataxia, visual field deficits, and diplopia. Altered mental status is common, but cognitive impairment in the absence of focal findings on exam or imaging is unusual. Cortical symptoms and signs, including seizures, frequently occur due to involvement of the juxtacortical white matter and the gray matter itself. While TE and PCNSL are characterized by contrast enhancement and mass effect on neuro-imaging, PML typically lacks these features. Classically, PML appears as asymmetric multifocal white matter lesions which do not respect vascular territories and lack contrast enhancement or mass effect. Lesions are hypodense on CT; MRI reveals hyperintense lesions on T_2-weighted and hypointense lesions on T_1-weighted images (Figure 62.5).

While lesions most commonly involve the periventricular and subcortical white matter, posterior fossa and basal ganglia lesions frequently occur. Brain biopsy reveals gross demyelination and histopathology shows oligodendrocytes with nuclear inclusions and atypical astrocytes. Immunohistochemistry staining for JCV identifies infected oligodendrocytes. Development and validation of PCR for CSF JCV DNA has obviated the need for brain biopsy in most HIV patients with PML. Before the advent of highly active antiretroviral therapy (HAART), CSF PCR for JCV had 72-92% sensitivity and 92-100% specificity; sensitivity is decreased in patients on ART. In cases with typical clinical and radiographic features, positive CSF JCV PCR is considered diagnostic. Even when CSF is negative, a presumptive diagnosis may be given if other etiologies are excluded. There is no effective JCV specific treatment available, but in HIV patients, reconstitution of the

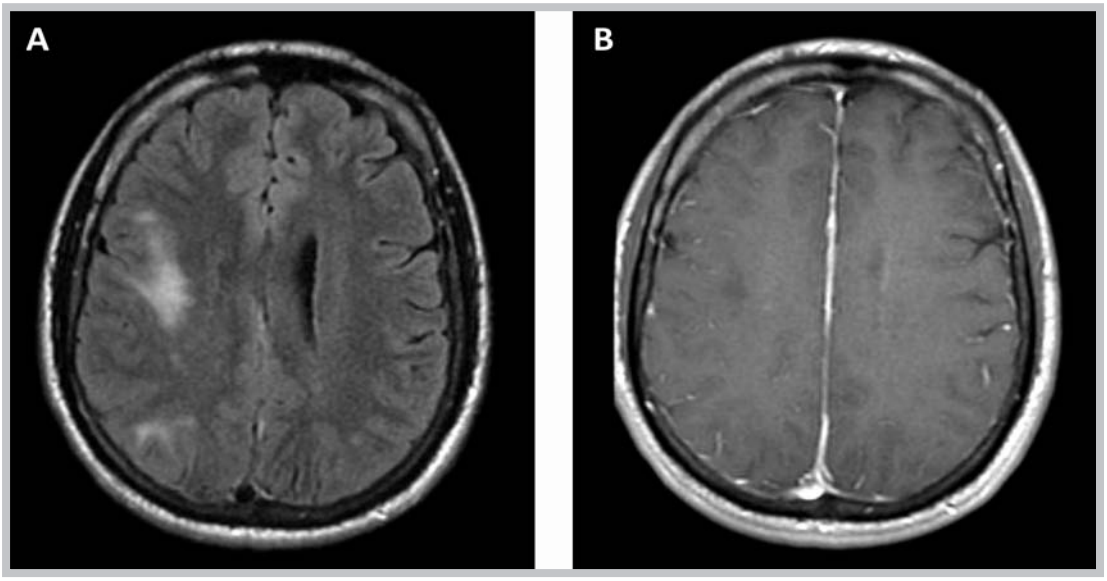

Figure 62.5. **Progressive multifocal leukoencephalopathy. FLAIR (A) and T1 post-contrast (B) MRI showing multifocal T2 hyperintense lesion in the right frontal and parietal subcortical white matter, with corresponding T1 hypointensity but no enhancement or mass effect.**

immune system with effective ART has led to great improvements in survival. Prior to HAART, the 1-year survival rate in patients with PML was only 10%; more recently this has improved to at least 50%. Even with longer survival, however, lesions caused by PML tend to persist, leaving residual deficits. A more recently recognized presentation occurs when there is a robust immune response – in the setting of IRIS from effective ART – which leads to symptomatic presentation of previously undiagnosed PML or worsening of known PML, with enhancement and edema on neuro-imaging. Although symptoms may worsen, this inflammation confers an improved prognosis for survival. Corticosteroids may be used cautiously in cases where this inflammation threatens essential neurological structures.

Although TE, PML, and PCNSL constitute the most common etiologies for focal brain lesions in patients with HIV, such patients are also at increased risk for other infections and for unusual manifestations of non-HIV-related infections. In many parts of the world, tuberculosis is an important cause of focal CNS lesions. Its incidence is increased further in patients with HIV, even at CD4 counts >200 cells/µl. Patients with HIV started on ART with virologic and immunologic improvement may unmask a previously asymptomatic tuberculoma. Distinguishing these lesions from toxoplasmosis or neurocysticercosis can be particularly difficult, and biopsy is often required. While HIV does not increase the

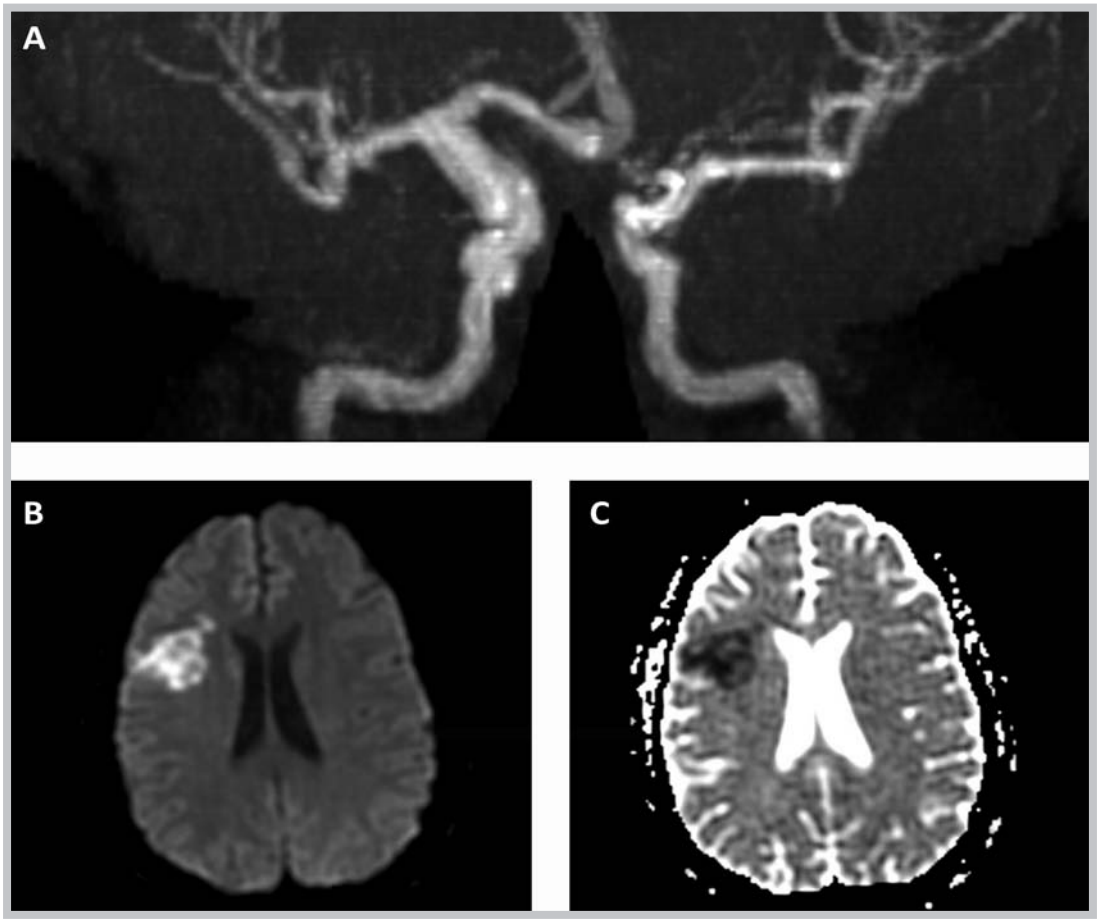

Figure 62.6. **HIV-arteriopathy. MRA circle of Willis (A) showing distal right ICA and proximal right MCA fusiform dilatation; diffusion weighted imaging (B) and apparent diffusion coefficient (C) sequences showing right MCA territory acute infarction.**

risk for neurocysticercosis, it may alter the presentation of this disease endemic to Latin America. There is some evidence suggesting that giant cysts and the racemose form of neurocysticercosis are more common in HIV-positive patients, possibly due to reduced immunity that allows for more chronic expansion of the cysts. In some cases, neurocysticercosis may be incidentally noted when imaging is obtained due to another HIV-related focal brain lesion. Rarer causes of focal brain lesions in HIV include fungal abscesses, including cryptococcus and histoplasmosis; aspergillosis may rarely cause a brain abscess in patients with HIV. Pyogenic bacteria, as well as atypical bacteria such as nocardia, are infrequent causes of focal brain lesions in HIV patients but are more common in injection drug users.

Occasionally, cerebral infarction is the presenting symptom of HIV or occurs in the course of known HIV infection. Basal meningitis/vasculitis due to tuberculosis, syphilis, and fungal infections – along with intracerebral vasculitis due to varicella-zoster virus (VZV) – are the usual etiologies for infarction. An unusual dilated cerebral arteriopathy affecting the extracranial and intracranial arterial stems and causing fusiform aneurysms has been increasingly recognized in patients with HIV and should be considered in the differential diagnosis of stroke of unknown etiology in young adults (Figure 62.6).

62.3 Diffuse Encephalitis

In addition to focal brain lesions, HIV patients are at risk for a number of more diffuse encephalitic processes. Acute HIV infection (or viral rebound from poor adherence or viral resistance) may rarely manifest with a fulminant HIV encephalitis (direct infection) or a peri- or post-infectious acute demyelinating encephalomyelitis (ADEM). Patients with more advanced HIV often develop HIV-associated dementia (HAD). Rarer causes of diffuse encephalitis in late HIV include cytomegalovirus (CMV), varicella-zoster virus (VZV), and neurosyphilis. Finally, in settings where patients have access to effective ART, longer survival has led to more typical causes of dementia in aging populations.

Among the processes that cause diffuse encephalitis in patients with HIV, the most frequent is HAD. This is typically a slowly progressive subcortical dementing process. As such, neurological sequelae from HAD will rarely require neurological-ICU care. Familiarity with this entity is nonetheless important for intensivists as these patients often have advanced disease and multiple simultaneous processes. HIV gains access to the CNS early in the course of infection via migration of infected monocytes. Replication within the CNS occurs in the microglia and macrophages. Damage occurs indirectly from cytokine-induced cytotoxicity. Early in the course of HAD, deficits develop in concentration, short-term memory, cognitive slowing, apathy, reading, and comprehension. Later on, patients may develop more florid dementia and frontal release signs. These are often accompanied by motor deficits which are predominantly extra-pyramidal. Neuro-imaging may reveal cortical and periventricular atrophy; often there is diffuse, symmetric subcortical white matter hypodensity on CT or hyperintensity on T_2-weighted MRI (Figure 62.7). Compared to PML, lesions due to HAD are more often symmetric, may be isointense on T_1-weighted MRI, and are potentially reversible. In untreated patients, HAD usually presents in advanced disease (CD4 count <150 cells/µl). But more recently with ART the proportion of cases presenting with CD4 counts of 200-350 cells/µl is increasing. CSF studies are nonspecific and may even be normal. The HIV viral load may be detectable, sometimes at high titres, in the CSF. In patients on ART, however, the CSF viral load does not correlate with HAD. Although biopsy may be unnecessary, classic pathology on brain biopsy or autopsy reveals multinucleated giant cells and myelin pallor.

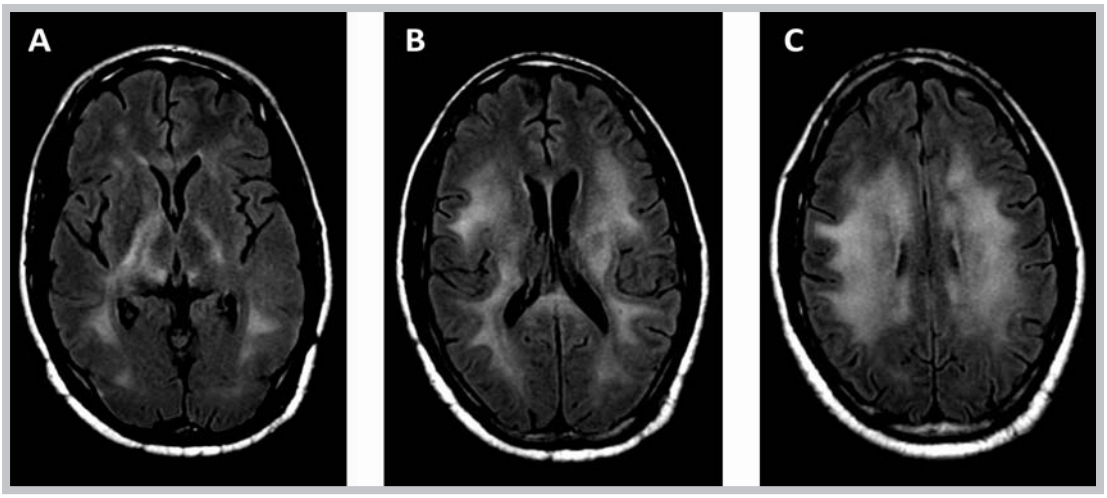

Figure 62.7. HIV-associated dementia. FLAIR MRI showing symmetric, confluent T2 hyperintense signal in subcortical white matter (A, B, C); there was no corresponding enhancement or mass effect.

While there are proposed criteria for diagnosis, HAD is ultimately a diagnosis of exclusion. Treatment with ART with suppression of serum viral load may lead to stabilization or even reversal; treatment is less effective late in the disease when significant atrophy is already present. There is ongoing debate on whether ART regimens with better CNS penetration (as measured in CSF) improve outcome.

Rarely HIV can cause a more fulminant meningoencephalitis. In HIV seroconversion, patients may present with an acute disseminated encephalomyelitis (ADEM)-like illness. In addition, in the setting of viral rebound due to cessation of ART or viral breakthrough due to the development of resistance to ART, patients may develop meningoencephalitis with a high CSF viral load. In both these scenarios, patients may improve rapidly with (re-)initiation of ART. More recently, it has been recognized that immune reconstitution from effective ART can lead to an exaggerated inflammatory response in the CNS, often in a similar but more fulminant pattern to HAD. This process often proves rapidly fatal, and steroids may be given in an attempt to attenuate the exaggerated immune response.

Cytomegalovirus (CMV) is a herpes virus that may be reactivated in profoundly immunocompromised patients (CD4 count <50 cells/μl) to cause neurologic disease in the retina, brain, spinal cord, nerve root, or peripheral nerves. Non-nervous system involvement includes colitis, esophagitis, and rarely pneumonitis. While the incidence of CMV disease in HIV has declined in populations with access to ART, it remains an important consideration in cases of diffuse encephalitis in immunocompromised patients. CMV encephalitis may present with subacute dementia similar to HAD but usually more rapid and more likely to have accompanying focal symptoms and signs. CMV ventriculo-encephalitis is a more fulminant syndrome, with accompanying focal signs including cranial nerve palsies, and is rapidly fatal. Patients with CMV encephalitis often have evidence of CMV disease elsewhere, especially retinitis. CT and MRI may reveal periventricular enhancement. The typical CSF profile is nonspecific, usually with mild-moderate pleiocytosis, normal to low glucose, and moderately elevated protein. In the appropriate clinical context, diagnosis is made by CSF CMV antigen testing or DNA PCR. Treatment consists of intravenous ganciclovir 5 mg/kg q12 and foscarnet 60 mg/kg q12 until improvement, with initiation of ART if there is a clinical response. Lifelong maintenance consists of oral valacyclovir 900 mg daily.

VZV is ubiquitous throughout temperate climates. Primary infection causes chicken pox, with latent virus persisting in the dorsal root and cranial nerve ganglia. Reactivation in the elderly and immunocompromised leads to herpes zoster or shingles. Patients with HIV have a 15-fold increase in zoster, which may occur at any CD4 count but usually when <200 cells/μl. VZV may rarely manifest as a neurologic syndrome, including encephalitis, myelitis, meningitis, retinitis, cranial nerve palsy, CNS vasculitis, or a combination thereof. Neurological involvement in zoster is more common in HIV than in other patients. Rash may not be present in a significant minority, so its absence does not exclude VZV as a cause of neurological symptoms. CSF typically reveals a mild lymphocytic pleiocytosis, moderately elevated protein, and normal glucose. CSF VZV DNA PCR or antibodies confirm the diagnosis. MRI may show multifocal T_2 hyperintensities and leptomeningeal enhancement, but such findings are nonspecific and may be normal. In VZV vasculitis, MRI may show single or multifocal cerebral infarctions, so VZV should be considered in the differential diagnosis of stroke syndromes in HIV patients. Treatment with intravenous acyclovir usually leads to recovery, except for visual loss from retinitis and infarctions from vasculopathy.

62.4 Meningitis

Meningitis is a frequent complication of advanced HIV. In patients with CD4 counts <200 cells/μl, the most common cause of meningitis is *Cryptococcus neoformans*, followed by tuberculosis and syphilis. HIV itself causes aseptic meningitis at seroconversion in up to one third of patients, which is usually self-limiting, as well as a rebound meningoencephalitis as noted above. Less common causes of meningitis include coccidioides, VZV, HSV-2, and pyogenic bacteria. Non-infectious meningitis may occur with leptomeningeal spread of systemic non-Hodgkin's lymphoma. Patients with advanced HIV may not present with classic symptoms and signs of meningitis, so the threshold for performing lumbar puncture to assess neurological symptoms should be lower for these patients. As these patients may also have multiple simultaneous neurological processes, neuro-imaging should be performed prior to lumbar puncture when possible to exclude mass lesions which might lead to downward herniation if CSF pressure is decreased.

C. neoformans is a ubiquitous encapsulated yeast found in the soil worldwide, as well as in pigeon droppings. This invasive fungus infects humans through the lungs, but the most common clinical manifestation is meningitis (meningoencephalitis), likely related to decreased complement activation and other factors that allow more growth in the CSF. It predominately affects immunocompromised patients; HIV patients with cryptococcal meningitis typically have CD4 counts <100 cells/μl, although it can rarely occur at higher counts. The incidence has decreased in populations with access to ART. Due to the lack of appropriate immune response, patients develop symptoms over days to weeks. Fever, malaise, and headache are the most common presenting symptoms, with classic symptoms of meningitis, as well as altered mental status, occurring in only about 25% on presentation. Rarely, patients may present with focal findings due to a mass lesion or cryptococcoma, usually in the deep white matter or basal ganglia, which occurs more often in non-HIV patients. Hence, mass lesions in patients with cryptococcal meningitis are more likely to be due to one of the causes listed in the section above. In some patients, cranial nerve palsies such as bilateral blindness and deafness can be presenting symptoms with only slight meningeal symptoms, due to the predilection of the infection to the CSF cisterns at the base of the brain. CT and MRI may be normal, but contrast studies may reveal perivascular nodules. CSF opening pressure is almost always elevat-

ed, often markedly so. CSF is often bland, with up to 30% of patients having normal CSF profiles. CSF India ink stain reveals numerous encapsulated yeast in 80% of cases. CSF cryptococcal antigen assay is highly sensitive and specific and is much more rapid than culture. Serum cryptococcal antigen assay is similarly sensitive in HIV patients and useful when lumbar puncture cannot be done immediately. Cryptococcal meningitis in HIV is treated with intravenous amphotericin B (0.7 mg/kg/day) plus oral flucytosine (100 mg/kg/day in 4 divided doses) for 14 days as induction. Consolidation treatment consists of oral fluconazole (400 mg/day) for at least 8 weeks. Once there is clinical improvement after 10 weeks, oral fluconazole (200 mg/day) provides maintenance therapy, which is continued indefinitely although discontinuation may be considered after ART leads to CD4 counts >100 cells/μl for at least 12 months. Even with successful chemotherapeutic treatment of cryptococcus, increased intracranial pressure (ICP) can pose ongoing problems. Patients may require daily lumbar puncture to remove enough CSF to maintain closing pressure <200 mmH_2O; patients who have ongoing elevated ICP after 4 weeks often require a ventriculoperitoneal shunt. Some patients without known cryptococcal meningitis, or with previously treated disease, may show worsening meningitis with inflammatory CSF in the setting of effective ART. This IRIS meningitis may be difficult to distinguish from worsening infection, but usually the organism burden is lower or undetectable in CSF and virologic and immunologic parameters show marked improvement. The timing of initiating ART in patients treated for cryptococcus is controversial, but waiting 2 weeks after specific cryptococcal treatment is reasonable.

HIV itself causes self-limiting aseptic meningitis in up to 30% of cases during acute seroconversion, but it may also persist as a low-grade chronic meningitis that is often asymptomatic. Symptoms include headache, meningismus, malaise, and photophobia. Focal symptoms are rare but may include cranial nerve deficits including bilateral facial palsies; few cases of encephalopathy have been reported. CSF reveals a mild lymphocytic pleiocytosis, normal glucose, and normal to mildly elevated protein. The CSF HIV viral load may be detectable and markedly high in some cases. Except in severe cases, the course is self-limiting and not an indication for initiation of ART (although the issue of starting ART early to reduce CNS penetration is under debate). As mentioned above, rebound HIV meningitis may occur in the setting of viral breakthrough from ART discontinuation or development of resistance. It is rapidly reversible with appropriate ART.

Coccidioides (*C. immitis* in California and *C. posadasii* in the American southwest, and Central and South America) are dimorphic fungi limited to arid and semi-arid regions of the Western hemisphere which infect humans by inhalation of spores. In normal hosts, it may cause a self-limiting respiratory illness. In immunocompromised patients, however, there is an increased risk for extrapulmonary dissemination during primary infection or through reactivation. Of these, meningitis is the most serious. Patients may present weeks to months after initial infection, most often with persistent headache. Tremor may be the only other neurological symptom, and overt signs of meningismus are often lacking. Later in the course of disease, cranial neuropathies and focal infarct may occur due to inflammation at the base of the brain with vasculopathy of the basal vessels. MRI may show nonspecific signs of basal meningitis, including leptomeningeal enhancement, infarction, and hydrocephalus. CSF studies show a mild to moderate lymphocytic pleiocytosis; although there may be neutrophilic predominance, early and mild eosinophilia is common. Compared to most other causes of aseptic meningitis, CSF glucose is more often depressed, sometimes markedly. CSF protein is moderately to severely elevated. Coccidioides symptoms and CSF profile can mimic tuberculosis and are both endemic in certain areas of Central and South America, so caution is warranted in the diagnosis. CSF culture of coccidioides is diagnostic but insensitive. Detection of antibodies to coccidioides more often yields the diagnosis, and rarely infection must be inferred from

detection at another site or in serum. Meningitis is treated with intravenous or oral fluconazole 400-800 mg daily acutely and 400 mg daily for life thereafter.
Meningitis is the most common CNS manifestation of tuberculosis and it is a major cause of HIV-associated meningitis in endemic areas. Syphilis more often progresses to early neurosyphilis in patients with HIV, requiring more aggressive diagnosis and treatment of syphilis in these patients. Organisms causing meningitis in immunocompetent hosts may also affect patients with HIV, and CSF should be routinely checked for pyogenic bacteria, mycobacteria, venereal disease research laboratory (VDRL) test, VZV, and HSV-2 as these have specific treatments. In addition, neoplastic meningitis – in particular leptomeningeal spread of systemic lymphoma – may cause subacute meningitis with cranial nerve palsies and/or polyradiculitis. CSF should be sent for cytology and flow cytometry where available. Unfortunately, leptomeningeal spread portends a poor prognosis even with appropriate treatment.

62.5 Myeloradiculitis

The most common myelopathy in patients with advanced disease is HIV vacuolar myelopathy. It has been detected in 25-50% of patients with AIDS, although it is symptomatic in only 5-10%. CMV is a rare but important cause of acute myelopathy in patients with advanced HIV and may cause conus medullaris or cauda equina syndrome. Other causes of myelopathy include human T-cell lymphotrophic virus-1 (HTL-1), tuberculosis, syphilis, toxoplasmosis, VZV, HSV-2, vitamin B12 deficiency, and lymphoma.
HIV vacuolar myelopathy shares features in common with subacute combined degeneration. HIV causes vacuolization of the lateral and posterior columns – particularly in the thoracic region – through unknown but indirect mechanisms rather than direct infection. It usually accompanies HIV-associated dementia. Patients present with slowly progressive but painless spastic paraparesis, sensory ataxia, and neurogenic bladder and sexual dysfunction. Rarely acute HIV infection is associated with an acute transverse myelitis, likely due to immune dysregulation. As with encephalitis, rebound viraemia in the setting of ART cessation or development of resistance may occasionally cause an acute myelitis. MRI in vacuolar myelopathy is most often normal but early in the process may show increased signal in the posterior and lateral columns and later may show atrophy of the thoracic cord. CSF typically reveals no white blood cells and mildly elevated protein. There is no specific treatment for HIV vacuolar myelopathy. By the time it is clinically manifest, irreversible damage has occurred. ART may help prevent progression, and typical symptomatic treatments for myelopathy should be applied. There is some evidence that methionine may offer some modest benefit.
CMV may cause axonal destruction, demyelination, or perineural vasculitis. Patients with CMV myeloradiculitis present over days to weeks with lower extremity weakness, saddle anaesthesia, and bowel and bladder paresis producing an acute conus medullaris or cauda equina syndrome. Reflexes are increased in myelitis and absent in polyradiculitis, which is often painful. Patients may have concomitant retinitis or encephalitis. MRI may be normal or show enlargement and enhancement of conus medullaris or cauda equina. CSF studies reveal moderate pleiocytosis (may be neutrophilic or lymphocytic), elevated protein, and normal to low glucose. Diagnosis is confirmed by CSF CMV DNA PCR, which has high sensitivity and specificity in the appropriate clinical setting. Treatment is the same as for CMV encephalitis (see above).
HTLV-1 causes a myelopathy which progresses over many years, ultimately resulting in symmetric spastic paraparesis, bladder dysfunction, and often lumbar and radicular

pain. Other causes of chronic myelopathy include tuberculosis, syphilis, subacute combined degeneration, and epidural compression from lymphoma. Acute myelitis may occur in the setting of infection with VZV, HSV-2, and syphilis. Appropriate serum and CSF studies should be sent to assess for these.

62.6 Peripheral Nervous System

While peripheral nervous system disease rarely causes acute critical illness, these syndromes are important to recognize. They may complicate the evaluation of weakness or sensory change in critically ill patients, and rarely may progress rapidly, leading to respiratory weakness and other serious complications.

The most common neurological complication of HIV infection is a distal symmetric polyneuropathy (DSPN) which primarily affects the sensory nerves. The virus causes a toxic dying back neuropathy through indirect immune activation and inflammation. Patients present with burning dysesthesias on the soles of the feet, decreased sensation in the distal lower extremities (especially vibration), and loss of ankle deep tendon reflexes. Certain ART medications – especially the dideoxnucleosides stavudine (d4T) and didanosine (ddI) – cause a toxic neuropathy indistinguishable from DSPN. The frequency with which this complication occurs may obscure the diagnosis of other causes of sensory loss, weakness, or ataxia such as myelopathy or critical illness neuropathy or myopathy.

Both acute and chronic demyelinating polyradiculoneuropathies occur in patients with HIV. Early in the infection, Guillain-Barré syndrome (GBS) may occur in the setting of seroconversion or as the first sign of HIV. GBS may rarely result from immune reconstitution with effective ART. In more advanced HIV infection, patients more often develop chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The clinical presentation of GBS and CIDP in patients with HIV is similar to that in non-infected patients, and the treatment and favourable response are the same. Clinical features and treatment of inflammatory demyelinating polyradiculoneuropathies are discussed elsewhere.

Mononeuropathy is rare but may occur at any point in the course of HIV infection. Compression may be related to cachexia or in presymptomatic nerve toxicity as in diabetes. Mononeuropathy may also develop into mononeuritis multiplex. Early in HV infection it is likely due to autoimmune vasculitis and has a good prognosis. In more advanced HIV, opportunistic infections including CMV, VZV, and hepatitis B and C play a more prominent role. These viruses should be sought and treated if present. If no explanation is found, biopsy may be necessary to assess for CMV inclusions or vasculitis. In more severe disease associated with vasculitis, treatment with immunomodulation (plasma exchange, intravenous immune globulin, or prednisone) may be helpful but prognosis is poor.

Some patients with HIV develop sicca symptoms with a Sjögren's-like syndrome with a CD8+ lymphocytosis infiltrating various tissues, including parotid gland, lung, kidney, and peripheral nerve. This diffuse infiltrative lymphocytosis syndrome (DILS) can cause an axonal neuropathy with pain and symmetric sensory loss or a picture of painful mononeuritis multiplex. Blood CD8 counts are elevated above 1200 cells/μl with a CD8 percentage >60%. Treatment consists of ART and/or steroids with typically good response.

Myopathy in HIV may be due to several different processes. HIV myopathy is a presumably immune mediated inflammatory myopathy which may occur at any point in the course of infection. It has clinical and pathologic characteristics similar to non-HIV polymyositis. Patients present with proximal lower more than upper extremity weak-

ness, muscle pain, and tenderness. Creatinine kinase (CK) is often elevated but may be normal. Electromyography (EMG) may be normal but often reveals changes consistent with necrotic myopathy (increased insertional activity, fibrillations, and polyphasic potentials). Muscle biopsy reveals mononuclear endomysial infiltrate, with predominantly CD8+ T cells and macrophages. Once other causes are excluded, treatment is similar to non-HIV polymyositis with high-dose prednisone slowly tapered after maximal response.

Zidovudine, a nucleoside reverse transcriptase inhibitor, may cause a toxic myopathy clinically indistinguishable from HIV myopathy. The pattern of weakness and CK elevation are similar. EMG and basic histopathology are typically milder than HIV myopathy, although evidence of mitochondrial toxicity may be apparent, with ragged red fibres on trichome stain and ultrastructural damage in electron microscopy. Cessation of the offending agent generally leads to recovery over many weeks.

Bacterial pyomyositis usually causes more focal muscle disease, and inflammatory changes overshadow any accompanying weakness. Toxoplasmosis may cause a more diffuse myositis, usually in the setting of disseminated disease including encephalitis. Muscle biopsy reveals more neutrophilic infiltrate and intracellular cysts containing the parasite, if seen, are diagnostic. Treatment is similar for CNS disease (see above).

A rare complication of the nucleoside reverse transcriptase inhibitor stavudine is HIV-associated neuromuscular weakness syndrome. Patients develop acute ascending weakness and respiratory failure over several days to weeks, with accompanying fatigue, abdominal pain, nausea, and vomiting. Weakness may be due to neuropathy, myopathy, or both. The clinical picture resembles Guillain-Barré syndrome, except for the accompanying systemic illness. Serum lactate is invariably elevated, and the mechanism is believed to be mitochondrial toxicity. Stavudine should be discontinued immediately and treatment is supportive. Prompt recognition in the early phase of this syndrome can result in marked improvement in the disorder which otherwise has high mortality.

62.7 General Issues

The optimal timing of initiating combination antiretroviral therapy has been an area of active research and ongoing debate. One issue is the possibility of worsening neurological outcome due to IRIS. Some argue that cART should be delayed until after specific antimicrobial treatment for opportunistic infections has obtained control of the infection, typically within 4-6 weeks. However, recent evidence suggests no difference if cART is started earlier. Although the evidence is mixed, a reasonable approach is to treat for any specific opportunistic infections for 2 weeks prior to initiating cART. For neurological infections, this primarily includes cryptococcal meningitis and toxoplasma encephalitis. Since PML and PCNSL have no effective specific antimicrobial therapy, cART should be initiated as soon as possible in these patients. An exception to this guideline is tuberculous involvement of the CNS, in which the risk for paradoxical worsening in the short term with cART is higher than for other opportunistic infections. For those with CD4 counts <100 cells/µl, cART should be started after 2 weeks of anti-Tb therapy. For those with higher CD4 counts (100-350 cells/µl), most recommend waiting until after the 2-month intensive phase of anti-Tb treatment before starting cART. For those with CD4 counts >350 cells/µl, cART may be delayed until Tb treatment is complete. For patients who develop CNS symptoms while on cART, this therapy should be continued and IRIS should be considered.

In addition to the neurological complications of HIV noted above, there are other important considerations in the neurological care of patients with HIV. Seizures are common in HIV, present in approximately 5-15% of HIV-positive patients. Conversely, patients with underlying seizure disorders – as from neurocysticercosis – may contract HIV. This poses particular challenges in treatment. Although data are limited, there does not appear to be any major effect of antiepileptic drugs (AEDs) on HIV or its course. AEDs, however, can have significant interactions with ART. Both the older AEDs (phenytoin, phenobarbital, carbamazepine, valproate) and certain antiretrovirals (protease inhibitors [PI's] > non-nucleoside reverse transcriptase inhibitors [NNRTIs] >> nucleoside reverse transcriptase inhibitors [NRTIs]) are significantly protein-bound and metabolized by the hepatic cytochrome P450 system.

Hence, while NRTIs may be safely co-administered with older AEDs, the use of protease inhibitors and NNRTIs with older AEDs poses the risk of increased AED toxicity due to protein displacement and enzyme inhibition, as well as subtherapeutic ART levels due to enzyme induction by the AEDs. When available, newer AEDs with effectiveness for the clinical context should be used when patients are taking concurrent ART. Levetiracetam, which has effectiveness in both generalized and partial seizures and is not hepatically metabolized or significantly protein bound, is a particularly useful agent in this situation.

62.8 Key Concepts

HIV infection can affect every part of the nervous system from focal brain lesions to inflammatory myopathy. The most frequent HIV-related syndromes seen in the ICU setting are focal brain lesions, diffuse encephalitis, and meningitis. In many instances, the neurological syndromes can be the presenting manifestations of AIDS. The accompanying symptoms and signs of systemic illness, such as weight loss, oral thrush or other systemic opportunistic infections and unexplained lymphopenia on routine blood count, provide clues to the diagnosis. Based on the clinical presentation, radiographic findings, and serological and antigen testing, the diagnosis is usually possible without resorting to biopsy. In cases where the clinical context so allows, an empiric trial of treatment for toxoplasmosis is reasonable given the usually quick response to treatment. If there is no response, other entities must be considered and sought aggressively.

Patients with advanced HIV may have more than one process occurring simultaneously, and typical presenting symptoms and signs may be lacking given the lack of immune activation. Furthermore, patients with HIV are also susceptible to neurological infections which occur in the immunocompetent host, in particular tuberculosis, syphilis, and neurocysticercosis. Once diagnosis is made in an ART-naïve patient, specific antimicrobial agents should be initiated in advance of ART to help avoid IRIS. In treating patients with comorbid HIV and epilepsy, newer AEDs pose less risk of harmful drug interactions.

The pathophysiology, diagnosis, and treatment of HIV-associated neurological disease are complicated and evolving. In this context, the increasingly recognized role of immune reconstitution in neurological disease should be considered in unusual cases. Consultation with infectious disease experts when possible is helpful to address the unique aspects of neurological complications in the setting of HIV, but the neurological intensivist should maintain a working knowledge of the most common and most devastating neurological manifestations of HIV and their treatment.

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Section 8.
Frequent Problems

63 Cerebral Protection

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63.1 Introduction

Acute brain Injury is due to several causes: traumatic brain injury (TBI), different medical conditions, such as subarachnoid hemorrhage (SAH), central nervous system infections or stroke, and some surgical procedures (mainly cardiothoracic, neurosurgical and vascular). Primary brain injuries can be divided into two major categories: focal injuries, stroke being the most representative example, and diffuse injuries, for instance patients who suffer coma following a cardiac arrest. In spite of considerable differences in clinical features and initial prognosis of primary lesions, all of them trigger a wide variety of secondary injuries, both at a systemic level (hypotension, hypoxemia, ventilatory and hydroelectrolitic alterations), and at a cerebral level (swelling, intracranial hypertension or seizures). These secondary injuries are responsible for the onset of ischemia.

Neurons are extremely sensitive to ischemia due to a low energy substrate disposal in the brain. Moreover, neuronal hypoxia-ischemia occurs not only because of cellular energy failure, but also because of the activation of the genetic transcription that contributes to apoptosis and inflammation, protein synthesis inhibition and oxidative stress. Consequences of neuronal ischemia vary from subtle neurocognitive deficits to catastrophic neurological morbidity. In any case, the result of the secondary injury is neuronal death, neurological deterioration and a worse functional outcome than those solely induced by the primary injury.

Cerebral protection can be defined as a set of interventions aimed at maintaining the integrity of neuronal interactions. In other words, it comprises any strategy, or combination of strategies, that antagonizes, interrupts, or slows the sequence of injurious biochemical and molecular events that, if left unchecked, would eventuate in irreversible ischemic injury [1]. This concept has been evolving as our knowledge of cerebral physiology and physiopathology has improved. Such knowledge is relevant to understanding the relevance of the interventions adopted, as well as the reasons why they are successful or not. **Neuroprotection** is the group of strategies applied before brain injury takes place, in order to modify the following cascade of events. The treatment that focuses on restoring normal homeostasis of cells already exposed to the insult is referred to as **neuro-resuscitation**. Although primary injury is often difficult to predict, cerebral protection should ideally be started before its appearance, and should be maintained during the phase of tissular reperfusion.

63.2 Pathophysiology of Brain Injury

Ischemia initiates a complex cascade of cellular events, encompassing many different pathways, that ultimately leads to irreversible tissue injury. It usually starts with rapid depletion of adenosine triphosphate (ATP) – which is synthesized by aerobic glucose metabolism –, and activation of anaerobic metabolism [2].

Extracellular liberation of excitatory mediators – mainly glutamate – is induced. These substances cause neuronal depolarization, via activation of N-methyl-D-aspartate (NMDA) and α-amino-3-hidroxy-5-methylisoxazole-4-propionic acid (AMPA) type of glutamate receptor, allowing calcium to enter the intracellular compartment. Dysfunction of ATP-sodium-potassium pumps facilitates this process. Water entering the cell together with sodium induces cytotoxic edema, while calcium acts as a coenzyme, and facilitates enzymes activation -proteases and lipases-, which are ultimately responsible for cellular membrane destruction and liberation of fatty acids, prostaglandins and thromboxanes.

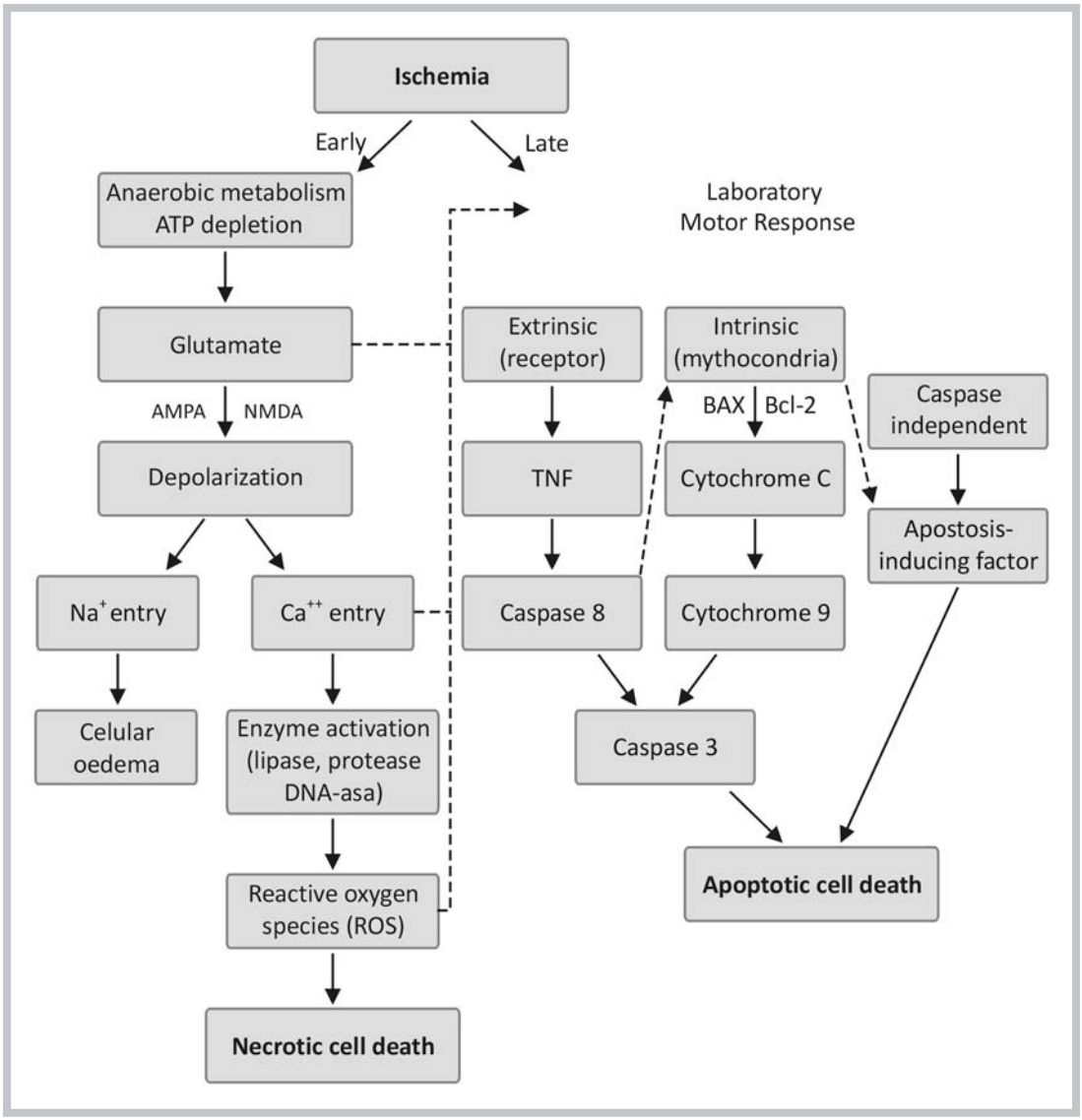

Figure 63.1. **Pathophysiology cascade of ischemic neuronal death associated to secondary brain damage.**

AMPA = α-amino-3-hidroxy-5-methylisoxazole-4-propionic acid type of glutamate receptors
ATP = Adenosin-triphosphate
BAX / Bcl-2 = pro and anti-apoptotic proteins in mytochondrial membrane
Ca^{++} = calcium
Na^{+} = sodium
NMDA = N-methyl-D-aspartate receptors
ROS = reactive oxygen species
TNF = Tumor necrosis factor

Oxidative stress is also induced by interrupting mitochondrial respiratory chain. It consists of an imbalance in the production and degradation of reactive oxygen species (ROS), which aggravates the ATP-sodium-potassium pump inhibition, lipid peroxidation, mitochondrial and cellular membrane disintegration, protein oxidation and nuclear DNA fragmentation.

The final result is cellular death due to necrosis (Figure 63.1). Activation of anaerobic metabolism generates acidosis, increasing neuronal damage. This type of cellular death is morphologically characterized by swelling and cellular pyknosis, karyolysis, cytoplasmic eosinophilia and inflammatory response [3].

Once ischemic insult ceases, perfusion is restored, and oxygen and glucose tissular deliveries are recovered. Nevertheless, reperfusion induces some adverse effects that worsen ischemic injury (largely the formation of more ROS). Moreover, a relative hypoperfusion state remains after reperfusion, due to platelet aggregation (mediated by thromboxane A2), calcium influx in endothelial cells (which causes vasoconstriction), cytotoxic edema, loss of red blood cells shape, and vasogenic swelling, generated by the blood brain barrier (BBB) disruption [4].

Free radicals and metalloproteinases (MMP) play a key role in the BBB alteration. The latter are synthesized by neutrophils, and alter the tight junctions which are present in the BBB. An initial disturbance of the BBB develops following an ischemic event. Such disturbance is usually repaired in the first 2 or 3 hours within reperfusion, and it may not be evident again until 24-48 hours later. This second disruption is related to vasogenic edema and haemorrhagic transformation in case of ischemic stroke, and has been associated with MMP-3 and MMP-9 [5].

Those strategies focused on interrupting or slowing down the aforementioned chain of events have a potentially protective role. In that sense, several techniques or pharmacological agents have demonstrated positive outcomes in neuroprotection, when evaluating short term histological parameters of neuronal loss (less than 15 days). On the other hand, many of those interventions failed to obtain a clinical benefit when evaluated at a longer term. This feature has lead to the discovery of a second pathway of ischemic neuronal death, which occurs at a later stage to necrosis. This pathway is more frequently present in the ischemia-penumbra areas. Ischemia is not critical enough to induce cellular necrosis in these penumbra areas; however a considerable degree of hypo perfusion may be still present. Apoptosis, a type of cellular death “genetically programmed”, is activated in these areas in response to stimuli as calcium, glutamate, ROS storage or ATP depletion. Important contributors to late apoptosis are cellular mitochondria and some enzymes, named caspases, which are ultimately responsible for that process [3].

This sort of cellular death is morphologically characterized by nuclear chromatine degradation, cytoplasmic and nuclear condensation and, finally, cellular fragmentation into “apoptotic bodies”. Apoptosis has also been described in functional cells, and it is originated inside the nucleus during certain cellular phases. Signals which trigger ischemic apoptosis include several pathways [6] (Figure 63.1):

- Intrinsic pathway, mediated by the mitochondria. It is characterized by cytochrome-C release, which activates caspase-9 that, in turn, activates caspase-3 and induces DNA fragmentation. This pathway can be early initiated, within 2 hours from onset of the injury, and it is modulated by mitochondrial membrane proteins, such as Bax (pro-apoptotic) or Bcl-2 (anti-apoptotic).
- Extrinsic pathway is characterized by receptor activation, mediated by binding molecules, such as tumor necrosis factor, which activates caspase-8 and this enzyme, in turn, activates caspase-3. Extrinsic pathway is established later than the intrinsic one.

- The third pathway is triggered by storage of anomalous proteins inside the endoplasmic reticulum. This phenomenon activates caspases 12 and 4, which are associated to caspase-3 activity.
- The fourth apoptotic pathway is caspase-independent. It is mediated by apoptosis induction factor, which is released in response to oxidative stress. This factor binds to DNA, promoting chromatine condensation and cellular death.

Apoptosis-mediated dead cells are phagocytized by cerebral microglia. This ends cellular death expansion and avoids response amplification. However, necrotic cells are phagocytized by macrophages, inducing a propagation reaction in the surrounding tissue. For some authors, changing from a necrotic cellular death to an apoptotic one could be a relevant cerebral-protective mechanism, due to its ability to control neuroinflammation spread. However, this is still a point of debate.

Observing this complex process of ischemic neuronal death helps us to understand some key issues. Firstly, different ischemia-mediated cellular death pathways are intimately related or at least, necrosis and apoptosis are. Secondly, strategies that seemed effective blocking necrotic cellular death may not be relevant in the long term with regards to patient outcome, since apoptotic mechanisms induce late cellular death (this is probably the case of anesthetics-mediated neuroprotection). Finally, it is difficult to imagine a single protective measure capable of slowing down all these events, or altering early features induced by ischemic cascade, owing to the fact that many patients arrive at the emergency area several hours after the onset of the ischemic injury.

In addition to negative effects, ischemia also activates repairing mechanisms. Thus, many processes which result harmful at one point in time can be beneficial at another. For instance, MMPs alter BBB in the early phases of an ischemic event, and therefore inhibition is beneficial at that moment. However they are associated with neurogenesis and angiogenesis later on, and consequently, late treatments based on MMPs-inhibitors might delay reparation mechanisms.

63.3 Cerebral Protection Goals

During early resuscitation, surgery or Intensive Care Unit (ICU) admission, our interventions in an acute brain injury, should focus on preventing and treating cerebral ischemia associated with secondary injury. The final purpose is to minimize cerebral damage and maximize neurological recovery. This objective is based on the fact that primary injuries – with the exception of those caused by some surgical procedures – are seldom predictable (traumatism, stroke, cardiac arrest, etc.) and thus, the initial damage cannot be avoided. Furthermore, secondary injury will decisively contribute to final neurological outcome unless effective neuroprotective measures are implemented. Finally, secondary injury consequences have probably been underestimated in the past. There is evidence supporting the hypothesis that cognitive dysfunction associated with mild cerebral injuries may be due to this secondary injury.

As well as precociousness, other factors seem to be of crucial importance for protective measures to be effective: intensity with which a treatment is applied (drugs given at different doses, levels of hypothermia, etc.), duration of the treatment, severity of primary injury and finally, injury extension – focal or diffuse. Moreover, neurons represent only 5% of cells in cortical grey matter, with glia and astrocytes being much more numerous. Accordingly, another field of interest is neuroprotection "beyond the neuron", focused on the so called "neurovascular unit" (neurons, muscular brain vessels cells, and support cells – astrocytes, oligodendrocytes and microglia).

Those strategies or treatments which have demonstrated major clinical impact and their applicability will be described hereafter, as well as clinical investigation lines which are currently being developed.

63.4 General Neuroprotection Strategies

Three different groups of neuroprotection strategies can be distinguished:
Neuronal loss reduction. This goal can be achieved by increasing tissular oxygen delivery and decreasing metabolic demands. Traditional neuroprotection was based on decreasing brain metabolism, i.e. administering high doses of barbiturates after an ischemic event. Nevertheless, this pathway is neither the only, nor the most relevant in order to establish neuroprotection. Consequently, other strategies aimed at modifying ischemic neuronal death cascades have been developed:

- Glutamate receptor inhibition (NMDA and AMPA).
- Gamma-amino butyric acid (GABA) system stimulation.
- Anti-inflammatory mechanisms.
- Apoptosis inhibition.
- Mitochondrial dysfunction prevention.
- Cellular hyperpolarization.

Ischemic preconditioning. It is an innate protective mechanism which reduces damage induced by ischemia-reperfusion. Basically, it consists of inducing cellular tolerance by provoking ischemic situations previous to a severe injury that otherwise would be lethal. It has been observed that patients who had suffered from transient ischemic events prior to a serious stroke showed better recovery than those who had not. Two different preconditioning types can be distinguished: early and late preconditioning. The former is developed within minutes to hours after the initial insult, and it is independent of protein synthesis, whilst the latter takes place between 12 and 24 hours after the preconditioning stimulus, lasts for 2 or 3 days, and depends on genetic regulation and protein synthesis.
Neuroprotection can be elicited by certain drugs such as inhaled anesthetics, opioids, adenosine, statins, etc.). They interfere with energetic cellular metabolism and are able to reproduce cellular responses similar to those occurring during preconditioning, such as vasodilatation, angiogenesis, neurogenesis reduction in energy consumption, antagonism of NMDA and AMPA glutamate type receptor [7].
Recently, two additional preconditioning pathways have sparked great interest. On the one hand, **remote preconditioning** can be elicited by applying brief periods of ischemia to tissues with ischemic tolerance, thus protecting vital organs more susceptible to ischemic damage. For instance, skeletal muscle ischemia is a potent preconditioning stimulus for heart and probably, for brain too [8]. It can be performed quickly and inexpensively, requiring only a blood pressure cuff applied in an arm or a lower limb. Some clinical trials are being carried out in order to test the neuroprotective effect of remote ischemic preconditioning on cardiac surgery (NCT 01231789) and for SAH (NCT01110239).
On the other hand, **postconditioning** entails brief ischemia periods (10 seconds approximately) applied during reperfusion and separated by 30-second intervals. It appears to be a promising strategy after myocardial ischemia, and its role in cerebral protection is being studied, since cellular injury mechanisms are similar. However, results in neuroprotection are less satisfactory than in the heart, so postconditioning might only be applicable to mild or moderate injuries. This fact might due to a greater cerebral sensitivity towards ischemia [9].

Neuronal reparation. It is mainly caused by a genetic upregulation, between 4 and 24 hours after reperfusion, which induces greater production of endothelial growth factor and erythropoietin (EPO). EPO stimulates neurogenesis in animal ischemia-reperfusion models, decreases neuronal damage and improves long-term cognitive outcomes. EPO and EPO-receptors have been detected throughout the central nervous system, as well as an increase in their levels following hypoxic events. EPO crosses BBB (despite a large molecular weight) and has a very interesting therapeutic window in ischemic events. Its effects involve several cellular levels in the brain: it increases tolerance to ischemia and regeneration of astrocytes, improves differentiation, regeneration and survival of neurons; increases regeneration of oligodendrocytes and preserves vascular regeneration as well as the integrity of the BBB following an ischemic vascular event [10].
GABA-A agonists, such as pregnanolone – a steroid with anaesthetic effects – and sevoflurane are other drugs with neuronal regeneration properties.

63.5 Concrete Strategies for Cerebral Protection

Global strategies for neuroprotection have been described in the section above. Nevertheless, from a practical point of view, it is more useful for physicians to know the potential and applications of measures at their disposal.

63.5.1 Control of Physiological Parameters

At present, this is probably the best modality of cerebral protection [11]. Control and maintenance of arterial pressure, oxygenation, hydroelectrolitic balance and CO_2 exchange are key points for final outcomes in several neurocritical pathologies; regardless of whether they are focal or diffuse. However, there is less clear evidence that ideal values of these parameters should be generalized for all patients. That is the reason why cerebral monitoring represents a helpful complement. Neuromonitoring – cerebral perfusion pressure (CPP), jugular bulb oxygen saturation (SjO_2), tissue oxygen pressure ($ptiO_2$), transcranial Doppler, cerebral microdialysis, electroencephalography, etc. – should be used, where possible, according to each patient's pathology, in order to optimize physiological parameters. Since the development of specific neurocritical ICUs has been shown to improve the prognosis of many of these pathologies when compared with general ICUs, admitting neurocritical patients into specialized units could be considered a neuroprotective measure.

Hypoxemia and Hypotension

Hypoxemia and hypotension during the acute phase of cerebral injury are associated with poor prognosis and should be treated aggressively [12]. Oxygen therapy should be focused on maintaining normal oxygenation ranges (SpO_2>94%) as hyperoxia during reperfusion may stimulate ROS synthesis and oxidative stress. Hyperoxia has also been shown to reduce lactate levels in cerebral microdialysis, but not the lactate/piruvate rate, which is a more reliable indicator of the energetic state. In addition, lactate may be used as an energetic substrate in case of severe metabolic depletion in the brain. These findings explain why hyperoxia may be harmful in this setting.
Hypotension induces a global reduction in CPP and cerebral blood flow. The initial objective should be to maintain CPP within a target range of 60 to 70 mmHg. Excessive fluid administration may be harmful, due to increased cerebral swelling in case of BBB disrup-

tion. Furthermore, arterial hypertension may contribute to vasogenic cerebral swelling in the case of cerebral autoregulation abnormalities, which are frequently established following severe acute injuries. Nevertheless, mild hypertension may be recommended after SAH secondary to cerebral aneurysm rupture, once endovascular coiling or surgical clipping has been performed, in an attempt to avoid vasospasm [13].

Control of arterial blood pressure may reduce cerebral swelling and the risk of hemorrhagic transformation following stroke. Nevertheless, this effect must be balanced against the risk of decreasing perfusion in the penumbra areas. Antihypertensive treatment is discouraged for patients who are non-candidate for thrombolytic therapy, unless diastolic blood pressure is above 120 mmHg or systolic above 220 mmHg. Anti-hypertensive drugs are recommended for patients following thrombolytic treatment, within the first 24 hours, if diastolic or systolic blood pressure are above 110 or 185 mmHg respectively [14]. Despite the lack of clear evidence in spontaneous cerebral hemorrhage, recent studies suggest that maintaining systolic blood pressure below 140 mmHg may reduce hematoma growth [15].

Fluid Management and Transfusion

As a rule, normovolemia is the therapeutic target and, in any case, hypovolemia and hypo-osmolarity should be avoided. Since the brain is very sensitive to secondary injury induced by ischemia, anemia should also be avoided. Hemoglobin levels of 7-8 g/dl appear to be safe for stable patients. On the other hand, acute patients may have a reduced tolerance to anemia. In those cases, the risk-benefit ratio of blood transfusion versus anemia should be assessed [16].

Recent studies have suggested that anemia can foster protective responses in the brain, mediated by ischemic preconditioning, EPO release, β2-adrenergic stimulation, and nitric oxide synthase; but these hypotheses still need clinical confirmation [17]. Monitoring can help in taking individualized decisions for these patients regarding transfusion therapy. Some coexisting diseases (such as coronary disease) may also affect the transfusion threshold.

Concerning osmotic treatment, mannitol is still the most used drug for neurocritical patients, particularly for treating intracranial hypertension [18]. Hypertonic saline solutions are a point of debate: they improve hemodynamic and blood viscosity, reduce endothelial swelling and capillary resistance, but they may cause renal failure, rebound intracranial hypertension, coagulopathy, hypervolemia and electrolytic disturbances [19].

Ventilation

Neurological patients frequently need mechanical ventilation, sometimes for long periods. Ventilation strategies should be aimed at maintaining an adequate gas exchange, minimizing the risk of ventilation-associated lung injury. Cerebral vessels are sensitive to extracellular pH changes caused by ventilation, thus in the range of a $paCO_2$ of 20 to 60 mmHg, cerebral blood flow varies about 3% per mmHg of $paCO_2$. Hypercapnia causes cerebral vasodilatation and, consequently, an increase in cerebral blood volume and blood flow, as well as in intracranial pressure. Hypocapnia (hyperventilation) induces the opposite effects; however, the possibility of critical reductions of blood flow in areas at risk of ischemia should be taken into account. Hyperventilation is effective during brief periods, because extracellular pH tends to normalize a few hours after its instauration, and a rebound phenomenon can even develop once intentional hypocapnia has ceased. After acute neurological injuries, normocapnia is generally recommended, with short periods of hypocapnia in case of severe neurological compromise, whenever unrespon-

sive to other therapies, and preferentially guided by cerebral oxygenation monitoring (SjO_2, $ptiO_2$) and/or microdialysis. Reducing ventilatory dead space, avoiding patient fight against the ventilator, checking permeability of orotracheal tube and procedures directed at increasing lung compliance (i.e. evacuating pleural effusions or severe ascites) are relevant issues for maintaining normocapnia. Hypercapnia is counterproductive and, basically, it should be avoided [20], although some recent investigations have suggested some neuroprotective effects of mild hypercapnia after global cerebral ischemia, possibly via the activation of the hypothalamic-pituitary-adrenal axis, exertion of anti-inflammatory and antioxidant effects, and release of neurotransmitters. However, the real role of hypercapnia in brain injuries remains to be clarified, since deleterious effects may outweigh the possible benefits [21].

There is controversy regarding the use of protective ventilation in patients with neurological injuries, based on a low fraction of inspired oxygen, low tidal volumes and high positive end-expiratory pressure (PEEP). This pattern is often associated to hypercapnia and decreased venous return – the latter mediated by high intrathoracic pressures –, both of which may increase intracranial pressure. PEEP can provide cerebral benefits when its value is lower than intracranial pressure and it enhances pulmonary compliance, thus improving CO_2 exchange -via alveoli recruitment- and contributing to cerebral blood flow redistribution (mainly venous). Nevertheless, if PEEP provokes pulmonary overdistension, the net effect can be deleterious [12]. In case of "conflict of interest" between the brain and the lung, putting cerebral protection before protective ventilation is highly recommended [22].

Glucose

Hyperglycemia could simply be a marker of severity of the brain injury; however, without an adequate oxygen supply, its presence increases anaerobic metabolism thus generating acidosis and worsening ischemic injury. Some clinical trials carried out in critical care populations showed a lower intracranial pressure, fewer complications and even lower mortality, when comparing a tight control of glucose blood level versus a liberal one. Whether glucose value *per se* is more relevant than the insulin administered to maintain that glucose blood level is still controversial, and so is the ideal glucose value (microdialysis patterns characteristic of metabolic neuronal suffering have been observed in patients with glucose levels considered normal in other critical patients) [23]. The glucose threshold in neurocritical patients might be about 140 mg/dl but no definitive data are available on this point.

63.5.2 Therapeutic Hypothermia

Despite not being a drug, it is considered a medical treatment. Its protective effect is beyond decreasing metabolic requirements since it reduces extracellular acidosis, swelling and the release of excitatory aminoacids and free radicals. Besides, it may play a role in repairing BBB integrity, reducing apoptosis and eliminating intracranial gradients of temperature [24]. Cerebral temperature is usually 1°C above core temperature, but differences up to 2°C among different areas of the brain can be observed [25].

Clinical benefits derived from hypothermia probably depend not only on the type of neurological pathology, but also on the precociousness and speed of cooling, the temperature achieved (the protective effect seems to disappear above 35°C, and the complications rate increases below 32°C), the method used for cooling, the duration of hypothermia – which should be guided by clinical targets such as the control of intracranial pressure – and finally, the rewarming rate (much of the benefit can be lost if the patient

is rewarmed too fast, independently of the nature of injury) [26]. Therefore, the experience of the centre where therapeutic hypothermia is instituted may be a critical factor.
Mild to moderate hypothermia (33-34°C) in comatose survivors of out-of-hospital cardiac arrest, induced within hours of resuscitation and maintained for 12-24 hours, has demonstrated a reduction in mortality [27]. One meta-analysis showed that the number of patients needed to be treated (NNT) in order to prevent one death was 6, and NNT in order to obtain an optimized neurological recovery was 7. According to this evidence, the 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care included the following recommendations [28]:

- Comatose (i.e., lack of meaningful response to verbal commands) adults patient, with return of spontaneous circulation (ROSC) after out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C-34°C for 12-24 hours.
- Induced hypothermia may also be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole.
- Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (>32°C) after resuscitation from cardiac arrest during the first 48 hours after ROSC.
- Patient core temperature should be closely monitored after ROSC and interventions should be performed to avoid hyperthermia.
- Additionally, the 2010 European resuscitation council guidelines for resuscitation stated that a child with ROSC but remaining comatose after cardiopulmonary arrest might benefit from being cooled to a core temperature of 32-34°C for at least 24 h. The successfully resuscitated child with hypothermia and ROSC should not be actively rewarmed unless the core temperature is below 32°C. Following a period of mild hypothermia, the child should be rewarmed slowly (at 0.25-0.5°C/h) [29].

Moderate whole-body hypothermia (rectal temperature of 33.5-34.5°C) for 72 hours in term neonates with clinical and electrophysiological evidence of perinatal hypoxic-ischemic encephalopathy attributable to perinatal asphyxia showed a strong neuroprotective effect [30], and substantially – although incompletely – reduces neurological disability [31]. Hypothermia must be started within 6 hours of birth and rewarming should last at least 4 hours
The NABISH study, one of the biggest trials run on moderate hypothermia (32.5-34°C), failed to demonstrate either reduction of mortality or functional improvement in adult patients suffering from severe TBI, except for the subgroup of patients younger than 45 who were hypothermic on admission [32]. The recently published NABISH II clinical trial, which evaluated moderate early hypothermia (33°C) for 48 hours in adults younger than 45, has been cancelled without completion of the estimated sample size due to futility, although the subgroup of patients with drainable mass lesions might benefit for hypothermia effect [33].
The methodology of the NABISH trials has been criticized, especially by those who claim that hypothermia contributes to better outcomes provided that it is used with a concrete therapeutic goal (i.e., control of intracranial pressure), without a pre-established duration and checking adverse effects. A systematic literature review concluded that there may be a trend to therapeutic benefits when using hypothermia in patients with severe head injury, but the recommendations are not strong enough due to a lack of studies with adequate methodological quality. The Cochrane Collaboration corroborated these findings [34] and showed an increased rate of pneumonia in TBI patients treated with hypothermia, especially when it was associated to barbiturates. Results for pediatric severe trauma are also contradictory: it appears to improve intermediate outcomes, such as intracranial pressure or cerebral edema, but it has not shown any definitive benefit in

terms of survival. Regarding spinal cord injury, there is not clear evidence to recommend for or against the practice of therapeutic hypothermia as a treatment [35]
Indeed, one of the major limitations of hypothermia as a therapeutic measure is the development of complications, especially infectious ones, but also thrombocytopenia, acidosis, insulin resistance, and pancreatitis, which appear to increase the deeper and the longer the hypothermia is. Consequently, physicians should be aware of these complications and treat them early. At present, at least two large randomized clinical trials for evaluating hypothermia in severe TBI patients are being developed: one in Japan and the European Eurotherm trial. Their results will clarify the role of hypothermia as a cerebral protective measure in this disease.
Concerning stroke, current evidence for hypothermia is still scarce and limited to case series and pilot studies. In these patients, hypothermia presents another limitation to its use, as most of them are conscious at the time of hospital admission and do not tolerate cooling. Furthermore, whether or not the association of hypothermia with fibrinolytic therapy enhances neuroprotection is currently being studied [24].
As far as HSA treatment and surgical aneurysm clipping are concerned, a clinical trial which included 1001 patients (IHAST trial), failed to demonstrate any benefit of intraoperative hypothermia in terms of mortality or neurological recovery. Moreover, an increase in the rate of bacteriemia, close to statistical significance, was found in the hypothermia-treated group, discouraging routine use for this indication [36].
Leaving aside the possible beneficial effect of hypothermia, it seems that hyperthermia in patients with neurological injuries is detrimental. Fever increases metabolic rate, triggers the release of excitatory aminoacids and free radicals, and aggravates the damage of the BBB and proteolysis of cellular cytoskeleton. Besides, fever duration influences both vital and neurological prognosis. Therefore fever should be prevented and treated [37], although each type of injury may have an optimal time-window for fever control.
Because we need a balance between limiting secondary injury and impairing the ability to fight against infections, it seems reasonable to control fever aggressively during the first hours to days after spinal cord injury, intracerebral hemorrhage and TBI. In SAH patients the risk period for hyperthermia consequences is more prolonged, since fever can favour vasospasm even some weeks after the hemorrhage [25]. Pharmacologic interventions (mainly acetaminophen), external cooling, maintaining infections surveillance and avoiding shivering can be an appropriate approach to fever prevention and management.

63.5.3 Thrombolysis, Anticoagulants and Antiplatelet Drugs

The main priority in the treatment of stroke is restoring normal cerebral blood flow. The only widely accepted treatment is reperfusion, mediated by intravenous administration of recombinant tissue plasminogen activator (r-tPA) at a dose of 0.9 mg/kg, with a maximum of 90 mg (10% administered as a bolus and the remainder as a continuous infusion for 1 hour). Nevertheless, few patients admitted to hospital with stroke may benefit from reperfusion due to the strict inclusion criteria for therapy that excludes the majority of patients from effective therapy [38] (Table 63.1).
Despite improvement in care after reperfusion, experimental and clinical data indicate that the benefits of thrombolysis with r-tPA are limited due to the narrow therapeutic range. The earlier the treatment is administered, the more effective it is. It has been approved for use within 3 hours from stroke onset. It should neither be given neither more than 4.5 hours after onset, nor in cases of extensive infarctions involving the middle cerebral artery. Elderly patients (>80) also benefit from thrombolysis, although they showed worse outcomes after the treatment than younger patients [39].

Inclusion criteria	Exclusion criteria
• Ischemic stroke with specific start point • Measureable neurological damage • Radiologic evidence ruling out hemorrhage	• Stroke or severe traumatic brain injury in the previous 3 months • Major surgery in the previous 14 days • Previous history of intracranial hemorrhage • SBP >185 mmHg or DBP >110 mmHg • Symptoms suggesting subarachnoid hemorrhage • Digestive bleeding or gross hematuria in the previous 21 days • Non-compressive arterial puncture in the previous 7 days • Seizures as the initial clinical presentation of stroke • Increase in aPTT, PT >15 seconds or INR >1.4 • Platelet count $<100x10^9/mm^3$ • Glucose blood level below 50 mg/dl or above 400 mg/dl

Table 63.1. **Criteria for intravenous tissue plasminogen activator administration after stroke.**

aPTT = activated partial thromboplastin time
DBP = diastolic blood pressure
INR = international normalized ratio
PT = prothrombin time
SBP = systolic blood pressure

Patients must be monitored intensively at least 24 hours after thrombolysis. Cerebral hemorrhage is the main adverse effect (6.4% versus 0.6% of patients not receiving r-tPA). If thrombolysis is delayed, the risk of bleeding increases, especially more than 3 hours after stroke, although, mortality does not appear to increase. Induced upregulation of MMP-9 alters BBB, facilitating bleeding. Despite these adverse effects, NNT of r-tPA to produce significant improvement in functional outcome is 3, while NNT to cause damage is 30 [40]. Induced hypothermia may have a preventive effect on hemorrhagic conversion after r-tPA administration, although results of studies in this regard are not conclusive; as well as minocycline, which reduces the activation of microglia and cytokines production, and inhibits MMPs. In the event that bleeding is suspected, r-tPA should be stopped (if still running) and CT-scan should be performed, as well as a blood cell count and a coagulation test. In addition to platelets, fresh frozen plasma or cryoprecipitate must be available. If CT-scan rules out hemorrhage, r- tPA infusion can be restored. When cerebral hemorrhage is confirmed, laboratory tests must be checked, plasma and platelets must be administered, and the neurosurgeon must be alerted.

Another relevant adverse effect of r-tPA is orolingual angiedema (5%). Antihistamines and corticosteroids may be effective in this case. Finally, it may have neurotoxic potential due to the activation of glutamate receptors, especially in astrocytes.

Use of anticoagulants is not recommended for stroke, except in cases of cerebral venous sinuses thrombosis. Unfractionated heparin is indicated for this particular condition during the acute phase, even in the presence of hemorrhagic infarction, continuing treatment with vitamin K antagonists for up to 12 months and maintaining an international normalized ratio (INR) of 2.0-3.0. In those patients suffering a stroke, who are not candidates for thrombolysis, antiplatelet drugs may be used. Acetylsalicylic acid at doses of 300 mg reduces the recurrence of ischemic stroke without increasing bleeding risk. Due to lack of evidence, neither clopidogrel nor platelet receptors inhibitors IIb/IIIa (e.g. abciximab) are recommended. After non-cardioembolic stroke, preventive treatment with an antiplatelet agent is encouraged. In cases of atrial fibrillation in patients who have suffered stroke or recent transient ischemic attack, anticoagulation (INR 2.0-3.0) is recommended. If anticoagulation is contraindicated, aspirin 75-325 mg a day may be a valid alternative. In patients with mitral valve prolapse and transient ischemic attack or stroke, antiplatelet therapy is encouraged.

Antiplatelet agents and intrathecal fibrinolytic agents have also been tested in SAH in order to reduce the risk of delayed cerebral ischemia secondary to vasospasm, although current evidence does not support the routine administration of these drugs [41,42].

63.5.4 Anesthetics

Anesthetics have the potential to reduce cerebral metabolism. In this respect, the mechanism of action of barbiturates, propofol or halogenated inhalational agents (isoflurane, sevoflurane, desflurane) is based on enhancing GABA stimulation – which is the main inhibitory neurotransmitter in the brain –, and counteracts the deleterious effects of glutamate. Nitrous oxide, ketamine and xenon act by inhibiting the NMDA receptor, which mediates the effect of glutamate. Thiopental and propofol may also act by reducing free radicals; and the latter exerts antiapoptotic and anti-inflammatory properties [43].
When administered before an ischemic event, and given at usual clinical doses, anesthetics can contribute to preconditioning, by opening potassium channels, thus hyperpolarizing the cell.
Thiopental is still considered the anesthetic benchmark in terms of protection, being the only one to have demonstrated neuroprotective efficacy in a clinical trial. That study included patients who underwent heart valve surgery with cardiopulmonary bypass [44]; but the result could not be replicated in other surgical populations or in patients who had suffered a cardiac arrest. Barbiturates are used for cerebral protection in many circumstances, including trauma, stroke, carotid endarterectomy and even the clipping of cerebral aneurysms, although benefits are not as obvious as it was thought in the past. Moreover, their use delays postoperative recovery and has immunosuppressive effects, due to which interest in these agents has declined.
Many authors support the effectiveness of anesthetics in neuroprotection based on two facts: firstly, the reduced incidence of stroke occurring during the intraoperative period. Secondly, the effectiveness of anesthetics in the prevention of neuronal death by necrosis and to a lesser extent, to apoptosis, has been demonstrated at an experimental level. Nevertheless, critics argue that these results have not been clinically proven yet, and that anesthetics may promote neuronal degeneration and apoptosis by altering the GABA-glutamate balance needed for an adequate neuronal maturing. More conciliatory positions suggest that anesthetics delay neuronal death by enhancing the ischemic threshold, thus they may be effective in protecting against mild brain damage and, in any case, they can increase the margin of time in order to implement other protective measures [3].
Lidocaine, administered at usual antiarrhythmic doses (1 mg/kg bolus and infusion at 1-2 mg/h), acts by blocking sodium channels which, added to its inhibitory effects on cerebral metabolism and leukocytes activation, confers neuroprotective potential. However, results in clinical trials, basically in cardiac surgery, have not been conclusive [45].

63.5.5 Corticosteroids

Corticosteroids exert anti-inflammatory properties and stabilize membranes; decrease brain edema and foster regeneration of the BBB. However there is only evidence of neuroprotective effectiveness in the peritumoral brain edema (mainly metastatic), in bacterial meningitis (mainly in children) and probably in tuberculosis meningitis [46].
The Cochrane Collaboration reviews have shown a lack of protection of corticoids after an acute ischemic or hemorrhagic stroke, although a recent trial has suggested an improvement in the functional outcome after SAH for patients receiving 16 mg/kg of meth-

ylprednisolone for three days [47]. In TBI, the CRASH trial had to be cancelled after the randomization of 10,000 patients (half of the estimated sample size), because one interim analysis reflected an increase in mortality for those patients receiving high doses of methylprednisolone, compared to those receiving placebo [48].
Concerning traumatic spinal cord injury, the NASCIS trials concluded with this recommendation: "Early administration of high doses of methylprednisolone (30 mg/kg bolus in 30 minutes + 5.4 mg/kg/h) for 24-48 hours can be used, considering that related complications might overcome anticipated benefits of this treatment" [49].
However, we should not confuse the protective and the therapeutic role of steroids. One systematic review of the literature suggests that pituitary dysfunction after TBI and SAH occurs about 27.5% and 47% respectively, although most of them can go unnoticed. The most common deficits are growth hormone and ACTH related. Diagnosis is based on stimulation tests, which are often not feasible in the neurocritical patient. However, cortisol basal levels can even be obtained in the acute phase of the injury. Cortisol levels below 7.2-18 μg/dl (200-500 mmol/l), when associated to adrenal gland deficit signs and symptoms (such as hyponatremia, hypoglycemia or hypotension), can be inadequate, and those patients might be good candidates to receive steroid therapy [50]. Finally, we should not forget that steroid therapy is considered an independent risk factor for the development of hyperglycemia, myopathies and critical patient neuropathy, which suggests that corticosteroids may have a harmful role for the Peripheral Nervous System.

63.5.6 Calcium Channel Blockers and Magnesium

Calcium channel blockers mainly exert their effect through decreasing the contraction of the vascular smooth muscle, promoting vasodilatation, increasing cerebral blood flow and avoiding vasospasm. Vasospasm is closely linked to the development of delayed ischemic deficits after a brain injury. Nimodipine 60 mg/4h per os has been associated to a decrease in vasospasm and improvement in the outcome of patients after SAH, with few side effects [51]. Nimodipine effectiveness has also been shown in patients suffering vasospasm after TBI, although the evidence is weaker in this pathology.
Most brain injuries are associated to low serum levels of magnesium and the benefit of maintaining blood values over 1.5 mmol/l for this group of patients has been proposed. On the one hand, magnesium acts by blocking glutamate in the NMDA receptor, lowering intracellular calcium concentration, and thus limiting enzyme activation and ischemic cellular necrosis. On the other hand, it enhances nimodipine action, and inhibits platelet aggregation and ROS liberation.
The effectiveness of magnesium sulphate was evaluated in the IMAGES trial, involving 2,589 patients, who were treated with magnesium or placebo in the following 12 hours after an acute ischemic stroke. After 90 days, there were no differences between groups in mortality or neurological recovery, even in the subgroup of patients treated in the first 6 hours after the stroke [18]. FAST-MAG trial, to evaluate field initiation (within 2 hours) of magnesium sulphate neuroprotective therapy after acute stroke (16 mmol over 15 minutes + 65 mmol over 24 hours) has reached 75% of enrolment by the end of May 2011 [52].
For patients suffering SAH, there is some evidence that after treatment of the aneurysm, daily intravenous infusion of 64-96 mmol of magnesium (8-12 g) for 14-21 days decreases the number of 90 days-delayed ischemic deficits and improves functional recovery, although no effect has been proven in terms of mortality [53]. However, the recently published data of the IMASH trial, which compared magnesium sulphate infusion

with placebo do not support a clinical benefit of magnesium sulphate infusion over placebo [54].
Regarding TBI, one recent trial involving more than 500 patients assessed the administration of magnesium in the first hours after injury. No benefit has been shown with magnesium treatment, and even those patients receiving higher doses of the drug developed a worse functional outcome. Currently there is no evidence to support the use of magnesium salts in patients with TBI [55].
Magnesium neuroprotective effects have been also tested in patients at risk for preterm delivery. The available evidence suggests that magnesium sulphate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Ideal candidates [56] and the dose regimen remain still unclear [57].
Magnesium related adverse effects are scarce: muscular weakness, areflexia, bradycardia and hypotension when magnesium blood level is over 3-5 mmol/l have been described. Minor reactions, such as pain on injection or nausea are more frequent, but they can be avoided by diluting the drug (<0.5 mmol/ml) and administering it slowly (<30 ml/h).

63.5.7 Statins

Statins are 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors used in the prevention of cardiovascular diseases and atherosclerosis associated to hypercholesterolemia, and they show high affinity with the enzyme about 1000 times higher than the natural particle HMG-CoA [18].
Statins treatment seems to develop protective properties in strokes, especially for high-risk patients (those with coronary artery disease, diabetes or hypertension). In a recent meta-analysis, a reduction of 21% of these events has been shown. These data have increased the interest in this group of drugs as neuroprotective. Several mechanisms have been proposed to explain this protective effect. Lipid metabolism effects, especially reduction in LDL lipoproteins and cholesterol have been associated to a reduction in the vascular wall thickness and platelet aggregation. Besides, statins cause an up-regulation in the endothelial nitric-oxide synthase, and they inhibit the activation in astrocytes of inducible nitric-oxide synthase, which exerts neurotoxicity. They enhance the activation of the plasminogen tissular activator and the inhibition of the plasminogen inhibitor, decreasing hypercoagulability states. Lastly, they exert antioxidant and anti-inflammatory properties, as well as fostering regeneration and neuronal plasticity by mobilizing endothelial stem-cells [58].
Due to this potential, these drugs are being tested in several studies. Recent evidence across phase II studies suggest a reduction in the incidence of vasospasm, and better outcome, after the administration of pravastatin 40-80 mg for 14-21 days after SAH. One recent meta-analysis dealing with statins therapy for SAH concludes that they reduce the incidence of vasospasm, with a NNT of 6.1 patients; the incidence of delayed ischemic deficits related to vasospasm (NNT of 5.0), and even mortality (NNT 6.7). The authors of this meta-analysis recommend the administration of statins to all patients, after SAH, where there is no contraindication, although there is a lack of knowledge of the ideal treatment length [59]. However, the small number of patients included in this meta-analysis (158) suggests that before extending statins administration on this indication, we should wait for the results of the large STASH trial, which is currently running. It seems suitable to maintain statin therapy in those patients previously taking these drugs, when admitted with acute neurological damage, especially in those patients suffering hemorrhagic or ischemic strokes.

Several adverse effects of statins have been described, but only liver enzymes elevation and myopathies seem relevant. These effects are mainly produced in elderly patients, those with liver failure or hypothyroidism, and those taking fibrates, cyclosporine, and antifungal drugs containing the azolic ring, macrolides, verapamil, diltiazem or amiodarone.

63.5.8 Erythropoietin (EPO)

EPO and its receptor are expressed in almost all cells within the Central nervous System. EPO improves tolerance to ischemia due to anti-apoptotic and preconditioning properties; acts as a free-radical scavenger of ROS and suits cellular regeneration. Weekly subcutaneous injection of 40,000 UI of EPO up to three doses is being tested in a phase III trial in TBI patients (NCT00987454). A German phase II study has shown positive results after the administration of recombinant EPO 33,000 IU/day for three days in stroke patients [60], but these results have not been confirmed in a subsequent trial using 40,000 IU/day for three days, and even mortality was increased in the EPO arm of the trial [61]. Three doses of 30,000 IU every 48 hours were associated with a reduction in the incidence of severe vasospasm and in the development of delayed ischemic deficits compared to placebo in patients suffering SAH [62], but 6 months outcome was not different between groups. Younger patients taking statins simultaneously seemed to get the most benefit from the EPO protective effect [63].

EPO studies are also being carried out after perinatal hypoxic encephalopathy. There seems to be a positive effect after the administration of 300-500 IU/kg of EPO every 48 hours for two weeks in terms of the neurological outcome; however, these results are awaiting confirmation in phase III studies.

Overall, high and repeated doses seem to be associated to better results in terms of neuroprotection, because of the low capability of EPO for BBB penetration. Potential thrombotic adverse effects of high doses of this drug, through an increase in blood viscosity and platelet activation, might stop the development of this treatment. That is why we cannot recommend the systematic administration of EPO for neuroprotection while waiting for the results of larger randomized clinical trials. Development of new recombinant forms of EPO, free of the hematopoietic properties might minimize side effects of this drug [64].

63.5.9 Antiepileptic Drugs

Seizures can be included in the clinical presentation of several injuries in neurocritical patients. Seizures worsen secondary brain injury because they increase oxygen consumption and intracranial pressure, and can impair the outcome, as well as delay recovery [65]. An electroencephalogram should be performed to every patient with high suspicion of seizures, and should be considered in patients without improvement in the level of consciousness after a neurological event, to rule out non-convulsive status epileptic.

Every clinical condition and even every patient needs an individual evaluation to start antiepileptic treatment. As a rule, we can say that prophylaxis or treatment is indicated for patients with witnessed seizures, or patients with high risk of development of seizures. However we should neither establish prophylactic treatment systematically to all neurocritical patients, nor extend treatment, since short-term adverse events and long term cognitive dysfunction associated to antiepileptic drugs, may overcome benefits of the treatment in low risk seizures patients.

Antiepileptic drugs can be used in addition to hypothermia in children with hypoxic perinatal encephalopathy.

63.5.10 Other

Several other drugs are being studied in order to evaluate their role as neuroprotection agents. Some examples are:

- **Caspase inhibitors**. Caspases are the enzymes in charge of apoptosis mechanisms. Minocycline and dexamethasone can act at this level. Promising results have been obtained with minocycline [66], and there are at least three clinical trials under investigation to evaluate its effects after an acute ischemic stroke.
- **Prevention of mitochondrial dysfunction**. The role that experts give to mitochondria in the maintenance or derangement of the cellular structure is becoming more and more relevant. Cyclosporine A might preserve the integrity of the transitional pore in mitochondrial membrane, avoiding the entry of calcium, edema and destruction. The optimal dose seems to be 2.5 mg/kg over two hours followed by a continuous infusion of 5 mg/kg/day for 72 hours [67]. Phase III studies with cyclosporine A are currently being developed in severe TBI. Voltage dependent calcium channel blockers may also act at the mitochondrial level, and they are being tested in some experimental studies.
- **Scavengers of free radicals**. After the failure of clinical trials with tirilazad [68] and NXY-059 [69] in patients with stroke, there are other promising scavengers being studied, such as edaravone and albumin, which in addition might decrease cerebral edema after an ischemic event. Its protective effects is being currently tested in the ALIAS trial (NCT 00235495), comparing 2.0 g/kg of iv albumin 25% and equivalent volume of saline control, infused over 2 hours, started within 5 hours of stroke onset [70].
- **Female hormones**. Oestrogens might inhibit apoptosis and promote vasodilatation, improving blood flow. Progesterone may improve brain edema by collaborating in the repair of the BBB, upregulating GABA receptors and inhibiting apoptosis. Current clinical evidence from three small randomized clinical trials indicates progesterone may improve the neurologic outcome of patients suffering TBI [71]. This evidence is still insufficient, and a multicentre, randomised double blind study is currently underway (NCT00822900).
- **Nitric oxide and nitric oxide synthase inhibitors**. Nitric oxide is produced from L-arginine, through different types of nitric oxide synthase (inducible, endothelial and neuronal), and plays a key role in the regulation of vascular tone. High concentrations of nitric oxide may be excitotoxic, damaging DNA and promoting apoptosis, as well as ROS. Therefore, blocking the inducible form of nitric oxide synthase may be beneficial.
- **Antagonism of bradykinins**. After cerebral damage, inflammatory kinins are released, worsening secondary brain damage. Therefore, blockade of bradykinin B2R might represent a therapeutic approach in the pharmacological treatment of TBI, however, there is no reliable evidence that B2R antagonists are effective in reducing mortality or disability after TBI, although well-designed randomized clinical trials are needed [72].
- **Neurotransmitters blockade**, neurotrophic factors and some proteins of coagulation cascade are also neuroprotective targets, which are being investigated in different pathologies.

63.6 Cerebral Protection in Cardiovascular Surgery

Patients undergoing cardiac surgery have a considerable risk of neurological injuries, due to embolic strokes, and the inherent risks of cardiopulmonary bypass, which is associated to hypoperfusion, ischemia-reperfusion injury, cellular edema and cerebral swelling. Stroke after cardiac surgery is below 1% in patients younger than 65 years old under coronary bypass, about 5% in patients between 65 to 75, and 7-9% in those above 75.

About 30-40% of cardiac surgery patients develop postoperative cognitive dysfunction several weeks after the surgical procedure. Apart from previous cerebral vascular diseases, advanced age and female sex are well known, but unmodifiable risk factors for neurological complications. Protective approaches in this setting are based on reducing sources of damage (embolism and hypoperfusion), as there is no current evidence of the effectiveness of any neuroprotective drug. Barbiturates have been the only agents showing protection in a randomized clinical trial, the methodology of which has been questioned [45].

The incidence of stroke for patients younger than 60 years old, undergoing aortic arch surgery is about 1%, but it rises to 20% in older patients. The traditional approach to brain protection used in this surgical procedure was deep hypothermic circulatory arrest (≤20°C). Brief periods of circulatory arrest (less than 20-25 minutes preferably) and deeper hypothermia improve the effectiveness and safety of this technique without the development of neurological damage in most patients. Rewarming must also be carefully carried out, taking at least 20-30 minutes to complete, and avoiding hyperthermia.

Alternatives that are more recent allow an increase of the period of circulatory arrest; such as antegrade brain perfusion (via arterial perfusion) or retrograde brain perfusion (via venous perfusion). These techniques decrease the risk of global cerebral hypoperfusion, but they also have some limitations. Retrograde perfusion has been associated to cerebral swelling, intracranial hypertension or hemorrhages, whilst antegrade perfusion extends the time period needed to control vessels in order to be perfused and increases the risk of embolic events because of dislodgement of a calcium plaque [73].

Antegrade perfusion may extend safety time for circulatory arrest up to 80 minutes. Blood flow should be started with 10 ml/kg/min and must be adjusted to maintain a cerebral perfusion pressure of 40-60 mmHg, at a temperature of 10-13°C. During this period, electroencephalographic burst suppression should be maintained, as well as jugular blood oxygen saturation, when available, above 90-95%. Transcranial Doppler monitoring of the flow in the medium cerebral artery is advisable. Retrograde perfusion can get homogeneous brain cooling, but it does not seem to extend the safety period for circulatory arrest longer than 30 minutes. Blood temperature should be 10-12°C and flow should avoid a pressure in the superior cava vein greater than 20-25 mmHg (100-150 ml/min) in order to decrease the risk of brain edema.

Different drugs have been used regarding pharmacological protection for aortic arch surgery. Some of them are barbiturates (5 mg/kg before circulatory arrest), lidocaine 200 mg to stabilize the neuronal membrane, 2 g of magnesium sulphate; mannitol (0.25-0.5 mg/kg) to decrease brain edema, steroids for stabilizing the BBB, nimodipine, aprotinine and even beta-blockers; but none of them is supported by evidence enough for the systematic administration to be recommended.

In carotid surgery, stroke incidence ranges between 1.5-2.8% of patients. Endovascular treatment (arterial dilation and stent placement) has not shown any definitive bene-

fit in terms of stroke or death, compared to open surgery, although the development of filters to capture embolic particles can improve the outcome after endovascular treatment. Patients undergoing stent placement must be treated with double antiplatelet drugs (acetylsalicylic acid + clopidogrel), while those undergoing open surgery may benefit from treatment with acetylsalicylic acid 50-100 mg/day.

Anesthetic technique is also a source of debate, because local anesthesia allows the early detection of intraoperative neurological deficits and optimizes shunt usage. In spite of some observational studies suggesting benefits with regional anesthesia in terms of mortality and cerebral stroke reduction, the GALA trial -which included more than 3,000 patients under carotid endarterectomy- has not demonstrated any benefit of regional anesthesia compared to general anesthesia in terms of stroke, myocardial infarct or mortality [74].

Blood pressure control after carotid procedures is very relevant. Pressure should be maintained at about 10-20% of baseline values, because hypertension can be associated to cerebral hyperperfusion injury, including frontal headache, focal seizures, edema and hemorrhage. Its incidence is about 0.2-0.7%, but it is associated with a high mortality rate. Etiology is probably linked to an increase in flow after the re-establishment of "normal" perfusion in a chronically maximally dilated arterial bed (hypoperfused brain).

63.7 Neuroprotection. From Past Failure to Future

Many potential neuroprotective therapies tested successfully in experimental models have failed when applied to humans in clinical trials. There are several explanations for this lack of positive results [1]. Firstly, there is great variability in the quality or scope of these pre-clinical studies as reflected in their adherence to the Stroke Therapy Academic and Industry Roundtable (STAIR) guidelines.

Secondly, some consequences triggered after a brain injury might be beneficial in the long term, such as the removal of dysfunctional tissue or ischemic preconditioning, and so, they should not be avoided, but rather promoted.

Thirdly, inappropriate dosage or temporary administration of neuroprotective therapies might mask beneficial effects. Besides, there is a chance that the design and statistical management of clinical trials may not be optimal. Furthermore, in preclinical studies, the targeted variable is usually a reduction in the damaged tissue, while in clinical studies we look for a reduction in mortality or an improvement in neurological outcomes, which are complex objectives, affected by a great number of variables.

Finally, the way of evaluating the outcome might not be the most adequate as it is usually based on "all or nothing type" variables (dead or alive, favourable or unfavourable outcome). New ways of evaluating the outcomes are being currently proposed, based on scales that combine several parameters, on secondary markers of patient outcome or on the "sliding dichotomy" (evaluate the outcome based on the initial severity of the patient). All these measures try to detect possible benefits for patients receiving neuroprotective therapies.

One less pessimistic view of neuroprotection points out that there is still a lack of knowledge about relevant aspects related to the complex progression of neuronal damage. That may be the reason why no one single therapy may provide adequate neuroprotection in all the circumstances, maintaining a reasonable therapeutic window and being free of adverse effects in humans. In the future, neuroprotection may turn towards the judicious combination of therapies at safe and lowest effective doses in order to get better results.

63.8 Summary and Key Points

- Neuroprotection is a challenge for critical care professionals.
- Pathophysiological knowledge of secondary brain damage plays a key role in understanding and applying neuroprotective therapies.
- Several potentially protective therapies or drugs have failed when applied to large populations of patients. For this reason, the development of clinical guidelines for neuroprotection is complex.
- According to the best evidence available, an adequate hemodynamic and respiratory management, cerebral monitoring, and the prevention and active treatment of hyperthermia are key factors in achieving a good outcome in neurocritical patients.
- According to phase III randomized clinical trials, mild hypothermia has proven neuroprotective properties in brain injury after cardiac arrest, in neonatal hypoxic encephalopathy and possibly in selected groups of TBI (young patients who are hypothermic on arrival to the hospital and patients with refractory intracranial hypertension unresponsive to conventional treatment).
- Anesthetic drugs may delay and reduce ischemic neuronal damage, especially when the damage is mild or moderate. They can also show preconditioning properties
- Corticosteroids have not been proven effective in TBI, nor in ischemic or hemorrhagic stroke, and so they should be restricted to tumour-related brain edema.
- Reperfusion with thrombolytic agents is the indicated treatment in the first 3 to 4.5 hours after an ischemic stroke. Early treatment is essential, because a delay impairs effectiveness and increases the risk of hemorrhagic complications.
- Statins may reduce the incidence of stroke and they might be effective in preventing vasospasm after SAH. Consequently, they could be used in the future for prevention of delayed ischemic injuries after SAH hemorrhage, in addition to nimodipine.
- Other potentially effective drugs in terms of neuroprotection are under clinical or preclinical studies.

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64 Antithrombotic Therapy for Secondary Stroke Prevention

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64.1 Introduction

Stroke is the leading cause of morbidity and long-term disability in Europe such as the third cause of death in United States [1]. The minimization of the very high risk of a recurrent stroke in the first 3 months (about 17% [95% confidence intervals (CI) 14-21]) represents an important aspect in the management of ischemic stroke patients [2] such as the reduction of long-term risk of recurrent stroke, myocardial infarction (MI), and death due to major vascular events, which is about 44% (95% CI 42-46) over 10 years [3]. Stroke patients show a high prevalence of coronary or peripheral artery disease (PAD), and an increased risk cardiovascular death [4].

Recurrent strokes are extremely dangerous [5]. Approximately 6-70% of first recurrent strokes have the same mechanism as the incident stroke [6]. Secondary stroke prevention depends on concomitant cardiovascular disorders and stroke subtypes [7]. Hypertension is the main stroke risk factor for intracerebral hemorrhage (ICH) and blood pressure control represents a valid prevention strategy. Risk factor associations differ in ischemic stroke subtypes. Hypertension, smoking, abdominal obesity, dyslipidemia and diabetes are common risk factors for small vessel disease (SVD) strokes [7]. Although the differences between SVD and the other ischemic stroke subtypes are not as great as previously suspected [8], the risk of recurrence varies between stroke subtypes, as well as the differences in degrees of severity and impairment. Lacunar (SVD) stroke shows lower 30-day risk of recurrence, lower 5-year mortality, and better functional outcomes when compared with other subgroups [9]. Large vessel disease (LVD) stroke presents the highest 30-day recurrence of ischemic stroke subtypes while cardioembolic stroke the highest (>80%) 5-year mortality [9].

In secondary stroke prevention, the different vascular mechanisms of stroke must have importance in the choice of strategies to reduce ischemic stroke risk; they depend on the underlying cause of ischemic stroke, and include carotid revascularization, vascular risk factor control, and antithrombotic therapy. Lifestyle and risk factor modifications such as low- fat and low-salt diet, exercise, smoking cessation, and control of blood pressure, glucose, and lipids are appropriate initiatives in all stroke patients who can benefit from them [10]. Endarterectomy or endovascular procedures such as angioplasty and stenting are appropriate procedures in patients with LVD strokes related to severe, extracranial internal carotid artery stenosis. Similarly, those with large vessel disease involving the extracranial vertebral arteries or intracranial arteries may also benefit from angioplasty and stenting, but these procedures are still considered investigational.

Antithrombotic therapy is a key component of any strategy for the secondary prevention of ischemic stroke. A better understanding of the various therapeutic options will lead to improved stroke prevention, better medication adherence, and fewer complications. Antiplatelet agents and anticoagulants are the two major classes of antithrombotic therapy used for stroke prevention. The etiology and mechanism of the stroke must be con-

sidered in order to make the best decision regarding which agent(s) to use for secondary stroke prevention. Antiplatelet therapy is recommended in patients with ischemic stroke of non-cardiac origin decreasing the stroke risk of 11-15% and the composite risk of stroke, MI, and vascular death of 15-22% [11]. Anticoagulant agents are indicated in patients with a high-risk source of embolism such as atrial fibrillation (AF) or prosthetic heart valves and cardioembolic stroke [12].

This chapter will review antithrombotic treatment strategies for secondary ischemic stroke prevention in the context of current best evidence and examine how they may affect the prophylactic antithrombotic management of patients with ischemic stroke.

64.2 Antiplatelet Regimens: Prevention of Recurrent Ischemic Stroke of Non-cardioembolic Stroke (Atherosclerotic, Lacunar, or Cryptogenic Infarcts)

The best antithrombotic regimen is antiplatelet therapy, of which aspirin (ASA) has been the mainstay for the prevention of recurrent ischemic stroke of arterial origin. The AHA/ASA guidelines [12-14] together with other international guidelines recommend antiplatelet agents rather than OAT in patients with non-cardioembolic ischemic stroke or transient ischemic attack (TIA) to reduce the risk of recurrent strokes. For patients with non-cardioembolic stroke, oral anticoagulants are generally not recommended because of both the lack of evidence of greater efficacy and the increased risk of bleeding complications (Table 64.1).

ASA, ticlopidine, clopidogrel, and a combination of ASA plus extended release dipyridamole (ER-DP) (ASA+ER-DP) are the four antiplatelet regimens approved by the US Food and Drug Administration (FDA) for secondary prevention of ischemic stroke. Ticlopidine is virtually no longer used because of its side-effects such as neutropenia, thrombotic thrombocytopenic purpura, gastrointestinal side effects. ASA, clopidogrel, and ASA+ER-DP are currently the recommended antiplatelet agents for secondary stroke prevention (Table 64.1).

Aspirin

Aspirin (ASA) reduces adverse cardiovascular events but increases bleeding in patients with stable cardiovascular disease [17,18]. In doses as low as 75 mg/day it reduces risk of vascular events in patients with previous stroke or transient ischemic attack [19]. Low-dose ASA are associated with low risk of major bleeding (NNH 769 per year) [20]. ASA increases risk of hemorrhagic stroke, but overall benefit on myocardial infarction and ischemic stroke incidence may outweigh its adverse effects on risk of hemorrhagic stroke in most populations [21]. Laboratory ASA resistance associated with increased risk of recurrent cardiovascular events in patients taking ASA for secondary prevention [22]. Concomitant nonsteroidal anti-inflammatory drugs (NSAID) may be associated with ASA resistance [23].

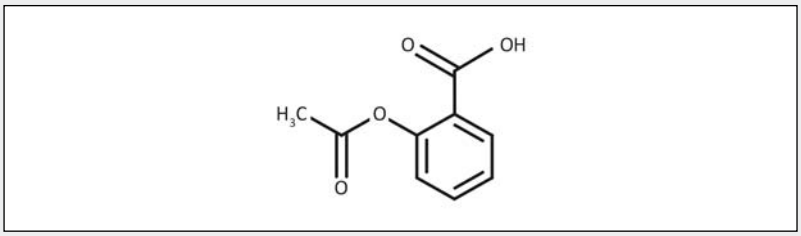
ASA inhibition of COX-1 decreases TXA2 production (Table 64.2) [24]. Like most other NSAIDs, ASA exerts its therapeutic effects by inhibiting prostaglandin G/H synthase 1 and 2, better known as cyclooxygenase-1 and -2 or simply COX-1 and -2. COX-1 and -2 catalyze the conversion of arachidonic acid to prostaglandin G2 and prostaglandin G2 to prostaglandin H2. ASA differs from other NSAIDs because it is an irreversible COX inhibitor. ASA irreversibly acetylates a serine side chain of COX rendering the enzyme inactive. Enzyme activity can only be regained by production of more cyclooxygenase. This

For patients with non-cardioembolic stroke or transient ischemic attack (TIA)	Antiplatelet agents recommended over anticoagulation (ACCP Grade 1B, AHA/ASA Class I, Level A, CSN Grade A). Options include: • Clopidogrel (Plavix) 75 mg once daily (AHA/ASA Class IIa, Level B) • Combination of ASA 25 mg plus extended-release DP 200 mg (Aggrenox, Asasantin) twice daily (AHA/ASA Class I, Level B) • ASA 50-325 mg/day (AHA/ASA Class I, Level A) • cilostazol (Pletal) 100 mg twice daily • Clopidogrel or combination ASA plus extended-release DP suggested over ASA alone (ACCP Grade 2B) • Combination of ASA plus clopidogrel not usually recommended (ACCP Grade 1B, AHA/ASA Class III, Level A, CSN Grade B)
For patients with cardioembolic stroke and contraindications to anticoagulant medication	Use ASA 75-325 mg daily (AHA/ASA Class I, Level A) or combination of ASA plus clopidogrel (ACCP Grade 1B) • Supporting evidence: ▪ ASA in doses as low as 75 mg/day reduces risk of vascular events in patients with previous stroke or TIA (Level 1 [likely reliable] evidence) ▪ Clopidogrel may be slightly more effective than ASA at reducing ischemic events (Level 2 [mid-level] evidence) ▪ Addition of DP to ASA reduces risk of vascular events after stroke or TIA (Level 1 [likely reliable] evidence) ▪ ASA plus extended-release DP appears similar to clopidogrel for prevention of recurrent stroke but may have slightly more major hemorrhagic events (Level 2 [mid-level] evidence) ▪ Combination of ASA plus clopidogrel for secondary stroke prophylaxis increases risk of life-threatening or major bleeding (level 1 [likely reliable] evidence) ▪ Cilostazol decreases risk of hemorrhagic stroke but increases risk of adverse events compared with ASA in patients with previous cerebral infarction (Level 1 [likely reliable] evidence); Pletal approved only for intermittent claudication • Other antiplatelet agents: ▪ Triflusal (Aflen, Disgren, Grendis, Triflux) appears as effective as ASA for secondary prevention of vascular events with lower risk of hemorrhage (level 2 [mid-level] evidence) ▪ Ticlopidine (Ticlid, Tiklid) may be slightly more effective than ASA at reducing ischemic events (Level 2 [mid-level] evidence), but less commonly used due to life-threatening hematologic toxicity
For patients who have ischemic stroke on antiplatelet therapy	No evidence to guide changing antiplatelet regimen (AHA/ASA Class IIb, Level C)
Use of antithrombotic therapy following intracerebral hemorrhage	Depends on risk for recurrent hemorrhage and risk for ischemic events (AHA/ASA Class IIb, Level B); antiplatelet therapy may not increase risk for recurrent hemorrhage after intracerebral hemorrhage (Level 2 [mid-level] evidence)

Table 64.1. **International recommendations of American College of Chest Physicians (ACCP) [15], American Heart Association (AHA) [13] and Canadian Stroke Network (CNS) [16] in noncardioembolic stroke about the use of antiplatelet therapy.**

unique property of ASA and its higher selectivity for COX-1 over COX-2 makes it an effective antiplatelet agent. Platelets contain COX-1, a key enzyme in the production thromboxane A2 (TXA2), which is a potent inducer of platelet aggregation. Since platelets lack the ability to make more enzyme, TXA2 production is inhibited for the lifetime of the platelet (approximately 8-12 days) [24]. It has a rapid effect, and antiaggregate activi-

ty occurs within 1 hour of administration. These effects last for the life of the anucleate platelet, approximately 7 to 10 days. Prostaglandin systems in the vessel wall, which produce prostacyclin, a vasodilator and platelet inhibitor, can recover after low-dose ASA.

Structure	 Chemical formula: $C_9H_8O_4$ SMILES: CC(=O)OC1=CC=CC=C1C(O)=O
Pharmacodynamics	ASA is an analgesic, antipyretic, antirheumatic, and anti-inflammatory agent. ASA's mode of action as an antiinflammatory and antirheumatic agent may be due to inhibition of synthesis and release of prostaglandins. ASA appears to produce analgesia by virtue of both a peripheral and CNS effect. Peripherally, ASA acts by inhibiting the synthesis and release of prostaglandins. Acting centrally, it would appear to produce analgesia at a hypothalamic site in the brain, although the mode of action is not known. ASA also acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of vasodilation and increased peripheral blood flow. ASA's antipyretic activity may also be related to inhibition of synthesis and release of prostaglandins
Mechanism of action	ASA directly and irreversibly inhibits the activity of both types of cyclooxygenase (COX-1 and COX-2) to decrease the formation of precursors of prostaglandins and thromboxanes from arachidonic acid. This makes ASA different from other NSAIDS (such as diclofenac and ibuprofen) which are reversible inhibitors. Salicylate may competitively inhibit prostaglandin formation. ASA's antirheumatic (nonsteroidal anti-inflammatory) actions are a result of its analgesic and anti-inflammatory mechanisms; the therapeutic effects are not due to pituitary-adrenal stimulation. Platelet-derived COX-1 generates thromboxane A2 (TXA2), a potent vasoconstrictor and platelet agonist. In contrast, endothelial cell COX-1 generates prostacyclin which possesses vasodilatory and antiplatelet actions. Platelet COX-1 is more sensitive than endothelial cell COX-1 is to this effect of ASA and this distinction explains the recommendation for using very low doses of ASA to retard platelet aggregation. Inhibiting platelet COX-1 without diminishing endothelial cell COX-1 is desirable in patients with cardiovascular disease Inhibition of platelet COX-1 results in decreased platelet aggregation, leading to a prolonged bleeding time. Hemostatic effects return to normal roughly 36 hours after the last dose of the drug. The platelet aggregation-inhibiting effect of ASA specifically involves the compound's ability to act as an acetyl donor to COX; the nonacetylated salicylates have no clinically significant effect on platelet aggregation. Irreversible acetylation renders COX inactive, thereby preventing the formation of the aggregating agent TXA2 in platelets. Since platelets lack the ability to synthesize new proteins, the effects persist for the life of the exposed platelets (7-10 days). ASA may also inhibit production of the platelet aggregation inhibitor, prostacyclin (prostaglandin I2), by blood vessel endothelial cells; however, inhibition prostacyclin production is not permanent as endothelial cells can produce more cyclooxygenase to replace the non-functional enzyme. ASA has little effect on thrombin-induced platelet aggregation. More recently, it has been proposed that the beneficial effect of ASA might be related to its ability to reduce circulating levels of C-reactive protein. In very high and toxic doses, ASA also exerts a direct inhibitory effect on vitamin K-dependent hemostasis. Prothrombin synthesis is impaired, resulting in hypoprothrombinemia

Absorption	Absorption is generally rapid and complete following oral administration but may vary according to specific salicylate used, dosage form, and other factors such as tablet dissolution rate and gastric or intraluminal pH	
Volume of distribution	Not available	
Protein binding	High (99.5%) to albumin. Decreases as plasma salicylate concentration increases, with reduced plasma albumin concentration or renal dysfunction, and during pregnancy	
Metabolism	ASA is rapidly hydrolyzed primarily in the liver to salicylic acid, which is conjugated with glycine (forming salicyluric acid) and glucuronic acid and excreted largely in the urine	
Route of elimination	Not available	
Half life	The plasma half-life is approximately 15 minutes; that for salicylate lengthens as the dose increases: doses of 300 to 650 mg have a half-life of 3.1 to 3.2 hours; with doses of 1 gram, the half-life is increased to 5 hours and with 2 grams it is increased to about 9 hours.	
Clearance	Not available	
Toxicity	Oral, mouse: LD_{50}=250 mg/kg; Oral, rabbit: LD_{50}=1010 mg/kg; Oral, rat: LD_{50}=200 mg/kg. Effects of overdose include: tinnitus, abdominal pain, hypokalemia, hypoglycemia, pyrexia, hyperventilation, dysrhythmia, hypotension, hallucination, renal failure, confusion, seizure, coma, and death.	
Drug Interactions	**Drug**	**Interaction**
	Acenocoumarol	Acetylsalicylic acid increases the effect of the anticoagulant, acenocoumarol
	Acetazolamide	Acetylsalicylic acid at high dose increases the effect of the carbonic anhydrase inhibitor, acetazolamide
	Acetohexamide	Acetylsalicylic acid increases the effect of sulfonylurea, acetohexamide
	Anisindione	Acetylsalicylic acid increases effect of the anticoagulant, anisindione
	Betamethasone	The corticosteroid, betamethasone, may decrease the effect of the salicylate, acetylsalicylic acid
	Chlorpropamide	Acetylsalicylic acid may increase the effect of the sulfonylurea, chlorpropamide
	Cortisone acetate	The corticosteroid, cortisone acetate, may decrease the effect of the salicylate, acetylsalicylic acid
	Dexamethasone	The corticosteroid, dexamethasone, may decrease the effect of the salicylate, acetylsalicylic acid
	Dichlorphenamide	Acetylsalicylic acid at high dose increases the effect of the carbonic anhydrase inhibitor, dichlorphenamide
	Dicumarol	Acetylsalicylic acid increases effect of the anticoagulant, dicumarol
	Fludrocortisone	The corticosteroid, fludrocortisone, may decrease the effect of the salicylate, acetylsalicylic acid
	Ginkgo biloba	Additive anticoagulant/antiplatelet effects may increase bleed risk. Concomitant therapy should be avoided
	Gliclazide	Acetylsalicylic acid increases the effect of the sulfonylurea, gliclazide
	Glipizide	Acetylsalicylic acid increases the effect of the sulfonylurea, glipizide
	Glisoxepide	Acetylsalicylic acid increases the effect of the sulfonylurea, glisoxepide

	Glyburide	Acetylsalicylic acid increases the effect of the sulfonylurea, glibenclamide
	Glycodiazine	Acetylsalicylic acid increases the effect of sulfonylurea, glycodiazine
	Griseofulvin	Griseofulvin may decrease the efficacy of acetylsalicylic acid
	Heparin	Increased risk of bleeding
	Hydrocortisone	The corticosteroid, hydrocortisone, may decrease the effect of the salicylate, acetylsalicylic acid
	Ibuprofen	Concomitant therapy of the NSAID, ketoprofen, and acetylsalicylic acid may result in additive adverse/toxic effects (e.g. GI bleeding). The NSAID may also limit the cardioprotective effect of acetylsalicylic acid. Occasional concomitant use may not cause clinically significant problems, but regular, frequent concomitant therapy is not recommended
	Ketoprofen	Concomitant therapy of the NSAID, ketoprofen, and acetylsalicylic acid may result in additive adverse/toxic effects (e.g. GI bleeding). The NSAID may also limit the cardioprotective effect of acetylsalicylic acid. Occasional concomitant use may not cause clinically significant problems, but regular, frequent concomitant therapy is not recommended
	Ketorolac	Acetylsalicylic acid may increase the adverse GI effects ketorolac
	Methazolamide	Acetylsalicylic acid at high dose increases the effect of the carbonic anhydrase inhibitor, methazolamide
	Methotrexate	Acetylsalicylic acid increases the effect and toxicity of methotrexate
	Methylprednisolone	The corticosteroid, methylprednisolone, may decrease the effect of the salicylate, acetylsalicylic acid
	Paramethasone	The corticosteroid, paramethasone, may decrease the effect of the salicylate, acetylsalicylic acid
	Prednisolone	The corticosteroid, prednisolone, may decrease the effect of the salicylate, acetylsalicylic acid
	Prednisone	The corticosteroid, prednisone, may decrease the effect of the salicylate, acetylsalicylic acid
	Probenecid	Acetylsalicylic acid decreases the uricosuric effect of probenecid
	Sulindac	Risk of additive toxicity (e.g. bleed risk). Acetylsalicylic acid may decrease the serum concentration of sulindac. Sulindac may counteract the cardioprotective effects of acetylsalicylic acid. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of both agents if the interacting agent is initiated, discontinued or dose changed
	Telmisartan	Concomitant use of relmisartan and acetylsalicylic acid may increase the risk of acute renal failure and hyperkalemia. Monitor renal function at the beginning and during treatment
	Tiaprofenic acid	Increased risk of gastrointestinal bleeding

	Ticlopidine	Increased effect of ticlopidine
	Tolazamide	Acetylsalicylic acid increases the effect of the sulfonylurea, tolazamide
	Tolbutamide	Acetylsalicylic acid increases the effect of the sulfonylurea, tolbutamide
	Tolmetin	Additive adverse effects increase the risk of gastrointestinal bleeding. Possible decrease in the cardioprotective effect of acetylsalicylic acid. Monitor for increased bleeding risk during concomitant therapy
	Trandolapril	Acetylsalicylic acid may reduce the efficacy of Trandolapril. Monitor for changes in Trandolapril efficacy if acetylsalicylic acid is initiated, discontinued or dose changed
	Treprostinil	The prostacyclin analogue, Treprostinil, increases the risk of bleeding when combined with the antiplatelet agent, Acetylsalicylic acid. Monitor for increased bleeding during concomitant thearpy
	Triamcinolone	The corticosteroid, triamcinolone, may decrease the effect of the salicylate, acetylsalicylic acid
	Valproic acid	Acetylsalicylic acid increases the effect of valproic acid
	Warfarin	The antiplatelet effects of acetylsalicylic acid may increase the bleed risk associated with warfarin
Food interactions	• Avoid alcohol, alcohol appears to cause a 50 to 100% increases in ASA serum levels • Take with a full glass of water • Take with food to reduce gastric irritation	

Table 64.2. **Aspirin (ASA) overview. SMILES indicates simplified molecular-input line-entry system [25].**

Effectiveness of ASA

ASA reduces the risk of recurrent stroke and other major vascular events of approximately 13-22% (mean 13%; 95% CI 6-19%) compared with control, when administered acutely and over the long-term (Figure 64.1) [26-36]. Antiplatelet therapy reduced the risk of secondary stroke, MI, or vascular death by 22% among the subset of patients with prior cerebrovascular disease (TIA or stroke) in the 2002 ATC; the absolute benefit was 36 events prevented per 1000 patients treated for 29 months [19]. The benefit was independent of age (greater or less than 65), sex, diabetes, or hypertension. These results were further confirmed in an implemented 2009 ATC meta-analysis of 16 placebo-controlled secondary prevention trials. ASA reduced the risk of any serious vascular event and the risk of ischemic stroke of 19% and 22%, respectively [37]. In high-risk patients, stopping antiplatelet therapy may increase the risk of stroke. In one study of patients hospitalized with cerebral infarction 4.5% patients (n=13 of 289) had recently stopped antiplatelet therapy. Most had been taking ASA and in all patients, the antiplatelet agent had been discontinued within 6 to 10 days of stroke onset, consistent with the known lifespan (about 10 days) of inhibited platelets [38]. Similar results were found in a case-control study comparing 309 patients with stroke to 309 matched controls. ASA discontinuation was associated with a significantly increased risk of a recurrent cerebrovascular event (TIA or ischemic stroke; OR 3.4, 95% CI 1.08-10.63) [39]. In addition, ASA decreases the risk of other cardiovascular events in a wide range of patients with established cardiovascular disease and the risk of death from certain cancers in the long-term use. However, ASA shows a limited efficacy and treatment failures should be expected in

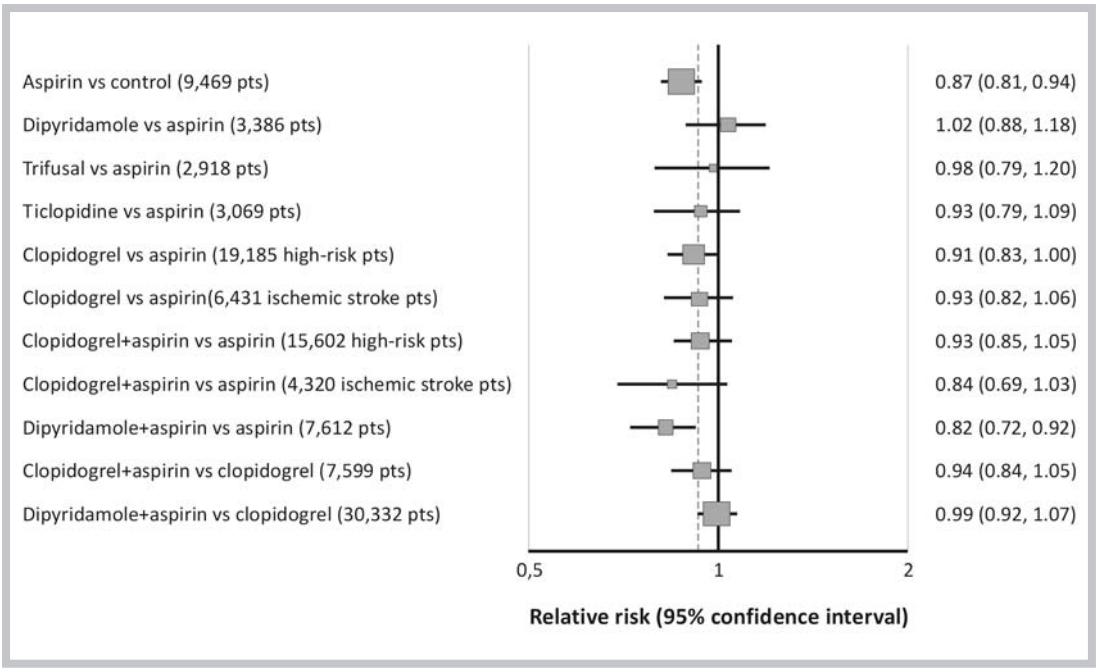


Figure 64.1. **Summary of the results of RCTs of antiplatelet drugs in patients with TIA or ischemic stroke of presumed arterial origin. Relative effects of antiplatelet regimens vs.placebo, aspirin, and clopidogrel in reducing the risk of stroke, myocardial infarction, or vascular death (major vascular events). The x-axis shows the degree of relative risk of stroke, myocardial infarction, or vascular events/death with each antiplatelet regimen. Point estimates and 95% CIs are shown. The data derived from a systematic review of all trials [26-31,33,35,36].**

most patients with TIA and stroke. The modest treatment effect of ASA in many patients may be attributable to non-compliance [40], and in some patients to suboptimum platelet inhibition by ASA, as shown by incomplete inhibition of TXA2 production or of platelet activation and aggregation [41,42].

Dose of ASA

The lack of proof of an optimal dose is a controversial issue concerning the efficacy of ASA in stroke prevention. In secondary stroke prevention studies, ASA doses range between 20 to 1300 mg; however, 50 to 325 mg/day of ASA is as effective as higher dose in most studies [11,43-48]. Lower doses within this range appear to provide the same benefit as higher doses [43-48]. Doses of 75 to 150 mg/day produced the same risk reduction, compared with placebo, as doses of 150 to 325 mg/day according to a review of 195 trials of secondary prevention by the ATC [11]. The ATC analysis of trials directly comparing ASA<75 mg/day to ASA ≥75 mg/day, showed comparable effectiveness between the two regimens. However, the ASA doses of<75 mg/day have been less widely assessed than doses of 75 to 150 mg/day, so uncertainty remains regarding the effectiveness of doses<75 mg/day compared with higher ASA doses in the ATC meta-analysis. No additional benefit with a greater risk of non-fatal major gastrointestinal hemorrhage was demonstrated in two further trials comparing higher with lower doses of ASA regimens [45,49]. The risk of major stroke, MI, or vascular death was 15% less with ASA than with placebo in the United Kingdom Transient Ischemic Attack trial (UK-TIA); in this trial, patients with minor ischemic stroke or TIA were randomized to 600 mg ASA twice daily, 300 mg ASA once daily, or placebo. The two ASA doses were equal in efficacy. Also in the Dutch TIA trial of patients with TIA or non-disabling stroke, there was no difference

in stroke prevention between the two doses of ASA 30 mg ASA vs. 283 mg in preventing vascular death, non-fatal stroke, or non-fatal MI. Again, however, the 30 mg dose group had fewer bleeding complications [45]. No clinical trial evidence supports an increase in the ASA dose for patients who have a stroke while receiving ASA. Lower doses may also be effective. The Dutch TIA Trial [49] demonstrated a similar efficacy for stroke prevention with 30 mg compared with 283 mg of ASA per day in patients who had had a TIA or minor ischemic stroke. Similarly, in the European Stroke Prevention Study-2 (ESPS-2), 50 mg of ASA daily reduced stroke risk by 18% compared with placebo (29 strokes prevented per 1000 treated), an effect of comparable magnitude to the other trials cited above [47]. This benefit is consistent with laboratory observations that 30 mg of ASA per day results in complete suppression of TXA2 production [50]. Both the Food and Drug Administration and the American College of Cardiology now support ASA doses between 50 and 325 mg, either alone or in combination with extended-release DP (ER-DP) for prevention of recurrent noncardioembolic TIA or stroke [51,52]. ASA in doses as low as 75 mg/day reduces risk of vascular events in patients with previous stroke or TIA [17,18].

Toxicity and Risk of Bleeding

Low-dose ASA are associated with low risk of major bleeding (number needed to harm [NNH] 769 per year) [20]. In the UK TIA trial, for example, gastrointestinal hemorrhage occurred in 1.6% of patients on placebo, 2.6% on 300 mg ASA, and 4.7% on 1200 mg ASA [43]. ASA doses ≤200 mg/day were associated with a significantly lower rate of major bleeding events compared with higher doses in an analysis of data from 31 randomized, controlled trials [53]. However, major bleedings were similar when ASA <100 mg/day was compared with 100 to 200 mg/day, the overall rate of bleeding complications (including major, minor and insignificant events) was associated with a lower risk in ASA <100 mg/day group compared with the 100 to 200 mg/day and >200 mg/day groups. A later meta-analysis of 22 randomized trials of low-dose ASA (75 to 325 mg/day) vs.placebo for cardiovascular prophylaxis reached similar conclusions within the low-dose range [20]. Compared with placebo, ASA increased the relative risk of any major bleeding, major gastrointestinal bleeding, and intracranial bleeding by 1.7- to 2.1-fold. However, the absolute annual increase in risk for any major bleeding episode (mostly gastrointestinal) and for intracranial bleeding was 0.13 and 0.03%, respectively. Furthermore, there was no evidence of an increased risk of bleeding with “high” low-dose ASA (>162 to 325 mg/day) compared with “low” low-dose ASA (75 to 162 mg/day). Although ASA increases the risk of major bleeding by about 70% (risk ratio [RR] 1.71 [95% CI 1.41-2.08]), the absolute annual increase is modest (0.13% [0.08-0.20%]), indicating that one additional major bleeding episode will occur each year for every 769 patients (95% CI 500-1250) treated with ASA [20]. The increased risk of bleeding is mainly due to an increase in major gastrointestinal bleeding (RR 2.07 [95% CI 1.61-2.66]; absolute annual increase 0.12% [0.07-0.19]) and intracranial bleeding (RR 1.65 [1.06-5.99]; absolute annual increase 0.03% [0.01-0.08]) [20]. Gastrointestinal hemorrhage was more common with the 1200 mg dose than the 300 mg dose. ASA increases risk of hemorrhagic stroke, but overall benefit on MI and ischemic stroke incidence may outweigh its adverse effects on risk of hemorrhagic stroke in most populations. ASA use associated with absolute risk increase in hemorrhagic stroke of 12 events per 10,000 persons (NNH 833) [21].

Nonresponse/resistance

About 10% of general population is resistant to antiplatelet effects of ASA [54]. Decreasing response to ASA is correlated independently with increasing risk of cardiovascular events. In a systematic review of 13 prospective cohort studies and 3 case-control studies among patients treated with ASA for secondary prevention of cardiovascular events,

5% to 65% range of ASA resistance by *ex vivo* nonresponsiveness to ASA based on any test of platelet TXA2 synthesis or platelet function, in a meta-analysis of 12 studies with 1813 patients 30.4% patients with vs. 12.7% patients without ASA resistance had cardiovascular events ($p<0.001$) although this meta-analysis is limited by heterogeneity ($p=0.03$) [55]. Studies showing that ASA is unable to protect against the onset of thrombotic complications. A high percentage (up to a barely believable 45%, depending on the study) of patients presents "treatment failure" or "ASA resistance," being more common in elderly people and women [41]. The mechanisms involved in ASA resistance are probably multifactorial and include the factors shown in Figure 64.2.

Potential causes of a reduced response to ASA include inadequate dose, genetic polymorphisms of *PTGS1* (which encodes prostaglandin G/H synthase 1, formerly cyclo-oxygenase 1) and other genes involved in TX biosynthesis, upregulation of non-platelet sources of TX biosynthesis, increased platelet turnover, and drug interactions (eg, with non-steroidal anti-inflammatory drugs [NSAIDs]), and occasional ASA allergy. *C*oncomitant NSAIDs may be associated with ASA resistance. Concomitant NSAID use is associated with increased risk of ASA nonresponsiveness as determined by arachidonate acid agonist (OR 2.17, $p=0.036$) and by determined by collagen agonist (OR 2.67, $p=0.001$) [23,41,56]. The specific NSAIDs that may lead to a less than expected inhibition of platelet function by ASA are ibuprofen, naproxen, and possibly other non-selective NSAIDs, because they compete with ASA for access to its target (the active site at position 530 of

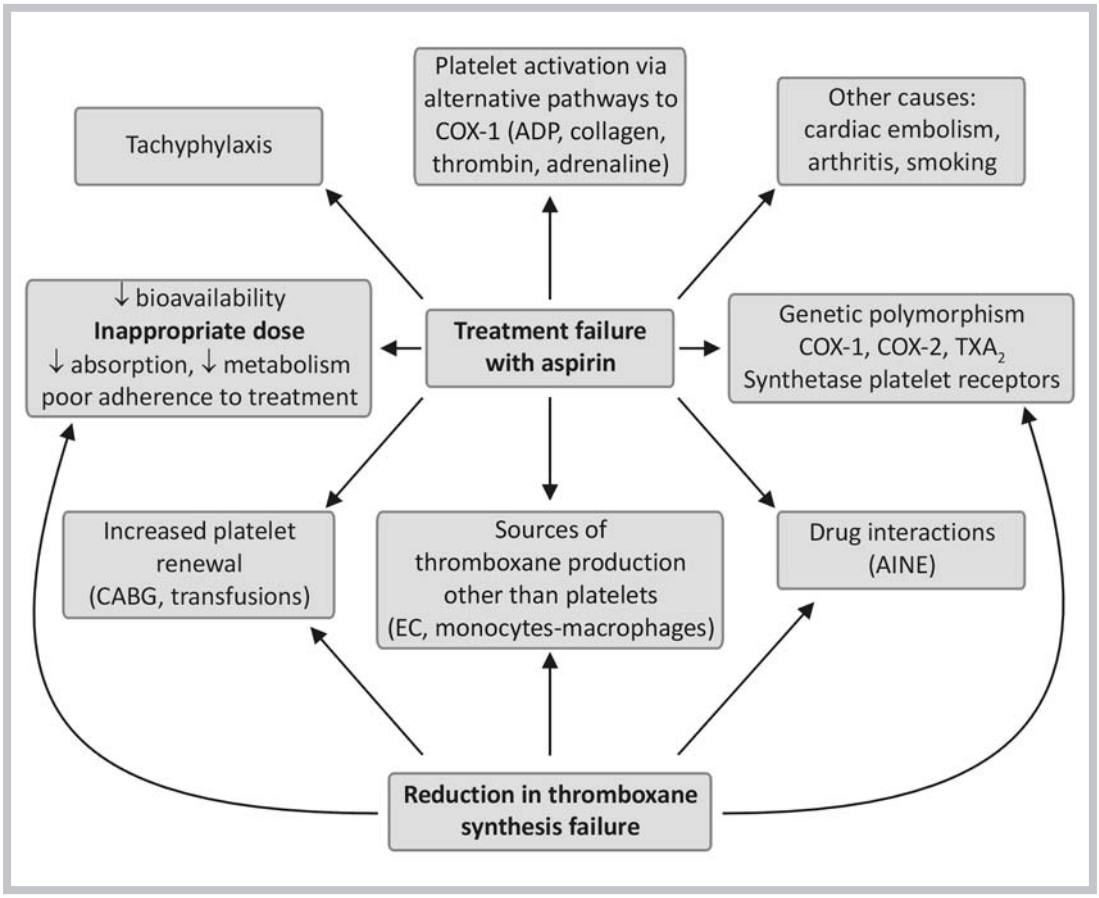


Figure 64.2. **Possible mechanisms involved in aspirin resistance. NSAIDS indicates non-steroid antiinflammatories; CABG, coronary artery bypass.**

a serine residue in the core of the cyclo-oxygenase enzyme) [57]. ASA hyporesponsiveness can potentially be overcome by increasing the dose or frequency of administration, and by avoiding drugs that interact with ASA. However, the benefit of these measures on clinical outcomes remains unproven. ASA resistance represents a controversial topic also because there is poor agreement on the best measurement of such resistance, as the methods of assaying platelet inhibition do not always agree, and there has also been little control for lack of adherence to the ASA regimen [40]. Likewise, switching to alternative antiplatelet agents has not been studied for ASA failures. In clinical practice ASACheck® and ASAWorks® are tests for ASA resistance which measure urine 11-dehydro-TXB2, high levels might suggest ASA resistance but could be due to other sources of TX production. Ultegra RPFA-ASA® is another point-of-care optical platelet function assay for ASA resistance. Laboratory ASA resistance is associated with increased risk of recurrent cardiovascular events in patients taking ASA for secondary prevention. To date, small studies have been conducted showing that incomplete TX synthesis suppression, despite sufficient doses (aspirin resistance), is a potential cardiovascular risk marker [58]. In the WARSS trial [59], a clinical trial of ASA vs. warfarin in non-cardioembolic stroke patients, the two agents had nonsignificant difference in efficacy. Moreover, patients who had already failed ASA when they had their index strokes had a higher risk of recurrent stroke in the course of the trial, but there was still no evidence of superior efficacy of warfarin over ASA. Established alternatives to ASA include clopidogrel and the combination of ASA and ER-DP.

Recommendations for ASA

American College of Chest Physicians (ACCP) (Ninth Edition) [15]

- Following noncardioembolic stroke or transient ischemic attack (TIA)
  - ASA 75-100 mg once daily recommended as an option for long-term antiplatelet therapy over: no antiplatelet therapy (ACCP Grade 1A), oral anticoagulants (ACCP Grade 1B), combination of clopidogrel plus ASA (ACCP Grade 1B), Triflusal (ACCP Grade 2B).
  - Among the recommended antiplatelet regimens, clopidogrel or combination of ASA plus extended-release DP suggested over ASA alone (ACCP Grade 2B) or triflusal (ACCP Grade 2C).
  - Benefit of clopidogrel over ASA for preventing major vascular events may be offset with long-term use (>5 years) by lower cancer-related mortality with ASA.
- Following cardioembolic stroke or TIA (that is, atrial fibrillation, including paroxysmal atrial fibrillation):
  - OAT recommended over: no antithrombotic therapy (ACCP Grade 1A), ASA (ACCP Grade 1B), combination therapy with ASA plus clopidogrel (ACCP Grade 1B).
  - For patients unsuitable for or who choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with ASA plus clopidogrel recommended over ASA (ACCP Grade 1B).
  - Use of ASA as bridging therapy suggested until anticoagulation reaches therapeutic level.

American Heart Association (AHA) [13]:

- For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents recommended rather than OAT (AHA/ASA Class I, Level A):
  - Acceptable options include: ASA 50-325 mg daily (AHA/ASA Class I, Level A), combination ASA 25 mg twice daily and extended-release DP 200 mg twice daily (AHA/ASA Class I, Level B), clopidogrel 75 mg daily (AHA/ASA Class iia, Level B).
  - Selection of antiplatelet agent should be individualized based on patient risk factors, cost, tolerance and other clinical factors.

  - Addition of ASA to clopidogrel increases risk of hemorrhage and is not routinely recommended for secondary prevention of stroke (AHA/ASA Class III, Level A).
  - Clopidogrel reasonable for patients allergic to ASA (AHA/ASA Class iia, Level C).
  - For patients who have ischemic stroke while taking ASA (AHA/ASA Class iib, Level C): no evidence for additional efficacy with increasing dose of ASA, alternative antiplatelet agents often considered, but no regimen specifically studied.
- For patients with ischemic stroke or TIA and paroxysmal or permanent atrial fibrillation:
  - If unable to take oral anticoagulants, ASA alone is recommended (AHA/ASA Class I, Level A).
  - Clopidogrel with ASA not recommended for patients with hemorrhagic contraindication to warfarin (AHA/ASA Class III, Level B).
- Optimal medical therapy for patients with extracranial arterial disease (carotid or vertebrobasilar) and TIA or stroke should include antiplatelet therapy (AHA/ASA Class I, Level B).
- For patients with stroke or TIA due to 50%-99% stenosis of major intracranial artery, ASA 50-325 mg/day is recommended over warfarin (AHA/ASA Class I, Level B).
- For patients with cardiomyopathy:
  - Insufficient evidence for use of warfarin in patients with prior stroke or TIA, sinus rhythm, cardiomyopathy and ejection fraction ≤ 35% (AHA/ASA Class iib, Level B).
  - Treatments to consider for patients with ischemic stroke or TIA and cardiomyopathy include (AHA/ASA Class IIb, Level B): warfarin (INR 2-3), ASA 81 mg/day, clopidogrel 75 mg/day, combination of ASA 25 mg twice daily and extended-release DP 200 mg twice daily.
- For patients with native valvular heart disease:
  - Antiplatelet therapy may be considered for patients with ischemic stroke or TIA and: native aortic or nonrheumatic mitral valve disease and no atrial fibrillation (AHA/ASA Class IIb, Level C), mitral annular calcification (AHA/ASA Class IIb, Level C), mitral valve prolapse (AHA/ASA Class IIb, Level C).
  - To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin (AHA/ASA Class III, Level C).
- For patients with ischemic stroke or TIA due to extracranial arterial dissection (carotid or vertebral):
  - Antithrombotic therapy for at least 3-6 months is reasonable (AHA/ASA Class IIa, Level B).
  - Relative efficacy of antiplatelet therapy vs. Anticoagulation is unknown (AHA/ASA Class iib, Level B).
- For patients with patent foramen ovale (PFO):
  - Antiplatelet therapy is reasonable for patients with ischemic stroke or TIA and PFO (AHA/ASA Class IIa, Level B).
  - Insufficient data to determine whether anticoagulation is as or more effective than ASA for secondary stroke prevention in patients with PFO (AHA/ASA Class IIb, Level B).

Canadian Stroke Network (CSN) [16]:

- All patients with ischemic stroke should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless indication for anticoagulation (CSN Grade A).
- Medications include (CSN Grade A):
  - ASA 80-325 mg/day (1-5 mg/kg/day in children [CSN Grade B]).
  - Combined ASA (25 mg) and extended-release DP (200 mg) twice daily.
  - Clopidogrel 75 mg/day.

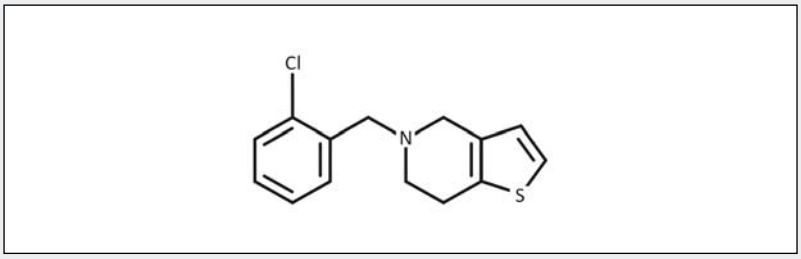
- Clopidogrel may be considered an alternative in pediatric patients with contraindication to ASA (CSN Grade C).
- Long term combination of ASA and clopidogrel is not recommended for secondary stroke prevention unless there is a compelling indication (CSN Grade B).

Thienopyridine Derivatives

Ticlopidine and clopidogrel decrease platelet aggregation by inhibiting the binding of adenosine 5'-diphosphate (ADP) receptor antagonists that inhibit ADP-induced fibrinogen binding to platelets [60]. Significant inhibition is present after 2 to 3 days of therapy with ticlopidine 500 mg/day or clopidogrel 75 mg/day, with maximal inhibition occurring between 4 and 7 days. As with ASA, the antiplatelet action persists for 7 to 10 days after therapy is stopped lasting for the lifespan of the platelet.

Ticlopidine

Ticlopidine is a thienopyridine structurally and pharmacologically similar to clopidogrel (Table 64.3) [25]. The active metabolite of ticlopidine prevents binding of adenosine diphosphate (ADP) to its platelet receptor, impairing the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. It is proposed that the inhibition involves a defect in the mobilization from the storage sites of the platelet granules to the outer membrane. No direct interference occurs with the GPIIb/IIIa receptor. As the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, its impaired activation prevents fibrinogen binding to platelets and inhibits platelet aggregation. By blocking the amplification of platelet activation by released ADP, platelet aggregation induced by agonists other than ADP is also inhibited by the active metabolite of ticlopidine.

Structure	 Chemical formula: $C_{14}H_{14}ClNS$; SMILES: ClC1=CC=CC=C1CN1CCC2=C(C1)C=CS2
Mechanism of action	The active metabolite of ticlopidine prevents binding of adenosine diphosphate (ADP) to its platelet receptor, impairing the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. It is proposed that the inhibition involves a defect in the mobilization from the storage sites of the platelet granules to the outer membrane. No direct interference occurs with the GPIIb/IIIa receptor. As the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, its impaired activation prevents fibrinogen binding to platelets and inhibits platelet aggregation. By blocking the amplification of platelet activation by released ADP, platelet aggregation induced by agonists other than ADP is also inhibited by the active metabolite of ticlopidine
Absorption	Absorption is greater than 80%. Food increases absorption
Volume of distribution	Not available
Protein binding	Binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins. The binding to albumin and lipoproteins is nonsaturable over a wide concentration range. Ticlopidine also binds to alpha-1 acid glycoprotein. At concentrations attained with the recommended dose, only 15% or less ticlopidine in plasma is bound to this protein

Metabolism	Metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine. At least 20 metabolites have been identified. It has been proposed that 1 or more active metabolites may account for ticlopidine's activity, because ticlopidine itself is an extremely weak platelet aggregation inhibitor in vitro at the concentrations achieved in vivo. However, no active metabolite has been identified	
Route of elimination	Ticlopidine hydrochloride is metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine. Approximately 1/3 of the dose excreted in the feces is intact ticlopidine hydrochloride, possibly excreted in the bile	
Half life	Half-life following a single 250-mg dose is approximately 7.9 hours in subjects 20 to 43 years of age and 12.6 hours in subjects 65 to 76 years of age. With repeated dosing (250 mg twice a day), half-life is about 4 days in subjects 20 to 43 years of age and about 5 days in subjects 65 to 76 years of age	
Clearance	Not available	
Toxicity	Single oral doses of ticlopidine at 1600 mg/kg and 500 mg/kg were lethal to rats and mice, respectively. Symptoms of acute toxicity were GI hemorrhage, convulsions, hypothermia, dyspnea, loss of equilibrium and abnormal gait	
Drug Interactions	**Drug**	**Interaction**
	Acetylsalicylic acid	Increased effect of ticlopidine
	Alteplase	Increased bleeding risk. Monitor for signs of bleeding
	Ambrisentan	Ticlopidine may decrease the metabolism and clearance of ambrisentan. Consider alternate therapy or monitor for adverse/toxic effects of ambrisentan if ticlopidine is initiated, discontinued or dose changed.
	Aminophylline	Ticlopidine increases the effect and toxicity of theophylline
	Bortezomib	Ticlopidine may decrease the metabolism and clearance of bortezomib. Consider alternate therapy or monitor for adverse/toxic effects of bortezomib if ticlopidine is initiated, discontinued or dose changed
	Carbamazepine	Ticlopidine increases the effect of carbamazepine
	Carisoprodol	Ticlopidine may decrease the metabolism and clearance of carisoprodol. Consider alternate therapy or monitor for adverse/toxic effects of carisoprodol if ticlopidine is initiated, discontinued or dose changed
	Cilostazol	Ticlopidine may decrease the metabolism and clearance of cilostazol. Consider alternate therapy or monitor for adverse/toxic effects of cilostazol if ticlopidine is initiated, discontinued or dose changed
	Cimetidine	Cimetidine may increase ticlopidine levels. Avoid concomitant therapy.
	Citalopram	Ticlopidine may decrease the metabolism and clearance of citalopram. Consider alternate therapy or monitor for adverse/toxic effects of citalopram if ticlopidine is initiated, discontinued or dose changed
	Clobazam	Ticlopidine may decrease the metabolism and clearance of clobazam. Consider alternate therapy or monitor for adverse/toxic effects of clobazam if ticlopidine is initiated, discontinued or dose changed
	Clomipramine	Ticlopidine may decrease the metabolism and clearance of clomipramine. Consider alternate therapy or monitor for adverse/toxic effects of clomipramine if ticlopidine is initiated, discontinued or dose changed

	Cyclosporine	Ticlopidine decreases the effect of cyclosporine
	Diazepam	Ticlopidine may decrease the metabolism and clearance of diazepam. Consider alternate therapy or monitor for adverse/toxic effects of diazepam if ticlopidine is initiated, discontinued or dose changed
	Digoxin	Ticlopidine may decrease digoxin levels. Monitor for digoxin levels with ticlopidine is initiated, discontinued or dose changed
	Dyphylline	Ticlopidine increases the effect and toxicity of theophylline
	Escitalopram	Ticlopidine may decrease the metabolism and clearance of escitalopram. Consider alternate therapy or monitor for adverse/toxic effects of ambrisentan if escitalopram is initiated, discontinued or dose changed
	Ethotoin	Ticlopidine increases the effect of hydantoin
	Fosphenytoin	Ticlopidine may decrease the metabolism and clearance of fosphenytoin. Consider alternate therapy or monitor for adverse/toxic effects of fosphenytoin if ticlopidine is initiated, discontinued or dose changed
	Ginkgo biloba	Additive anticoagulant/antiplatelet effects may increase bleed risk. Concomitant therapy should be avoided
	Heparin	Increased bleeding risk. Monitor aPTT
	Ifosfamide	Ticlopidine may decrease the metabolism and clearance of ifosfamide. Consider alternate therapy or monitor for adverse/toxic effects of ifosfamide if ticlopidine is initiated, discontinued or dose changed
	Imipramine	Ticlopidine may decrease the metabolism and clearance of Imipramine. Consider alternate therapy or monitor for adverse/toxic effects of Imipramine if ticlopidine is initiated, discontinued or dose changed
	Mephenytoin	Ticlopidine increases the effect of hydantoin
	Methsuximide	Ticlopidine may decrease the metabolism and clearance of methsuximide. Consider alternate therapy or monitor for adverse/toxic effects of methsuximide if ticlopidine is initiated, discontinued or dose changed
	Moclobemide	Ticlopidine may decrease the metabolism and clearance of moclobemide. Consider alternate therapy or monitor for adverse/toxic effects of moclobemide if ticlopidine is initiated, discontinued or dose changed
	Nilutamide	Ticlopidine may decrease the metabolism and clearance of nilutamide. Consider alternate therapy or monitor for adverse/toxic effects of nilutamide if ticlopidine is initiated, discontinued or dose changed
	Oxtriphylline	Ticlopidine increases the effect and toxicity of theophylline
	Pentamidine	Ticlopidine may decrease the metabolism and clearance of pentamidine. Consider alternate therapy or monitor for adverse/toxic effects of pentamidine if ticlopidine is initiated, discontinued or dose changed
	Phenobarbital	Ticlopidine may decrease the metabolism and clearance of phenobarbital. Consider alternate therapy or monitor for adverse/toxic effects of phenobarbital if ticlopidine is initiated, discontinued or dose changed

	Phenytoin	Ticlopidine may decrease the metabolism and clearance of phenytoin. Consider alternate therapy or monitor for adverse/toxic effects of phenytoin if ticlopidine is initiated, discontinued or dose changed
	Reteplase	Increased bleeding risk. Monitor for signs of bleeding
	Sodium bicarbonate	Sodium bicarbonate may decrease ticlopidine levels. Administer agents 1 to 2 hours apart
	Streptokinase	Increased bleeding risk. Monitor for signs of bleeding
	Tamoxifen	Ticlopidine may decrease the therapeutic effect of tamoxifen by decreasing the production of active metabolites. Consider alternate therapy
	Tamsulosin	Ticlopidine, a CYP2D6 inhibitor, may decrease the metabolism and clearance of Tamsulosin, a CYP2D6 substrate. Monitor for changes in therapeutic/adverse effects of tamsulosin if ticlopidine is initiated, discontinued, or dose changed
	Tenecteplase	Increased bleeding risk. Monitor for signs of bleeding
	Theophylline	Ticlopidine increases the effect and toxicity of theophylline
	Thioridazine	Ticlopidine may decrease the metabolism of thioridazine. Concomitant therapy is contraindicated
	Tizanidine	Ticlopidine may decrease the metabolism and clearance of tizanidine. Consider alternate therapy or use caution during co-administration
	Tramadol	Ticlopidine may decrease the effect of tramadol by decreasing active metabolite production
	Treprostinil	The prostacyclin analogue, Treprostinil, increases the risk of bleeding when combined with the antiplatelet agent, Ticlopidine. Monitor for increased bleeding during concomitant thearpy
	Trimipramine	The strong CYP2C19 inhibitor, ticlopidine, may decrease the metabolism and clearance of trimipramine, a CYP2C19 substrate. Consider alternate therapy or monitor for changes in therapeutic and adverse effects of trimipramine if ticlopidine is initiated, discontinued or dose changed
	Warfarin	Increased bleeding risk. Monitor INR
Class effects	Thienopyridines may be slightly more effective than *ASA* for preventing serious vascular events in high-risk patients (Level 2 [mid-level] evidence) [35]	

Table 64.3. **Ticlopidine overview. SMILES indicates simplified molecular-input line-entry system.**

When taken orally, ticlopidine causes a time- and dose-dependent inhibition of both platelet aggregation and release of platelet granule constituents, as well as, a prolongation of bleeding time. The intact drug has nonsignificant in vitro activity at the concentrations attained in vivo; and, although analysis of urine and plasma indicates at least 20 metabolites, no metabolite which accounts for the activity of ticlopidine has been isolated. Ticlopidine was initially approved for the secondary prevention of stroke and was subsequently found to be beneficial for other types of vascular events [61]. It is typically administered twice daily with food. It is associated with a significant risk for severe neutropenia (approximately 1%), mainly in the first 2-3 months of treatment. A lesser risk of thrombotic thrombocytopenic purpura is also present. Because of these hematological adverse effects, complete blood counts are recommended every 2 weeks for the first 3

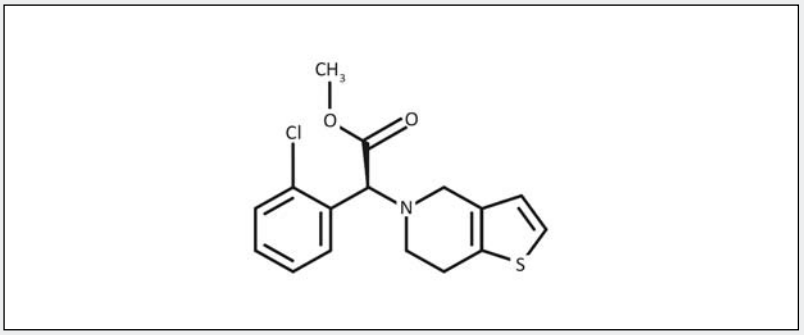
months that patients are on the drug [61]. Diarrhea occurs in more than 20% of patients as well. These side effects have significantly limited its use.

Effectiveness of ticlopidine. Three major trials involving patients with TIA and stroke evaluated its role in stroke prevention. The Canadian American Ticlopidine Study, which included 1072 patients with ischemic stroke, compared ticlopidine with placebo [62]. Patients in the ticlopidine group had a significant 23.3% reduction in the combined end point of stroke, MI, or vascular death compared with the placebo group (11.3% per year vs. 14.8% per year; p=0.02). The CATS trial compared ticlopidine vs.placebo in patients who had suffered a significant stroke. At a mean of 24 months follow-up, the primary composite end point of stroke, MI, and vascular death was significantly lower with ticlopidine compared with placebo (10.8% vs. 15.3%, relative risk reduction [RRR] 30%) [62]. Analysis by intention-to-treat gave a smaller estimate of RRR for stroke, MI, or vascular death (23%). The Ticlopidine ASA Stroke Study (TASS) trial compared ticlopidine (500 mg/day) to ASA (1300 mg/day) in 3,069 patients with a recent TIA or mild stroke [63]. There was a 12% reduction in the primary end point of nonfatal stroke or death in patients receiving ticlopidine compared with those receiving ASA (17% vs. 19%; p=0.048). Ticlopidine treatment was also associated with a significant reduction in the rate of fatal and nonfatal stroke compared with ASA (10% vs. 13%, respectively; RRR 21% [95% CI 4-38]). A TASS subgroup analysis showed a larger benefit for ticlopidine in African Americans prompting the African American Antiplatelet Stroke Prevention Study (AAASPS), in which ticlopidine was compared with ASA for secondary stroke prevention in African American stroke/TIA patients [64]. The AAASPS trial compared ticlopidine (500 mg/day) to ASA (650 mg/day) in 1809 black patients with noncardioembolic ischemic stroke [64]. At two-year follow-up, there was nonsignificant difference in the primary end point (stroke, MI, vascular death) between ticlopidine and ASA in African Americans. However, for the end point of fatal or non-fatal stroke, there was a trend favoring ASA over ticlopidine. The hematologic side effects and the availability of clopidogrel have significantly reduced the use of ticlopidine for recurrent stroke prevention in patients with ischemic stroke. Despite the evidence of benefit in the CATS and TASS trials, ticlopidine is not considered a first-line antiplatelet agent for stroke prevention because of side effects and relatively high cost.

Side effects of ticlopidine. Severe neutropenia, which occurs in approximately 1% of patients is the most serious complication of ticlopidine therapy. Thus, for the first three months of treatment, patients must undergo biweekly complete blood counts. This side effect limits the utility of ticlopidine. Other common side effects, which occur more frequently with ticlopidine than ASA, are rash and diarrhea.

Clopidogrel

Clopidogrel is a thienopyridine that inhibits ADP-dependent platelet aggregation (Table 64.4) [60]. Clopidogrel, an antiplatelet agent structurally and pharmacologically similar to ticlopidine, is used to reduce atherosclerotic events such as myocardial infarction, stroke, and vascular death in patients who have had a recent stroke, recent MI, or have established peripheral vascular disease. The active metabolite of clopidogrel prevents binding of adenosine diphosphate (ADP) to its platelet receptor, impairing the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. It is proposed that the inhibition involves a defect in the mobilization from the storage sites of the platelet granules to the outer membrane. No direct interference occurs with the GPIIb/IIIa receptor. As the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, its impaired activation prevents fibrinogen binding to platelets and inhibits platelet aggregation. By blocking the amplification of platelet activation by released ADP, platelet aggregation induced by agonists other than ADP is also inhibited by the active metabolite of clopidogrel.

Structure	 Chemical formula: $C_{16}H_{16}ClNO_2S$ SMILES: COC(=O)[C@@H](N1CCC2=C(C1)C=CS2)C1=CC=CC=C1Cl
Pharmacodynamics	Clopidogrel, an antiplatelet agent structurally and pharmacologically similar to ticlopidine, is used to reduce atherosclerotic events such as myocardial infarction, stroke, and vascular death in patients who have had a recent stroke, recent MI, or have established peripheral vascular disease
Mechanism of action	The active metabolite of clopidogrel prevents binding of adenosine diphosphate (ADP) to its platelet receptor, impairing the ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. It is proposed that the inhibition involves a defect in the mobilization from the storage sites of the platelet granules to the outer membrane. he drug specifically and irreversibly inhibits the P2Y12 subtype of ADP receptor, which is important in aggregation of platelets and cross-linking by the protein fibrin. No direct interference occurs with the GPIIb/IIIa receptor. As the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, its impaired activation prevents fibrinogen binding to platelets and inhibits platelet aggregation. By blocking the amplification of platelet activation by released ADP, platelet aggregation induced by agonists other than ADP is also inhibited by the active metabolite of clopidogrel
Absorption	Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites. Bioavailability has not been found to be affected by food.
Volume of distribution	Not available
Protein binding	98%
Metabolism	Hepatic, extensive and rapid, by hydrolysis to the main circulating metabolite, a carboxylic acid derivative, which accounts for approximately 85% of the circulating drug-related compounds. A glucuronic acid derivative of the carboxylic acid derivative has also been found in plasma and urine. Neither the parent compound nor the carboxylic acid derivative has a platelet inhibiting effect
Route of elimination	Following an oral dose of 14C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-dosing
Half life	Carboxylic acid derivative: 8 hours (after single and multiple doses). Covalent binding to platelets has accounted for 2% of radiolabeled clopidogrel with a half-life of 11 days
Clearance	Not available
Toxicity	Symptoms of acute toxicity include vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage

Drug interactions	Drug	Interaction
	Bortezomib	Moderate CYP2C19 Inhibitors like bortezomib may decrease serum concentrations of the active metabolite(s) of Clopidogrel. Avoid concurrent use of moderate CYP2C19 inhibitors with clopidogrel whenever possible. If such a combination must be used, monitor closely for evidence of reduced clinical response to clopidogrel
	Drotrecogin alfa	Antiplatelet agents such as clopidogrel may enhance the adverse/toxic effect of Drotrecogin Alfa. Bleeding may occur. Increase monitoring for signs/symptoms of bleeding during concomitant therapy. If possible, avoid use of drotrecogin within 7 days of use of any IIb/IIIa antagonists, higher dose aspirin (more than 650 mg/day), or use of other antiplatelet agents
	Esomeprazole	Esomeprazole may decrease serum concentrations of the active metabolite(s) of clopidogrel. Due to the possible risk for impaired clopidogrel effectiveness with this combination, clinicians should carefully consider the need for concurrent esomeprazole therapy in patients receiving clopidogrel. Monitor response to clopidogrel closely when using clopidogrel with esomeprazole. Whether there are differences among individual proton pump inhibitors is unclear. Other acid-lowering therapies (e.g., H2-receptor antagonists, antacids, etc.) do not appear to share this interaction with clopidogrel
	Ginkgo biloba	Additive anticoagulant/antiplatelet effects may increase bleed risk. Concomitant therapy should be avoided
	Lansoprazole	Lansoprazole may decrease serum concentrations of the active metabolite(s) of clopidogrel. Due to the possible risk for impaired clopidogrel effectiveness with this combination, clinicians should carefully consider the need for concurrent lansoprazole therapy in patients receiving clopidogrel. Monitor response to clopidogrel closely when using clopidogrel with lansoprazole. Whether there are differences among individual proton pump inhibitors is unclear. Other acid-lowering therapies (e.g., H2-receptor antagonists, antacids, etc.) do not appear to share this interaction with clopidogrel
	Omeprazole	Omeprazole may decrease serum concentrations of the active metabolite(s) of clopidogrel. Clopidogrel prescribing information recommends avoiding concurrent use with omeprazole, due to the possibility that combined use may result in decreased clopidogrel effectiveness
	Pantoprazole	Pantoprazole may decrease serum concentrations of the active metabolite(s) of clopidogrel. Due to the possible risk for impaired clopidogrel effectiveness with this combination, clinicians should carefully consider the need for concurrent pantoprazole therapy in patients receiving clopidogrel. Monitor response to clopidogrel closely when using clopidogrel with pantoprazole. Whether there are differences among individual proton pump inhibitors is unclear. Other acid-lowering therapies (e.g., H2-receptor antagonists, antacids, etc.) do not appear to share this interaction with clopidogrel

	Rabeprazole	Rabeprazole may decrease serum concentrations of the active metabolite(s) of clopidogrel. Due to the possible risk for impaired clopidogrel effectiveness with this combination, clinicians should carefully consider the need for concurrent rabeprazole therapy in patients receiving clopidogrel. Monitor response to clopidogrel closely when using clopidogrel with rabeprazole. Whether there are differences among individual proton pump inhibitors is unclear. Other acid-lowering therapies (e.g., H_2-receptor antagonists, antacids, etc.) do not appear to share this interaction with clopidogrel
	Rivaroxaban	Antiplatelet agents such as clopidogrel may enhance the anticoagulant effect of rivaroxaban. Avoid concurrent use of clopidogrel with rivaroxaban unless the anticipated benefits outweigh the risks of bleeding. Canadian rivaroxaban labeling recommends avoiding concurrent use with any antiplatelet agent, while the U.S. rivaroxaban labeling recommends caution and increased monitoring if used with any other antiplatelet agent. Any combined use should only be undertaken with increased monitoring for evidence of bleeding
	Treprostinil	The prostacyclin analogue, Treprostinil, increases the risk of bleeding when combined with the antiplatelet agent, clopidogrel. Monitor for increased bleeding during concomitant thearpy
	Warfarin	Increased bleed risk may occur as a result of additive anticoagulant effects. Increase monitoring for signs and symptoms of bleeding during concomitant therapy.
Food interactions	Take without regard to meals	
Class effects	Thienopyridines may be slightly more effective than ASA for preventing serious vascular events in high-risk patients (Level 2 [mid-level] evidence) [35]	

Clopidogrel plus ASA	• Combination of ASA plus clopidogrel not usually recommended for secondary prevention of stroke or transient ischemic attack (TIA) in patients without atrial fibrillation:
	  ▪ Single-agent antiplatelet therapy recommended over combination of clopidogrel plus ASA for long-term antiplatelet therapy (ACCP Grade 1B) [15]
	  ▪ Addition of ASA to clopidogrel increases risk of hemorrhage and is not routinely recommended for secondary prevention of stroke (AHA/ASA Class III, Level A) [13]
	  ▪ Long term combination of ASA and clopidogrel is not recommended for secondary stroke prevention unless there is a compelling indication (CSN Grade B) [16]
	• For patients with cardioembolic stroke or TIA (that is, atrial fibrillation):
	  ▪ For patients unsuitable for or who choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with ASA plus clopidogrel recommended over ASA (ACCP Grade 1B) [15]
	  ▪ Clopidogrel with ASA not recommended for patients with hemorrhagic contraindication to warfarin (AHA/ASA Class III, Level B) [2]
	• Combination of ASA plus clopidogrel for secondary stroke prophylaxis increases risk of life-threatening or major bleeding (Level 1 [likely reliable] evidence) [31,66]	

Table 64.4. **Clopidogrel overview. SMILES indicates simplified molecular-input line-entry system.**

Clopidogrel is structurally similar to ticlopidine, differing by the addition of a carboxymethyl side group. The 2- to 3-day lag from initiation of clopidogrel to platelet inhibition can be overcome by oral clopidogrel loading (300-600 mg), which can result in platelet inhibition in 2 to 3 hours. Much of the evidence for a benefit with this drug comes from the cardiac literature, where it has been shown to reduce recurrent events in patients with an acute MI and lower reocclusion rates in patients undergoing coronary angioplasty and stenting. Safety profile is much better for clopidogrel than ticlopidine and carries a minimal risk for neutropenia. It has largely replaced ticlopidine in practice. Clopidogrel is significantly but marginally more effective than ASA: it reduced the long-term risk of stroke and other major vascular events by 8.7% (95% CI 0.3-16.5) compared with ASA among 19,185 patients at high vascular risk, and by 7.3% (−5.7-18.7%) among a subgroup of 6431 patients with ischemic stroke [26,35]. The Clopidogrel vs. ASA in Patients at Risk of Ischemic Events (CAPRIE) trial [26] compared clopidogrel (75 mg) to ASA (325 mg) in more than 19,000 patients with symptomatic vascular disease, defined by either recent ischemic stroke (within 1 week to 6 months), MI (within 35 days), or documented peripheral arterial disease. Among all patients, clopidogrel was associated with a significant 8.7% RRR compared with ASA for the primary end point of ischemic stroke, MI, or vascular death (5.32% vs. 5.83% per year; p=0.043). The benefit of clopidogrel over ASA was most pronounced for patients in the peripheral arterial disease subgroup (3.71% vs. 4.86% per year; p=0.0028) but ineffective for the 6,431 patients in the stroke subgroup (7.15% vs. 7.71% per year; p>0.2). However, the strength of these observations is limited, since they are based on subgroup analyses. Although the overall relative benefit of clopidogrel over ASA in the CAPRIE trial was modest (absolute risk reduction of 0.5% per year) and there was no statistically significant benefit over ASA for the stroke patients in this study, clopidogrel has become an important treatment option for patients with stroke. Hemorrhagic risk was similar between the groups.

Reccomendations

American College of Chest Physicians (ACCP) recommendations (Ninth Edition) [15]:

- Following noncardioembolic stroke or transient ischemic attack (TIA):
  - Clopidogrel 75 mg once daily recommended as an option for long-term antiplatelet therapy over: no antiplatelet therapy (ACCP Grade 1A), oral anticoagulants (ACCP Grade 1B), combination of clopidogrel plus ASA (ACCP Grade 1B), Triflusal (ACCP Grade 2B).
  - Among the recommended antiplatelet regimens, clopidogrel or combination of ASA plus extended-release DP suggested over ASA alone (ACCP Grade 2B) or triflusal (ACCP Grade 2C).
  - Benefit of clopidogrel over ASA for preventing major vascular events may be offset with long-term use (>5 years) by lower cancer-related mortality with ASA.
- Following cardioembolic stroke or TIA (that is, atrial fibrillation, including paroxysmal atrial fibrillation):
  - OAT recommended over:no antithrombotic therapy (ACCP Grade 1A), ASA (ACCP Grade 1B), combination therapy with ASA plus clopidogrel (ACCP Grade 1B).
  - For patients unsuitable for or who choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with ASA plus clopidogrel recommended over ASA (ACCP Grade 1B).

American Heart Association (AHA) recommendations [13]:

- For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents recommended rather than OAT (AHA/ASA Class I, Level A):
  - Acceptable options include: ASA 50-325 mg daily (AHA/ASA Class I, Level A), combination ASA 25 mg twice daily and extended-release DP 200 mg twice daily (AHA/ASA Class I, Level B), clopidogrel 75 mg daily (AHA/ASA Class IIa, Level B).

  - Selection of antiplatelet agent should be individualized based on patient risk factors, cost, tolerance and other clinical factors.
  - Addition of ASA to clopidogrel increases risk of hemorrhage and is not routinely recommended for secondary prevention of stroke (AHA/ASA Class III, Level A).
  - Clopidogrel reasonable for patients allergic to ASA (AHA/ASA Class IIa, Level C).
- For patients who have ischemic stroke while taking ASA (AHA/ASA Class IIb, Level C): no evidence for additional efficacy with increasing dose of ASA, alternative antiplatelet agents often considered, but no regimen specifically studied.
- For patients with ischemic stroke or TIA and paroxysmal or permanent atrial fibrillation:
  - If unable to take oral anticoagulants, ASA alone is recommended (AHA/ASA Class I, Level A).
  - Clopidogrel with ASA not recommended for patients with hemorrhagic contraindication to warfarin (AHA/ASA Class III, Level B).
  - Optimal medical therapy for patients with extracranial arterial disease (carotid or vertebrobasilar) and TIA or stroke should include antiplatelet therapy (AHA/ASA Class I, Level B).
- For patients with stroke or TIA due to 50%-99% stenosis of major intracranial artery, ASA 50-325 mg/day is recommended over warfarin (AHA/ASA Class I, Level B).
- For patients with cardiomyopathy:
  - Insufficient evidence for use of warfarin in patients with prior stroke or TIA, sinus rhythm, cardiomyopathy and ejection fraction ≤ 35% (AHA/ASA Class IIb, Level B)
  - Treatments to consider for patients with ischemic stroke or TIA and cardiomyopathy include (AHA/ASA Class IIb, Level B): Warfarin (INR 2-3), ASA 81 mg/day, clopidogrel 75 mg/day, combination of ASA 25 mg twice daily and extended-release DP 200 mg twice daily.
- For patients with native valvular heart disease:
  - Antiplatelet therapy may be considered for patients with ischemic stroke or TIA and: native aortic or nonrheumatic mitral valve disease and no atrial fibrillation (AHA/ASA Class IIb, Level C), mitral annular calcification (AHA/ASA Class IIb, Level C), mitral valve prolapse (AHA/ASA Class IIb, Level C).
- To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin (AHA/ASA Class III, Level C).

National Institute of Health and Clinical Excellence (NICE) guidance on clopidogrel and modified-release DP in prevention of occlusive vascular events [65]:

- Guidance applies to people with history of occlusive vascular event or with symptomatic peripheral arterial disease
- Clopidogrel alone (within licensed indications) recommended for people intolerant of low-dose ASA (proven hypersensitivity or history of severe dyspepsia) who have had occlusive vascular event or symptomatic peripheral arterial disease.

Canadian Stroke Network (CSN) recommendations [16]:

- All patients with ischemic stroke should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless indication for anticoagulation (CSN Grade A).
- Medications include (CSN Grade A):
  - ASA 80-325 mg/day (1-5 mg/kg/day in children [CSN Grade B]).
  - Combined ASA (25 mg) and extended-release DP (200 mg) twice daily.
- Clopidogrel 75 mg/day.
- Clopidogrel may be considered an alternative in pediatric patients with contraindication to ASA (CSN Grade C)
- Long term combination of ASA and clopidogrel is not recommended for secondary stroke prevention unless there is a compelling indication (CSN Grade B).

Side effects of clopidogrel. The side effect profile of clopidogrel is favorable compared with ASA, with lower frequency of gastric upset or gastrointestinal bleeding but a slightly higher frequency of rash and diarrhea [20]. Severe neutropenia is not seen more frequently with clopidogrel than with ASA [26]. Clopidogrel causes less gastrointestinal bleeding than 325 mg ASA daily (RR 0.69 [95% CI 0.48-1.00]; absolute annual decrease 0.12% [0.00-0.28%]), but does not reduce the risk of other types of bleeding [26,35].

Platelets response to clopidogrel treatment varies, and may be due to clinical, cellular, or genetic factors [58,67-69]. Clopidogrel is an inactive prodrug that requires two-step oxidation by the hepatic cytochrome P450 (CYP) system to generate its active compound, the thiol metabolite, which targets and irreversibly inhibits the ADP P2Y purinoceptor 12 on circulating platelets. The hepatic CYP isoenzymes involved in this two-step metabolization process of clopidogrel include CYP2C19, CYP3A4/5, CYP1A2, CYP2B6, and CYP2C9. Several genetic polymorphisms have been described that may be associated with impaired pharmacokinetic and pharmacodynamic response to clopidogrel, with possible clinical consequences [58,67-69]. The first genome-wide association study of clopidogrel response has recently reported that the loss-of-function *CYP2C19*2* genotype was associated with diminished effect of clopidogrel inhibition of ADP-induced platelet aggregation and poorer cardiovascular outcomes [58]. Whether the *CYP2C19*2* polymorphism is associated with higher cardiovascular risks that are independent from the diminished conversion of the prodrug to the active form of clopidogrel remains to be determined. A genomic profile may identify patients at risk of ischemic events for whom an alternative antiplatelet approach may be more effective while taking clopidogrel. This hypothesis remains to be validated externally. At the moment, no convincing prospective data support routine testing for clopidogrel resistance with in vitro tests of platelet function or genotyping in patients with cardiovascular disease, particularly for those with a history of stroke or TIA. A 2010 clinical alert from the American College of Cardiology Foundation and the American Heart Association noted that adherence to existing guidelines for the use of antiplatelet therapy should remain the basis for therapy, and further that there is insufficient evidence to recommend routine platelet function testing or genetic testing for clopidogrel [70]. Concomitant administration of clopidogrel with a proton pump inhibitor, particularly omeprazole, to minimize the risk of gastrointestinal bleeding complications, also attenuates clopidogrel's antiplatelet action in about a third of patients [58,67-69]. The mechanism is thought to be a drug-drug interaction at the level of the hepatic CYP system, because hepatic metabolization of omeprazole is also CYP dependent. However, although treatment with a proton pump inhibitor attenuates the pharmacodynamic effects of clopidogrel, the effect is modest and apparently insufficient to affect the clinical outcome of patients on clopidogrel (or prasugrel – another thienopyridine) [71,72]. In the long-term use (18 months), ASA plus clopidogrel is no more effective than clopidogrel alone in prevention of ischemic stroke, MI, vascular death, and rehospitalization for acute ischemia (RR 0.94 [95% CI 0.84-1.05]) [31]; while it was associated with an increase in life threatening bleeding (2.6% on ASA and clopidogrel vs. 1.3% on ASA; absolute risk increase 1.3% [0.6-1.9]) [40].

ASA Plus Clopidogrel

The combined use of ASA plus clopidogrel does not offer greater benefit for stroke prevention than either agent alone but increases the risk of bleeding complications [28,31,73]. Combination therapy with clopidogrel plus ASA has been shown to be more effective than ASA monotherapy in patients with acute MI, unstable angina, or coronary interventions [74,75], and its use is common, especially in patients with coronary artery disease. The combination therapy in patients with stroke was tested in the Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) trial, in which clopidogrel plus ASA was compared with clopidogrel monotherapy [31]. This specific compari-

son was based on the assumption that clopidogrel monotherapy is the gold standard for antiplatelet secondary prevention [28]. This study enrolled 7,599 patients with stroke or TIA who also had some additional "high-risk" feature, defined as prior MI, prior stroke (in addition to the index event), diabetes, angina, or symptomatic peripheral artery disease (PAD). The primary end point was a composite of ischemic stroke, MI, vascular death, or rehospitalization for acute ischemia. Patients were randomly assigned to the combination of clopidogrel (75 mg daily) plus ASA (75 mg daily) vs. clopidogrel (75 mg daily) alone. Follow-up was 18 months. The main results of this trial were [31]: 1) ASA plus clopidogrel treatment did not reduce the risk of major vascular events compared with clopidogrel alone (RRR 6.4%, 95% CI -4.6-16.3); 2) ASA plus clopidogrel was associated with a significant increase in life-threatening bleeding complications, mainly intracranial and gastrointestinal, compared with clopidogrel alone with an absolute excess of 1.3% for life-threatening hemorrhage (95% CI 0.6-1.9) over the 18-month trial period and an additional 1.3% for major hemorrhage in patients assigned combination therapy. (3) Overall, the combination treatment with ASA and clopidogrel compared with clopidogrel alone might prevent 10 ischemic events per 1000 treated (not statistically significant) at the cost of 13 life-threatening hemorrhages per 1000 treated. However, MATCH trial has several limitations such as 54% of MATCH subjects qualified for trial entry because of a lacunar stroke, a stroke subtype that has the lowest recurrence risk [76], and data regarding interaction between treatment and stroke mechanism were not reported, raising the question of whether combination therapy might still play a role in particular stroke subtypes. In conclusions, the MATCH results do not support the use of combination therapy of clopidogrel plus ASA for patients with stroke. Future trials to evaluate the benefit and safety of the combination of ASA and clopidogrel when administered immediately after TIA and ischemic stroke (ie, within 12 to 24 hours rather than 15 days) with a loading dose of clopidogrel (300 mg or 600 mg) and for a short period of 3 months, when the benefits are likely to be greatest and the cumulative risks of bleeding avoided could be of interest and useful [77]. The combination of ASA and clopidogrel has been shown to have benefit over ASA alone in patients with acute coronary syndromes. However, there are important differences between patients with coronary and cerebrovascular disease [78], and between short-term therapy initiated in the acute setting, and longer term preventative therapy. On the contrary, the CHARISMA trial evaluated ASA plus clopidogrel vs. ASA alone in patients with symptomatic cardiovascular disease or asymptomatic multiple cardiovascular risk factors [28]. CHARISMA enrolled 15,603 patients with either documented cardiovascular disease (coronary, ischemic cerebrovascular, or peripheral arterial) or, in 21% of patients, multiple atherothrombotic risk factors (eg, diabetes, hypertension, primary hypercholesterolemia, current smoking, asymptomatic carotid stenosis ≥70%) and randomly assigned them to low-dose ASA (75 to 162 mg/day) plus either clopidogrel (75 mg/day) or placebo. The combination of ASA plus clopidogrel was not more effective than ASA alone for reducing the rate of MI, stroke, or death from cardiovascular causes [28]. Combined ASA plus clopidogrel treatment did not reduce the risk of the composite primary end point (MI, stroke of any cause, or death from cardiovascular causes) compared with ASA alone (6.8% vs. 7.3%, RR 0.93, 95% CI 0.83-1.05). Combination therapy compared with ASA alone was associated with a significant increase in moderate bleeding (2.1% vs. 1.3%) and a nonsignificant increase in severe bleeding (1.7% vs. 1.3%).

The use of dual antiplatelet therapy with ASA plus clopidogrel has also been studied in different subtypes of ischemic stroke, including small vessel disease and large artery atherosclerosis. In the randomized Secondary Prevention of Small Subcortical Strokes (SPS3) trial evaluating patients with subcortical (ie, lacunar) stroke confirmed by MRI, the arm testing the combination of ASA plus clopidogrel was terminated before completion because a preliminary review of trial data found a higher frequency of bleeding events (mostly sys-

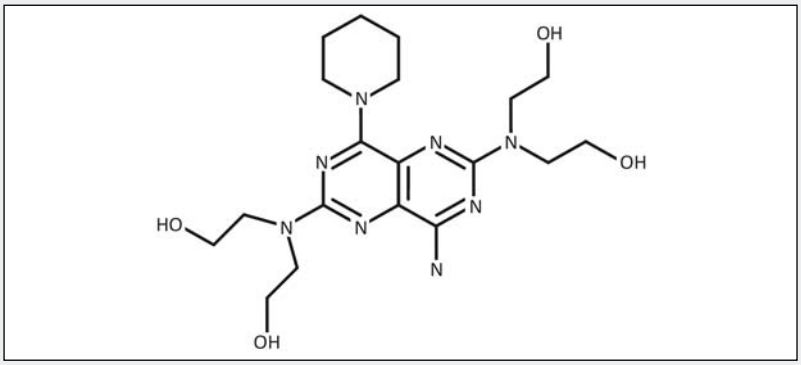
temic) in patients assigned to ASA and clopidogrel compared with those assigned to ASA alone (6.5% vs. 3.3%) [79]. The dual antiplatelet therapy group showed a higher mortality rate from all causes compared with the ASA alone group (5.8% vs. 4.1%; hazard ratio [HR], 1.5; p=0.005). This result was not confirmed in a meta-analysis of twelve trials included 90,934 participants. There was nonsignificant increase in mortality with the combination therapy either in 4 short-term (14 days-3 months; OR, 0.93, 95% CI 0.87- 0.99) or in 7 long-term (>3 months; HR 0.97, 95% CI 0.91-1.04) trials after the SPS3 trial was excluded because of heterogeneity. It was confirmed that addition of clopidogrel was associated with an increase in fatal hemorrhage (OR 1.35, 95% CI 0.97-1.90) and a reduction in MI (OR 0.82, 95% CI 0.74-0.91) [80]. These results, together with those of the MATCH trial, suggest that dual antiplatelet therapy with ASA and clopidogrel is harmful for patients with lacunar stroke. Two small trials (CARESS and CLAIR) of patients with recently symptomatic large artery stenosis found that, compared with ASA alone, early treatment with ASA plus clopidogrel reduced the number of microembolic signals detected on transcranial Doppler ultrasound [81,82]. However, whether this surrogate measure would translate into clinical benefit for patients with symptomatic large artery stenosis remains uncertain. In the SAMMPRIS trial, all subjects with recently symptomatic intracranial large artery stenosis, received combined ASA and clopidogrel for the first 90 days after enrollment to evaluate angioplasty and stenting plus intensive medical management vs. intensive medical management alone [83]. The results were notable for a reduced rate of recurrent stroke and death in the medical management arm compared with historical controls, suggesting that short-term dual antiplatelet therapy is beneficial in this scenario. Therefore, we suggest dual antiplatelet therapy with ASA plus clopidogrel for 90 days, followed by antiplatelet monotherapy, for patients with recently symptomatic intracranial large artery disease.

Dipyridamole

Dipyridamole (DP) likely inhibits both adenosine deaminase and phosphodiesterase, preventing the degradation of cAMP, an inhibitor of platelet function (Table 64.5). This elevation in cAMP blocks the release of arachidonic acid from membrane phospholipids and reduces thromboxane A2 activity. DP also directly stimulates the release of prostacyclin, which induces adenylate cyclase activity, thereby raising the intraplatelet concentration of cAMP and further inhibiting platelet aggregation [84].

Because of its short half-life, the regular form is taken every 8 hours and the ER form is taken twice per day. DP is currently available in two forms: an immediate-release form, usually given as 50 to 100 mg three times per day and a proprietary formulation containing both ER-DP 200 mg and 25 mg ASA, given two times per day.

Structure



Chemical formula: $C_{24}H_{40}N_8O_4$
SMILES: CCN(CCO)C1=NC2=C(N=C(N=C2N2CCCCC2)N(CCO)CCO)C(=N1)N1CCCCC1

Pharmacodynamics	DP, a non-nitrate coronary vasodilator that also inhibits platelet aggregation, is combined with other anticoagulant drugs, such as warfarin, to prevent thrombosis in patients with valvular or vascular disorders. DP is also used in myocardial perfusion imaging, as an antiplatelet agent, and in combination with aspirin for stroke prophylaxis	
Mechanism of action	DP likely inhibits both adenosine deaminase and phosphodiesterase, preventing the degradation of cAMP, an inhibitor of platelet function. This elevation in cAMP blocks the release of arachidonic acid from membrane phospholipids and reduces thromboxane A2 activity. DP also directly stimulates the release of prostacyclin, which induces adenylate cyclase activity, thereby raising the intraplatelet concentration of cAMP and further inhibiting platelet aggregation	
Absorption	70%	
Volume of distribution	1 to 2.5 l/kg	
Protein binding	99%	
Metabolism	Hepatic	
Route of elimination	DP is metabolized in the liver to the glucuronic acid conjugate and excreted with the bile	
Half life	40 minutes	
Clearance	2.3-3.5 ml/min/kg	
Toxicity	Hypotension, if it occurs, is likely to be of short duration, but a vasopressor drug may be used if necessary. The oral LD_{50} in rats is greater than 6,000 mg/kg while in the dogs, the oral LD_{50} is approximately 400 mg/kg. LD_{50}=8.4g/kg (orally in rat)	
Affected organisms	Humans and other mammals	
Interactions	**Drug**	**Interaction**
	Adenosine	DP may increase the effect/toxicity of adenosine
	Fludarabine	DP may decrease the effect of fludarabine
	Ginkgo biloba	Additive anticoagulant/antiplatelet effects may increase bleed risk. Concomitant therapy should be avoided
	Topotecan	The p-glycoprotein inhibitor, DP, may increase the bioavailability of oral topotecan. A clinically significant effect is also expected with IV topotecan. Concomitant therapy should be avoided
	Treprostinil	The prostacyclin analogue, Treprostinil, increases the risk of bleeding when combined with the antiplatelet agent, DP. Monitor for increased bleeding during concomitant thearpy. Additive hypotensive effect. Monitor antihypertensive therapy during concomitant use
Food interactions	Coffee and tea can decrease the effect of DP Take with food to reduce irritation	
Combination formulation with ASA	• Aggrenox FDA approved to reduce risk of stroke in patients who have had transient ischemia of brain or completed ischemic stroke due to thrombosis: ▪ Each capsule contains extended-release DP 200 mg plus immediate-release ASA 25 mg ▪ 1 capsule orally twice daily, swallow whole; do not crush, chew or open ▪ Cautions: peripheral vasodilation so caution if hypotension or severe coronary artery disease, amount of ASA may be inadequate for protection against myocardial infarction, Pregnancy Category D ▪ Adverse reactions: headache, dizziness, gastrointestinal upset, flushing, weakness, syncope, rash, pruritus, increased liver enzymes ▪ available in Europe as Asasantin/Aggrenox • Expensive, but generic substitutions with immediate-release DP may be less effective	

Efficacy	• Addition of DP to ASA reduces risk of vascular events after stroke or TIA (Level 1 [likely reliable] evidence) [33,66,85,86] • Extended-release DPis effective alone and more effective in combination with ASA in secondary prevention of stroke (Level 1 [likely reliable] evidence) [44,87] • Addition of DP to ASA may reduce risk of combined outcome of cardiovascular events (Level 2 [mid-level] evidence) [86] • Addition of DP to ASA might not reduce vascular events in patients after severe disabling stroke (level 2 [mid-level] evidence) [88] • Initiating DP plus ASA after 7 days of ASA therapy alone may be as effective as initiating within 24 hours of TIA or stroke (Level 2 [mid-level] evidence) [89] • Oatients>80 years old may still have reduced risk of stroke or death with ASA plus DP (level 2 [mid-level] evidence) [90]
Triple therapy	Antiplatelet therapy with combination ASA, clopidogrel, and DP associated with increased adverse events and bleeding complications (Level 2 [mid-level] evidence) [91]
Comparative efficacy	• ASA plus extended-release DP appears similar to clopidogrel for prevention of recurrent stroke but may have slightly more major hemorrhagic events (Level 2 [mid-level] evidence) [36,89] • ASA plus extended-release DP appears similar to clopidogrel in short-term functional outcome, recurrence and death (Level 2 [mid-level] evidence) [92] • DP plus ASA reported to be more effective than clopidogrel, ticlopidine or ASA for prevention of serious vascular events after TIA or stroke (Level 3 [lacking direct] evidence) [93]

Table 64.5. **Dipyridamole (DP) overview. SMILES indicates simplified molecular-input line-entry system [25].**

In the European Stroke Prevention Study 2 (ESPS-2) trial 6602 patients with a recent TIA or ischemic stroke were randomly assigned to four treatment groups: 25 mg ASA, 200 mg ER -DP, 25 mg ASA plus ER-DP, and placebo using a factorial design [44]. The three active treatments significantly reduced the incidence of stroke compared with placebo: (ASA vs. placebo: 12.5% vs. 15%, RRR 18.1%, p=0.01; ER-DP vs. placebo: 12.7% vs. 15%, RRR 16.3%, p=0.04; ASA combined with ER-DP: 9.5% vs. 15%, RRR 37.0%, p=0.001). The benefit of combination ER-DP plus ASA was significantly greater still than the two components alone and significantly greater than placebo (OR 0.59, 95% CI 0.48-0.73). A subsequent meta-analysis of individual patient data from all available randomized trials found that DP alone was effective for reducing recurrent stroke compared with control (OR 0.82, 95% CI 0.68-1.0) [85]. Since the ESPS-2 trial [44] provided 57% of the data in this meta-analysis, it is possible that ESPS-2 was the primary driver behind the results [85]. When ESPS-2 data were excluded, the effectiveness of DP alone compared with control did not achieve statistical significance. Whether this is related to the lower doses and immediate-release formulation used in trials other than ESPS-2 remains unclear.

Side Effects of DP

Headache is a well-known side effect of DP [85], and was the most frequent adverse event associated with ER-DP in two large clinical trials, ESPS-2 and ESPRIT [44,86]. DP causes headache in 24-70% of patients, in 39.7% after a single dose [94], which is sufficient to prompt discontinuation in about 10% of patients, usually within the first 3 months. Headache is more likely to occur in women, non-smokers, and patients with an absence of relevant ischemic lesions on brain imaging [95]. The headaches associated with ASA plus ER-DP treatment were mostly self-limited, and treatment with acetaminophen was not significantly better than with placebo, as measured by response at two hours (75.5% and 69.4%). The overall incidence of headache declined markedly over seven days to less than 20%. Gastric upset and/or diarrhea requiring drug cessation was

also more common with DP compared with ASA or placebo in ESPS-2. Notably, ASA use was associated with significantly greater overall bleeding and gastrointestinal bleeding compared with DP or placebo in ESPS-2 and a subsequent meta-analysis [44,85]. In fact, in ESPS-2, the frequency of bleeding complications with DP was comparable to placebo.

Cardiac Effects

Concern that DP use might lead to increased rates of myocardial ischemia has been largely laid to rest by data from two large clinical trials (ESPS-2 and ESPRIT) and a meta-analysis [85,86,96]. This concern is related to the potential for DP to cause vasodilation of coronary vessels [97], with the use of intravenous DP in cardiac stress testing [98]. The 2002 American College of Cardiology/American Heart Association guideline for the management of patients with chronic stable angina recommend avoidance of DP in patients with stable angina [99]. An analysis of data from ESPS-2 found that use of ER-DP was not associated with increased cardiac ischemia or mortality in patients with a history of coronary artery disease [96]. A meta-analysis found that oral DP had a neutral cardiac effect and did not alter the rate of MI in patients with previous stroke or TIA, either when compared with control, or when administered in combination with ASA and compared with ASA alone [85]. In ESPRIT, the use of combination therapy with ASA and DP, mainly ER-DP, was associated with a nonsignificant decrease in the outcome of first cardiac event, and a significant decrease in the primary composite outcome that included death from all vascular causes and nonfatal MI [86]. The cited observations suggest that ER-DP use for stroke prevention is NOT associated with an increased risk of myocardial ischemia or infarction.

ASA plus DP

Currently, the most commonly used preparation combines the ER form of DP (200 mg) with ASA (25 mg) into one pill. The combination of 25 mg ASA with 200 mg ER-DP costs substantially more than ASA but less than clopidogrel. In the USA, use of clopidogrel and the combination of ASA and ER-DP increased between 2001 and 2005, as their superior efficacy to ASA was recognized, despite the greater costs of the drugs [87]. In patients with previous TIA or ischemic stroke, the combination of ASA and ER-DP is significantly more effective than ASA alone in reducing the risk of stroke and other major vascular events (HR 0.82, 95% CI 0.72-0.92) without excessive bleeding or MI [33]. The combination of ASA and DP has been compared with ASA monotherapy for stroke prevention among patients with TIA or stroke in several clinical trials. Stroke risk was significantly reduced with ASA plus DP (including immediate and ER formulations) compared with ASA alone (RR 0.77, 95% CI 0.67-0.89) as reported in a meta-analysis of six randomized trials with 7,648 patients [86]. The beneficial effects of ASA and DP for secondary stroke prevention appear to be additive such that the combination of ASA plus ER-DP is significantly more effective than ASA alone for stroke prevention. In the ESPS-2 trial, the stroke rate at 24 months of follow-up was significantly reduced in the ASA plus ER-DP group compared with the ASA alone group (9.9% vs. 12.9%; RRR 23%, 95% CI 9.2-37.0) [44]. The risk of death and bleeding complications was not significantly different between the ASA plus ER-DP group and the ASA monotherapy group, whereas both groups experienced a greater frequency of bleeding complications than the placebo group. In the ESPRIT trial, the composite primary outcome (death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complication) was significantly less frequent in the ASA plus DP group than the ASA group (13% vs. 16%, HR 0.80, 95% CI 0.66-0.98, absolute risk reduction 1.0% per year) over a mean follow-up of 3.5 years [88]. In this trial, 2,739 patients within six months of a TIA or minor stroke of presumed arterial origin were randomly assigned to open-label treatment with ASA (30 to 325 mg/day) alone or ASA plus

DP (200 mg twice daily). The median ASA dose was 75 mg/day in both treatment groups, and the DP formulation used by most patients (83%) was ER rather than immediate release [88] ESPRIT included patients using ASA doses ranging from 30 to 325 mg daily, allaying concerns that the very low ASA dose (25 mg twice daily) used in ESPS-2 was in part responsible for the benefit of combined ASA plus ER-DP over ASA alone. The specific DP preparation may also be important because the combination of ASA and immediate-release DP was nonsignificantly better than ASA alone for secondary prevention of stroke (RR 0.83, 95% CI 0.59-1.15); on the contrary ASA plus ER-DP was associated with a significant reduction in stroke risk compared with ASA alone (RR 0.76, 95% CI 0.65-0.89) [86]. Extended release DP was used in all or the vast majority of patients in the much larger ESPS-2 and ESPRIT trials [47,88].

Recommendations for Use of DP for Secondary Prevention of Stroke

American College of Chest Physicians (ACCP) recommendations (Ninth Edition) [15]:

- Following noncardioembolic stroke or transient ischemic attack (TIA):
  - Combination of ASA 25 mg plus DP extended-release 200 mg twice daily recommended as an option for long-term antiplatelet therapy over: no antiplatelet therapy (ACCP Grade 1A), oral anticoagulants (ACCP Grade 1B), combination of clopidogrel plus ASA (ACCP Grade 1B), triflusal (ACCP Grade 2B).
  - Among the recommended antiplatelet regimens, clopidogrel or combination of ASA plus extended-release DP suggested over ASA alone (ACCP Grade 2B) or triflusal (ACCP Grade 2C).

American Heart Association (AHA) recommendations [13]:

- For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents recommended rather than OAT (AHA/ASA Class I, Level A):
  - Acceptable options include. ASA 50-325 mg daily (AHA/ASA Class I, Level A), combination ASA 25 mg twice daily and extended-release DP 200 mg twice daily (AHA/ASA Class I, Level B), clopidogrel 75 mg daily (AHA/ASA Class IIa, Level B).
  - Selection of antiplatelet agent should be individualized based on patient risk factors, cost, tolerance and other clinical factors.
  - Addition of ASA to clopidogrel increases risk of hemorrhage and is not routinely recommended for secondary prevention of stroke (AHA/ASA Class III, Level A).
  - Clopidogrel reasonable for patients allergic to ASA (AHA/ASA Class IIa, Level C).
  - For patients who have ischemic stroke while taking ASA (AHA/ASA Class IIb, Level C): no evidence for additional efficacy with increasing dose of ASA, alternative antiplatelet agents often considered, but no regimen specifically studied.
- For patients with ischemic stroke or TIA and paroxysmal or permanent atrial fibrillation:
  - If unable to take oral anticoagulants, ASA alone is recommended (AHA/ASA Class I, Level A).
  - Clopidogrel with ASA not recommended for patients with hemorrhagic contraindication to warfarin (AHA/ASA Class III, Level B).
- Optimal medical therapy for patients with extracranial arterial disease (carotid or vertebrobasilar) and TIA or stroke should include antiplatelet therapy (AHA/ASA Class I, Level B).
- For patients with stroke or TIA due to 50%-99% stenosis of major intracranial artery, ASA 50-325 mg/day is recommended over warfarin (AHA/ASA Class I, Level B).
- For patients with cardiomyopathy:
  - Insufficient evidence for use of warfarin in patients with prior stroke or TIA, sinus rhythm, cardiomyopathy and ejection fraction ≤ 35% (AHA/ASA Class IIb, Level B).
  - Treatments to consider for patients with ischemic stroke or TIA and cardiomyopathy include (AHA/ASA Class IIb, Level B): warfarin (INR 2-3), ASA 81 mg/day,

clopidogrel 75 mg/day, combination of ASA 25 mg twice daily and extended-release DP 200 mg twice daily.

- For patients with native valvular heart disease:
  - Antiplatelet therapy may be considered for patients with ischemic stroke or TIA and: native aortic or nonrheumatic mitral valve disease and no atrial fibrillation (AHA/ASA Class IIb, Level C), mitral annular calcification (AHA/ASA Class IIb, Level C), mitral valve prolapse (AHA/ASA Class IIb, Level C).

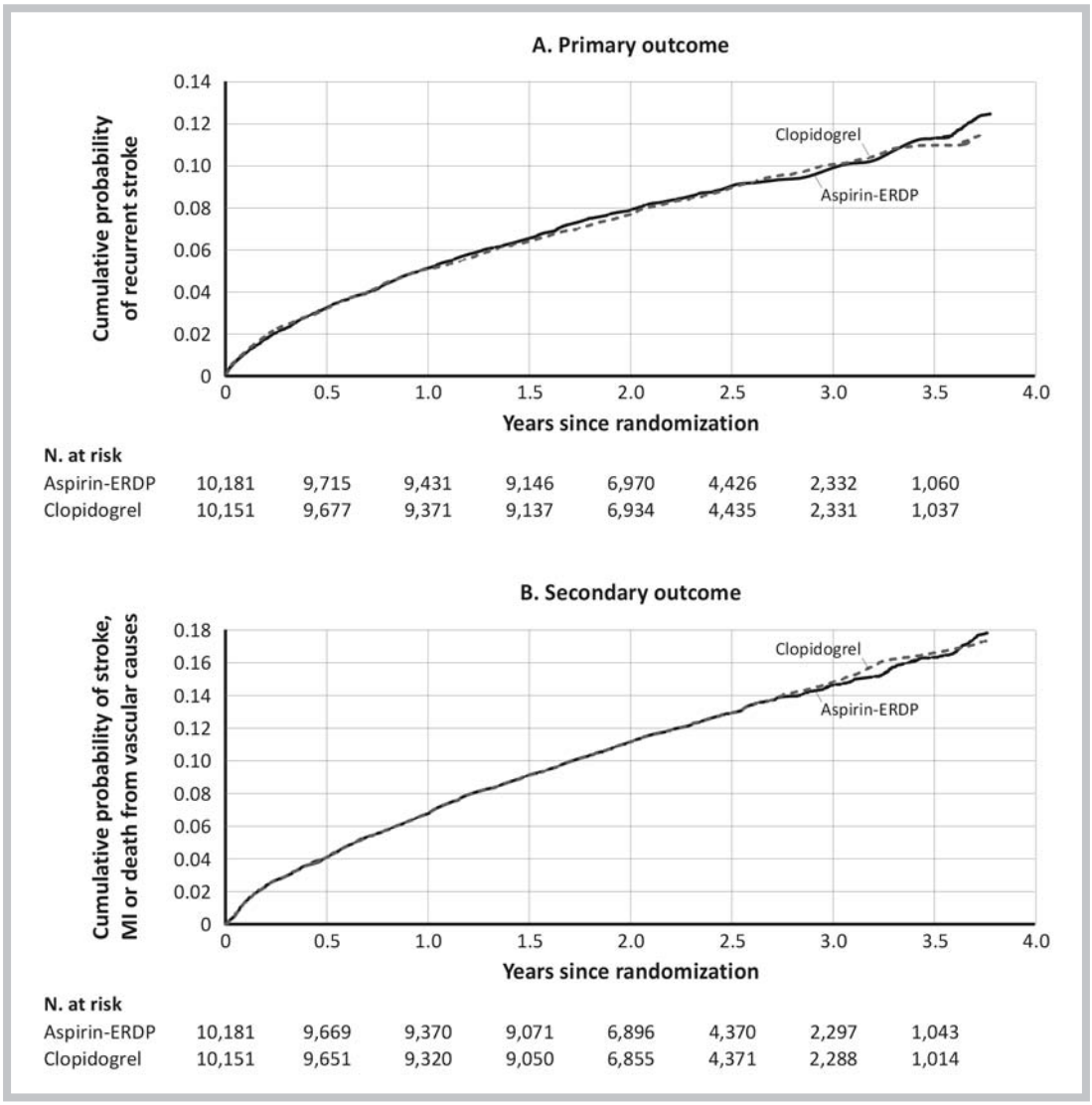


Figure 64.3. **Kaplan-Meier estimates of the cumulative probability of primary and secondary outcomes, according to treatment group. The primary outcome of first recurrence of stroke (Panel A) occurred in 916 of 10,181 patients (9.0%) treated with aspirin plus extended-release dipyridamole (ERDP) and in 898 of 10,151 patients (8.8%) treated with clopidogrel (hazard ratio for aspirin-ERDP, 1.01; 95% confidence interval [CI], 0.92 to 1.11). The main secondary outcome of stroke, myocardial infarction (MI), or death from vascular causes (Panel B) occurred in 1333 patients (13.1%) in each of the two groups (hazard ratio for aspirin-ERDP, 0.99; 95% CI, 0.92 to 1.07). The estimated hazard ratios are based on a Cox model with covariates of baseline values of age, use or nonuse of angiotensin-converting-enzyme inhibitors, diabetes status, and score on the modified Rankin scale. Adapted from [36].**

  - To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin (AHA/ASA Class III, Level C).
- For patients with ischemic stroke or TIA due to extracranial arterial dissection (carotid or vertebral):
  - Antithrombotic therapy for at least 3-6 months is reasonable (AHA/ASA Class IIa, Level B).
  - Relative efficacy of antiplatelet therapy vs. anticoagulation is unknown (AHA/ASA Class IIb, Level B).
- For patients with patent foramen ovale (PFO):
  - Antiplatelet therapy is reasonable for patients with ischemic stroke or TIA and PFO (AHA/ASA Class IIa, Level B).
  - Insufficient data to determine whether anticoagulation is as or more effective than ASA for secondary stroke prevention in patients with PFO (AHA/ASA Class IIb, Level B).

National Institute of Health and Clinical Excellence (NICE) guidance on clopidogrel and modified-release DP in prevention of occlusive vascular events [65]:

- Guidance applies to people with history of occlusive vascular event or with symptomatic peripheral arterial disease.
- Combination of modified-release DP and ASA recommended for people who had ischemic stroke or transient ischemic attack for 2 years from most recent event then continue with low-dose ASA.

Canadian Stroke Network (CSN) recommendations [16]:

- All patients with ischemic stroke should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless indication for anticoagulation (CSN Grade A).
- Combined ASA (25 mg) and extended-release DP (200 mg) twice daily is an option for antiplatelet therapy.

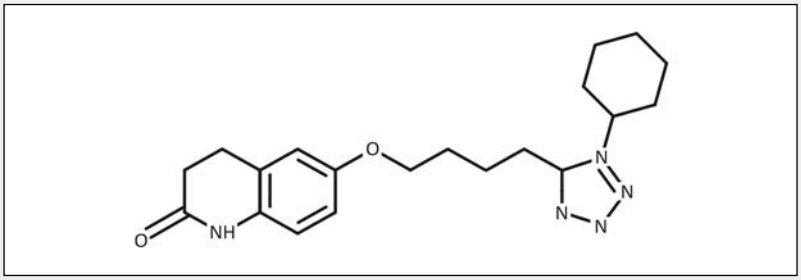
ASA Plus Extended-release Dipyridamole vs. Clopidogrel

In the PRoFESS trial clopidogrel monotherapy and ASA plus ER-DP showed similar risks and benefits for secondary stroke prevention [36]. Using a 2x2 factorial design in which the patients were also randomly assigned to telmisartan or placebo, the trial enrolled 20,332 patients with noncardioembolic ischemic stroke and randomly assigned them to treatment with either ASA plus ER-DP (25/200 mg twice daily) or clopidogrel (75 mg once daily). At an average follow-up of 2.5 years, a direct comparison of 75 mg clopidogrel daily with the combination of 25 mg ASA and 200 mg ER-DP twice daily in 20,332 patients with ischemic stroke showed nonsignificant difference between either regimen in the prevention of recurrent stroke (9.0% on ASA plus ER-DP vs. 8.8% on clopidogrel; HR 1.01, 95% CI 0.92-1.11), MI (1.7% vs. 1.9%; HR 0.90, 0.73-1.10), and the composite secondary outcome of stroke, MI, and vascular death (13.1% vs. 13.1%; HR 0.99, 0.92-1.07; Figure 64.3). The trial failed to meet the prespecified noninferiority criteria for treatment with ASA plus ER-DP, the rate of recurrent ischemic stroke was slightly lower in those assigned to ASA plus ER-DP compared with clopidogrel (7.7% vs. 7.9%) among patients who had recurrent strokes, while ICH were slightly increased (0.9% vs. 0.5%). The benefit-risk ratio (the combination of recurrent stroke plus major hemorrhage) was not significantly different between ASA plus ER-DP and clopidogrel (11.7% vs. 11.4%; HR 1.03, 95% CI 0.95-1.11). Discontinuation due to headache was significantly more frequent in patients assigned to ASA plus ER-DP than in those assigned to clopidogrel (5.9% vs. 0.9%) while New or worsening heart failure was slightly less frequent in patients assigned to ASA plus ER-DP compared to those assigned to clopidogrel (1.4% vs. 1.8%, 95% CI 0.62-0.96).

64.2.1 Other Antithrombotic Regimens

Cilostazol

The antiplatelet agent cilostazol is a phosphodiesterase 3 inhibitor that is used in the alleviation of the symptom of intermittent claudication in individuals with peripheral vascular disease (Table 64.6). The mechanism of the effects of cilostazol on the symptoms of intermittent claudication and in the prevention of recurrent ischemic stroke is not fully understood. Cilostazol and several of its metabolites are cyclic AMP (cAMP) phosphodiesterase III inhibitors (PDE III inhibitors), inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation [84].

Structure	 Chemical formula: $C_{20}H_{27}N_5O_2$ SMILES: O=C1CCC2=C(N1)C=CC(OCCCCC1=NN=NN1C1CCCCC1)=C2
Indication	For the reduction of symptoms of intermittent claudication (pain in the legs that occurs with walking and disappears with rest)
Pharmacodynamics	Cilostazol is a quinolinone derivative indicated for the reduction of symptoms of intermittent claudication, as indicated by an increased walking distance. Intermittent claudication is pain in the legs that occurs with walking and disappears with rest. The pain occurs due to reduced blood flow to the legs
Mechanism of action	Cilostazol and several of its metabolites are cyclic AMP (cAMP) phosphodiesterase III inhibitors (PDE III inhibitors), inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation
Absorption	Cilostazol is absorbed after oral administration. A high fat meal increases absorption, with an approximately 90% increase in C_{max} and a 25% increase in AUC. Absolute bioavailability is not known
Volume of distribution	Not available
Protein binding	95-98%
Metabolism	Hepatic. Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly 3A4, and, to a lesser extent, 2C19, with metabolites largely excreted in urine. Two metabolites are active, with one metabolite appearing to account for at least 50% of the pharmacologic (PDE III inhibition) activity after administration of cilostazol
Route of elimination	Cilostazol is extensively metabolized by hepatic cytochrome P-450 enzymes, mainly 3A4, and, to a lesser extent, 2C19, with metabolites largely excreted in urine. Cilostazol is eliminated predominately by metabolism and subsequent urinary excretion of metabolites. The primary route of elimination was via the urine (74%), with the remainder excreted in feces (20%). No measurable amount of unchanged cilostazol was excreted in the urine, and less than 2% of the dose was excreted as 3,4-dehydro-cilostazol. About 30% of the dose was excreted in urine as 4'-trans-hydroxy-cilostazol

Half life	11-13 hours	
Clearance	Not available	
Toxicity	Information on acute overdosage with cilostazol in humans is limited. The signs and symptoms of an acute overdose can be anticipated to be those of excessive pharmacologic effect: severe headache, diarrhea, hypotension, tachycardia, and possibly cardiac arrhythmias. The oral LD_{50} of cilostazol is >5.0 g/kg in mice and rats and >2.0 g/kg in dogs	
Drug interactions	**Drug**	**Interaction**
	Diltiazem	Diltiazem, a moderate CYP3A4 inhibitor, may increase the serum concentration of cilostazol by decreasing its metabolism. Monitor for changes in the therapeutic and adverse effects of cilostazol if diltiazem is initiated, discontinued or dose changed
	Erythromycin	Erythromycin increases the effect of cilostazol
	Fluconazole	Fluconazole may decrease the effect of cilostazol
	Fluoxetine	Fluoxetine, a moderate CYP2C19 inhibitor, may decrease the metabolism of cilostazol. Monitor for changes in the therapeutic and adverse effects of cilostazol if fluoxetine is initiated, discontinued or dose changed
	Fluvoxamine	Fluvoxamine increases the effect of cilostazol
	Ginkgo biloba	Additive anticoagulant/antiplatelet effects may increase bleed risk. Concomitant therapy should be avoided
	Itraconazole	Itraconazole may increase the effect of cilostazol
	Josamycin	Erythromycin increases the effect of cilostazol
	Ketoconazole	Ketoconazole may increase the effect of cilostazol
	Nefazodone	Nefazodone increases the effect of cilostazol
	Omeprazole	Omeprazole increases the effect of cilostazol
	Sertraline	Sertraline increases the effect of cilostazol
	Telithromycin	Telithromycin may reduce clearance of cilostazol. Consider alternate therapy or monitor for changes in the therapeutic/adverse effects of cilostazol if telithromycin is initiated, discontinued or dose changed
	Ticlopidine	Ticlopidine may decrease the metabolism and clearance of cilostazol. Consider alternate therapy or monitor for adverse/toxic effects of cilostazol if ticlopidine is initiated, discontinued or dose changed
	Treprostinil	The prostacyclin analogue, treprostinil, increases the risk of bleeding when combined with the antiplatelet agent, cilostazol. Monitor for increased bleeding during concomitant thearpy
	Voriconazole	Voriconzole may increase the serum concentration of cilostazol by decreasing its metabolism. Monitor for increased therapeutic/adverse effects of cilostazol and consider reducing the dose during concomitant therapy
Food interactions	• Grapefruit and grapefruit juice should be avoided throughout treatment, grapefruit can significantly increase serum levels of this product • Take on an empty stomach, a lipid rich meal will increase absorption	

Efficacy	• Cilostazol decreases risk of hemorrhagic stroke but increases risk of adverse events compared with ASA in patients with previous cerebral infarction (Level 1 [likely reliable] evidence) [89] • Cilostazol decreases stroke but increases minor adverse events compared to ASA in patients with previous cerebral infarction (Level 1 [likely reliable] evidence) [91] • Cilostazol is at least as effective as ASA for reducing risk of recurrent stroke (Level 1 [likely reliable] evidence) [92] • Cilostazol may reduce risk of pneumonia (Level 2 [mid-level] evidence) [93]

Table 64.6. **Cistazol overview. SMILES indicates simplified molecular-input line-entry system [60].**

Several controlled trials have found that cilostazol is effective for preventing cerebral infarction. For longer term secondary prevention, cilostazol (100 mg twice daily) reduced the risk of stroke (RRR 42%, 95% CI 9.2-62.5) compared with placebo among 1095 Japanese patients with ischemic stroke [94], and by about 38% (−26-70%) compared with ASA in a pilot trial involving 720 Chinese patients with ischemic stroke (3.3% vs. 5.6%, HR 0.62, 95% CI 0.30-1.26) but this result was not statistically significant [92]. In the non-inferiority CSPS II trial, 2757 Japanese patients with a recent noncardioembolic cerebral infarction were randomly assigned to cilostazol (100 mg twice daily) or ASA (81 mg daily) [91]. Cilostazol is non-inferior to ASA for stroke prevention, the yearly rates of recurrent stroke (infarction or hemorrhage) for cilostazol and ASA were 2.7% and 3.7% (HR 0.74, 95% CI 0.56-0.98) at a mean follow-up of 29 months. Annual rates of hemorrhagic events (ICH, subarachnoid hemorrhage, or other hemorrhage requiring hospitalization) were lower with cilostazol than with ASA (0.8% vs. 1.8%, HR 0.46, 95% CI 0.30-0.71).

However, side effects (headache, diarrhea, palpitation, dizziness, and tachycardia) were more frequent with cilostazol, and more patients discontinued cilostazol than ASA (20% vs. 12%). These data support the safety and efficacy of cilostazol for secondary stroke prevention in Asian populations. However, there are as yet no high-quality data regarding the use of cilostazol for secondary stroke prevention in non-Asian ethnic groups. Furthermore, drugs similar to cilostazol have increased the risk of death in patients with congestive heart failure, studies of significant size have not addressed people without the disease. Finally, the lower tolerability and higher cost of cilostazol compared with ASA may limit its more widespread use for stroke prevention.

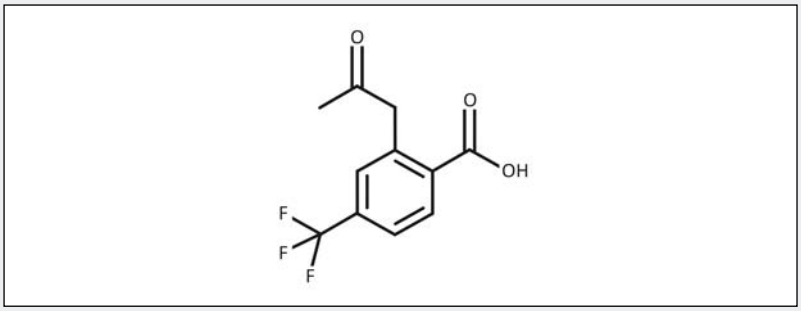
Recommendations for Use of Cilostazol for Secondary Prevention of Stroke

American College of Chest Physicians (ACCP) recommendations (Ninth Edition) for secondary prevention of stroke [15]:

- Following noncardioembolic stroke or transient ischemic attack (TIA), cilostazol 100 mg twice daily recommended as an option for long-term antiplatelet therapy over:
  - No antiplatelet therapy (ACCP Grade 1A).
  - Oral anticoagulants (ACCP Grade 1B).
  - Combination of clopidogrel plus ASA (ACCP Grade 1B).
  - Triflusal (ACCP Grade 2B).

Triflusal

Triflusal is an antiplatelet agent that is structurally related to ASA (Table 64.7).

Structure	 Chemical formula: $C_{10}H_7F_3O_4$ SMILES: CC(=O)Oc1cc(C(F)(F)F)ccc1C(=O)O	
Pharmacodynamics	Triflusal is an antithrombotic anticoagulant. It irreversibly inhibits the production of thromboxane-B2 in platelets by acetylating cycloxygenase-1. Triflusal affects many other targets such as NF kappa B, which is a gene expression regulatory factor for cycloxygenase-a and cytokines. Numerous studies comparing the efficacy and safety profile (i.e. systemic hemorrhage) between triflusal and acetylsalsylic acid has shown either nonsignificant difference or a better effacy and safety profile for triflusal. Triflusal has been shown to protect cerebral tissue due to its inhibition of lipid peroxidation resulting from anoxia-reoxygenation	
Mechanism of action	Triflusal is chemically related to acetylsalicylic acid (ASA) and irreversibly inhibits cycloxygenase-1 (COX-1) in platelets. Acetylation of the active group of COX-1 prevents the formation of thromboxane-B2 in platelets. However, it is unique because it spares the arachidonic acid metabolic pathway in endothelial cells. In addition, it favors the production of nitric oxide, a vasodilator	
Absorption	Absorbed in the small intestine with a bioavailability range from 83% to 100%. There is nonsignificant difference between the absorption of the oral solution and capsule formulation	
Volume of distribution	34 l	
Protein binding	Binds to plasma proteins almost entirely (99%)	
Metabolism	In the liver, triflusal undergoes deacetylation, forming its main metabolite 2-OH-4-trifluoromethyl benzoic acid (HTB)	
Route of elimination	Primarily renal	
Half life	In healthy human, the half life is 0.5 ± 0.1h, while that of HTB is 34.3 ± 5.3 h	
Clearance	Renal clearance is 0.8 ± 0.2 l/h and 0.18 ± 0.04 l/h for triflusal and HTB, respectively	
Toxicity	Excessive bleeding. The risk of bleeding is less than that of acetylsalicylic acid	
Affected organisms	Not available	
Drug Interactions	**Drug**	**Interaction**
	Ibuprofen	The metabolite of triflusal, 2-hydroxy-4-trifluoro-methyl-benzoic acid (HTB), impairs the serum protein binding of ibuprofen to the same extent as acetylsalisylic acid. Thus, the free fraction of glisentide may be increased. A dosage reduction may be required if used in combination
	Naproxen	The metabolite of triflusal, 2-hydroxy-4-trifluoro-methyl-benzoic acid (HTB), impairs the serum protein binding of naproxen to the same extent as acetylsalisylic acid. Thus, the free fraction of glisentide may be increased. A dosage reduction may be required if used in combination

	Piroxicam	The metabolite of triflusal, 2-hydroxy-4-trifluoro-methyl-benzoic acid (HTB), impairs the serum protein binding of glisentide to the same extent as acetylsalisylic acid. Thus, the free fraction of glisentide may be increased. A dosage reduction may be required if used in combination
	Warfarin	The metabolite of triflusal, 2-hydroxy-4-trifluoro-methyl-benzoic acid (HTB), impairs the serum protein binding of warfarin to the same extent as acetylsalisylic acid. Thus, the free fraction of glisentide may be increased. A dosage reduction may be required if used in combination
Food interactions	Gingko bilboa Herbs with anticoagulant/antiplatelet activity such as alfalfa, feverfew, ginger, ginseng, grape seed, green tea, horseradish	
Efficacy	Triflusal appears as effective as ASA with less hemorrhagic complications for secondary prevention of vascular events (level 2 [mid-level] evidence) [29,95]	

Table 64.7. **Triflusal overview. SMILES indicates simplified molecular-input line-entry system [25].**

Approved by the European Stroke Organization, triflusal is recommended as lone therapy for the secondary prevention of atheroembotic stroke. Triflusal appears to be equally effective with a better safety profile than ASA plus DP and clopidogrel alone based on a double blind, randomized TACIP and TAPIRSS trials [95,96]. The effectiveness of triflusal was similar to ASA (325 mg/day) at preventing vascular events after stroke, but it did have a lower rate of hemorrhagic complications [95]. Similar findings were noted in a smaller randomized trial and a meta-analysis of four trials [29,96]. It is not clear whether triflusal would have had a lower rate of hemorrhagic complications than lower-dose ASA [98].

Recommendations for Use of Triflusal for Secondary Prevention of Stroke

American College of Chest Physicians (ACCP) recommendations (Ninth Edition) for secondary prevention of stroke [15]:

- For antiplatelet therapy for secondary prevention of stroke, triflusal is not suggested over clopidogrel or combination of ASA plus extended-release dipyridamole (ACCP Grade 2C).

Sarpogrelate

Sarpogrelate acts as an antagonist at the $5HT_{2A}$ and $5\text{-}HT_{2B}$ receptors and blocks serotonin-induced platelet aggregation. In S-ACCESS trial, sarpogrelate (100 mg 3 times daily plus placebo ASA) was not as effective as ASA (81 mg daily plus placebo sarpogrelate) for secondary prevention of cerebral infarction in 1510 Japanese patients with ischemic stroke in previous 1 week to 6 months randomized to sarpogrelate vs. ASA (level 2 [mid-level] evidence) [100].

Terutroban

Terutroban is selective TX-prostaglandin receptor antagonist. In PERFORM trial, terutroban (30 mg orally per day) was no more effective than ASA (100 mg orally per day) in 19,120 patients with ischemic stroke during prior 3 months or TIA within prior 8 days followed for mean 28.3 months for reducing vascular events (level 1 [likely reliable] evidence) [101]. The trial comparing terutroban with 100 mg ASA daily in 18,000 patients with a history of recent ischemic stroke or TIA has recently been halted because interim analyses suggested that continuation of the study would be futile [101].

64.2.2 Special Antithrombotic Regimens

In acute TIA and ischemic stroke, the combination of ASA plus clopidogrel may be more effective than ASA alone if administered immediately and for only the first few months, when the risk of recurrent stroke is highest [99]. This strategy reduces the long-term risks of bleeding associated with the combination of clopidogrel and ASA compared with ASA or clopidogrel alone [28,33].

The POINT (Platelet-Oriented Inhibition in New TIA) trial, are being planned to establish the relative safety and efficacy of the combination of clopidogrel and ASA compared with ASA in patients with acute TIA and mild ischemic stroke [102]. In the acute phase of ischemic stroke, short-term abciximab is not more effective than ASA (OR 0.97 [95% CI 0.70-1.36]) [34,103].

64.2.3 Antiplatelets vs. Anticoagulants

Warfarin has been shown in multiple trials to be superior to ASA for patients with AF, and is clearly indicated in patients with stroke caused by AF if they have no contraindications to therapy. Two recent trials have failed to show that OAT was better than ASA for other ischemic stroke subtypes [59,104].

The Warfarin ASA Recurrent Stroke Study (WARSS) was a superiority trial that compared ASA to warfarin for secondary stroke prevention in 2206 patients with recent noncardioembolic stroke. The goal INR in this study was 1.4 to 1.8. Event rates (17.8% for warfarin vs. 16.0% for ASA) as well as major hemorrhage rates (3.4% for warfarin vs. 2.7% for ASA) were nonsignificantly higher in the warfarin arm. In subgroup analyses, no patient subgroup clearly benefited from warfarin compared with ASA, including those with antiphospholipid antibodies, patent foramen ovale, and posterior circulation strokes [59]. In addition, patients who were taking ASA at the time of their initial stroke did not benefit from warfarin compared with ASA.

The Warfarin vs. ASA for Symptomatic Intracranial Disease (WASID) study compared high-dose ASA (1300 mg) to warfarin (INR goal 2-3) in patients with symptomatic atherosclerotic intracranial stenosis [104]. The study was stopped prematurely after enrollment of 569 of the planned 806 patients due to concerns about the safety of patients randomized to warfarin. Compared with ASA, warfarin was associated with a higher rate of death (9.7% vs. 4.3%, p=0.02), major hemorrhage (8.3% vs. 3.2%, p=0.01), and MI or sudden death (7.3% vs. 2.9% p=0.02). We recommend antiplatelet agents over OAT for most patients with noncardioembolic stroke. For the subset of patients with noncardioembolic stroke with well-documented prothrombotic disorders, we suggest OAT over antiplatelet agents.

64.2.4 National Guidelines and Consensus Statements Regarding Choice of Antiplatelet Agents

American Heart Association/American Stroke Association (AHA/ASA) and the American College of Chest Physicians (ACCP) current guidelines recommend that patients with a noncardioembolic (ie, atherothrombotic, lacunar, or cryptogenic) stroke or TIA and no contraindication receive an antiplatelet agent to reduce the risk of recurrent stroke [13,15].

These guidelines note that ASA, clopidogrel, and the combination of ASA plus ER-DP are all acceptable options for preventing recurrent noncardioembolic ischemic stroke

or TIA. The 2011 AHA/ASA guidelines recommend the use of the combination of ASA and ER-DP instead of ASA [13]. The 2012 ACCP guidelines include cilostazol in this group of recommended antiplatelet agents, and further suggest the use of the combination of ASA plus ER-DP or clopidogrel over aspirin or cilostazol. However, the publication of the PRoFESS trial provides high-quality evidence that clopidogrel monotherapy and ASA plus ER-DP are equivalent in terms of effectiveness and safety for secondary prevention of ischemic stroke [36]. The most important guidelines are summarized in Table 64.8.

American College of Chest Physicians (ACCP) guidelines (Ninth Edition) [15,117]	• Following noncardioembolic stroke or transient ischemic attack (TIA):
	  ▪ Long-term antiplatelet therapy recommended with 1 of: clopidogrel 75 mg once daily, combination of ASA 25 mg plus DP extended-release 200 mg twice daily, ASA 75-100 mg once daily, cilostazol 100 mg twice daily
	  ▪ Any of these antiplatelet agents recommended over, no antiplatelet therapy (ACCP Grade 1A), oral anticoagulants (ACCP Grade 1B), combination of clopidogrel plus ASA (ACCP Grade 1B), triflusal (ACCP Grade 2B)
	  ▪ Among the recommended antiplatelet regimens, clopidogrel or combination of ASA plus extended-release DP suggested over ASA alone (ACCP Grade 2B) or triflusal (ACCP Grade 2C)
	  ▪ Benefit of clopidogrel over ASA for preventing major vascular events may be offset with long-term use (>5 years) by lower cancer-related mortality with ASA
	• Following cardioembolic stroke or TIA (that is, atrial fibrillation, including paroxysmal atrial fibrillation):
	  ▪ OAT recommended over: no antithrombotic therapy (ACCP Grade 1A), ASA (ACCP Grade 1B), combination therapy with ASA plus clopidogrel (ACCP Grade 1B)
	  ▪ OAT with dabigatran 150 mg twice daily suggested over adjusted-dose vitamin K agonist therapy (target range 2-3) (ACCP Grade 2B); dabigatran contraindicated if creatinine clearance ≤ 30 ml/minute
	  ▪ For patients unsuitable for or who choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with ASA plus clopidogrel recommended over ASA (ACCP Grade 1B)
	  ▪ OAT should generally be started within 1-2 weeks after stroke onset, but timing may vary with risk for bleeding
	  ▪ Use of ASA as bridging therapy suggested until anticoagulation reaches therapeutic level
	• With history of symptomatic primary intracerebral hemorrhage, long-term use of antithrombotic therapy for prevention of ischemic stroke suggested against (ACCP Grade 2C)
	• If cerebral venous sinus thrombosis, anticoagulation during acute and chronic phases suggested over no anticoagulant therapy (ACCP Grade 2C)

National Institute for Health and Clinical Excellence (NICE) [65]	• NICE guidance on clopidogrel and modified-release DP in prevention of occlusive vascular events:
	  ▪ Guidance applies to people with history of occlusive vascular event or with symptomatic peripheral arterial disease
	  ▪ Combination of modified-release DP and ASA recommended for people who had ischemic stroke or transient ischemic attack for 2 years from most recent event then continue with low-dose ASA
	  ▪ Clopidogrel alone (within licensed indications) recommended for people intolerant of low-dose ASA (proven hypersensitivity or history of severe dyspepsia) who have had occlusive vascular event or symptomatic peripheral arterial disease

American Heart Association (AHA) guidelines [13]	• For patients with noncardioembolic ischemic stroke or TIA, antiplatelet agents recommended rather than OAT (AHA/ASA Class I, Level A):
	  ▪ Acceptable options include: ASA 50-325 mg daily (AHA/ASA Class I, Level A), combination ASA 25 mg twice daily and extended-release DP 200 mg twice daily (AHA/ASA Class I, Level B), clopidogrel 75 mg daily (AHA/ASA Class IIa, Level B)
	  ▪ Selection of antiplatelet agent should be individualized based on patient risk factors, cost, tolerance and other clinical factors
	  ▪ Addition of ASA to clopidogrel increases risk of hemorrhage and is not routinely recommended for secondary prevention of stroke (AHA/ASA Class III, Level A)
	  ▪ Clopidogrel reasonable for patients allergic to ASA (AHA/ASA Class IIa, Level C)
	  ▪ For patients who have ischemic stroke while taking ASA (AHA/ASA Class IIb, Level C): no evidence for additional efficacy with increasing dose of ASA, alternative antiplatelet agents often considered, but no regimen specifically studied
	• For patients with ischemic stroke or TIA and paroxysmal or permanent atrial fibrillation:
	  ▪ If unable to take oral anticoagulants, ASA alone is recommended (AHA/ASA Class I, Level A)
	  ▪ Clopidogrel with ASA not recommended for patients with hemorrhagic contraindication to warfarin (AHA/ASA Class III, Level B)
	• Optimal medical therapy for patients with extracranial arterial disease (carotid or vertebrobasilar) and TIA or stroke should include antiplatelet therapy (AHA/ASA Class I, Level B)
	• For patients with stroke or TIA due to 50%-99% stenosis of major intracranial artery, ASA 50-325 mg/day is recommended over warfarin (AHA/ASA Class I, Level B)
	• For patients with cardiomyopathy:
	  ▪ Insufficient evidence for use of warfarin in patients with prior stroke or TIA, sinus rhythm, cardiomyopathy and ejection fraction ≤ 35% (AHA/ASA Class IIb, Level B)
	  ▪ Treatments to consider for patients with ischemic stroke or TIA and cardiomyopathy include (AHA/ASA Class IIb, Level B): warfarin (INR 2-3), ASA 81 mg/day, clopidogrel 75 mg/day, combination of ASA 25 mg twice daily and extended-release DP 200 mg twice daily
	• For patients with native valvular heart disease:
	  ▪ Antiplatelet therapy may be considered for patients with ischemic stroke or TIA and: native aortic or nonrheumatic mitral valve disease and no atrial fibrillation (AHA/ASA Class IIb, Level C), mitral annular calcification (AHA/ASA Class IIb, Level C), mitral valve prolapse (AHA/ASA Class IIb, Level C)
	  ▪ To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin (AHA/ASA Class III, Level C)
	• For patients with ischemic stroke or TIA due to extracranial arterial dissection (carotid or vertebral):
	  ▪ Antithrombotic therapy for at least 3-6 months is reasonable (AHA/ASA Class IIa, Level B)
	  ▪ Relative efficacy of antiplatelet therapy vs. anticoagulation is unknown (AHA/ASA Class IIb, Level B)
	• For patients with patent foramen ovale (PFO)
	  ▪ Antiplatelet therapy is reasonable for patients with ischemic stroke or TIA and PFO (AHA/ASA Class IIa, Level B)
	• Insufficient data to determine whether anticoagulation is as or more effective than ASA for secondary stroke prevention in patients with PFO (AHA/ASA Class IIb, Level B)

Canadian Stroke Network/Heart and Stroke Foundation of Canada [16]	• All patients with ischemic stroke should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke unless indication for anticoagulation (CSN Grade A) • Medications include (CSN Grade A): · ASA 80-325 mg/day · Combined ASA (25 mg) and extended-release DP (200 mg) · Clopidogrel • Long term combination of ASA and clopidogrel are not recommended for secondary stroke prevention (CSN Grade B)	
Other reviews	• Recommended initial antiplatelet therapy (Grade B recommendation [inconsistent or limited evidence]) [97], based on literature review: · ASA or clopidogrel is agent of choice for transient ischemic attack, stroke, chronic stable angina, and peripheral arterial disease · ASA plus DP is an alternative for first episode of TIA or stroke in absence of clinically apparent coronary artery disease • ASA or combination extended-release DP plus ASA appear cost-effective for prevention of second strokes [118]: · Clopidogrel not considered cost-effective • Age >80 years should not be deterrent to using antiplatelet drugs (grade B recommendation [inconsistent or limited evidence]) [90], based on subgroup analysis of randomized trial: · 1306 patients with TIA or stroke randomized to combination of ASA 330 mg plus DP 75 mg vs. placebo orally 3 times daily for 2 years · Statistically significant decreases in combined outcome of stroke or death occurred in subgroups with ages>60 years,>70 years and>80 years; 40 patients were>80 years old	
Recommendation grading systems used	American College of Chest Physicians (ACCP) grades	• Grade 1: strong recommendation based on clear risk/benefit balance • Grade 2: weak recommendation based on unclear or close risk/benefit balance • Grade A: high-quality evidence based on consistent evidence from randomized trials without important limitations or exceptionally strong evidence from observational studies • Grade B: moderate-quality evidence based on randomized trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise results) or very strong evidence from observational studies • Grade C: low- or very low-quality evidence based on observational studies, case series, or randomized trials with serious flaws or indirect evidence • Reference: ACCP Evidence-Based Clinical Practice Guidelines (Ninth Edition) Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines [119]
	Canadian Stroke Network (CSN)/Heart and Stroke Foundation of Canada definitions of strength of recommendations [16]	• Grade A: strong recommendation · Evidence from randomized controlled trials or meta-analyses of randomized controlled trials · Desirable effects clearly outweigh undesirable effects, or vice versa

		• Grade B: · Single randomized controlled trial or well-designed observational study with strong evidence, or · Well-designed cohort or case-control analytic study, or · Multiple time series or dramatic results of uncontrolled experiment · Desirable effects closely balanced with undesirable effects. • Grade C: · At least 1 well-designed, nonexperimental descriptive study (such as comparative studies, correlation studies, case studies), or · Expert committee reports, opinions and/or experience of respected authorities, including consensus from development and/or reviewer groups
	American Heart Association/American Stroke Society (AHA/ASA) grading system for recommendations [12]	• Classifications of recommendations: · Class I: procedure or treatment should be performed or administered · Class IIa: reasonable to perform procedure or administer treatment, but additional studies with focused objectives needed · Class IIb: procedure or treatment may be considered; additional studies with broad objectives needed, additional registry data would be useful · Class III: procedure or treatment should not be performed or administered because it is not helpful or may be harmful · Class III ratings may be subclassified as Class III No Benefit or Class III Harm • Levels of evidence: · Level A: data derived from multiple randomized clinical trials or meta-analyses · Level B: data derived from single randomized trial or nonrandomized studies · Level C: only consensus opinions of experts, case studies, or standard of care

Table 64.8. **Guidelines regarding the choice of antiplatelets agents.**

64.2.5 Implications for Clinicians: Choosing Initial Therapy

The most important priority in the management of patients with ischemic stroke and TIA of arterial origin is to ensure that they are prescribed, taking, and tolerating an effective antiplatelet drug. ASA is effective for secondary stroke prevention in patients with noncardioembolic TIA and ischemic stroke. However, clopidogrel treatment was better than ASA as measured by a composite outcome of stroke, MI, or vascular death in the CAPRIE study [26], and the combination of ASA and ER-DP had greater benefit for secondary stroke risk reduction than ASA alone in two clinical trials (ESPS-2 and ESPRIT) [44,88]. Immediate-release DP cannot be routinely recommended for secondary prevention of ischemic stroke, given the limited evidence supporting its effectiveness and

the significant pharmacokinetic differences between it and ER-DP. Ticlopidine is rarely used because of its side-effect profile and lack of clear superiority over the other available agents. ASA and clopidogrel should not be used in combination for stroke prevention, given the lack of greater efficacy compared with either agent alone, and given the substantially increased risk of bleeding complications.

Because ASA is widely available, affordable, and albeit modestly effective, it is arguably the first-line treatment of choice, noting that the alternative antiplatelet regimens (clopidogrel or combined ASA and ER-DP) have an apparent modest advantage in benefit that is offset by a severe disadvantage in cost. However, if patients are intolerant of or allergic to ASA, at high risk of a recurrent stroke (more than 15-20% per year) [3], or have experienced a recurrent ischemic event of arterial origin while taking ASA, then one of the two more effective, although more expensive, regimens is indicated. As with any medication choices, individual patient characteristics play a role in the decision to start clopidogrel or the combination of ASA and ER-DP. Factors to keep in mind include medication costs and patient comorbidities.

Costs

The costs of prescription medications can be important in medication decisions. Clopidogrel and the combined ER-DP plus ASA each costs approximately $115 per month. The potential benefits of these two alternatives to ASA, which has a monthly cost of only a few dollars, must be carefully considered.

Medical Comorddidities

Stroke patients with unstable coronary artery disease or recent MI will generally benefit from the use of clopidogrel. ASA plus ER-DP has not been proven to be effective for the treatment of patients with coronary artery disease, but was not associated with any excess MI as an outcome event in stroke patients [31,36]. Patients with gastric ulcers may best be served with low-dose ASA or one of the other antiplatelet choices (major bleeding in 4.1% of patients on ASA with ER-DP vs. 3.6% on clopidogrel). For patients with headaches (headache 6% of patients on ASA with ER DP vs. 1% on clopidogrel), the potential side effect of worsening headache with ER-DP should be discussed at the time treatment is started, or another antiplatelet agent could be chosen.

Recurrent events on treatment. No clinical trials have directly addressed the issue of subsequent therapy for patients who experience recurrent episodes of brain ischemia while taking ASA. The WARSS trial demonstrated that patients who had their baseline event while on ASA had higher recurrent-event rates then the overall study population, regardless of treatment with warfarin or ASA, suggesting that these patients constituted a population at higher risk [59]. Some physicians select an alternative antiplatelet drug for patients who have an event while taking ASA but no regimen specifically studied neither evidence for additional efficacy with increasing dose of ASA (AHA/ASA class IIb, level C) [13]. Measuring platelet aggregation may be useful for identifying patients who have incomplete platelet inhibition on ASA or clopidogrel. The effect of increasing antiplatelet dosages on subsequent stroke risk has not been studied.

64.2.6 Antiplatelet Use in Secondary Prevention After Intracerebral Hemorrhage

The use of antiplatelet agents, especially ASA, after an episode of ICH is based on the proven benefits of these agents for the prevention of coronary and cerebrovascular ischemic events. Because ischemic vascular disease and ICH share risk factors, it is not unusu-

al for a patient who has suffered an ICH to need antiplatelet treatment. This raises the concern about an increased risk of ICH recurrence in the setting of continuing or starting antiplatelet therapy after the index episode of ICH. The clinical decision making in this situation depends on the magnitude of the risk of recurrent ICH under antiplatelet treatment. No data from randomized trials to guide secondary prevention of stroke after intracranial hemorrhage. Few data are available to assist the clinician in this decision. In patients with history of symptomatic primary ICH, Flynn and colleagues assessed the risk of recurrent ICH in a hospital-based cohort of 417,417 ICH patients who survived to discharge [105]. Of these, 120 patients were prescribed subsequent antiplatelet medicines (28.8%). The median time from discharge to antiplatelet use was 14.8 months (range, 2 days-7.5 years). HRs associated with antiplatelet exposure were 1.07 (95% CI 0.24-4.84) for recurrent ICH, 0.23 (95% CI 0.03-1.68) for ischemic stroke, and 0.72 (95% CI 0.25-2.02) for ischemic strokes or MI. Similarly, Viswanathan and colleagues addressed this issue by prospectively assessing the risk of recurrent ICH in a hospital-based cohort of 207 survivors of ICH (127 lobar, 80 deep), 46 (22%) of whom were treated with antiplatelet agents [106]. In a median of 19.5 months of follow-up, they observed 39 instances of recurrent ICH, which corresponded to a 2-year recurrence rate of 22% for lobar ICH patients and 4% for deep ICH patients. Exposure to antiplatelet agents resulted in no increase in the risk of recurrent ICH in survivors of lobar and deep ICH (Figure 64.4) [106].

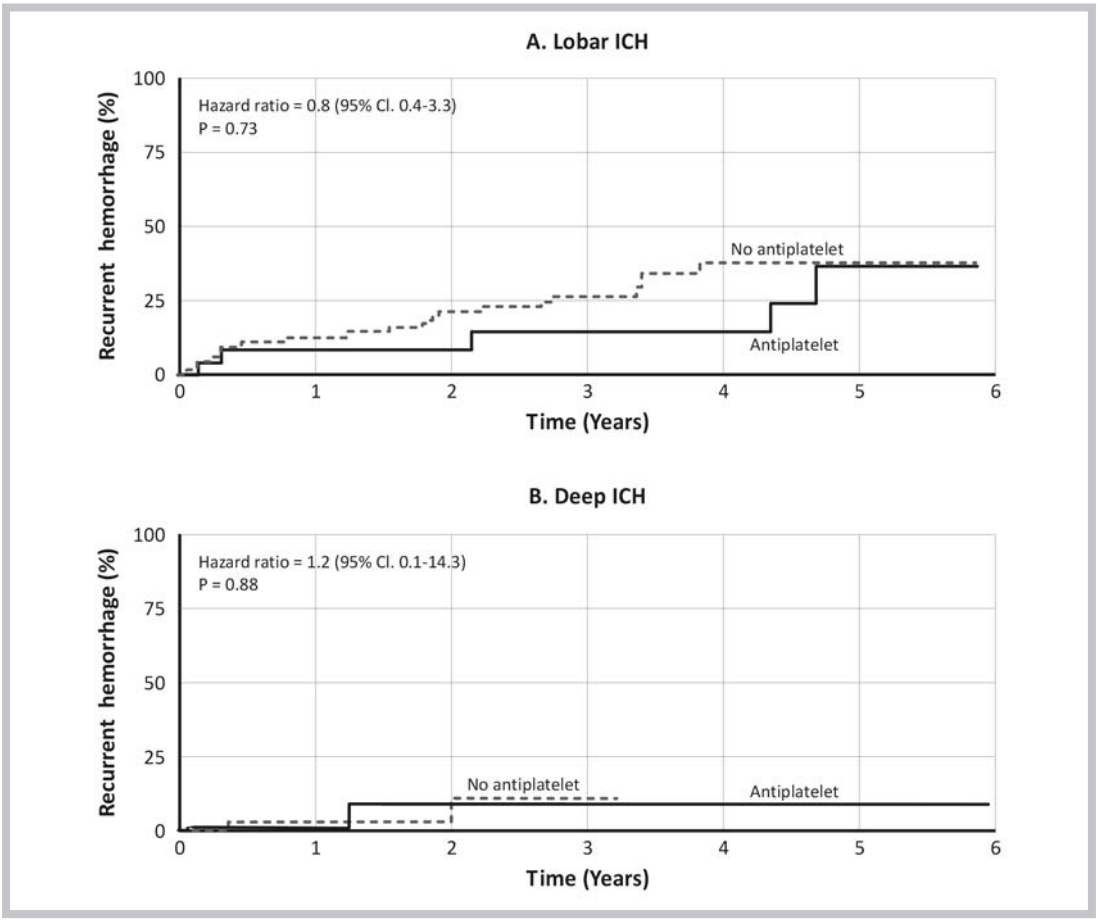


Figure 64.4. **Modified Kaplan-Meier plot of the effect of antiplatelet use on the rate of recurrent intracerebral hemorrhage (ICH) in survivors of lobar (A) and deep (B) ICH. Redrawn from [106].**

Factors to consider in restarting antiplatelet therapy include type of ICH, patient age, risk factors for recurrent ICH, risk factors for ischemic stroke, and indications for antithrombotic therapy. Risk factors for recurrent ICH include lobar hemorrhage, microbleeds on magnetic resonance imaging (MRI), advanced age, hypertension, dialysis, leukoaraiosis, and degree of anticoagulation [107]. These results suggest that there should be a compelling reason (such as active coronary artery disease or AF) for using antiplatelet agents after ICH (at a low dose [81 mg aspirin once daily]), especially if the ICH is deep in location. Furthermore, those with features suggestive of cerebral amyloid angiopathy as the underlying condition should require "the most compelling indication" because of their markedly increased risk of recurrent ICH [108]. For these reasons, the American College of Chest Physicians (ACCP Grade 2C) is against the long-term use of antithrombotic therapy for prevention of ischemic stroke in ICH patients [15]. The American Heart Association/American Stroke Association recommendations for use of antithrombotic therapy following ICH suggest [13] to restart antithrombotic therapy after ICH related to antithrombotic therapy depending on risk of subsequent arterial or venous thromboembolism, risk of recurrent ICH, and overall status of patient (AHA/ASA Class IIb, Level B). For patients with comparatively lower risk of cerebral infarction (such as AF without prior ischemic stroke) and higher risk of amyloid angiopathy (such as elderly patients with lobar ICH) or with very poor overall neurological function, an antiplatelet agent may be considered for prevention of ischemic stroke. For patients with very high risk of thromboembolism, it may be reasonable to restart warfarin therapy at 7-10 days after onset of ICH. For patients with hemorrhagic cerebral infarction, it may be reasonable to continue anticoagulation, depending on specific clinical scenario and underlying indication for anticoagulant therapy (AHA/ASA Class IIb, Level C).

On the basis of these limited data, it seems appropriate to limit the use of antiplatelet agents after ICH to those patients who are at high risk of coronary events and have sustained a deep ICH. Likewise, in those with suspected cerebral amyloid angiopathy (by virtue of having a history of lobar ICH preceding the lobar index event, a high load of microhemorrhages at baseline, and prominent white matter hypodensity on CT scan), antiplatelet treatment should be reserved for only those patients with the strongest indication.

64.2.7 Summary and Recommendations

ASA, clopidogrel, and the combination of ASA plus ER-DP are all acceptable options for preventing recurrent noncardioembolic ischemic stroke. For patients with a history of noncardioembolic stroke or TIA of atherothrombotic, lacunar (small vessel occlusive type), or cryptogenic type, we recommend treatment with an antiplatelet agent. Initial therapy with ASA is appropriate for patients who cannot afford or cannot obtain the more effective antiplatelet agents (clopidogrel or ASA plus extended-release DP). Although the optimal dose of ASA is uncertain, there is no compelling evidence that any specific dose is more effective than another, and fewer gastrointestinal side effects and bleeding occur with lower doses (≤325 mg a day). We recommend a dose of 50 to 100 mg daily when using ASA for the secondary prevention of ischemic stroke. In the absence of a substantial financial burden, initial antiplatelet therapy using either clopidogrel (75 mg daily) as monotherapy, or the combination of ASA plus ER-DP (25 mg/200 mg twice a day), rather than ASA should be preferred. The choice between clopidogrel and ASA plus ER-DP is dependent mainly on patient tolerance and contraindications. ER-DP contains ASA and should not be used in patients who cannot tolerate ASA. Clopidogrel (75 mg/day) is an obvious alternative for patients who cannot tol-

erate ASA. Ticlopidine should be reserved for patients intolerant of ASA and clopidogrel. For most patients with a noncardioembolic stroke or TIA, we recommend NOT using ASA and clopidogrel in combination for long-term stroke prevention, given the lack of greater efficacy compared with clopidogrel alone and the substantially increased risk of bleeding complications. However, selected patients with a recent acute MI, other acute coronary syndrome, or arterial stent placement are treated with clopidogrel plus ASA could be beneficed from a short (3-months) period.

64.3 Anticoagulation Regimens: Stroke Anticoagulation and Prophylaxis

64.3.1 Role of Anticoagulants

Drugs vitamin K antagonists (VKA) represent one of the major classes of drugs used in cardiovascular medicine; 1-1.5% of general population in Western countries is subject to VKA therapy, so-called oral anticoagulant therapy (OAT) [109], with a widespread use over the last two decades [110,111]. The controlled therapeutic inhibition of blood clotting by means of appropriate drugs (ie, anticoagulants) is defined anticoagulation. For many years, anticoagulation was used routinely in acute ischemic stroke. However, in the past 2 decades, randomized, controlled studies have helped to better define the role of anticoagulants in the acute treatment and prevention of stroke changing the actual role of anticoagulants in the treatment of cerebral ischemia. Furthermore in the last years, several new oral and parenteral anticoagulants are in different stages of clinical trials for use in the prophylaxis of ischemic thromboembolic stroke. Current data do not support the routine use of anticoagulation for acute ischemic stroke, limiting its use in secondary prevention. In fact, several randomized, controlled trials with IV heparinoids, subcutaneous low-molecular-weight heparin (LMWH), or subcutaneous unfractionated heparin (UFH) failed to show a significant overall benefit in their early use after ischemic stroke.

No difference in morbidity and mortality from stroke was shown between the group treated with aspirin and the group treated with UFH in the International Stroke Study

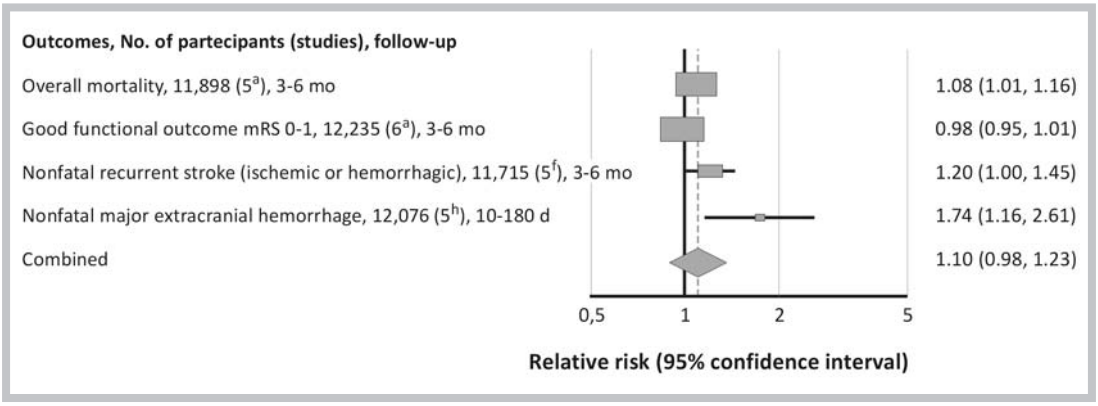


Figure 64.5. **Summary of findings: anticoagulants compared with antiplatelets in patients with acute ischemic stroke or TIA [113].**

[a]IST (1997), RAPID (2005), TAIST (2001), HAEST (2000), FISS-tris (2007). [f]IST (1997), RAPID (2005), HAEST (2000), TAIST (2001). [h]IST (1997), Pince (1981), TAIST (2001), HAEST (2000), FISS-tris (2007). Mo indicates months; d, days.

(IST) compared aspirin with subcutaneous UFH at 2 different doses (5000 units or 12,500 units bid). Although UFH seemed to decrease the risk of pulmonary embolism and deep venous thrombosis (DVT), it increased the risk of hemorrhagic complications [112]. The anticoagulation with UFH, LMWH, heparinoids, oral anticoagulants, or thrombin inhibitors did not decrease the odds of death or development of dependency from stroke in the last systematic review by the Cochrane collaboration [113]. It provides high-quality evidence that treatment with treatment-dose anticoagulation compared with aspirin results in more deaths, fewer patients with a favorable outcome, and more nonfatal major extracranial bleeding events [113]. Although anticoagulants prevent pulmonary embolism and determine a small decrease in recurrent ischemic strokes, they also increase the risk of hemorrhage, leading to the conclusion that anticoagulation cannot be recommended for the treatment of acute ischemic stroke [113]. Figure 64.5 summarizes the effect of parenteral anticoagulation compared with antiplatelet therapy according to data from updated Cochrane review [113]. If early anticoagulation after ischemic stroke is indicated but UFH is contraindicated because of large brain infarctions, hemorrhagic infarctions, or pronounced microangiopathic changes in the brain, LMWH (in a bodyweight-adapted dose) could be used because of lower bleeding risk, although this recommendation is not based on solid evidence. There is also not a net benefit of acute anticoagulant therapy over antiplatelet therapy in stroke patients with AF [114]. In patients with acute ischemic stroke and AF, a controlled, randomized study (Heparin in Acute Embolic Stroke Trial [HAEST]) failed to show the superiority of LMWH (dalteparin 100 IU/kg subcutaneously bid) to aspirin (160 mg/d) [115]. The risk for extracerebral hemorrhages was greater with anticoagulation than with antiplatelet therapy (5.8% vs. 1.8%, p=0.028). On the basis of this evidence, patients with acute ischemic stroke and AF should be treated with aspirin in the acute phase (and then placed on anticoagulation). When long-term anticoagulation is indicated, the use of UFH or LMWH has been advocated to serve as a bridge while a therapeutic international normalized ratio (INR) is achieved with warfarin. A small pilot study found that LMWH (enoxaparin 1 mg/kg subcutaneously bid) was safer than IV UFH for this purpose in patients with subacute cerebral ischemia [116]. However, further studies are needed to confirm this finding before this approach can be recommended generally. Despite evidence from the randomized clinical trials discussed above, anticoagulation continues to be recommended for some specific clinical situations. These recommendations are based on uncontrolled studies and expert opinion. Even among experts there is disagreement about the best level of anticoagulation, route of administration, timing and duration of treatment, use of a bolus dose, and safety of the therapy, given the severity of neurologic deficits, size of infarction on baseline CT, vascular distribution, or presumed cause of stroke. Some of the indications currently proposed by many experts for early full-dose IV heparin after stroke or TIA are summarized in Table 64.9.

Apparently, patients with acute ischemic stroke ipsilateral to a severe stenosis or occlusion of the internal carotid artery could be an exception to the lack of anticoagulation benefit. This group appeared to benefit from early IV administration of the LMWH danaparoid in the TOAST (Trial of Org 10172 in Acute Stroke Treatment) trial. Although the Trial of Org 10172 in Acute Stroke Treatment (TOAST) reported that a favorable functional outcome at 3 months occurred more frequently in the subgroup of patients with large artery atherosclerotic stroke who were treated with danaparoid (68.1% vs. 54.7%, p=0.04), the rates of recurrent stroke were similar between treatment regimens, and there was no benefit of danaparoid in the overall trial population. However, this was a post hoc analysis with a small number of individuals, so the effect of chance cannot be excluded [120]. A recent systematic review based on observational studies failed to demonstrate a significant difference between antiplatelet therapy and anticoagula-

- Symptomatic extracranial or intracranial arteriosclerotic stenosis with crescendo TIAs or early progressive stroke
- Basilar artery occlusion before or after intra-arterial pharmacological or mechanical thrombolysis.
- Conditions with potential high risk of early cardiogenic reembolization, such as atrial fibrillation with proven intracardial thrombus on echocardiography, artificial valves, left atrial or ventricular thrombi, or myocardial infarction during the last 4 weeks
- Symptomatic dissection of the arteries supplying the brain (after exclusion of subarachnoid hemorrhage on CT scan)
- Known hypercoagulable states (e.g., protein C and S deficiencies, activated protein C [APC] resistance, antithrombin deficiency, relevant titer of antiphospholipid antibodies)
- Cerebral venous sinus thrombosis

Table 64.9. **Early anticoagulation in subpopulations.**

tion for the acute treatment of patients with stroke secondary to cervical artery dissection [121]. No convincing evidence supports anticoagulation for patients with stroke due to large artery atherosclerosis. Conclusive data are also lacking about the management of anticoagulation in patients with hemorrhagic conversion of ischemic brain infarction or primary ICH who have an absolute indication for anticoagulation for the prevention of embolism (ie, AF or mechanical heart valves). Small retrospective case series of patients with urgent need for anticoagulation (eg, with artificial heart valves) showed a better outcome for those treated with full-dose IV heparin (only after normalization of INR values by administration of prothrombin complex and/or other warfarin antagonists) than for those treated with low-dose subcutaneous heparin; however, these studies lack concomitant control subjects, thus making any conclusions about true efficacy and safety difficult. The use of anticoagulation in cerebral venous sinus thrombosis is based on open case series with no controls. Anticoagulation has been used even in the presence of hemorrhagic infarctions typical of this condition. Obviously, at the present time, patients with acute ischemic stroke treated with intravenous recombinant tissue plasminogen activator (rtPA) clearly should not be treated with anticoagulation for at least 24 hours post thrombolysis. ASA therapy is therefore recommended for all patients with acute ischemic stroke based on high-quality evidence in favor of antiplatelet therapy and the lack of evidence to support anticoagulation over antiplatelet therapy for any subpopulation of ischemic stroke patients thus far investigated. In conclusion, early (within 48 h) ASA therapy with an initial dose of 160 to 325 mg over therapeutic parenteral anticoagulation (Grade 1A) in patients with acute ischemic stroke or TIA [15]. There are, however, some patients at particularly high risk for recurrent embolic events (eg, those with mechanical heart valves or intracardiac thrombi) who were either not included or underrepresented in the acute antithrombotic therapy stroke trials. Although long-term anticoagulation for secondary stroke prevention may be indicated for these patients, the optimal choice of acute antithrombotic therapy is uncertain. As a result, there is considerable variation in clinical practice. Acute anticoagulation could be considered in this setting when the risk of hemorrhagic complications is low (eg, small ischemic burden and no evidence of hemorrhage on imaging).

64.3.2 Prevention of Recurrent Ischemic Stroke of Cardiac Origin

Cardioembolic strokes account for one third of ischemic strokes and AF represents the main source of this stroke subtype [122]. The rate of stroke is 5%/year in patients with AF. Patients with AF have a 2-7 fold increased risk of stroke compared to patients without AF [10,122-124]. Cardioembolic strokes have poorer prognosis compared to other subtypes of ischemic strokes, such as atherotrombotic and lacunar forms, due to wider

ischemic damage and major risk of hemorrhagic transformation with the consequence of higher risk of in-hospital, 30-days and 12-months mortality and severe disability [125-127]. Stroke prevention in AF (SPAF) is therefore of utmost importance and represents a major point in the modern management of AF [10,123,124]. The risk of stroke is high in patients with AF associated to severe mitral stenosis, mechanical prosthetic valve, history of previous cerebrovascular ischemic event, moderate when AF is associated to age over than 75 years, systemic blood hypertension, diabetes mellitus, heart failure with depressed contractility and finally is low but consistent when AF is associated to female sex, vascular disease such as coronary artery disease or peripheral artery disease, age 65 to 74 years and thyrotoxicosis [10,123,124,128]. Practical prognostic scores, such as $CHADS_2$ [129] and the most recent CHA2DS2-VASC (see Appendix), help in predicting stroke risk in patients with AF [123]. For information on how to calculate the CHADS2 score, see You et al. [130]. CHA2DS2-VASC score seems to better predict the low risk of stroke or systemic embolism respect CHADS2 [123]. The most important function of these and similar schemes is to identify patients with AF who are likely to benefit from OAT, and thus accurately discriminate patients at high risk of stroke or systemic embolism (for whom OAT is indicated) from those at moderate risk (OAT or ASA) and low risk (ASA). Although the CHADS2 score might not be as accurate as the other schemes in predicting stroke risk, its discriminative capacity is sufficiently adequate to guide thromboprophylactic treatment decisions, and it can be calculated at the bedside or in the clinic from simple clinical features (without requiring access to echocardiography). The choice of drugs aimed to reduce the cardioembolic risk should take in account the risk of bleedings and carefully weighted. Several risk stratification models have been proposed to calculate bleeding risk in patients on antithrombotic treatment to reduce the thromboembolic risk in AF. Much recently, two practical scores named HAS-BLED [131] and ATRIA respectively (Appendix) [132], have been proposed. They identify categories of patients at different risk of bleeding assigning points to the considered risk factors. Unfortunately many risk factors are at the same time risks for thromboembolic and for bleeding events, making choice difficult.

Almost all patients with AF, including paroxysmal AF, who are at high risk of stroke ($CHADS_2 \geq 2$) should be treated with anticoagulation. This includes all patients with a history of stroke or TIA, as a history of stroke or TIA alone accounts for two points on the $CHADS_2$ score. For patients with TIA or ischemic stroke due to cardioembolism, particularly those with AF, the use of oral VKAs (i.e., warfarin) maintaining an international normalized ratio (INR) of 2.0-3.0, has been the cornerstone of antithrombotic therapy for more than 20 years [133,134]. Recommendations for patients with AF and a

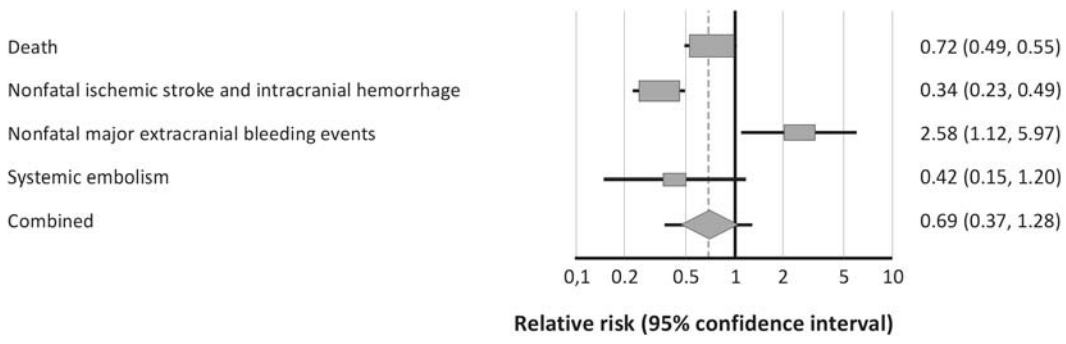


Figure 64.6. **Anticoagulation compared with no anticoagulation for secondary prevention in patients with AF and a history of ischemic stroke or TIA.**

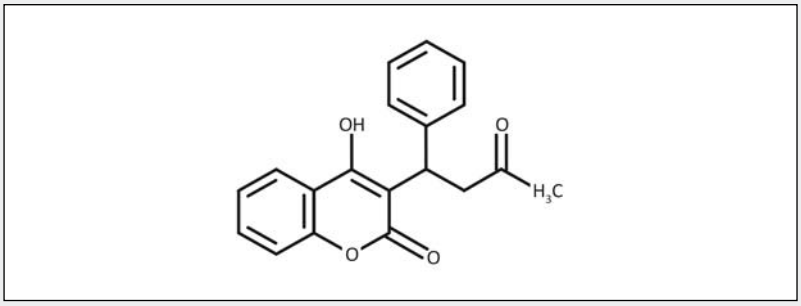
history of stroke or TIA are based on the pooled effect of anticoagulation in primary and secondary prevention studies as the data exclusively on secondary prevention are limited to only two trials [135,136]. Pooled data from these anticoagulation trials are summarized in Figure 64.6. Recommendations for antithrombotic therapy in patients with AF with a history of stroke or TIA therefore follow the recommendations for patients with AF at high risk of stroke [130]. Patients with AF and with a history of stroke or TIA showed a much higher recurrence stroke rate in the two secondary prevention trials (8.0% per year) [135,136] compared with the nine mainly primary prevention trials (2.6% per year) [135,137-144]. In the two secondary-prevention trials, the benefit of anticoagulation was represented by a lower incidence of any (ischemic or hemorrhagic) recurrent stroke (52 fewer per 1000 over 1-2.3 years); although at a cost of more major extracranial bleeding events (12 more per 1000 over 1-2.3 years) [134]. Both primary and secondary prevention studies showed a neutral effect of anticoagulation therapy on mortality [134].

The optimal time to begin OAT following a cardioembolic stroke depends primarily on the balance of risks of early ischemic stroke recurrence and hemorrhagic transformation of the index stroke. Few studies can help guide the timing of anticoagulation after stroke secondary to AF. There is ≈5% risk of symptomatic hemorrhagic transformation between AF patients in the 2 weeks after presentation with an acute ischemic stroke and the risk is greater in patients with larger infarcts [145]. No increase in ICH was apparent in patients started early (<2 weeks) vs. later (2 weeks to 3 months) in the European Atrial Fibrillation Trial (EAFT) [136], where about half of the patients receiving anticoagulation were randomized within 2 weeks after symptom onset. In this trial patients with previous stroke or TIA who also were diagnosed with AF were randomized to oral anticoagulation, 300 mg aspirin daily, or placebo. Similar results were found in the Heparin in Acute Embolic Stroke Trial (HAEST) study where patients with AF presenting with acute ischemic stroke were randomized to early treatment (within 30 h of stroke onset) with LMWH or ASA. It did not find evidence of a statistically significant difference in recurrent ischemic stroke (the primary outcome) or ICH [115]. A subgroup analysis of 3,169 patients with AF enrolled in the IST showed no net advantage to early treatment with UFH compared with no heparin; patients who received heparin experienced reductions in ischemic stroke that were offset by an increase in ICH within the first 14 days [146]. In summary, there is no net benefit or harm associated with the early initiation of anticoagulation, but that the risk of symptomatic hemorrhagic transformation is greater with large infarcts. From this low-quality evidences, it is therefore recommended initiation of OAT within 2 weeks of a cardioembolic stroke; however, for patients with large infarcts or other risk factors for hemorrhage, additional delays are appropriate. Before anticoagulation is initiated and during the time that anticoagulation is started but has not yet reached therapeutic levels (ie, INR<2.0), treatment with ASA is recommended. ASA is beneficial in the early treatment of acute stroke and indirect data from randomized trials of ASA in patients with AF who have not yet had a stroke that suggest a RRR of recurrent stroke of approximately 20% [130]. The benefit of ASA over placebo is also suggested by EAFT subanalyses [136]. Long-term ASA use was associated with a 14% reduction in the annual rate of stroke (HR 0.86; 95% CI 0.64-1.15) between ASA (300 mg/d) arm when compared to placebo in patients with AF who had suffered a stroke or TIA; although this difference was not statistically significant.

Vitamin K Antagonists (VKA)

VKA drugs available are represented by warfarin, acenocoumarol and phenprocoumon, which differ for the different plasma half-life. Up to now, VKA drugs have demonstrated to be the most effective choice in SPAF and clinical guidelines have suggested to consid-

er these as the first choice [10,123]. Between VKA, warfarin is the most frequent used. Warfarin inhibits vitamin K reductase, resulting in depletion of the reduced form of vitamin K (vitamin KH2) (Table 64.10) [147,148]. As vitamin K is a cofactor for the carboxylation of glutamate residues on the N-terminal regions of vitamin K-dependent proteins, this limits the gamma-carboxylation and subsequent activation of the vitamin K-dependent coagulant proteins. The synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S is inhibited. Depression of three of the four vitamin K-dependent coagulation factors (factors II, VII, and X) results in decreased prothrombin levels and a decrease in the amount of thrombin generated and bound to fibrin.

Structure	 Chemical formula: $C_{19}H_{16}O_4$ SMILES: CC(=O)CC(C1=CC=CC=C1)C1=C(O)C2=C(OC1=O)C=CC=C2
Pharmacodynamics	Warfarin, a coumarin anticoagulant, is a racemic mixture of two active isomers. It is used in the prevention and treatment of thromboembolic disease including venous thrombosis, thromboembolism, and pulmonary embolism as well as for the prevention of ischemic stroke in patients with atrial fibrillation (AF)
Mechanism of action	Warfarin inhibits vitamin K reductase, resulting in depletion of the reduced form of vitamin K (vitamin KH2). As vitamin K is a cofactor for the carboxylation of glutamate residues on the N-terminal regions of vitamin K-dependent proteins, this limits the gamma-carboxylation and subsequent activation of the vitamin K-dependent coagulant proteins. The synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S is inhibited. Depression of three of the four vitamin K-dependent coagulation factors (factors II, VII, and X) results in decreased prothrombin levels and a decrease in the amount of thrombin generated and bound to fibrin. This reduces the thrombogenicity of clots
Absorption	Rapidly absorbed following oral administration with considerable interindividual variations. Also absorbed percutaneously
Volume of distribution	0.14 l/kg
Protein binding	99% bound primarily to albumin
Metabolism	Metabolized stereo- and regio-selectively by hepatic microsomal enzymes. S-warfarin is predominantly metabolized by cytochrome P450 (CYP) 2C9 to yield the 6- and 7-hydroxylated metabolites. R-warfarin is metabolized by CYP1A1, 1A2, and 3A4 to yield 6-, 8-, and 10-hydroxylated metabolites. Hydroxylated metabolites may be further conjugated prior to excretion into bile and urine. UGT1A1 appears to be responsible for producing the 6-O-glucuronide of warfarin, with a possibly contribution from UGT1A10. Five UGT1As may be involved in the formation of 7-O-glucuronide warfarin. S-warfarin has higher potency than R-warfarin and genetic polymorphisms in CYP2C9 may dramatically decrease clearance of and increase toxicity of the medication

Route of elimination	The elimination of warfarin is almost entirely by metabolism. Very little warfarin is excreted unchanged in urine. The metabolites are principally excreted into the urine; and to a lesser extent into the bile	
Half life	R-warfarin $t_{1/2}$=37-89 hours; S-warfarin $t_{1/2}$=21-43 hours	
Clearance	0.065 ± 0.025 ml/min/kg [CYP2C9 Genotype 1/1] 0.041 ± 0.021 [CYP2C9 Genotype 1/2 or 1/3] 0.020 ± 0.011 [CYP2C9 Genotype 2/2, 2/3, or 3/3]	
Toxicity	LD_{50}=374 (orally in mice)	
Drug interactions	**Drug**	**Interaction**
	Acetaminophen	Acetaminophen increases the anticoagulant effect of warfarin. Monitor for changes in the therapeutic and adverse effects of warfarin if acetaminophen is initiated, discontinued or dose changed
	Acetylsalicylic acid	The antiplatelet effects of acetylsalicylic acid may increase the bleed risk associated with warfarin
	Allopurinol	Allopurinol may increase the anticoagulant effect of warfarin. Monitor for changes in prothrombin times and therapeutic effects of warfarin if allopurinol is initiated, discontinued or dose changed
	Aminoglutethimide	Aminoglutethimide may decrease the anticoagulant effect of warfarin by increasing its metabolism. Monitor for changes in prothrombin time and therapeutic effects of warfarin if aminoglutethimide is initiated, discontinued or dose changed
	Aminosalicylic Acid	The antiplatelet effects of aminosalicylic acid may increase the bleed risk associated with warfarin
	Amiodarone	Amiodarone may increase the anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if amiodarone is initiated, discontinued or dose changed
	Amobarbital	Amobarbital may decrease the serum concentration of warfarin by increasing its metabolism. Monitor for changes in the therapeutic and adverse effects of warfarin if amobarbital is initiated, discontinued or dose changed
	Amprenavir	Amprenavir may increase the anticoagulant effect of warfarin by increasing its serum concentration
	Aprepitant	Aprepitant may decrease the anticoagulant effect of warfarin by decreasing its serum concentration
	Atazanavir	The protease inhibitor, atazanavir, may increase the anticoagulant effect of warfarin
	Azathioprine	Azathioprine may decrease the anticoagulant effect of warfarin
	Azithromycin	Azithromycin may increase the anticoagulant effect of warfarin by increasing its serum concentration
	Betamethasone	The corticosteroid, betamethasone, alters the anticoagulant effect of warfarin
	Bezafibrate	Bezafibrate may increase the anticoagulant effect of warfarin. Monitor prothrombin time and therapeutic and adverse effects of warfarin if bezafibrate is initiated, discontinued or dose changed

	Bosentan	Bosentan may decrease the anticoagulant effect of warfarin by increasing its metabolism
	Butabarbital	Butabarbital may decrease the serum concentration of warfarin by increasing its metabolism. Monitor for changes in the therapeutic and adverse effects of warfarin if butabarbital is initiated, discontinued or dose changed
	Butalbital	Butalbital may decrease the serum concentration of warfarin by increasing its metabolism. Monitor for changes in the therapeutic and adverse effects of warfarin if butalbital is initiated, discontinued or dose changed
	Capecitabine	Capecitabine may increase the serum concentration of warfarin by decreasing its metabolism. Monitor for changes in prothrombin time and therapeutic effects of warfarin if capecitabine is initiated or discontinued. Subsequent cycles of capecitabine may increase this effect
	Carbamazepine	Carbamazepine may decrease the anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic and adverse effects of warfarin if carbamazepine is initiated, discontinued or dose changed
	Cefotetan	The cephalosporin, cefotetan, may increase the anticoagulant effect of warfarin
	Cefoxitin	The cephalosporin, cefoxitin, may increase the anticoagulant effect of warfarin
	Ceftriaxone	The cephalosporin, ceftriaxone, may increase the anticoagulant effect of warfarin
	Celecoxib	Celecoxib may increase the anticoagulant effect of warfarin
	Cholestyramine	The bile acid sequestrant, cholestyramine, may decrease the anticoagulant effect of warfarin by decreasing its absorption
	Cimetidine	Cimetidine may increase the serum concentration of warfarin. Monitor for changes in prothrombin time and therapeutic and adverse effects of warfarin if cimetidine is initiated, discontinued or dose changed
	Ciprofloxacin	The quinolone antibiotic, ciprofloxacin, may increase the anticoagulant effect of warfarin
	Cisapride	Cisapride may increase the anticoagulant effect of warfarin
	Citalopram	The SSRI, citalopram, increases the effect of anticoagulant, warfarin
	Clarithromycin	The macrolide, clarithromycin, may increase the anticoagulant effect of warfarin
	Clofibrate	The fibrate increases the anticoagulant effect
	Clopidogrel	Increased bleed risk may occur as a result of additive anticoagulant effects. Increase monitoring for signs and symptoms of bleeding during concomitant therapy

	Colestipol	The bile acid sequestrant, colestipol, may decrease the anticoagulant effect of warfarin by decreasing its absorption
	Cyclophosphamide	The antineoplastic agent, cyclophosphamide may alter the anticoagulant effect of warfarin
	Danazol	Danazol may increase the serum concentration and anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if danazol is initiated, discontinued or dose changed
	Delavirdine	Delavirdine, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if delavirdine is initiated, discontinued or dose changed
	Demeclocycline	The tetracycline, demeclocycline, may increase the anticoagulant effect of warfarin
	Desogestrel	Desogestrol may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if desogestrol is initiated, discontinued or dose changed
	Dexamethasone	The corticosteroid, dexamethasone, alters the anticoagulant effect of warfarin
	Dextrothyroxine	The thyroid hormone, dextrothyroxine, increase the anticoagulant effect of warfarin
	Diclofenac	The antiplatelet effects of oral diclofenac may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Dicloxacillin	Dicloxacillin may decrease the anticoagulant effect of warfarin
	Diflunisal	The antiplatelet effects of diflunisal may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Disulfiram	Disulfiram may increase the anticoagulant effect of warfarin
	Doxycycline	The tetracycline, doxycycline, may increase the anticoagulant effect of warfarin
	Drospirenone	Drospirenone may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if drospirenone is initiated, discontinued or dose changed
	Drotrecogin alfa	Increased risk of bleeding
	Erythromycin	The macrolide, erythromycin, may increase the anticoagulant effect of warfarin
	Ethchlorvynol	Ethchlorvynol may decrease the anticoagulant effect of warfarin
	Ethinyl estradiol	Ethinyl estradiol may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if ethinyl estradiol is initiated, discontinued or dose changed

	Ethynodiol diacetate	Ethynodiol diacetate may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if ethynodiol diacetate is initiated, discontinued or dos
	Etodolac	The antiplatelet effects of etodolac may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Etonogestrel	Etonogestrel may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if etonogestrel is initiated, discontinued or dose changed.
	Etoricoxib	Etoricoxib may increase the anticoagulant effect of warfarin
	Fenofibrate	Fenofibrate may increase the anticoagulant effect of warfarin. Monitor prothrombin time and therapeutic and adverse effects of warfarin if fenofibrate is initiated, discontinued or dose changed
	Fenoprofen	The antiplatelet effects of fenoprofen may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Floxuridine	Floxuridine, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if floxuridine is initiated, discontinued or dose changed
	Fluconazole	Fluconazole, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if fluconazole is initiated, discontinued or dose changed
	Fludrocortisone	The corticosteroid, fludrocortisone, alters the anticoagulant effect of warfarin
	Fluorouracil	Fluorouracil, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if fluorouracil is initiated, discontinued or dose changed
	Fluoxetine	The SSRI, fluoxetine, increases the effect of anticoagulant, warfarin
	Fluoxymesterone	Fluoxymesterone may increase the serum concentration and anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if fluoxymesterone is initiated, discontinued or dose changed
	Flurbiprofen	Flurbiprofen, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. The antiplatelet effect of flurbiprofen may also increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if flurbiprofen is initiated, discontinued or dose changed

	Fluvastatin	Fluvastatin may increase the anticoagulant effect of warfarin. Monitor for changes in the therapeutic and adverse effects of warfarin if fluvastatin is initiated, discontinued or dose changed
	Fluvoxamine	Fluvoxamine may increase the anticoagulant effect of warfarin by increasing its serum concentration
	Fosamprenavir	The protease inhibitor, fosamprenavir, may increase the anticoagulant effect of warfarin
	Fosphenytoin	Increased hydantoin levels and risk of bleeding
	Gefitinib	Gefitinib may increase the anticoagulant effect of warfarin
	Gemcitabine	Gemcitabine may increase the anticoagulant effect of warfarin
	Gemfibrozil	Gemfibrozil, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if gemfibrozil is initiated, discontinued or dose changed
	Ginkgo biloba	Additive anticoagulant/antiplatelet effects may increase bleed risk. Concomitant therapy should be avoided
	Ginseng	Additive anticoagulant effects increase the risk of bleeding. Concomitant therapy should be avoided
	Glutethimide	Glutethimide may decrease the serum concentration of warfarin by increasing its metabolism. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if glutethimide is initiated, discontinued or dose changed.
	Griseofulvin	Griseofulvin may decrease the anticoagulant effect of warfarin
	Hydrocortisone	The corticosteroid, hydrocortisone, alters the anticoagulant effect of warfarin
	Ibuprofen	Ibuprofen, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. The antiplatelet effect of ibuprofen may also increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if ibuprofen is initiated, discontinued or dose changed
	Imatinib	Imatinib may increase the anticoagulant effect of warfarin increasing the risk of bleeding. Monitor for changes in prothrombin time and therapeutic and adverse effects of warfarin if imatinib is initiated, discontinued or dose changed
	Indinavir	The protease inhibitor, indinavir, may increase the anticoagulant effect of warfarin
	Indomethacin	Indomethacin, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. The antiplatelet effect of indomethacin may also increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if indomethacin is initiated, discontinued or dose changed

	Isoniazid	Isoniazid may increase the anticoagulant effect of warfarin
	Itraconazole	Itraconazole may increase the anticoagulant effect of warfarin by decreasing its metabolism
	Ketoconazole	Ketoconazole, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if ketoconazole is initiated, discontinued or dose changed
	Ketoprofen	The antiplatelet effects of ketoprofen may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Ketorolac	The antiplatelet effects of ketorolac may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Leflunomide	Leflunomide may increase the anticoagulant effect of warfarin
	Levamisole	Levamisole may increase the anticoagulant effect of warfarin.
	Levofloxacin	The quinolone antibiotic, levofloxacin, may increase the anticoagulant effect of warfarin
	Levonorgestrel	Levonorgestrel may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if levonorgestrel is initiated, discontinued or dose changed
	Levothyroxine	Levothyroxine may contribute to the anticoagulant effect of warfarin by increasing the metabolism of vitamin K-dependent clotting factors. Monitor for changes in prothrombin time and anticoagulant effects if levothyroxine is initiated, discontinued or dose changed
	Liothyronine	Liothyronine may contribute to the anticoagulant effect of warfarin by increasing the metabolism of vitamin K-dependent clotting factors. Monitor for changes in prothrombin time and anticoagulant effects if liothyronine is initiated, discontinued or dose changed
	Liotrix	Liotrix may contribute to the anticoagulant effect of warfarin by increasing the metabolism of vitamin K-dependent clotting factors. Monitor for changes in prothrombin time and anticoagulant effects if liotrix is initiated, discontinued or dose changed
	Lovastatin	Lovastatin may increase the anticoagulant effect warfarin. Monitor for changes in the therapeutic and adverse effects of warfarin if lovastatin is initiated, discontinued or dose changed
	Lumiracoxib	Lumiracoxib may increase the anticoagulant effect of warfarin

	Meclofenamic acid	The antiplatelet effects of meclofenamic acid may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Medroxyprogesterone	Medroxyprogesterone may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if medroxyprogesterone is initiated, discontinued or dose changed
	Mefenamic acid	Mefenamic acid, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. The antiplatelet effect of mefenamic acid may also increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if mefenamic acid is initiated, discontinued or dose changed
	Mefloquine	Mefloquine may increase the anticoagulant effect of warfarin
	Meloxicam	The antiplatelet effects of meloxicam may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Mercaptopurine	Mercaptopurine may decrease the anticoagulant effect of warfarin
	Mestranol	Mestranol may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if mestranol is initiated, discontinued or dose changed
	Methimazole	Methimazole may decrease the anticoagulant effect of warfarin. Monitor for changes in the therapeutic and adverse effects of warfarin if methimazole is initiated, discontinued or dose changed
	Methohexital	Methohexital may decrease the serum concentration of warfarin by increasing its metabolism. Monitor for changes in the therapeutic and adverse effects of warfarin if methohexital is initiated, discontinued or dose changed
	Metronidazole	Metronidazole may increase the serum concentration of warfarin by decreasing its metabolism. Consider alternate therapy or a dose reduction in warfarin. Monitor for changes in prothrombin time and therapeutic and adverse effects of warfarin if metronidazole is initiated, discontinued or dose changed
	Miconazole	Miconazole, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if miconazole is initiated, discontinued or dose changed
	Minocycline	The tetracycline, minocycline, may increase the anticoagulant effect of warfarin

	Mitotane	Mitotane may decrease the anticoagulant effect of warfarin
	Moxifloxacin	The quinolone antibiotic, moxifloxacin, may increase the anticoagulant effect of warfarin
	Nabumetone	The antiplatelet effects of nabumetone may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Nafcillin	Nafcillin may increase the anticoagulant effect of warfarin increasing the risk of bleeding. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if nafcillin is initiated, discontinued or dose changed
	Nalidixic acid	The quinolone antibiotic, nalidixic acid, may increase the anticoagulant effect of warfarin
	Nandrolone decanoate	Nandrolone may increase the serum concentration and anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if nandrolone is initiated, discontinued or dose changed
	Nandrolone phenpropionate	Nandrolone may increase the serum concentration and anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if nandrolone is initiated, discontinued or dose changed
	Naproxen	The antiplatelet effects of naproxen may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Nelfinavir	The protease inhibitor, nelfinavir, may increase the anticoagulant effect of warfarin
	Nevirapine	Nevirapine may decrease the anticoagulant effect of warfarin by increasing metabolism of R-warfarin via CYP3A4
	Nicardipine	Nicardipine, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if nicardipine is initiated, discontinued or dose changed
	Norethindrone	Norethindrone may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if norethindrone is initiated, discontinued or dose changed
	Norfloxacin	The quinolone antibiotic, norfloxacin, may increase the anticoagulant effect of warfarin
	Norgestimate	Norgestimate may alter the anticoagulant effect of warfarin. Concomitant therapy should be avoided. Monitor for changes in coagulation status if norgestimate is initiated, discontinued or dose changed
	Ofloxacin	The quinolone antibiotic, ofloxacin, may increase the anticoagulant effect of warfarin
	Orlistat	Orlistat may increase the anticoagulant effect of warfarin

	Oxandrolone	Oxandrolone may increase the serum concentration and anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if oxandrolone is initiated, discontinued or dose changed
	Oxaprozin	The antiplatelet effects of oxaprozin may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Oxymetholone	Oxymetholone may increase the serum concentration and anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if oxymetholone is initiated, discontinued or dose changed
	Oxyphenbutazone	The NSAID, oxyphenbutazone, may increase the anticoagulant effect of warfarin
	Paroxetine	The SSRI, paroxetine, increases the effect of the anticoagulant warfarin
	Pentobarbital	Pentobarbital may decrease the serum concentration of warfarin by increasing its metabolism. Monitor for changes in the therapeutic and adverse effects of warfarin if pentobarbital is initiated, discontinued or dose changed
	Pentoxifylline	Pentoxifylline may increase the anticoagulant effect of warfarin
	Phenobarbital	Phenobarbital may decrease the serum concentration of warfarin by increasing its metabolism. Monitor for changes in the therapeutic and adverse effects of warfarin if phenobarbital is initiated, discontinued or dose changed
	Phenylbutazone	The NSAID, phenylbutazone, may increase the anticoagulant effect of warfarin
	Phenytoin	Warfarin may increase the serum concentration of phenytoin possibly by competing for CYP2C9 metabolism. Phenytoin may increase the anticoagulant effect of warfarin. Monitor phenytoin levels, prothrombin time, and therapeutic and adverse effects of both agents during concomitant therapy
	Phytonadione	Phytonadione (vitamin K) may antagonize the anticoagulant effects of warfarin. Monitor for changes in prothrombin time if phytonadione intake (either via supplements or vitamin K-rich foods) is increased or decreased
	Piroxicam	Piroxicam, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. The antiplatelet effect of piroxicam may also increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if piroxicam is initiated, discontinued or dose changed
	Prednisolone	The corticosteroid, prednisolone, alters the anticoagulant effect of warfarin

	Prednisone	The corticosteroid, prednisone, alters the anticoagulant effect of warfarin
	Primidone	The barbiturate, primidone, decreases the anticoagulant effect of warfarin
	Propafenone	Propafenone may increase the anticoagulant effect of warfarin
	Propoxyphene	Propoxyphene may increase the anticoagulant effect of warfarin
	Propylthiouracil	Propylthiouracil may decrease the anticoagulant effect of warfarin. Monitor for changes in the therapeutic and adverse effects of warfarin if propylthiouracil is initiated, discontinued or dose changed
	Quinidine	Quinidine may increase the anticoagulant effect of warfarin
	Quinine	Quinine, a moderate CYP2C9 inhibitor, may increase the serum concentration of S-warfarin by decreasing its metabolism via CYP2C9
	Ranitidine	Ranitidine may increase the anticoagulant effect of warfarin (conflicting evidence)
	Rifabutin	Rifabutin may decrease the anticoagulant effect of warfarin by increasing its metabolism.
	Rifampin	Rifampin may decrease the anticoagulant effect of warfarin by increasing its metabolism
	S-adenosylmethionine	Additive anticoagulant effects increase the risk of bleeding. Concomitant therapy should be avoided
	Salicylate-sodium	The antiplatelet effects of sodium salicylate may increase the bleed risk associated with warfarin
	Secobarbital	Secobarbital may decrease the serum concentration of warfarin by increasing its metabolism. Monitor for changes in the therapeutic and adverse effects of warfarin if secobarbital is initiated, discontinued or dose changed
	Sitaxentan	Sitaxentan, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Warfarin doses should be decreased by 80% upon initiated of concomitant therapy. Monitor for changes in the therapeutic and adverse effects of warfarin if sitaxentan is initiated, discontinued or dose changed
	St. John's Wort	St. John's Wort may decrease the serum concentration of warfarin by increasing its metabolism. Concomitant therapy should be avoided. Monitor for changes in the therapeutic and adverse effects of warfarin if St. John's Wort is initiated, discontinued or dose changed
	Sucralfate	Sucralfate may reduce the absorption of warfarin. Warfarin should be administered at least 2 hours before or 6 hours after sucralfate administration. Monitor for changes in prothrombin time if sucralfate is initiated, discontinued or dose changed

	Sulfadiazine	Sulfadiazine, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if sulfadiazine is initiated, discontinued or dose changed
	Sulfamethoxazole	Sulfamethoxazole may increase the anticoagulant effect of warfarin by decreasing its metabolism. Consider alternate therapy or monitor for changes in prothrombin time if sulfamethoxazole is initiated, discontinued or dose changed
	Sulfinpyrazone	Sulfinpyrazone may increase the anticoagulant effect of warfarin by decreasing its metabolism and protein binding
	Sulfisoxazole	Sulfisoxazole, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if sulfisoxazole is initiated, discontinued or dose changed
	Sulindac	The antiplatelet effects of sulindac may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Tamoxifen	Tamoxifen, a CYP2C9 inhibitor, may increase the serum concentration of warfarin by decreasing its metabolism. Concomitant therapy is contraindicated due to significant increase in bleed risk
	Telithromycin	Telithromycin may increase the anticoagulant effect of warfarin. INR should be monitored and warfarin dose adjusted accordingly during concomitant therapy
	Tenoxicam	The NSAID, tenoxicam, may increase the anticoagulant effect of warfarin
	Testolactone	Testolactone may increase the serum concentration and anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if testolactone is initiated, discontinued or dose changed
	Testosterone	Testosterone may increase the serum concentration and anticoagulant effect of warfarin. Monitor for changes in prothrombin time and therapeutic effects of warfarin if testosterone is initiated, discontinued or dose changed
	Testosterone Propionate	The androgen, testosterone, may incrase the anticoagulant effect of the Vitamin K antagonist, warfarin. Monitor for changes in the therapeutic effect of warfarin if testosterone is initiated, discontinued or dose changed
	Tetracycline	Tetracycline may increase the anticoagulant effect of warfarin
	Thiopental	Thiopental may decrease the serum concentration of warfarin by increasing its metabolism. Monitor for changes in the therapeutic and adverse effects of warfarin if thiopental is initiated, discontinued or dose changed

	Tiaprofenic acid	The antiplatelet effects of tiaprofenic acid may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	Ticlopidine	Increased bleeding risk. Monitor INR
	Tigecycline	Tigecycline may increase the serum concentration of warfarin
	Tolbutamide	Tolbutamide, a strong CYP2C9 inhibitor, may decrease the metabolism of warfarin. Consider alternate therapy or monitor for changes in the therapeutic and adverse effects of warfarin if tolbutamide is initiated, discontinued or dose changed
	Tolmetin	The antiplatelet effects of tolmetin may increase the bleed risk associated with warfarin. Consider alternate therapy or monitor for signs and symptoms of bleeding during concomitant therapy
	transdermal testosterone gel	The androgen, Testosterone, may incrase the anticoagulant effect of the vitamin K antagonist, and warfarin. Monitor for changes in the therapeutic effect of warfarin if testosterone is initiated, discontinued or dose changed
	Treprostinil	The prostacyclin analogue, treprostinil, increases the risk of bleeding when combined with the anticoagulant, Warfarin. Monitor for increased bleeding during concomitant thearpy
	Triamcinolone	The corticosteroid, triamcinolone, alters the anticoagulant effect of warfarin
	Triflusal	The metabolite of triflusal, 2-hydroxy-4-trifluoro-methyl-benzoic acid (HTB), impairs the serum protein binding of warfarin to the same extent as acetylsalisylic acid. Thus, the free fraction of glisentide may be increased. A dosage reduction may be required if used in combination
	Trimetrexate	The anticoagulant effect of Warfarin, a Vitamin K antagonist, may be altered by antineoplastics such as Trimetrexate. Monitor for changes in the anticoagulant effects of warfarin and other coumarin derivatives during concomitant use
	Trisalicylate-choline	The antiplatelet effects of trisalicylate-choline may increase the bleed risk associated with warfarin
	Vilazodone	Increased risk of bleeding with concomitant use of warfarin and vilazodone
Food interactions	• Avoid alcohol • Avoid drastic changes in dietary habit • Avoid St. John's Wort • Consult your doctor before ingesting large amounts of dietary Vitamin K (e.g. from green leafy vegetables) • Limit garlic, ginger, gingko, and horse chestnut	

Efficacy (vs. no anticoagulant)	• Warfarin with INR target≥2 associated with decreased risk of systemic embolism compared to antiplatelet agents and placebo, but higher rate of major bleeding compared to placebo and low-dose warfarin (Level 2 [mid-level] evidence) [159] • For patients with nonvalvular atrial fibrillation and with no history of stroke or transient ischemic attack (TIA), warfarin with target INR 2-3 reduces risk of stroke (Level 1 [likely reliable] evidence) [160] • For patients with nonrheumatic atrial fibrillation and recent TIA or minor ischemic stroke, anticoagulants reduce risk of stroke (Level 1 [likely reliable] evidence) [133] • Risks and benefits of warfarin treatment for atrial fibrillation vary by age, gender, and medical history (Level 2 [mid-level] evidence) [161]
Clinical outcome rates on warfarin (noncomparative data)	• Warfarin use associated with low annual rate of stroke or systemic embolism in patients with nonvalvular atrial fibrillation (Level 2 [mid-level] evidence) [162] • Warfarin use in clinical practice associated with outcomes similar to those in randomized trials except increased risk for minor bleeding [163] • Rates of stroke and bleeding complications in actual practice were similar to rates reported in randomized trials [164] • Long-term warfarin did not worsen self-reported perceptions of health except in patients who bled (even minor bleeding) [165]

Target INR	• INR 2.5-3.5 if rheumatic mitral stenosis or prosthetic heart valve
	• INR 2-3 if heart failure within 3 months, history of hypertension, echocardiography shows left ventricular systolic dysfunction, left atrial enlargement by echocardiography, left ventricular hypertrophy (LVH) by echocardiography, prior myocardial infarction, diabetes mellitus, significant mitral annular calcium, age>65 years, history of stroke or transient ischemic attack, clinical coronary artery disease, mitral stenosis, thyrotoxicosis
	• INR<2 or>3 associated with adverse outcomes (Level 2 [mid-level] evidence) [166]
	  ▪ optimum INR range is 2.0-3.9, INR<2 not protective against stroke, INR>5 associated with major bleeding [167]
	  ▪ INR<2 much less protective in reducing risk for stroke [168]
	• INR target of 1.8 does not appear to decrease risk of thromboembolic events and major bleeding compared with standard target INR among elderly patients with nonvalvular atrial fibrillation (Level 2 [mid-level] evidence) [169]

Table 64.10. **Warfarin overview. SMILES indicates simplified molecular-input line-entry system [25].**

This reduces the thrombogenicity of clots. Meta-analyses of the RCTs aimed to evaluate the antithrombotic efficacy of VKA in SPAF, in fact, have previously demonstrated that these drugs produce a RRR of stroke and systemic embolism of 64% (95% CI 49-74%) when compared to placebo and 39% (95% CI 19-53%) when compared to ASA [134]. Specifically, warfarin reduces the risk of recurrent stroke or systemic embolism by about 61% (95% CI 37-75%) compared with control in AF patients with recent TIA or ischemic stroke [133,134]. This proportional risk reduction is consistent with that observed for the prevention of first-ever stroke among individuals with AF, including the elderly [134,142]. Warfarin also increases the odds of major extracranial hemorrhage (OR 4.3 [95% CI 1.5-12.1]) [133]. Much recently the BAFTA trial (Birmingham Atrial Fibrillation Treatment of the Aged Study) has confirmed the superiority of VKA drugs on ASA in SPAF [149]. The superiority of VKA is clear only when the time spent in therapeutic range (TTR) measured by INR 2.0-3.0 is over than 40% [150].

Once the decision has been made to start OAT with VKA in patients with AF who are at medium or high risk of stroke, a clinical algorithm or fixed-dose approach is common-

ly used. However, adverse effects can arise while finding the appropriate maintenance dose, which can vary by a factor of ten among patients. VKA have a narrow therapeutic window; the risk of stroke and systemic embolism is increased at lower levels of anticoagulation (INR<2.0) and the bleeding risk is higher when INR is over 3.0 [151]. VKA have a slower onset and offset of action requiring a bridging therapy with parenteral antithrombotic drugs such as intravenous or subcutaneous heparins. Moreover VKA have an unpredictable pharmacologic profile in different patients, based on genetic polimorphisms in *CYP2C9* and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) genes and multiple food and drug interactions. VKA require close laboratory monitoring of INR with frequent dose adjustments and patients' discomfort. Due to these limitations TTR is often sub-optimal in the real practice, being less than 60% [152]. An algorithm for estimating the appropriate warfarin dose that is based on clinical and genetic data has been developed and validated, and provided significantly better predictions of appropriate dose of warfarin than either the clinical algorithm or a fixed-dose approach [153]. This suggests that testing for variants in genes involved in warfarin metabolism and sensitivity (*CYP2C9*2*, *CYP2C9*3*, and/ or *VKORC1*) might allow more personalized dosing of warfarin during the induction phase than would standard warfarin induction [153]. However, any clinical benefits of genotyping are unproven in terms of fewer future strokes or bleeds, and the additional cost of genotype testing is unlikely to be cost-effective for typical patients with non-valvular AF. Actually, the best way to determine the genotype of a patient is to measure their INR when starting OAT [153]. Despite strong literature evidence, VKA are underused in real clinical practice. A much recent meta-analysis shows that only 60% of patients suitable for treatment with VKA receives these drugs [154]. The reasons for this underuse must be researched in their many limitations. VKA limitations have lead to development and clinical experimental use of new anticoagulant molecules aimed to overcome these limits. In the last years new oral anticoagulants have reached phase III of clinical experimentation. Their targets on coagulation cascade are the direct inhibition of thrombin (actived factor II) and actived factor X.

Recommendations for Use of Warfarin for Secondary Prevention of Stroke

Recommendations apply to patients with permanent, persistent, or paroxysmal atrial fibrillation, atrial flutter, and patients managed with rhythm control strategy:

- For risk stratification consider CHADS2 score (CCS Strong recommendation, High-quality evidence):
  - 1 point for each of congestive heart failure, hypertension, age≥75 years, diabetes mellitus; 2 points for prior stroke or transient ischemic attack.
  - various risk scores predict risk for stroke; CHADS2 risk score may be simplest and most accurate (Level 2 [mid-level] evidence).
  - HAS-BLED score predicts risk of bleeding in patients with atrial fibrillation taking warfarin (Level 1 [likely reliable] evidence).
- Most patients with atrial fibrillation or atrial flutter should receive either oral anticoagulant or aspirin (ACC/AHA Class I, Level A, CCS Strong recommendation, High-quality evidence):
  - Warfarin with INR target ≥2 associated with decreased risk of systemic embolism compared to antiplatelet agents and placebo, but higher rate of major bleeding compared to placebo and low-dose warfarin (Level 2 [mid-level] evidence)-
  - OAT recommended for patients.
- Non-vitamin K antagonist (VKA) anticoagulantswith intermediate risk for stroke (for example, CHADS2 score=1) (CCS Strong recommendation, High-quality evidence, ACCP Grade 1B compared to no therapy, ACCP Grade 2B compared to antiplatelet therapy); high risk for stroke (for example, CHADS2 score≥2) (CCS Strong recom-

mendation, High-quality evidence, ACCP Grade 1A compared to no therapy, ACCP Grade 1B compared to antiplatelet therapy); mitral stenosis (considered high risk for stroke) (ACC/AHA Class I, Level A, ACCP Grade 1B compared to no therapy or antiplatelet therapy); history of cardioembolic stroke or transient ischemic attack (TIA) (ACC/AHA Class I, Level A, ACCP Grade 1A compared to no therapy, ACCP Grade 1B compared to antiplatelet therapy); for patients with nonrheumatic atrial fibrillation and history of stroke or TIA, anticoagulants reduce risk of stroke compared to placebo (Level 1 [likely reliable] evidence) or antiplatelet therapy (Level 2 [mid-level] evidence); if low risk for stroke (for example, CHADS2 score=0); no therapy suggested rather than antithrombotic therapy (ACCP Grade 2B), especially if male<65 years old without vascular disease (CCS Conditional recommendation, Low-quality evidence); aspirin 75-325 mg once daily suggested if antithrombotic therapy used (ACCP Grade 2B) and suggested for patients<65 years old if female or if vascular disease (CCS Conditional recommendation, Low-quality evidence); oral anticoagulant suggested if patient>65 years old, or female with vascular disease (CCS Conditional recommendation, Low-quality evidence); for patients with nonvalvular atrial fibrillation and with no history of stroke or TIA; warfarin with target INR 2-3 reduces risk of stroke (Level 1 [likely reliable] evidence); aspirin may reduce risk of stroke and major vascular events (Level 2 [mid-level] evidence).

- For patients using oral anticoagulation:
  - New anticoagulant (dabigatran, rivaroxaban, or apixaban) preferred over warfarin (CCS Conditional recommendation, High-quality evidence).
  - Dabigatran 150 mg twice daily suggested rather than adjusted-dose VKA therapy (target INR range 2-3) (ACCP Grade 2B, ACC/AHA Class I, Level B).
  - Compared to warfarin, dabigatran (Pradaxa) 150 mg twice daily further reduces risk for stroke with similar bleeding risk (Level 1 [likely reliable] evidence) and possibly higher incidence of myocardial infarction (Level 2 [mid-level] evidence).
  - Rivaroxaban (Xarelto) may be as effective as warfarin for preventing stroke or systemic embolism in patients with nonvalvular atrial fibrillation (Level 2 [mid-level] evidence).
  - Apixaban (Eliquis) associated with reduced risk of stroke and major bleeding and might reduce risk of mortality compared to warfarin (Level 2 [mid-level] evidence).
- If patient is unsuitable for or chooses not to take oral anticoagulant (for reasons other than concerns about major bleeding):
  - Combination therapy with aspirin and clopidogrel suggested rather than aspirin alone (ACC/AHA Class IIb, Level B, ACCP Grade 2B for intermediate-risk patients, ACCP Grade 1B for high-risk patients).
  - Addition of clopidogrel to aspirin associated with reduced risk for major vascular events and increased risk for major hemorrhage in patients with atrial fibrillation for whom VKA therapy is unsuitable (Level 2 [mid-level] evidence).
  - Apixaban reduces risk of stroke without increased risk of major bleeding or intracranial hemorrhage compared to aspirin in patients with atrial fibrillation for whom VKAs are unsuitable (Level 1 [likely reliable] evidence).

American College of Chest Physicians (ACCP) guidelines (Ninth Edition) on antithrombotic therapy in atrial fibrillation [130]:

- All antithrombotic therapy recommendations for atrial fibrillation (AF) apply to patients with:
  - Permanent, persistent, or paroxysmal AF (recommendations do not apply to patients with single, transient, self-limited AF associated with acute illness).
  - Atrial flutter.

  - Patients with AF being managed with a rhythm control strategy (pharmacologic or catheter ablation), regardless of apparent persistence of normal sinus rhythm (ACCP Grade 2C).
- OAT refers to use of dabigatran or adjusted-dose vitamin K antagonist (VKA) therapy; cautions with dabigatran include:
  - Dabigatran contraindicated if creatinine clearance ≤30 ml/minute.
  - There is no antidote for dabigatran.
- For risk stratification, consider CHADS2 score:
  - Congestive heart failure=1 point.
  - Hypertension=1 point.
  - Age ≥75 years=1 point.
  - Diabetes mellitus=1 point.
  - Prior Stroke or transient ischemic attack=2 points.
- For patients with nonrheumatic AF:
  - If low risk for stroke (for example, CHADS2 score=0): no therapy suggested rather than antithrombotic therapy (ACCP Grade 2B); for patients who choose antithrombotic therapy, aspirin (75-325 mg once daily) suggested rather than either OAT (ACCP Grade 2B) or combination therapy with aspirin and clopidogrel (ACCP Grade 2B).
  - If intermediate risk for stroke (for example, CHADS2 score=1): OAT recommended rather than no therapy (ACCP Grade 1B); OAT with dabigatran 150 mg twice daily suggested rather than adjusted-dose vitamin K antagonist (VKA) therapy (target INR range 2-3) (ACCP Grade 2B); OAT suggested rather than either aspirin (75-325 mg once daily) (ACCP Grade 2B) or combination therapy with aspirin and clopidogrel (ACCP Grade 2B);
  - If patient is unsuitable for or chooses not to take oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with aspirin and clopidogrel suggested rather than aspirin (75-325 mg once daily) (ACCP Grade 2B).
  - If high risk for stroke (for example, CHADS2 score≥2): OAT recommended rather than any of: no therapy (ACCP Grade 1A); aspirin (75-325 mg once daily) (ACCP Grade 1B); combination therapy with aspirin and clopidogrel (ACCP Grade 1B); OAT with dabigatran 150 mg twice daily suggested rather than adjusted-dose VKA therapy (target INR range, 2-3) (ACCP Grade 2B); if patient is unsuitable for or chooses not to take an oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with aspirin and clopidogrel recommended rather than aspirin (75-325 mg once daily) (ACCP Grade 1B).
- For patients with AF and mitral stenosis:
  - Adjusted-dose VKA therapy (target INR range 2-3) recommended rather than no therapy, aspirin (75-325 mg once daily), or combination therapy with aspirin and clopidogrel (all ACCP Grade 1B)
  - If patient is unsuitable for or chooses not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), combination therapy with aspirin and clopidogrel recommended rather than aspirin (75-325 mg once daily) alone (ACCP Grade 1B).
- For patients with AF and stable coronary artery disease (for example, no acute coronary syndrome [ACS] within the previous year):
  - If patient chooses oral anticoagulation, adjusted-dose VKA therapy alone (target INR range 2-3) suggested rather than combination of adjusted-dose VKA therapy and aspirin (ACCP Grade 2C).

- For patients with AF and intracoronary stent placement (with or without recent ACS):
  - If high risk of stroke (for example, CHADS2 score ≥2): during first month after placement of bare-metal stent or first 3-6 months after placement of drug-eluting stent, triple therapy (with VKA therapy, aspirin, and clopidogrel) suggested rather than dual antiplatelet therapy (with aspirin and clopidogrel) (ACCP Grade 2C); after initial period of triple therapy, VKA therapy (target INR 2-3) plus single antiplatelet drug suggested rather than VKA alone (ACCP Grade 2C); at 12 months after intracoronary stent placement, if patient chooses oral anticoagulation, adjusted-dose VKA therapy alone (target INR range 2-3) suggested rather than combination of adjusted-dose VKA therapy and aspirin (ACCP Grade 2C).
  - If low to intermediate risk for stroke (for example, CHADS2 score 0 or 1): during first 12 months after placement of intracoronary stent (bare metal or drug-eluting), dual antiplatelet therapy suggested rather than triple therapy (ACCP Grade 2C); at 12 months after intracoronary stent placement, if patient chooses oral anticoagulation, adjusted-dose VKA therapy alone (target INR range 2-3) suggested rather than combination of adjusted-dose VKA therapy and aspirin (ACCP Grade 2C).
- For patients with AF and ACS and no intracoronary stent placement:
  - If intermediate to high risk of stroke (for example, CHADS2 score≥1): for first 12 months, adjusted-dose VKA therapy (target INR 2-3) plus single antiplatelet therapy suggested rather than dual antiplatelet therapy (for example, aspirin and clopidogrel) or triple therapy (for example, warfarin, aspirin, and clopidogrel) (ACCP Grade 2C); after 12 months, if patient chooses oral anticoagulation, adjusted-dose VKA therapy alone (target INR range 2-3) suggested rather than combination of adjusted-dose VKA therapy and aspirin (ACCP Grade 2C)
  - If low risk for stroke (for example, CHADS2 score=0): dual antiplatelet therapy (for example, aspirin and clopidogrel) suggested rather than adjusted-dose VKA therapy (target INR 2-3) plus single antiplatelet therapy or triple therapy (for example, warfarin, aspirin, and clopidogrel) (ACCP Grade 2C); after 12 months, if patient chooses oral anticoagulation, adjusted-dose VKA therapy alone (target INR range 2-3) suggested rather than combination of adjusted-dose VKA therapy and aspirin (ACCP Grade 2C).
- For patients having cardioversion:
  - Same approach suggested for both atrial fibrillation and atrial flutter.
  - For patients having elective cardioversion (pharmacologic or electrical): for atrial fibrillation of≥48 hours or of unknown duration; therapeutic anticoagulation recommended rather than no anticoagulation (ACCP Grade 1B); pre-cardioversion treatment options are: therapeutic anticoagulation for at least 3 weeks before cardioversion, using any of: adjusted-dose vitamin K antagonist (VKA) therapy (target INR range 2-3); low-molecular-weight heparin (LMWH) at full venous thromboembolism (VTE) treatment doses; dabigatran; transesophageal echocardiography (TEE)-guided approach with abbreviated anticoagulation before cardioversion; start LMWH at full venous thromboembolism treatment doses or IV unfractionated heparin (UFH) (to maintain activated partial thromboplastin time [aPTT] prolongation equal to plasma heparin levels of 0.3-0.7 units/ml antifactor Xa activity); TEE screening for thrombus in either atrial appendage or atrium. If no thrombus seen, cardioversion within 24 hours: therapeutic anticoagulation recommended for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline risk of stroke (ACCP Grade 1B); anticoagulation decisions beyond 4 weeks should be made in accordance with risk-based recommendations for long-term antithrombotic therapy. For atri-

al fibrillation of known duration<48 hours: starting anticoagulation (with LMWH or IV UFH at full VTE treatment doses) at presentation and proceeding to cardioversion suggested rather than delaying cardioversion (for 3 weeks of therapeutic anticoagulation or for TEE-guided approach) (ACCP Grade 2C). After successful cardioversion to sinus rhythm, therapeutic anticoagulation recommended for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk (ACCP Grade 2C): anticoagulation decisions beyond 4 weeks should be made in accordance with risk-based recommendations for long-term antithrombotic therapy.
    - For urgent cardioversion in hemodynamically unstable patient: initiation of therapeutic-dose parenteral anticoagulation suggested before cardioversion, if possible (ACCP Grade 2C); initiation of anticoagulation should not delay any emergency intervention (ACCP Grade 2C); therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm suggested rather than no anticoagulation, regardless of baseline stroke risk (ACCP Grade 2C); anticoagulation decisions beyond 4 weeks should be made in accordance with risk-based recommendations for long-term antithrombotic therapy.
- For secondary stroke prevention after cardioembolic stroke or transient ischemic attack (TIA) (that is, in patients with atrial fibrillation, including paroxysmal atrial fibrillation) [15]:
    - OAT recommended over: no antithrombotic therapy (ACCP Grade 1A); aspirin (ACCP Grade 1B); combination therapy with aspirin plus clopidogrel (ACCP Grade 1B); OAT with dabigatran 150 mg twice daily suggested over adjusted-dose vitamin K antagonist therapy (target range 2-3) (ACCP Grade 2B); dabigatran contraindicated if creatinine clearance ≤30 ml/minute.
    - For patients unsuitable for or who choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with aspirin plus clopidogrel recommended over aspirin (ACCP Grade 1B)
    - OAT should generally be started within 1-2 weeks after stroke onset, but timing may vary with risk for bleeding.
    - Use of aspirin as bridging therapy suggested until anticoagulation reaches therapeutic level.

American College of Cardiology/American Heart Association (ACC/AHA) guidelines:

- Antithrombotic therapy to prevent thromboembolism is recommended for all patients with atrial fibrillation, except patients with lone atrial fibrillation (age<60 years old without heart disease or risk factors for thromboembolism) or contraindications (ACC/AHA Class I, Level A) [155].
- Antithrombotic therapy is recommended for patients with atrial flutter (ACC/AHA Class I, Level C) [155].
- Long-term anticoagulation with vitamin K antagonist (VKA) not recommended for primary prevention of stroke in patients<60 years old without heart disease (lone atrial fibrillation) or any risk factors for thromboembolism (ACC/AHA Class III, Level C) [155].
- Selection of antithrombotic agent:
    - Should be based upon absolute risks of stroke and bleeding and relative risk and benefit for a given patient (ACC/AHA Class I, Level A) irrespective of pattern of atrial fibrillation (paroxysmal, persistent, or permanent) (ACC/AHA Class IIa, Level B) [155].
    - VKA recommended for [155]: patients at high risk of stroke due to prior thromboembolism (stroke, transient ischemic attack, or systemic embolism) or rheumatic mitral stenosis (ACC/AHA Class I, Level A); patients with>1 moderate risk factor

such as age≥75 years, hypertension, heart failure, impaired left ventricular systolic function (ejection fraction ≤ 35% or fractional shortening<25%) and diabetes mellitus (ACC/AHA Class I, Level A).
  - Either aspirin or VKA is reasonable for primary prevention of thromboembolism in patients with only 1 moderate risk factor such as age≥75 years, hypertension, heart failure, impaired left ventricular systolic function (ejection fraction ≤ 35% or fractional shortening<25%) and diabetes mellitus (ACC/AHA Class IIa, Level A) [155].
  - Either aspirin or VKA is reasonable for patients with less well-validated risk factors such as age 65-74 years, female gender or coronary artery disease (ACC/AHA Class IIa, Level B) [155].
  - Dabigatran is useful as an alternative to warfarin for prevention of stroke and thromboembolism in patients with paroxysmal, persistent, or permanent atrial fibrillation and risk factors for stroke or systemic embolization who do not have any of (ACC/AHA Class I, Level B) [156]: prosthetic heart valve; hemodynamically significant valve disease; severe renal failure (creatinine clearance<15 ml/minute); advanced liver disease (impaired baseline clotting function).
  - Aspirin 81-325 mg daily is recommended as an alternative to VKAs in low-risk patients or in patients with contraindications to OAT (ACC/AHA Class I, Level A) [155].
  - Addition of clopidogrel to aspirin might be considered in patients for whom warfarin is considered unsuitable due to patient preference or concern for ability to safely sustain anticoagulation (ACC/AHA Class IIb, Level B) [157].
- For patients on VKA [155]:
  - INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable (ACC/AHA Class I, Level A).
  - Target INR 2-3 in patients without mechanical heart valves (ACC/AHA Class I, Level A).
  - For patients with mechanical heart valves, target INR should be based on type of prosthesis, maintaining INR≥2.5 (ACC/AHA Class I, Level B).
  - Lower target INR of 2 (range 1.6-2.5) may be considered for patients≥75 years old or other patients at increased risk of bleeding but without contraindications to oral anticoagulant therapy (ACC/AHA Class IIb, Level C).
  - If ischemic stroke or systemic embolism on anticoagulation within INR 2-3, increasing target INR to 3-3.5 may be reasonable instead of adding antiplatelet agent (ACC/AHA Class IIb, Level C).
  - For surgical or diagnostic procedures with bleeding risk: for patients without mechanical heart valves, interruption of OAT for up to 1 week without substituting heparin is reasonable (ACC/AHA Class IIa, Level C); for high-risk patients requiring interruption of OAT for>1 week, subcutaneous unfractionated heparin or low-molecular-weight heparin may be given (ACC/AHA Class IIb, Level C)
  - Following percutaneous coronary intervention or revascularization surgery, low-dose aspirin<100 mg/day and/or clopidogrel 75 mg/day may be given with anticoagulation (ACC/AHA Class IIb, Level C).
  - Reasonable to reevaluate need for anticoagulation at regular intervals (ACC/AHA Class IIa, Level C).

American Heart Association/American Stroke Association (AHA/ASA) guidelines for secondary prevention of stroke in patients with paroxysmal or permanent atrial fibrillation [13]:

- Use vitamin K antagonist for anticoagulation (AHA/ASA Class I, Level A).
- Use aspirin if patient unable to take OAT medications (AHA/ASA Class I, Level A).

- Clopidogrel with aspirin not recommended for patients with hemorrhagic contraindication to warfarin (AHA/ASA Class III, Level B).
- Use bridging therapy with subcutaneous low-molecular-weight heparin if temporary interruption of OAT in patient at high risk (such as TIA within 3 months, mechanical valve disease) (AHA/ASA Class IIa, Level C).

Canadian Cardiovascular Society (CCS) guidelines:

- Use predictive index for stroke risk (such as CHADS2) and for risk of bleeding (such as HAS-BLED) to assess all patients with atrial fibrillation or atrial flutter (paroxysmal, persistent, or permanent) (CCS Strong recommendation, High-quality evidence) [158].
- Most patients with atrial fibrillation or atrial flutter should receive either oral anticoagulant or aspirin (CCS Strong recommendation, High-quality evidence) [158].
- When oral anticoagulant is indicated [158]:
  - New anticoagulant (dabigatran, rivaroxaban, or apixaban) preferred over warfarin (CCS Conditional recommendation, High-quality evidence).
  - Consider dose reduction of new anticoagulant, especially dabigatran, in patients>75 years old.
- Risk-based selection of antithrombotic therapy for stroke prevention [158]:
  - If CHADS2 score ≥2, give oral anticoagulant (CCS Strong recommendation, High-quality evidence).
  - If CHADS2 score=1: give most patients oral anticoagulant (CCS Strong recommendation, High-quality evidence); consider aspirin as reasonable alternative based on individual risk/benefit considerations (CCS Conditional recommendation, Moderate-quality evidence).
  - If CHADS2 score=0: consider additional risk factors for stroke (age 65-74 years, female gender, vascular disease) (CCS Conditional recommendation, Moderate-quality evidence); oral anticoagulant suggested if patient >65 years old, or female with vascular disease (CCS Conditional recommendation, Low-quality evidence); aspirin 75-325 mg/day suggested if patient is male with vascular disease or female without vascular disease (CCS Conditional recommendation, Low-quality evidence); consider no antithrombotic therapy for patients with no additional risk factors for stroke (CCS Conditional recommendation, Low-quality evidence)-
  - For patients with coronary artery disease and atrial fibrillation/atrial flutter. For patients with stable coronary artery disease, select antithrombotic therapy based on risk of stroke (CCS Conditional recommendation, Moderate-quality evidence): consider oral anticoagulant for most patients with CHADS2 score ≥1; consider aspirin for most patients with CHADS2 score=0. For patients with recent acute coronary syndrome or percutaneous coronary intervention, select antithrombotic therapy based on assessment of risks of stroke, recurrent coronary artery events, and hemorrhage (CCS Conditional recommendation, Low-quality evidence): consider aspirin plus clopidogrel plus oral anticoagulant in patients with CHADS2 score ≥2; consider aspirin plus clopidogrel in patients with CHADS2 score ≤1.
- Renal function considerations in patients with atrial fibrillation receiving oral anticoagulant [158]:
  - Assess renal function at least annually by measuring serum creatinine and calculating estimated glomerular filtration rate (egfr) (CCS Strong recommendation, Moderate-quality evidence)
  - Regularly consider alteration of OAT drug or dose based on egfr (CCS Strong recommendation, Moderate-quality evidence).
  - If EGFR>30 ml/minute: give antithrombotic therapy according to CHADS2 score as recommended for patients with normal renal function (CCS Strong recommen-

dation, High-quality evidence); if EGFR 30-50 ml/minute, consider more frequent egfr measurements and oral anticoagulant dose reductions with conditions that may transiently reduce egfr, especially if patient >75 years old.

- If EGFR 15-30 ml/minute and patient not on dialysis, give antithrombotic therapy according to CHADS2 score as recommended for patients with normal renal function but warfarin suggested as preferred agent for OAT (CCS Conditional recommendation, Low-quality evidence).
- If EGFR <15 ml/minute and patient on dialysis, oral anticoagulant or aspirin suggested not to be used routinely (CCS Conditional recommendation, Low-quality evidence).

64.3.3 Oral Direct Thrombin Inhibitors

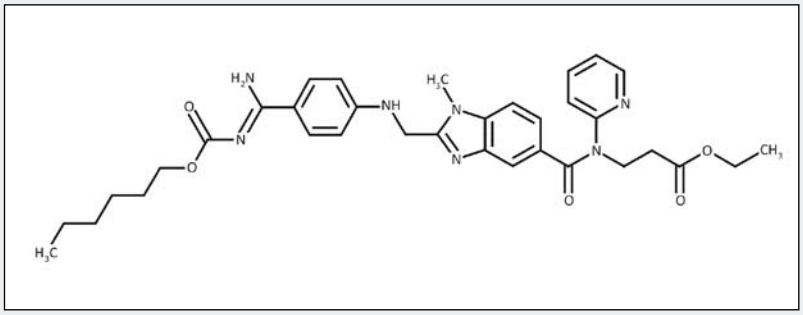
Dabigatran Etexilate

Dabigatran is a selective and reversible inhibitor of thrombin. It derives from a binding between a N-α-naphthylsulphonylglycyl-4-amidino-phenylalanine-piperidine compound to a benzamidine which leads to antithrombotic activity (Table 64.11) [170-172]. Dabigatran reversibly binds to active site of thrombin both when free and when clot-bound.

Dabigatran is administered as pro-drug (dabigatran etexilate); non specific enzymes convert the pro-drug to the active molecule (dabigatran). This is of utmost importance because high polarity of dabigatran proves the impossibility of gastro-intestinal absorption [170-172]. Dabigatran has a quick onset of action when orally administrated and a predictable anticoagulant effect. Therapeutic dose does not lead to interactions with coagulation parameters such as prothombin time (PT) and actived partial thromboplastin (aPTT). Sovra-therapeutic dose could be detected by aPTT. The coagulation parameters thrombin time (TT) and echarin clotting (ECT) time are both altered by dabigatran, but, unfortunately, these assays are not widely diffuse in laboratories. After administration bioavailability is near 6.5%. Time to reach maximum plasma concentration is 90-270 minutes. Volume of distribution is around 60-70 liters. Metabolism starts in gastro-intestinal tract and end in liver, but it is not mediated by cytochrome P450. Dabigatran have not interactions with food. Contemporary adiministration of protonic pump inhibitors reduces the max concentration of 20-25% whereas food decreases the plasma peak of two hours. Halflife of dabigatran is near 8 hours after the first dose and 6 hours after multiple doses; after 4-6 hours max concentration is reduced for 30%. Therefore dabigatran needs of two administrations in a day. Steady-state is reached in 3 days. Dabigatran is excreted for 80% from kidneys, therefore renal failure could prove a reduced excrection. Dabigatran is contraindicated in patients with severe renal failure (creatinine clearance, ClCr, <30 ml/min). Hepatotoxicity with dabigatran has not been demonstrated [170-172]. Dabigatran has not a specific antidote for urgent reversal. Up to now fresh frozen plasma (FFP), FEIBA, recombinant actived Factor VII (raFVII) and dyalisis seem to be possible choices in this context [173]. Two doses of dabigatran, 110 mg twice daily and 150 mg twice daily, administered in blinded fashion, have been compared with adjusted doses to INR 2.0-3.0 of warfarin administered in un-blinded fashion, in patients with AF in the RE-LY study, a randomized clinical trial (RCT) of phase III aimed to demonstrate the non-inferiority of dabigatran in terms of cardioembolic risk (effectiveness) and bleeding risk (safety) [174]. The RE-LY trial has demonstrated that lower dosage of dabigatran, 110 mg twice daily, is not inferior to warfarin in preventing combined ischemic and hemorrhagic strokes and systemic embolism (RR 0.90, 95% CI 0.74-1.10, p<0.001 for non-inferiori-

ty, p=0.29 for superiority), while it is superior to warfarin in reduce total (RR 0.78, 95% CI 0.73-0.83, p<0.001) and major bleeding risk (RR 0.80, 95% CI 0.70-0.93, p=0.003) [174,175]. Higher dosage of dabigatran, 150 mg twice daily, results superior to warfarin in reducing the above mentioned combined endpoint (RR 0.65, 95% CI 0.52-0.81, p<0.001 both for non-inferiority and superiority) and non inferior to warfarin in major bleedings (RR 0.93, 95% CI 0.81-1.07, p<0.31), with the exception of gastrointestinal bleedings, significantly higher for dabigatran (RR 1.48, 95% CI 0.18-1.85, p=0.001 for warfarin superiority) [174,175]. Lower doses of dabigatran reduce the risk of intracranial bleeding of 70% compared to warfarin, whereas higher doses prove a RRR of 59% [174,175]. Based on the results of RE-LY, dabigatran is now recommended by ACCF/AHA/HRS as an alternative to VKA in high risk patients (IB) [156]. A specific question is whether the overall results of RE-LY can be generalised to patients with AF and a history of stroke or TIA. Among the 3,623 (20%) patients with a previous stroke or TIA who were enrolled, the results were consistent with the overall trial results (annual rate of the primary outcome event: warfarin, 2.75%; 110 mg dabigatran, 2.32%; 150 mg dabigatran, 2.07%), without significant differences between the HRs for patients with or without a history of cerebral ischemia (p=0.34 for interaction). However, the 95% CIs for patients with a history of cerebral ischemia were wide, indicating that evidence for the efficacy of dabigatran compared with warfarin in patients with a history of cerebral ischemia is still limited.

Dabigatran has been approved for this indication in many countries of the world. However, the potential benefits of dabigatran compared with warfarin may be reduced in poorly compliant patients (because the longer half-life of warfarin could provide them with a more consistent anticoagulant effect) and in patients taking potent P-glycoprotein inhibitors, which can increase serum concentrations of dabigatran (Table 64.11).

Structure	 Chemical structure: $C_{34}H_{41}N_7O_5$ SMILES: CCCCCCOC(=O)N=C(N)C1=CC=C(NCC2=NC3=C(C=CC(=C3)C(=O)N(CCC(=O)OCC)C3=CC=CC=N3)N2C)C=C1
Pharmacodynamics	Dabigatran etexilate is an inactive pro-drug that gets converted to dabigatran, the active form, by esterase-catalyzed hydrolysis in the plasma and liver. Dabigatran, the main active principle in plasma, is a rapid-acting competitive and reversible direct inhibitor of thrombin. Thrombin, a serine protease, is responsible for the conversion of fibrinogen to fibrin during the coagulation cascade. Inhibition of thrombin consequently prevents thrombus development. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.
Mechanism of action	Esterase-catalysed hydrolysis of dabigatran etexilate in the plasma and liver yields the active form, dabigatran. Dabigatran competitively and reversibly binds to thrombin thereby inhibiting its ability to convert fibrinogen to fibrin during the coagulation cascade

Absorption	Peak plasma concentrations were achieved in 6 hours in post surgical patients. In healthy patients, maximum concentrations were achieved in 0.5 to 2 hours. The absolute bioavailability of dabigatran in the body after administration of dabigatran etexilate was 6.5%. Food does not affect the bioavailability of dabigatran etexilate, but it delays the time to peak plasma concentrations by 2 hours. Oral bioavailability may increase by up to 75% when pellets are taken out of the hydroxypropylmethylcellulose (HPMC) capsule. Therefore, capsules should not be opened and pellets taken alone	
Volume of distribution	Moderate tissue distribution with V_d of 60-70 l	
Protein binding	Relatively low binding (34-35%) to plasma proteins	
Metabolism	Dabigatran is typically metabolised by esterases and microsomal carboxylesterases. CYP450 enzymes do not seem to be involved. Pharmacologically active acylglucoronides are formed via conjugation. Four positional isomers, 1-O, 2-O, 3-O, and 4-O, acylglucuronides exist, each accounting for less than 10% of total plasma dabagatran	
Route of elimination	Mainly excreted in urine (85%). Fecal excretion accounts for 6% of the orally administered dose. Dabigatran is primarily eliminated unchanged via the kidneys at a rate of 100 ml/min corresponding to the glomerular filtration rate	
Half life	12-14 hours in healthy volunteers. 14-17 hours in patients treated for prevention of venous thromboembolism following hip- or knee-replacement surgery.	
Clearance	Not available	
Toxicity	The most common adverse reactions include dyspepsia or gastritis-like symptoms. The approximate lethal dose in rats and mice was observed at single oral doses of>2000 mg/kg. Oral doses of 600 mg/kg did not induce any toxicologically meaningful changes in dogs and Rhesus monkeys. Dabigatran was well-tolerated in rats and Rhesus monkeys during repeat-dose toxicity studies. No evidence of mutagenic potential	
Drug interactions	**Drug**	**Interaction**
	Amiodarone	Amiodarone may increase the serum concentration of dabigatran etexilate, resulting in increased risk of bleeding. Consider modifying therapy.
	Carbamazepine	P-Glycoprotein inducers such as carbamazepine may decrease the serum concentration of dabigatran etexilate. This combination should be avoided.
	Dexamethasone	P-Glycoprotein inducers such as dexamethasone may decrease the serum concentration of dabigatran etexilate. This combination should be avoided.
	Doxorubicin	P-Glycoprotein inducers such as doxorubicin may decrease the serum concentration of dabigatran etexilate. This combination should be avoided.
	Ginkgo biloba	Additive anticoagulant/antiplatelet effects of gingko may increase bleed risk for patients on dabigatran. Concomitant therapy should be avoided.
	Nefazodone	P-Glycoprotein inducers such as nefazodone may decrease the serum concentration of dabigatran etexilate. This combination should be avoided.
	Prazosin	P-Glycoprotein inducers such as prazosin may decrease the serum concentration of dabigatran etexilate. This combination should be avoided.
	Quinidine	Quinidine may increase the serum concentration of dabigatran etexilate, resulting in increased bleeding. Consider modification of therapy.
	Rifampin	P-Glycoprotein inducers such as rifampin may decrease the serum concentration of dabigatran etexilate. This combination should be avoided

	Rivaroxaban	Using additional anticoagulants such as dabigatran can increase the anticoagulant effect of rivaroxaban. Avoid concurrent use of rivaroxaban with other anticoagulants whenever possible, other than during transition periods, due to the possible increased for bleeding
	Tipranavir	P-Glycoprotein inducers such as tipranavir may decrease the serum concentration of dabigatran etexilate. This combination should be avoided
	Trazodone	P-Glycoprotein inducers such as trazodone may decrease the serum concentration of dabigatran etexilate. This combination should be avoided
	Verapamil	Verapamil may increase serum concentrations of the active metabolite(s) of dabigatran etexilate, resulting in an increased risk of bleeding. Therapy modification should be considered
	Vinblastine	P-Glycoprotein inducers such as vinblastine may decrease the serum concentration of dabigatran etexilate. This combination should be avoided
Food interactions	St. John's Wort	
Efficacy	• Compared to warfarin, dabigatran 150 mg twice daily further reduces risk for stroke with similar bleeding risk, while dabigatran 110 mg twice daily has similar efficacy to warfarin and lower bleeding risk (Level 1 [likely reliable] evidence); dabigatran associated with nonsignificant increase in incidence of myocardial infarction (Level 2 [mid-level] evidence) [174,177,178] · dabigatran may reduce major bleeding in patients<75 years old but not in patients≥75 years old [179] · prior vitamin K antagonist (VKA) exposure does not appear to influence efficacy of dabigatran or warfarin (Level 2 [mid-level] evidence) [180] · dabigatran 110 mg or 150 mg twice daily has similar efficacy as warfarin in reducing stroke or systemic embolism, while dabigatran 110 mg dose reduces bleeding risk in patients with previous stroke or TIA (Level 1 [likely reliable] evidence) [181] · dabigatran 110 mg or 150 mg appears as effective as warfarin for prevention of stroke or systemic embolism within 30 days of cardioversion (Level 2 [mid-level] evidence) [182] • Dabigatran associated with decreased risk of stroke compared with placebo, ASA monotherapy, or ASA plus clopidogrel (Level 2 [mid-level] evidence) [183] • Dabigatran associated with small increase in risk of myocardial infarction (MI) and acute coronary syndrome (ACS) compared with other anticoagulants or placebo (Level 2 [mid-level] evidence) [184]	

Table 64.11. **Dabigatran overview. SMILES indicates simplified molecular-input line-entry system [25].**

Several general concerns remain about its safety in ederly with moderate renal impairment, its long-term safety and efficacy (ie,>2 years mean follow-up), which is currently being assessed in an follow-up study of RE-LY patients, and the absence of an antidote to dabigatran, although dabigatran can be eliminated by means of dialysis. Dabigatran might be a safe and effective alternative to warfarin for patients with AF at risk of stroke. If, and once, the drug is approved, clinicians are likely to have a choice of doses, which they can tailor to the patient's risks of stroke and bleeding; the more efficacious 150 mg dose is likely to be appropriate for patients at high risk of stroke, and the safer 110 mg dose for those at high risk of bleeding or drug interactions, such as those taking potent P-glycoprotein inhibitors [176]. However, patients who are already taking and tolerating once-daily warfarin with good INR control may prefer to stay on warfarin and not switch to dabigatran. Despite the potential benefits of dabigatran in lowering rates of stroke and ICH and not requiring coagulation monitoring, these patients may be discour-

aged from a switch because dabigatran will need to be administered twice daily and has a greater risk of non-hemorrhagic side-effects (ie, dyspepsia), which may increase the likelihood of drug discontinuation [176].

Recommendations for Use of Dagibatran for Secondary Prevention of Stroke

Dabigatran may be preferred over warfarin for oral anticoagulation:

- For oral anticoagulation, dabigatran 150 mg twice daily suggested rather than adjusted-dose vitamin K antagonist (VKA) therapy (target INR range 2-3) (ACCP Grade 2B) [15].
- New anticoagulant (such as dabigatran) preferred over warfarin when oral anticoagulant therapy used (CCS Conditional recommendation, High-quality evidence) [158]
- Dabigatran is a direct thrombin inhibitor and alternative oral anticoagulant to warfarin for prevention of stroke and thromboembolism in patients with paroxysmal, persistent, or permanent atrial fibrillation and risk factors for stroke or systemic embolization who do not have any of (ACC/AHA Class I, Level B) [156]:
  - Prosthetic heart valve.
  - Hemodynamically significant valve disease.
  - Severe renal failure (creatinine clearance <15 ml/minute).
  - Advanced liver disease (impaired baseline clotting function).

Ximelagatran

Ximelagatran was the first oral direct thrombin inhibitors to be studied in phase III clinical trials for stroke and systemic embolism prevention in AF. In the SPORTIF III and SPORTIF V trials [185], ximelagatran showed promise in terms of being non-inferior to warfarin with a better bleeding profile. Among 7329 patients with AF who were randomly assigned to warfarin (INR 20-3.0) or ximelagatran (36 mg twice daily) and followed for 11,346 patient-years (mean 18.5 months per patient), ximelagatran was considered not inferior to warfarin in prevention of stroke and systemic embolism (1.62% vs. 1.65% per year; p=0·94) or in causing major bleeding (1.88% vs. 2.46% per year; p=0.054) [185,186]. However, after marketing, clinical practice revealed increased hepatotoxicity and adverse cardiovascular events with the drug and hence, ximelagatran was withdrawn from the market and further developments of ximelagatran in AF were precluded [187].

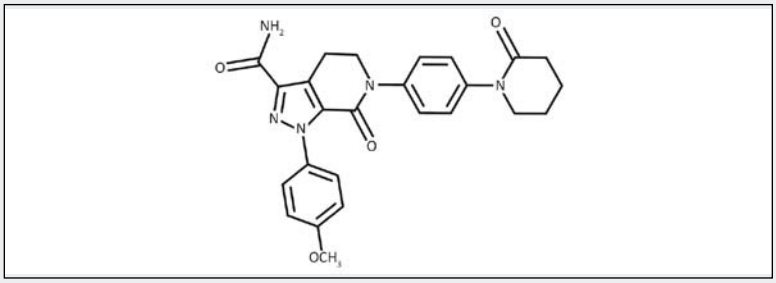
64.3.4 Factor Xa Inhibitors

Several oral and subcutaneous factor Xa inhibitors are currently undergoing clinical evaluation. These include apixaban, rivaroxaban, and edoxaban, which are currently being compared with warfarin.

Apixaban

Apixaban has been compared both with warfarin and with ASA in antithrombotic prevention of patients with AF (Table 64.12) [188,189].

Apixaban is a factor Xa inhibitor



New anticoagulant (such as apixaban, once approved by Health Canada) preferred over warfarin when oral anticoagulant therapy used (CCS Conditional recommendation, High-quality evidence) [158]	

Apixaban associated with reduced risk of stroke and major bleeding and might reduce risk of mortality compared to warfarin (Level 2 [mid-level] evidence) [188]	• Based on randomized trial with high dropout rate
	• 18,201 patients (median age 70 years) with atrial fibrillation and≥1 additional risk factor for stroke randomized to apixaban 5 mg twice daily vs. Warfarin (target inr 2-3)
	• Discontinuation of study drug before end of trial in
	  · 25.3% with apixaban (3.6% of discontinuations due to death)
	  · 27.5% with warfarin (3.8% of discontinuations due to death)
	• Comparing apixaban vs. Warfarin at median 1.8-year follow-up
	  · Any stroke or systemic embolism in 1.27% per year vs. 1.6% per year (p=0.01, nnt 303 per year)
	  · Hemorrhagic stroke in 0.24% per year vs. 0.47% per year (p<0.001, nnt 435 per year)
	  · Jo ischemic or uncertain type of stroke in 0.97% per year vs. 1.05% per year (not significant)
	  · Systemic embolism in 0.09% per year vs. 0.1% per year (not significant)
	  · Major bleeding in 2.13% per year vs. 3.09% per year (p<0.001, NNT 105 per year)
	  · All-cause mortality 3.52% vs. 3.94% (p=0.047, NNT 238)
	• Rates of stroke or systemic embolism comparing apixaban vs. Warfarin in subgroup analysis by previous stroke or transient ischemic attack [190]
	  · 2.46% per year vs. 3.24% per year in subgroup of 3,436 (19%) patients with previous stroke or transient ischemic attack (hazard ratio 0.76, 95% ci 0.56-1.03)
	• 1.01% per year vs. 1.23% per year in subgroup without prior stroke or transient ischemic attack (hazard ratio 0.82, 95% ci 0.65-1.03)

Apixaban reduces risk of stroke without increased risk of major bleeding or intracranial hemorrhage compared to ASA in patients with atrial fibrillation for whom vitamin K antagonists are unsuitable (Level 1 [likely reliable] evidence) [189]	• Based on randomized trial
	• 5,599 patients with atrial fibrillation at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable were randomized to apixaban (factor Xa inhibitor) 5 mg twice daily vs. ASA 81-324 mg/day and followed for mean 1.1 years
	  · Increased risk for stroke based on≥1 $CHADS_2$ criteria or documented peripheral artery disease
	• Patients unsuitable for vitamin K therapy included those proven to have problems with INR control, unlikely to comply with monitoring, refusing
	• Comparing apixaban vs. ASA
	  · Any stroke in 1.7% vs. 3.8% (p<0.001, nnt 48): ischemic stroke in 1.3% vs. 3.3% (p<0.001, nnt 50), disabling or fatal stroke in 1.1% vs. 2.6% (p<0.001, nnt 67)
	  · Systemic embolism in 0.007% vs. 0.5% (p=0.01, nnt 203)
	  · All-cause death in 4% vs. 5% (p=0.07)
	  · Major bleeding in 1.6% vs. 1.4% (not significant)
	  · Intracranial bleeding in 0.4% vs. 0.5% (not significant)
	  · First hospitalization for cardiovascular causes in 13.1% per year vs. 16.3% per year (p<0.001, nnt 31)
	• Similar findings in patients with or without prior vitamin K antagonist exposure, and according to $CHADS_2$ score

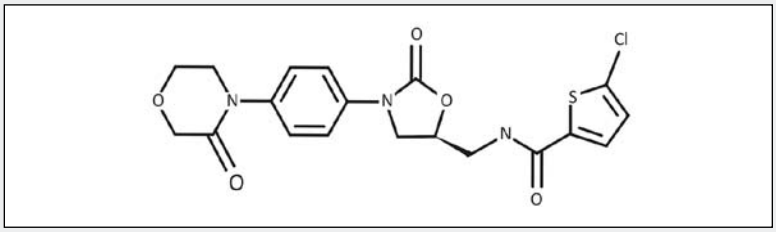
Table 64.12. **Apixaban: Summary of clinical data.**

The ARISTOTLE study, a double blind, double dummy, randomized clinical trial of phase III which has compared apixaban 5 mg (2.5 in patients with at least two of age>80 years, weight<60 Kg, creatinine levels>1.5 mg/dl) twice daily with adjusted doses of warfarin (range INR 2.0-3.0) with the aim of demonstrating non-inferiority and superiority [188]. The ARISTOTLE trial has demonstrated the superiority of apixaban on warfarin in reducing the combined endpoint ischemic and hemorrhagic stroke and systemic embolism (HR 0.79, 95% CI 0.66-0.95, p=0.01, RRR -21%), deaths from any cause (HR 0.89, 95% CI 0.80-0.99, p=0.047, RRR -11%) and major and clinically relevant nonmajor bleedings events (HR 0.68, 95% CI 0.61-0.75, p<0.001, RRR -32%) [188]. Apixaban reduces the risk of intracranial bleeding of 58% [188]. In subgroup analysis of patients with previous stroke or TIA, apixaban group showed lower rates of stroke and systemic embolism (2.46% per year vs. 3.24% per year (HR 0.76, 95% CI 0.56-1.03) [190].
The AVERROES study is a double-blind randomized clinical trial of phase III which has compared apixaban 5 mg twice daily (2.5 in patients with at least two of age>80 years, weight<60 Kg, creatinine levels>1.5 mg/dl) with ASA 81-324 mg in prevention of thromboembolic events in patients with AF [189]. This trial has clearly demonstrated the superiority of apixaban on ASA in terms of effectiveness and non inferiority of apixaban on ASA in terms of safety. Apixaban was associated to 55% of RRR of combined endpoint stroke and systemic embolism (HR 0.45, 95% CI 0.32-0.62, p<0.001) and 36% when death was added to the above mentioned endpoint (HR 0.64, 95% CI 0.51-0.78, p<0.001). Major and clinically relevant non major bleedings rate was similar in apixaban and ASA groups (1.4 vs. 1.2%/yr, HR 1.13, 95% CI 0.74-1.75, p=0.57 and 3.1 vs. 2.7%/yr, HR 1.15, 95% CI 0.86-1.54, p=0.35), whereas the rate of intracranial bleedings was the same (0.4 vs. 0.4%/yr, p=0.69) [189]. The substantial net clinical benefit of apixaban on ASA proved the early termination of this study [189].

Rivaroxaban

Rivaroxaban is an oxazolidinone derivate which acts making a strong inhibition of FXa binding to its active site both when free and prothrombin (factor II)-bound (Table 64.13) [170,191]. Rivaroxaban has not a pro-drug; it has an optimal adsorbent profile by gastrointestinal tract when orally administered. Bio-availability is very high (80%). Plasma peak is reached in 180 minutes. Halflife ranges from 6-8 hours in adults to 12 hours in the elderly. Rivaroxaban is metabolized from liver with a mechanism which is independent from cytochrome P450. Excretion is guaranteed from kidneys for 65%, whereas 65% is due to biliary system with the interaction of P-glyco-protein. The anticoagulant effect of rivaroxaban is viewable by interaction with PT and aPTT, but its effect on these parameters is very short and detectable only at concentration peak, therefore close laboratory monitoring is not routinariely recommended. Rivaroxaban does not interact with food, whereas it could have interactions with drugs with action on cytochromo P 3A4 and on P-glyco-protein, such as ketokonazol and ritonavir. Rivaroxaban is contraindicated in patients with sever liver or kidney disease (ClCr<20 ml/min). Rivaroxaban is administered once daily [170,191]. Rivaroxaban has not a specific antidote for urgent reversal. Up to prothrombin complex concentrates (PCC), FFP, FEIBA and raFVII [173,192].
The ROCKET-AF study, a randomized double blind, double dummy, controlled clinical trial of phase III which has compared rivaroxaban 20 mg once daily (15 mg in patients with moderate renal failure which means ClCr 30-50 ml/min) with adjusted doses of warfarin at therapeutic range 2.0-3.0 with the aim to demonstrate the non-inferiority of rivaroxaban in terms of effectiveness and safety; superiority of rivaroxaban was tested in the safety profile [193]. ROCKET-AF has demonstrated that rivaroxaban is not inferior to warfarin in combined endpoint ischemic and hemorrhagic strokes and systemic embolism (HR 0.79, 95% CI 0.66-0.96, p<0.001 for non-inferiority in per-protocol population

and HR 0.88, 95% CI 0.75-1.13, p<0.001 for non-inferiority in intention to treat population) [193]. Moreover ROCKET-AF has demonstrated that rivaroxaban is not-inferior to warfarin in terms of safety (major and clinically relevant non-major bleedings HR 1.03, 95% CI 0.96-1.11, p=0.44 for superiority), with exception of gastrointestinal bleedings (3.2% vs. 2.2%/yr, p<0.001 for warfarin superiority). Total and major bleedings rate is statistically not significant higher for rivaroxaban (14.9% vs. 14.5%/yr and 3.6% vs. 3.4%/yr respectively), while rivaroxaban is significantly superior to warfarin for reduction of intracranial bleeding rate (RRR -33%) [193].

Rivaroxaban is a direct factor Xa inhibitor FDA approved for reducing risk of stroke in patients with abnormal heart rhythm (nonvalvular atrial fibrillation)	
New anticoagulant (such as rivaroxaban) preferred over warfarin when oral anticoagulant therapy used (CCS Conditional recommendation, High-quality evidence) [158]	

Rivaroxaban may be as effective as warfarin for preventing stroke or systemic embolism in patients with nonvalvular atrial fibrillation (level 2 [mid-level] evidence) [193]	• Based on randomized noninferiority trial with high dropout rate
	• 14,264 patients with nonvalvular atrial fibrillation and at increased risk for stroke randomized to rivaroxaban 20 mg once daily (or 15 mg once daily if creatinine clearance 30-49 ml/minute) vs. Dose-adjusted warfarin
	• Patients followed for median 707 days
	• Patients stopping treatment before endpoint event and before trial termination 23.7% with rivaroxaban vs. 22.2% with warfarin
	• Noninferiority based on 1-sided significance level of 0.025 and superiority based on 2-sided significance level of 0.05
	• Comparing rivaroxaban vs. Warfarin
	  - Stroke or systemic embolism in 2.1% per year vs. 2.4% per year in intention-to-treat population (p<0.001 for noninferiority, not significant for superiority)
	  - Stroke or systemic embolism in 1.7% per year vs. 2.2% per year in per-protocol population (p<0.001 for noninferiority)
	  - Major and nonmajor clinically relevant bleeding in 14.9% per year vs. 14.5% per year (not significant for superiority)
	  - Intracranial hemorrhage in 0.5% vs. 0.7% (p=0.02 for superiority)
	• Fatal bleeding in 0.2% vs. 0.5% (p=0.003 for superiority)

Rivaroxaban may be as effective as warfarin for preventing stroke or systemic embolism in patients with nonvalvular atrial fibrillation and moderate renal impairment (level 2 [mid-level] evidence) [194]	• Based on subgroup analysis of ROCKET AF trial
	• 2,950 patients (mean age 79 years) with moderate renal impairment (creatinine clearance 30-49 ml/minute) who were randomized to rivaroxaban 15 mg once daily vs. Dose-adjusted warfarin in ROCKET AF trial were analyzed
	• Comparing rivaroxaban vs. warfarin
	  - Stroke or systemic embolism in 2.32% per year vs. 2.77% per year in intention-to-treat population (not significant)
	  - Major and nonmajor clinically relevant bleeding in 17.8% per year vs. 18.3% per year (not significant)

Table 64.13. **Rivaroxaban: summary of clinical data.**

Overall, phase III clinical trials on new oral anticoagulants for SPAF reveal good profile of effectiveness and safety of new molecules. With exception of dabigatran at higher doses and rivaroxaban in terms of gastrointestinal bleedings, new drugs seem to be at least not inferior to VKA, taking in account that for many endpoints they could be significantly superior. Furthermore pharmacoeconomic studies seem to demonstrate advantage of the new oral anticoagulants on VKA from a cost/benefit point of view [195-198].

64.3.5 Special Treatment Regimens in Secondary Prevention of Atrial Fibrillation Patients

ASA

ASA is considered as alternative to VKA in high risk patients when VKA are contraindicated or unsuitable and in moderate risk patients; when compared to placebo ASA produces a RRR of stroke and systemic embolism of 19% (95% CI 1-35%) [134], while reduces the risk of recurrent stroke and other major vascular event in patients with AF by about 17% (HR 0.83, 95% CI 0.65-1.05) compared with control [136]. Adjusted-dose warfarin is significantly more effective than antiplatelet therapy for preventing recurrent stroke (OR 0.49, 95% CI 0.33-0.72) in patients with AF, similarly to the effect of adjusted-dose warfarin compared with antiplatelet therapy in primary prevention (RR 0.61, 95% CI 0.48-0.78) [133,134]. The absolute benefit of OAT (vs. antiplatelet therapy) increases with older age because stroke risk increases with age and the relative efficacy of OAT to prevent ischemic stroke does not change while the relative efficacy of antiplatelet therapy to prevent ischemic stroke seems to decrease as patients with AF get older [199].

ASA Plus Clopidogrel vs. Warfarin and ASA Plus Clopidogrel vs. ASA Alone

The efficacy and safety of the association between ASA and clopidogrel in SPAF has been recently verified. The ACTIVE-W trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-Warfarin) [200] was aimed to compare ASA plus clopidogrel vs. VKA while the ACTIVE-A (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-Aspirin) [200] compared ASA plus clopidogrel vs. ASA. Clopidogrel (75 mg once daily) plus ASA (75-100 mg daily) treatment was associated with a significant increase in the primary outcome of stroke, myocardial infarction, non-CNS systemic embolism, or death from vascular causes, after a median follow-up of 1.3 years, compared with assignment to warfarin (target INR 2.0-3.0; 5.6% per year for those on clopidogrel plus ASA vs. 3.9% per year on warfarin; RR 1.44, 95% CI 1.18-1.76). Random assignment to 75 mg clopidogrel once daily plus ASA was associated with a reduction in the primary outcome of stroke, myocardial infarction, non-CNS systemic embolism, or death from vascular causes, after a median of 3·6 years of follow-up, compared with placebo plus ASA (6.8% vs. 7.6% per year; RR 0.89, 95% CI 0.81-0.98) [200]. However, major bleeding was greater among patients assigned clopidogrel plus ASA vs. those on ASA alone (2.0% vs. 1.3% per year; RR 1.57, 95% CI 1.29-1.92). These RCTs have found that the association ASA/clopidogrel does not reduce the risk of cardioembolic stroke when compared with VKA, at least when TTR is≥65% [201], but it is more effective when compared to ASA alone. The combination of ASA and clopidogrel is not as effective as warfarin, particularly for patients who are taking warfarin without complication [200]. However in these RCTs the bleeding risk associated to the ASA/clopidogrel use is higher both when compared to VKA and when it is compared with ASA alone [200]. Moreover the association of ASA/clopidogrel seems to be not superior to ASA alone when the con-

sidered endpoints are mortality and mortality plus disability after ischemic and hemorrhagic strokes [202]. However the association of ASA/clopidogrel for SPAF is now considered as potential alternative to VKA in patients with low risk of bleeding in ACCF/AHA/HRS guidelines but with a low grade of recommendation (IIb) [157].

ASA and Warfarin

Both warfarin and ASA are thought to be needed to prevent thrombus formation in the left atrium and arteries in patients with AF who have coexisting atherosclerotic vascular disease (such as ischemic heart disease). This principle appears valid in patients with AF with unstable vascular disease such as an acute coronary syndrome, or subjects with recent percutaneous coronary or carotid intervention or stenting. Warfarin prevents the formation of fibrin-rich thrombus (so-called "red clot") associated with AF, whereas antiplatelet treatment prevents the formation of the platelet-rich thrombus (so-called "white clot") associated with arterial vascular disease. For such AF patients, the long-term benefit-to-harm ratio of combination therapy is not known and should be left to the clinician's discretion. However, for AF patients with stable vascular disease, there is no reliable evidence to indicate that adding ASA (or clopidogrel) to warfarin is safe and effective compared with warfarin alone. Indeed, warfarin can be an effective drug for stable coronary and cerebrovascular disease, and the hemorrhage rate seems to be greater with the combination of ASA and warfarin [203-205].

64.3.6 Other Cardioembolic Sources

These special populations include patients with recent MI, left ventricular (LV) thrombus, and low ejection fraction mechanical heart valves, nonbacterial thrombotic endocarditis, infective endocarditis, mitral valve prolapse, mitral valve strands, and aortic arch atheroma [117,206]. Although the recommendations in these patients are focus on long-term antithrombotic therapy for primary stroke prevention, they also apply to patients who have suffered a stroke in the setting of one of these conditions (ie, secondary stroke prevention) [130,206]. Absolute indications for OAT (primary and secondary stroke prevention) are summarized in Table 64.14.

Although ASA and clopidogrel are superior to warfarin for the prevention of acute stent thrombosis, their relative effect on the prevention of systemic embolization in patients with LV thrombus is largely unknown. Physicians must attempt to weigh the potential benefits and risks of adding warfarin to dual antiplatelet therapy (low-dose ASA plus clopidogrel 75 mg daily) in these patients. Given the increased risk of major bleeding, the duration of triple therapy (warfarin [INR 2.0-3.0], low-dose ASA, clopidogrel 75 mg daily), if chosen, should be minimized. Although the formation of LV thrombus was observed in most patients in the first few weeks, additional clots developed up to 3 months after anterior MI. For patients at risk for LV thrombus (but no thrombus identified on initial echocardiogram) in whom warfarin therapy is withheld, repeat echocardiogram in 1 to 2 weeks to rule out subsequent development of thrombus may be advisable. The minimal duration of dual antiplatelet therapy should be 1 month following BMS and 3 to 6 months following DES.

For patients with anterior MI and LV thrombus or at high risk for LV thrombus (ejection fraction<40%, anteroapical wall motion abnormality) who do not undergo stenting warfarin (INR 2.0-3.0) plus low-dose aspirin 75 to 100 mg daily is the recommend therapy over single antiplatelet therapy or dual antiplatelet therapy for the first 3 months (Grade 1B) [165]. Triple therapy (warfarin [INR 2.0-3.0], low-dose aspirin, clopidogrel 75 mg daily) for 1 month over dual antiplatelet therapy (Grade 2C) is suggested for patients with

Cardiac	• Mechanical heart valve (target INR depending on type and location of valve, mostly 3.0, range 2.5-3.5) • Mitral valve stenosis with any prior embolic event (target INR 2.5, range 2-3) • Left atrial myxoma (target INR 2.5, range 2-3) • Intraventricular thrombus (target INR 2.5, range 2-3) • Ventricular aneurysm with thrombus (target INR 2.5, range 2-3) • Mobile thrombus in the ascending aorta (target INR 2.5, range 2-3) • Dilated cardiomyopathy (target INR 2.5, range 2-3) • Mitral valve prolapse with myxomatous leaflets (target INR 2.5, range 2-3; not evidence based) • Rupture of chordae tendineae (target INR 2.5, range 2-3) • Dyskinetic ventricular wall segment (target INR 2.5, range 2-3) • Mitral ring calcifications (target INR 2.5, range 2-3) • Persistent or paroxysmal atrial fibrillation (target INR 2.5, range 2-3) • Left ventricular thrombus (target INR 2.5, range 2-3) • Left ventricular aneurysm (target INR 2.5, range 2-3) • Extensive wall motion abnormalities resulting in a left ventricular ejection fraction (LVEF)<25% (target INR 2.5, range 2-3)
Thrombophilia and hypercoagulable states	• Antithrombin III deficiency (target INR 2.5, range 2-3) • Protein C deficiency (target INR 3, range 3-3.5) • Protein S deficiency (target INR 2.5, range 2-3) • Activated protein C (APC) resistance (factor V Leiden; target INR 2.5, range 2-3) • Plasminogen deficiency/inhibition (target INR 2.5, range 2-3) • Dysfibrinogenemia (target INR 2.5, range 2-3)

Table 64.14. **Absolute indications for OAT (primary and secondary stroke prevention).**

anterior MI and LV thrombus, or at high risk for LV thrombus (ejection fraction<40%, anteroapical wall motion abnormality) [165], who undergo BMS placement, while a longer triple therapy (3 to 6 months) is suggested for patients with anterior MI and LV thrombus or at high risk for LV thrombus (ejection fraction<40%, anteroapical wall motion abnormality) who undergo DES placement [165]. Thereafter, discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months as per the ACS recommendations. After 12 months, single antiplatelet therapy is recommended as per the established CAD recommendations [165].

VKA are recommended in rheumatic mitral disease, when the left atrial diameter is>55 mm (Grade 2C) or when complicated by left atrial thrombus (Grade 1A) [206], in candidates for percutaneous mitral valvotomy with left atrial thrombus until thrombus resolution (Grade 1A) [206]. Long-term VKA therapy is We recommended for all mechanical valves (Grade 1B): target INR 2.5 for aortic (Grade 1B) and 3.0 for mitral or double valve (Grade 2C). In patients with mechanical valves at low bleeding risk, addition of low-dose aspirin (50-100 mg/d) can be also used (Grade 1B) [206].

In patients with aortic atheromas identified on echocardiography, the ideal strategy for stroke prevention remains uncertain. Mixed outcomes have been reported for anticoagulation therapy; plaque stabilization with statins appears promising. Neither approach has been tested in randomized, controlled trials [207].

64.3.7 Patent Foramen Ovale (PFO)

The risk of stroke recurrence is estimated to be only 1% to 2% per year among stroke patients with a PFO [208,209]. The PICSS (PFO in Cryptogenic Stroke Study) trial did not show any significantly increased 2-year risk of recurrent stroke or death compared with those without a PFO, neither any significant difference in the 2-year event rates among

those treated with warfarin vs. aspirin [210]. Given the known increased risk of bleeding complications with anticoagulation and the lack of data to demonstrate a benefit in terms of reduction of recurrent ischemic cardiovascular events, the American College of Chest Physicians (ACCP) suggests the use of ASA (50-100 mg/day) over no ASA (ACCP Grade 1A) and the use of VKA (target INR 2.5, range 2-3) if recurrent events occur despite ASA therapy (ACCP Grade 2C) and in the presence of evidence of deep vein thrombosis (target INR 2.5, range 2-3, for 3 months) (ACCP Grade 1B) [15]. OAT is also indicated for patients with a large PFO and co-occurrence with atrial septal aneurysm. The target INR in such cases is 2.5 (range 2-3). The duration of anticoagulation is usually 2 years or longer. As an alternative to anticoagulation, operative or transcatheter occlusion of the PFO may be considered. However, although systematic reviews of observational studies showed that percutaneous and transcather closure of PFO is associated with reduced incidence of recurrent stroke compared to anticoagulant or antiplatelet therapy [211,212]; these results were not confirmed by the CLOSURE I trial where 909 patients aged 18-60 years with cryptogenic stroke or TIA and PFO were randomized to closure device plus antiplatelet therapy (clopidogrel 75 mg daily for 6 months and aspirin 81 mg or 325 mg daily for 2 years) vs. medical therapy alone (warfarin [target INR of 2-3], aspirin 325 mg daily, or both at discretion of principal investigator at each site). The addition of closure of PFO with STARFlex percutaneous transcatheter to antiplatelet therapy did not reduce the risk of recurrent stroke (2.9% vs. 3.1% p=0.79) or TIA (at 2 years in 3.1% vs. 4.1% p=0.44) but increased the risk of developing AF (5.7% vs. 0.7%; p<0.001) [213].

64.3.8 Venous Sinus Thrombosis

Several smaller studies demonstrated that of patients with venous sinus thrombosis, those treated with full-dose heparin had better outcomes than those treated with placebo. A Cochrane systematic review summarized two randomized trials of anticoagulation for patients with symptomatic cerebral sinus thrombosis [214]. This includes patients who present with headache, focal neurologic deficits, seizures, alterations of consciousness, and/or papilledema [215]. The overall quality of evidence is low for venous sinus thrombosis and the suggestion to treat patients with symptomatic cerebral sinus thrombosis with anticoagulation therefore reflects the expert's judgment based on the best available, albeit low-quality, evidence. After improvement under heparin therapy, patients usually are switched to OAT (target INR 2.5, range 2-3). Although the optimal duration has not been determined in randomized studies, OAT is recommended for at least 6 months. It is unclear whether the decision to stop anticoagulation should be based on the result of venography (magnetic resonance or conventional venography) after 6 months. In a recent study of 39 patients placed on anticoagulation, recanalization occurred only within the first 4 months, but not thereafter [216]. The two trials included in the meta-analysis had a relatively high percentage of patients who had some degree of ICH prior to anticoagulation therapy (three of 10 in one trial and 15 of 30 in the second trial) [217]. Despite this, no occurrences of new symptomatic ICH were observed in patients treated with anticoagulation. Anticoagulation is therefore recommended even in the presence of hemorrhage within a venous infarction. However, for patients with venous infarcts and large parenchymal hematomas the risk of hemorrhage extension is likely high. The uncertain benefits of anticoagulation do not outweigh the potential for harm. Either dose-adjusted heparin or LMWH can be used for the initial treatment of patients with cerebral venous sinus thrombosis. Heparin should be continued until the patient has stabilized clinically. For patients who demonstrate progressive neurologic deterioration despite adequate anticoagulation, other options, such as endovascular thrombec-

tomy [218] or local intrathrombus infusion of a thrombolytic agent [217], together with IV heparin, can be considered [219,220]. Patients who have stabilized can be switched from heparin to oral anticoagulation. OAT is generally recommended for a period of 3 to 6 months [221]. Lifelong anticoagulation could be considered in the presence of permanent risk factors for recurrent events [221].

64.3.9 Dissections of Internal Carotid and Vertebral Arteries

The majority (85-95%) of ischemic symptoms after dissection of brain-supplying arteries are caused by emboli from the site of the dissection, while the remainder are due to vessel narrowing with hemodynamic insufficiency. Many experts recommend anticoagulation with IV heparin in the acute phase and subsequent OAT for 3-24 months (target INR 2.5, range 2-3) followed by antiplatelet agents for at least 2 years. To present the results of the nonrandomized arm of the Cervical Artery Dissection in Stroke Study (CADISS-NR) trial [222], comparing anticoagulation and antiplatelets for prevention of recurrent stroke after carotid and vertebral dissection, shows no evidence for superiority of anticoagulation or antiplatelet therapy in prevention of stoke after carotid and vertebral artery dissection. A systematic meta-analysis confirms these results showing that there was nonsignificant difference between the 2 treatments in recurrent stroke risk [222]. The practice of anticoagulation is supported only by several published case series demonstrating good outcome with low complication rates in patients undergoing anticoagulation. However, these studies do not have a control or comparative group to establish efficacy. Only in rare cases (eg, with persistent high-grade proximal stenosis of the internal carotid artery or with severe hemodynamic impairment) should an operation or stenting be considered. No evidence of a higher embolic activity of pseudoaneurysms due to dissection exists; after OAT for 3-6 months, a platelet antiaggregant is sufficient in most cases. Only in selected cases, continuation of anticoagulation or interventional therapy may be preferable, but this practice is not supported by randomized, controlled studies. Anticoagulation is contraindicated in intracranial dissections complicated by subarachnoid hemorrhage.

64.3.10 Thrombophilia and hypercoagulable states

In patients with cerebral ischemia of unknown origin who are younger than 40 years, a search for hereditary thrombophilia is generally recommended [223]. The yield of hypercoagulable testing in patients with stroke is low overall, but somewhat higher in patients with stroke of undetermined cause [224,225]. Data associating stroke with the factor V Leiden and prothrombin G20210A mutations, and protein C, protein S, and antithrombin III deficiencies are limited and conflicting, but on the whole do not demonstrate any clear association. In the case of homocysteine, the association with stroke risk is stronger, but evidence for a stroke preventative effect of homocysteine lowering is inconclusive [226]. OAT after cerebral ischemia is usually recommended for patients with hypercoagulable states such as activated protein C (APC) resistance; protein C, protein S, or antithrombin III (ATIII) deficiencies; or antiphospholipid syndrome (APS) are treated with anticoagulants for stroke prophylaxis, especially if deep vein thrombosis (DVT) is present or recurrent thrombotic events have occurred (Table 64.15) [223,227].
The anticoagulation regimen usually is started with intravenous (IV) heparin, maintaining the aPTT at 2-3 times normal, until an oral anticoagulant (ie, warfarin) is able to achieve a therapeutic PT (INR). As an alternative to oral anticoagulants, patients with thrombophilia may be treated with fixed, low-dose subcutaneous UFH or LMWH. Patients with

ATIII deficiency can receive ATIII concentrates for acute intervention or LMWH. After a single event of thrombosis or thromboembolism, anticoagulation should be continued for at least 6 months. After recurrent or life-threatening thrombosis or in the case of a combination of different thrombophilias, lifelong anticoagulation is usually recommended. Starting heparin before warfarin is imperative to avoid warfarin-induced skin necrosis in protein C and S deficiencies. The level of anticoagulation in terms of PT (INR) required for stroke prophylaxis is uncertain.

Several studies have addressed secondary prevention of stroke in patients with antiphospholipid antibodies (APLA). This group includes patients with medium or high-titer APLA or the presence of lupus anticoagulants. The Antiphospholipid Antibodies and Stroke Study (APASS) found no difference in recurrent thrombotic events between those with and without Antiphospholipid Antibodies (APLA), and no benefit to warfarin compared with aspirin in patients with APLA [228]. However, in the APASS study, APLA were measured only one time (and were present in 41% of the 1770 patients enrolled) and the population enrolled was older (mean age 62) with a high prevalence of typical vascular risk factors. Extrapolation from this data to younger patients meeting diagnostic criteria for APLA syndrome is probably unwise. Based on the APASS data, patients with first ischemic stroke and a single positive APLA test result who do not have another indication for anticoagulation may be treated with aspirin (325 mg/day) or warfarin (INR 1.4-2.8). Aspirin is likely to be preferred because of its ease of use and lack of need for laboratory monitoring. Patients with ischemic stroke due to cerebral arterial thrombosis and a positive APLA test who have a history of venous thrombosis but were not receiving anticoagulant drugs when suffering the stroke should be treated with moderate-intensity warfarin (target INR 2.5, range 2-3). In the treatment of APS, high-intensity warfarin (target INR 3.5, range 3-4) was not superior to moderate-intensity warfarin (target INR 2.5, range 2-3) in preventing recurrent thrombosis and was associated with an increased rate of minor hemorrhagic complications [228,229].

In stroke patients with cancer, marantic endocarditis is found in up to 20%, and an additional 10% have other definite embolic sources consistent with a hypercoagulable state on transesophageal echocardiography (TEE) [230]. LMWH is the preferred treatment strategy for patients with venous thrombosis associated with cancer, and this may also be applicable to patients with cancer-associated stroke, particularly if mediated by marantic endocarditis [231].

64.3.11 Recurrent Thrombosis

Patients with recurrent thrombotic events despite warfarin pose a challenge for clinicians. The INR at the time of recurrence is important. An INR below the target therapeutic range represents inadequate anticoagulation as opposed to warfarin failure. These patients may be treated in the same manner as a patient presenting with new thrombosis without warfarin. Possible treatment options for recurrent thrombosis despite an INR in the target range include increasing the intensity of warfarin anticoagulation to achieve a higher target INR (target INR, 2.5-3.5 or 3.0-4.0), switching from warfarin to therapeutic doses of UFH or LMWH, or adding an antiplatelet agent to warfarin [232].

64.3.12 Summary and Recommendations

OAT is clearly superior to single or double antiplatelet therapy in patients with cardioembolic stroke, mainly caused by AF. National Guidelines and Consensus Statements regarding thromboembolic prophylaxis in AF are given in (Table 64.15).

American College of Chest Physicians (ACCP) guidelines (Ninth Edition) on antithrombotic therapy in atrial fibrillation [130,206]	• For secondary stroke prevention after cardioembolic stroke or transient ischemic attack (TIA) (that is, in patients with atrial fibrillation, including paroxysmal atrial fibrillation): ▪ OAT recommended over: no antithrombotic therapy (ACCP Grade 1A), ASA (ACCP Grade 1B), combination therapy with ASA plus clopidogrel (ACCP Grade 1B) ▪ OAT with dabigatran 150 mg twice daily suggested over adjusted-dose vitamin K antagonist therapy (target range 2-3) (ACCP Grade 2B); dabigatran contraindicated if creatinine clearance ≤ 30 ml/minute ▪ Ffor patients unsuitable for or who choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), combination therapy with ASA plus clopidogrel recommended over ASA (ACCP Grade 1B) ▪ OAT should generally be started within 1-2 weeks after stroke onset, but timing may vary with risk for bleeding • Use of ASA as bridging therapy suggested until anticoagulation reaches therapeutic level
American College of Cardiology/ American Heart Association (ACC/ AHA) guidelines [13]	• American Heart Association/American Stroke Association (AHA/ASA) guidelines for secondary prevention of stroke in patients with paroxysmal or permanent atrial fibrillation ▪ use vitamin K antagonist for anticoagulation (AHA/ASA Class I, Level A) ▪ use ASA if patient unable to take OAT medications (AHA/ASA Class I, Level A) ▪ clopidogrel with ASA not recommended for patients with hemorrhagic contraindication to warfarin (AHA/ASA Class III, Level B) • Use bridging therapy with subcutaneous low-molecular-weight heparin if temporary interruption of OAT in patient at high risk (such as TIA within 3 months, mechanical valve disease) (AHA/ASA class IIa, level C)
Canadian Cardiovascular Society (CCS) guideline:	• For patients with recent TIA or minor ischemic stroke, ASA is safe and probably effective for secondary prevention of cerebral ischemia in patients with nonrheumatic atrial fibrillation (level 2 [mid-level] evidence) [233] • antiplatelet therapy appears effective for preventing stroke in patients with nonvalvular atrial fibrillation (level 2 [mid-level] evidence) [234]
Comparative efficacy vs. anticoagulation	For patients with atrial fibrillation and recent transient ischemic attack (TIA) or minor ischemic stroke, anticoagulation appears superior to antiplatelet therapy for secondary prevention of stroke (level 2 [mid-level] evidence) [235]
Anticoagulant plus antiplatelet	Combination of antiplatelet and low-intensity anticoagulant therapy may further reduce risk of vascular death (level 2 [mid-level] evidence) [140]

Table 64.15. **National Guidelines and Consensus Statements regarding thromboembolic prophylaxis in atrial fibrillation.**

Dose-adjusted warfarin has been the mainstay of therapy. Warfarin has also been shown to be more effective than ASA or the combination of ASA plus clopidogrel for secondary prevention of stroke in patients with AF. Warfarin therapy aimed at a target INR of 2.5 (range 2.0-3.0) is recommended for stroke prevention in patients with paroxysmal or permanent AF. ASA alone is recommended in patients with AF who are unable to take oral anticoagulants.

Bridging anticoagulation with LMWH is recommended for patients at the highest risk for stroke (defined as having a stroke or TIA within 3 months, a CHADS2 score of at least 5, a mechanical cardiac valve, and rheumatic valve disease) in circumstances in which OAT must be temporarily interrupted.

Patients with TIA or ischemic stroke and acute MI complicated by left ventricular mural thrombus should be anticoagulated to a target INR of 2.5 for a minimum of 3 months. However, warfarin has no demonstrated benefit for secondary stroke prevention in the presence of systolic cardiac dysfunction alone.

Long-term warfarin therapy with a target INR of 2.5 is reasonable for secondary stroke prevention in patients with rheumatic mitral valve disease. Antiplatelet agents should not be combined with warfarin due to additional bleeding risk.
Antiplatelet agents are reasonable for secondary stroke prevention in patients with non-rheumatic native valve disease, mitral annular calcification, and mitral valve prolapse in the absence of AF. Warfarin with a target INR of 3.0 is recommended for prevention of stroke in patients with mechanical heart valves. The addition of ASA at 75-100 mg/day is reasonable in those who have had TIA or stroke despite adequate OAT and in whom the bleeding risk is not excessive. New oral anticoagulants seem promising a new era in antithrombotic prophylaxis of patients with AF. Up to now, all the published phase III trials have demonstrated at least the non-inferiority of direct thrombin inhibitor dabigatran and direct FXa inhibitors rivaroxaban and apixaban when compared with warfarin. For many endpoints, such as intracranial bleedings, new oral anticoagulants result superior to warfarin. New oral anticoagulants could become an effective and safe choice in this context.

64.4 Appendix

64.4.1 CHADS2 and CHA2DS2-VASC Scores

Risk factor	Points
C – Congestive heart failure	1
H – Hypertension	1
A – Age>75 years	1
D – Diabetes	1
S2 – Prior Stroke/TIA	2
Results: annual rate of stroke and systemic embolism	
Points	**Rate**
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%

Table 64.16. CHADS2 score.

Risk factor	Points
C – Congestive heart failure	1
H – Hypertension	1
A2 – Age>75 years	2
D – Diabetes	1
S2 – Prior Stroke/TIA	2
V – Vascular diseases	1
A – Age 65-74	1
SC – Sex Category (females)	1
Results: annual rate of stroke and systemic embolism	
Points	**Rate**
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Table 64.17. CHA2DS2-VASC score.

64.4.2 HAS-BLED and ATRIA Scores

	Risk factor	Points
H	Hypertension	1
A	Abnormal renal and liver function	1 o 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age>65 years)	1
D	Drugs and alchool	1 or 2
Results		
Score ≥ 3 indicates bleeding risk > 3.5% at 12 months		

Table 64.18. HAS-BLED score.

Risk factor	Points
Anemia	3
Severe renal failure	3
Age>75 years	2
Previous bleeding	1
Hypertension	1
Results	

Risk classification		Annual bleedings rate
0-3	Low	0.8%
4	Moderate	2.6%
5-10	High	5.8%

Table 64.19. ATRIA score.

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65 The Consciousness Disorders, Definitions and Clinical Assessment

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65.1 Alterated States of Consciousness

An accurate and reliable evaluation of the level and content of consciousness in severely brain-damaged patients is of paramount importance for their appropriate management. Progress in medicine has increased the number of patients who survive severe acute brain damage. Although the majority of these patients recover from coma within the first days after the insult, some permanently lose all brainstem functions (brain death), while others evolve to a state of "wakeful unawareness" (vegetative state; VS). Those who recover, typically progress through different stages before fully or partially recovering consciousness (minimally conscious state; MCS) (Figure 65.1).

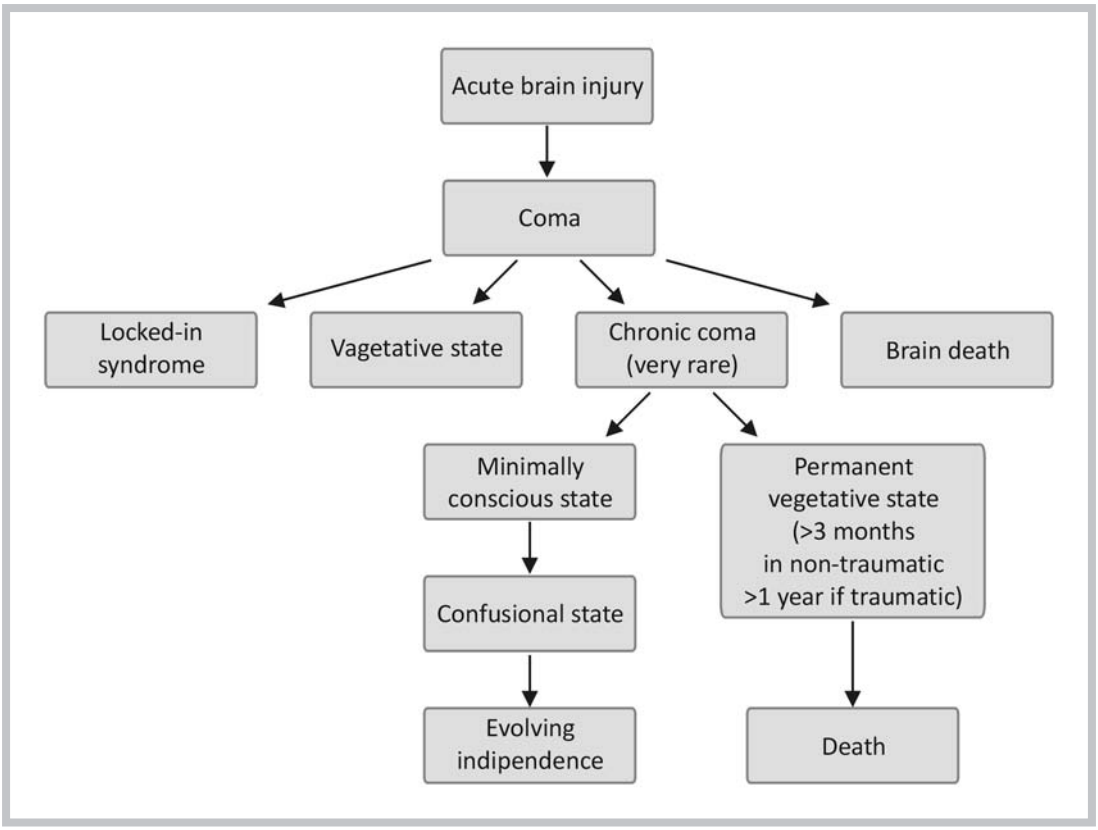

Figure 65.1. **Flow chart of the different conditions that follow a cerebral insult. Classically vegetative state follows a coma; after 1 month the term "persistent vegetative state" is used; after 3 months (non-traumatic insult) or 1 year (traumatic insult) some authors use the term "permanent vegetative state" which implies no chance of recovery. Adapted from [Laureys et al.,** *Lancet Neurology* **2005].**

Clinical practice shows that recognizing unambiguous signs of conscious perception of the environment and of the self in such patients with disorders of consciousness can be very challenging. This difficulty is reflected in the frequent misdiagnoses of VS, MCS and locked-in syndrome (LIS) [1-7]. Bedside evaluation of residual brain function in severely brain-damaged patients is difficult because motor responses may be very limited or inconsistent. In addition, consciousness is not an all-or-none phenomenon [8] and its clinical assessment relies on inferences made from observed responses to external stimuli at the time of the examination [7].

After briefly defining consciousness as it can be assessed at the patient's bedside and reviewing the major clinical entities of altered states of consciousness following severe brain damage, we will here review evaluation scales available for the assessment of patients suffering from disorder of consciousness.

65.1.1 Consciousness, Awareness and Arousal

Consciousness is a multifaceted concept that has two major components: awareness of environment and of self (i.e., content of consciousness) and wakefulness (i.e., level of consciousness). One needs to be awake in order to be aware (REM-sleep being a notorious exception). Figure 65.2 shows that in normal physiological states (green); level and content are positively correlated (with the exception of the oneiric activity during REM-sleep). Patients in pathological or pharmacological coma (that is, general anesthesia) are unconscious because they cannot be awakened (red). The vegetative state (blue) is a unique persistent dissociated state of consciousness (i.e., patients being seemingly awake but lacking any behavioral evidence of "voluntary" or "willed" behavior).

Arousal is supported by several brainstem neuronal populations that directly project to both thalamic and cortical neurons [9]. Therefore depression of either brainstem or both cerebral hemispheres may cause reduced wakefulness. Brainstem reflexes are a key to the assessment of the functional integrity of the brainstem (Figure 65.3). However, profound impairment of brainstem reflexes can sometimes coexist with intact function of the reticular activating system if the tegmentum of the rostral pons and mesen-

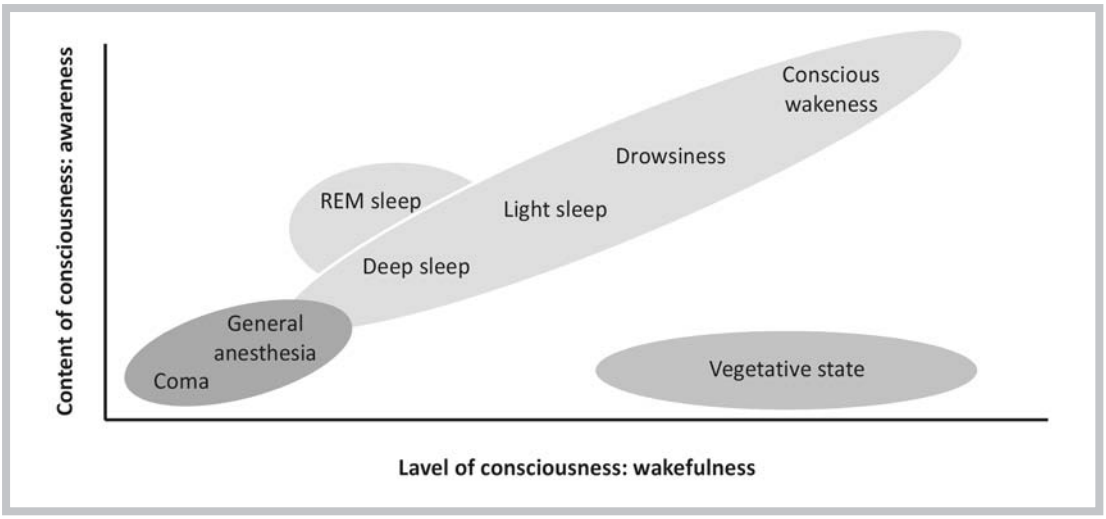

Figure 65.2. **Oversimplified illustration of consciousness' two major components: the level of consciousness (i.e., wakefulness or arousal) and the content of consciousness (i.e., awareness or experience). Adapted from [Laureys,** *Trends in Cognitive Sciences* **2005].**

cephalon are preserved. Awareness is thought to be dependent upon the functional integrity of the cerebral cortex and its reciprocal subcortical connections; each of its many aspects resides to some extent in anatomically defined regions of the brain [10-12]. Unfortunately, for the time being, consciousness cannot be measured objectively by any machine. Its estimation requires the interpretation of several clinical signs. Many scoring systems have been developed for a standardized assessment of consciousness in severely brain damaged patients (For review see [13]).

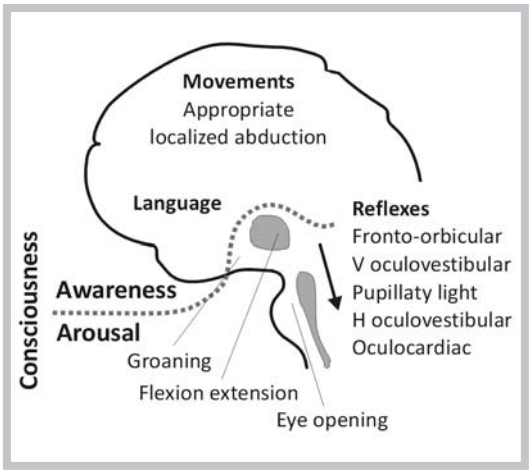

Figure 65.3. **A simplified scheme of consciousness and its two major components: arousal and awareness. Note: the gray area represents the reticular activating system encompassing the brainstem and thalamus; the arrow near the brainstem denotes the progressive disappearance of brainstem reflexes during rostral-caudal deterioration (i.e., evolution from coma to brain death). Adapted from [13].**

H = horizontal

V = vertical

65.1.2 Clinical Definitions

Survivors of severe traumatic or hypoxic-ischemic brain damage classically go through different clinical entities before partially or fully recovering consciousness. Coma is defined as "unarousable unresponsiveness". Irreversible coma may in some conditions equal brain death. After some days to weeks, comatose patients who recover will eventually open their eyes. When this return of "wakefulness" is accompanied by reflexive motor activity only, devoid of any voluntary interaction with the environment, the condition is called a vegetative state. The vegetative state may be a transition to further recovery, or not. Signs of voluntary motor activity should be actively searched for in vegetative state patients, as they herald the minimally conscious state (MCS). Functional communication indicates the next boundary – emergence from MCS – in the course of recovery. We will here briefly define brain death, coma, VS, MCS and LIS.

Brain Death

The concept of brain death as defining the death of the individual is largely accepted [14]. Most countries have published recommendations for the diagnosis of brain death but the diagnostic criteria differ from country to country [15]. Some rely on the death of the brainstem only [16] others require death of the whole brain including the brain stem [17]. However, the clinical assessments for brain death are very uniform and based on the loss of all brainstem reflexes and the demonstration of continuing cessation of respiration in a persistently comatose patient [procedures of a standardized apnea test can be found in 18]. There should be an evident cause of coma and confounding factors (including hypothermia, drugs, electrolyte, and endocrine disturbances) should be excluded. A repeat evaluation in 6h is advised, but the time period is considered arbitrary [19]. Confirmatory neurophysiological tests such as EEG, ERP, angiography, Doppler sonography, or scintigraphy or are only required when specific components of the clinical testing cannot be reliably evaluated and are recommended by a number of national professional societies to confirm the clinical diagnosis of brain death [20].

Coma

Coma is characterized by the absence of arousal and thus also of consciousness. It is a state of unarousable unresponsiveness in which the patient lies with the eyes closed and has no awareness of self and surroundings. The patient lacks the spontaneous periods of wakefulness and **eye-opening induced by stimulation** that can be observed in the VS [21]. To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least one hour. In general, comatose patients who survive begin to awaken and recover gradually within 2 to 4 weeks. This recovery may go no further than VS or MCS, or these may be stages (brief or prolonged) on the way to more complete recovery of consciousness.

Vegetative state

Patients in a VS are awake but are unaware of self or of the environment [22, 23]. Jennett and Plum cited the Oxford English Dictionary to clarify their choice of the term "vegetative": to vegetate is to "live merely a physical life devoid of intellectual activity or social intercourse" and vegetative describes "an organic body capable of growth and development but devoid of sensation and thought". "**Persistent VS**" has been arbitrarily defined as a vegetative state still present one month after acute traumatic or non-traumatic brain damage but does not imply irreversibility [24]. "**Permanent VS**" denotes irreversibility. The Multi-Society Task Force on PVS concluded that three months following a non-traumatic brain damage and 12 months after traumatic injury, the condition of VS patients may be regarded as 'permanent' and therefore irreversible. However, these guidelines are best applied to patients who have suffered diffuse traumatic brain injuries and post anoxic events; other non-traumatic etiologies may be less well predicted (see for example [25,26]) and require further considerations of etiology and mechanism in evaluating prognosis. Even after these long and arbitrary delays, some exceptional patients may show some limited recovery. This is more likely in patients with non-traumatic coma without cardiac arrest, who survive in VS for more than 3 months. The diagnosis of VS should be questioned when there is any degree of sustained visual pursuit, consistent and reproducible visual fixation, or response to threatening gestures [24] but these responses are observed in some patients who remain in VS for years. It is essential to establish repetitively the formal absence of any sign of conscious perception or deliberate action before making the diagnosis.

It is very important to stress the difference between persistent and permanent vegetative state which are, unfortunately, too often abbreviated identically as PVS, causing unnecessary confusion [27]. When the term "persistent vegetative state" was first described [22], it was emphasized that persistent didn't mean permanent and it is now recommended to **omit "persistent"** and to describe a patient as having been vegetative for a certain time. When there is no recovery after a specified period (depending on etiology three to twelve months) the state can be declared permanent and only then do the ethical and legal issues around withdrawal of treatment arise [28,29]. The vegetative state can also be observed in the end-stages of some chronic neurodegenerative diseases, such as Alzheimer's, and in anencephalic infants.

65.2 Clinical Evaluation of the Neurocritical Care Patient: The Coma Scales

The adequate evaluation of consciousness in patients suffering from severe brain damage is of a major importance for their optimal management over from the emergency

department throughout their acute hospital stay and their rehabilitation. On this evaluation will indeed depend, not only the therapeutic surgical or medical decisions, but also often cares limitation. Before the development and the diffusion of the scales of coma and in particular of the scale of Glasgow [30], the evaluation of the patient presenting with altered consciousness was based on a rather vague nomenclature. The description of the depth of coma was made by means of terms often vague such as: drowsy, **comatose**, somnolent, obtunded, obnubilated, obstreperous or combative.

During the World War II and later, during the Korean and Vietnam campaigns, it appeared important to physician to set up methods making it possible to evaluate patients after a traumatic brain injury so as to facilitate the transmission of information on the clinical state of wounded between the doctors of ground and the doctors ensuring the continuation of the treatment [31]. From these efforts were born the first classifications for altered consciousnesses states [32]. The neurosurgical literature on head injuries sustained in the Vietnam conflict classified their initial state in three grades, variously defined [33,34]. These classification suffered from their lack of precision and from the hence ambiguity of the terms employed. This type of classification should be abandoned for the assessment of altered consciousnesses.

65.2.1 The Glasgow Coma Scale

The publication of the Glasgow coma scale (GCS) in 1974 by Teasdale and Jennet [30] brought a major change in the clinical assessment of patients presenting with post-traumatic altered consciousness. These authors took special care to the construction of their scale to overcome the ambiguities that arose when information about comatose patients was presented and groups of patients compared. Among the objectives of its originators, there was the desire to establish an evaluation tool based on simple, clear, unambiguous items that could be easily translated in various languages. Moreover, the scale had to be utilizable in a reliable way not only by any doctor but also by nurses and paramedics. Considering that the deterioration of consciousness varies according to a continuum and thus does not lend to a categorization, these authors preferred to create an instrument based on the distinct clinical evaluation from three aspects of the behavioral response to the stimulation of the patient with altered consciousness (Figure 65.4): eye opening (E, 4 levels), verbal activity (V, 5 levels) and motor response (M, 5 then 6 levels [35]).

Eye Opening

Eye opening in response to pain should be tested by stimulation at the level of the limbs, because the grimacing associated with supra-orbital or jaw-angle pressure may cause eye closure. The eye opening either spontaneously or on stimulation defines the transition from coma to vegetative state.

Verbal Activity

The presence of verbal responses indicates the restoration of a high degree of interaction with the environment (i.e., awareness). An oriented conversation implies awareness of the self and environment. Confused speech is recorded when the patient is capable of producing language, for instance phrases and sentences, but is unable to answer the questions about orientation. When the patient presents intelligible articulation but exclaims only isolated words in a random way (often swear words, obtained by physical stimulation rather than by a verbal approach), this is scored as ‘‘inappropriate speech’’. Incomprehensible sounds refer to moaning and groaning without any recognizable words. This rudimentary vocalization does not necessitate awareness and is

thought to depend upon sub cortical functioning as it can be observed in anencephalic children and vegetative patients.

Motor Response

The motor response first assesses whether the patient obeys simple commands, given in verbal, gestural or written form. A non-specific sound stimulus may induce a reflex

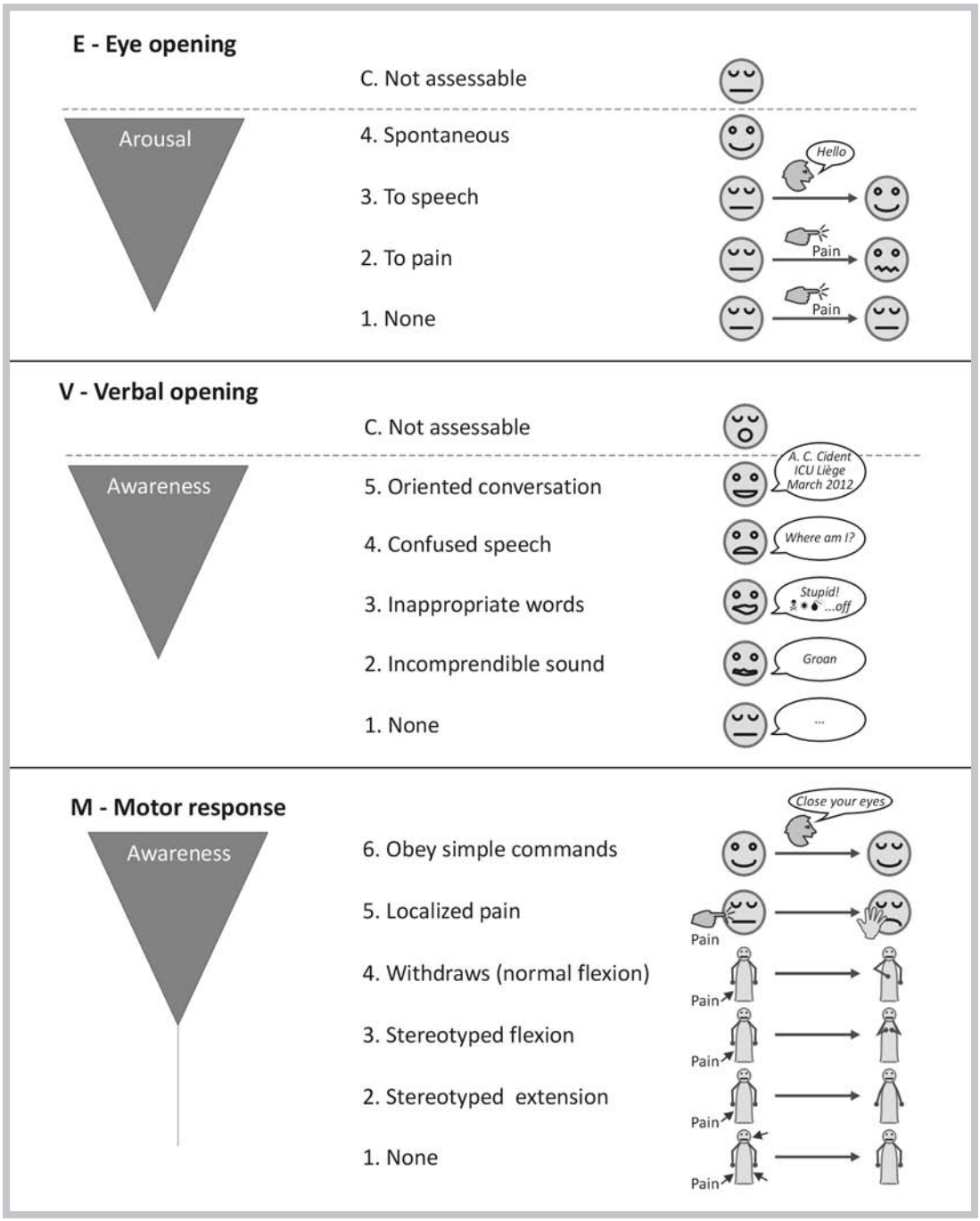

Figure 65.4. **Pictographic representation of the Glasgow coma scale. Adapted from [13].**

contraction of the patient's fingers or alternatively such a reflex response can result from the physical presence of the examiner's fingers against the palm of the patient (i.e., grasping reflex). Before accepting that the patient is truly obeying commands, it is advised to test that the patient will also release and squeeze again to repeated commands. If there is no response on command a painful stimulus is applied. First, pressure is applied to the fingernail bed. If flexion is observed, stimulation is then applied to other sites (applying pressure to the supra-orbital ridge, pinching the trapezium or rubbing the sternum) to differentiate between localization (i.e., attempt to remove a noxious stimulus by crossing the midline), withdrawal flexion (i.e., flexion of the elbow associated with abduction of the shoulder) or stereotyped flexion (i.e., stereotyped flexion of the elbow with adduction of the shoulder that can be achieved when stimulated at other sites). Extensor posturing is more easily distinguished and is usually associated with adduction, internal rotation of the shoulder and pronation of the forearm. Abnormal flexion and extension motor responses often coexist [36].

In a paper published the year following the original publication, numbers were ascribed to each level of response so that the responsiveness could be easily expressed, for example as E4, V3, M5, making communication more easy [37]. The use of these scores allowed, by summation the three component of the scale, to obtain a single total score [35]. This led to a score that ranged from 3 for deepest coma to 15 points for fully alert and oriented. The total score allows assessing the link between the gravity of altered consciousnesses and patients' outcome. However, in spite of its interest, the use of the total score induces a loss of information during the individual evaluation [38,39]. Moreover, the sum of the components causes a mathematical problem since weighting is in favor of motor response (6 points) as compared to eye opening (4 points) and verbal activity (5 points). The total score is consequently more influenced by the motor response than by the other two components [40]. It therefore appears essential, on the clinical level, to communicate the Glasgow coma scale by giving its three components (E, V, M) rather than their sum alone [41]. Although the Glasgows coma scale was initially built for post-traumatic brain injury evaluation, it was later also validated for the assessment of patients suffering from nontraumatic consciousness disorders [42,43].

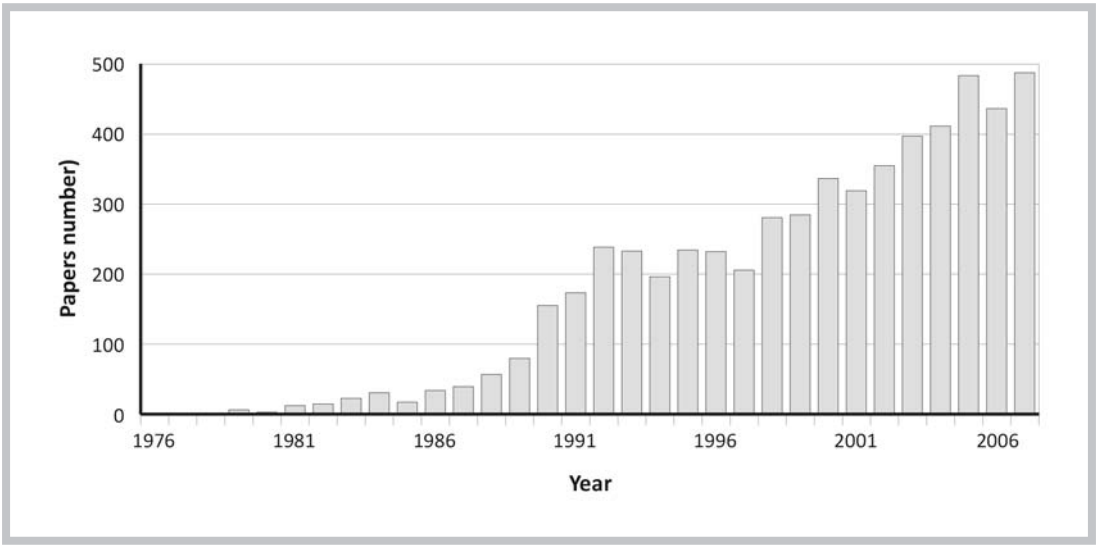

Figure 65.5. **Number of publication making reference to the Glasgow coma scale (Medline research from July 1974 to June 2008).**

The Glasgow coma scale was also studied in General Intensive Care [44] and, in addition, it is integrated in several general scores of gravity such as APACHE II [45], SAPS II [46] and SAPS 3 [47] where it has an important weight in the hospital risk of death prediction. The Glasgow coma scale remains to date the most internationally used coma scale with, since its publication, more than 5900 citations (Medline research from July 1974 to June 2008) (Figure 65.5). Apart from the Apgar score [48] with nearly 6500 quotations over the same period of time, there is probably no patients other severity of illness score which is quoted as much in the literature nor which has such an extended clinical application.

In spite of its undeniable qualities, the scale of Glasgow suffers from a certain number of imperfections. Its use causes problem in mechanically ventilated patients which a very common situation for patients with severe consciousness disorders. Indeed, in this circumstance, it is not possible to evaluate the verbal component of the scale and consequently the provided information is somewhat truncated in a substantial proportion of patients. Murray et al. indeed showed, in a study including 1000 head injured patients, that 40% of these patients could not be assessed by the Glasgow coma scale on the prior their hospital admission; this rate of unevaluable patients raised up to 50% when patients were assessed in the intensive care [49]. Another shortcoming of the Glasgow coma scale is that eye opening is insufficient to properly assess activity in the brainstem arousal system. This limitation induces a considerable loss of information for the prognosis assessment of brain injured patients. The **Glasgow-Liege scale** (Figure 65.6) is an adaptation of the scale of Glasgow; it combines the Glasgow coma scale with five brainstem reflexes [50]. This allows an approach of the brain as a whole and consequently

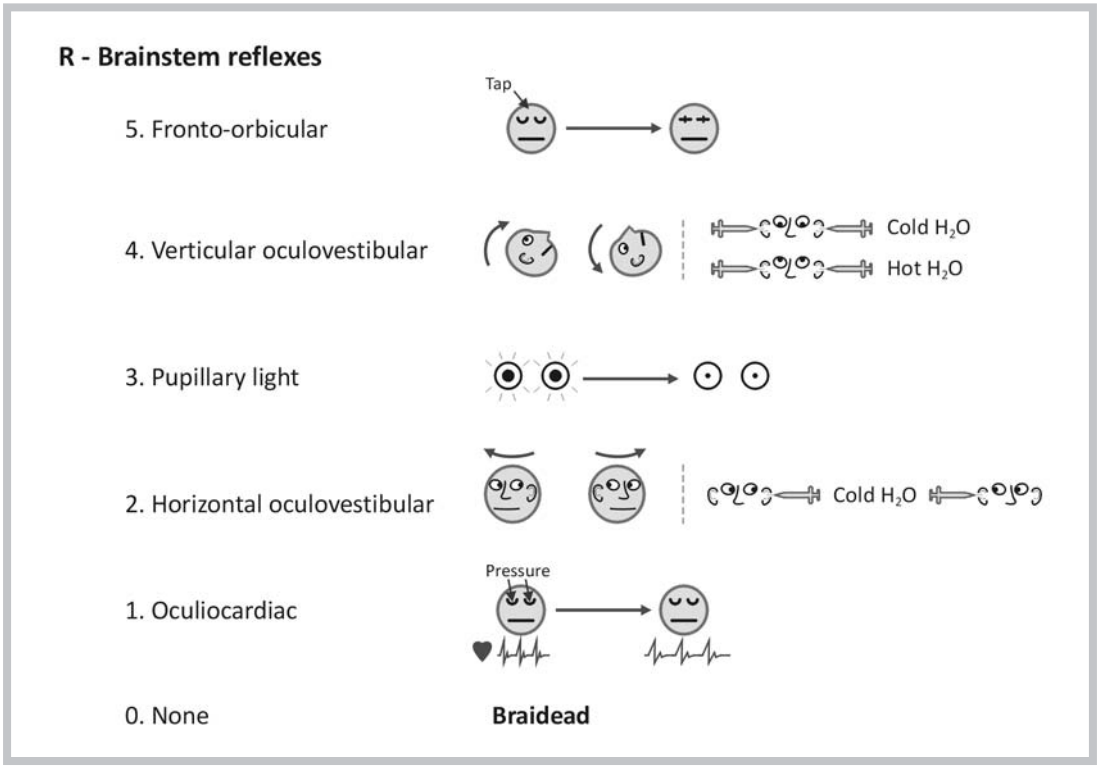

Figure 65.6. **Pictographic representation of the Glasgow-Liège scale (Born et al. 1982). Note: when oculocephalic reflexes (doll's eyes) cannot be tested or are absent, the (vertical and horizontal) oculovestibular reflexes (ice water testing) should be evaluated. Adapted from [13].**

provides more elements to evoke the diagnosis of brain death. Finally the Glasgow coma scale lacks reliability when assessing patients progressively recovering from their coma and entering a vegetative or minimally conscious state [51]. It also fails to detect more subtle the state of consciousness such as Locked-in Syndrome (LIS). For these patients, more sensitive scales are the coma recovery scale-revised, sensory modality assessment and rehabilitation technique, or Wessex head injury matrix [52-54]. These scales, however, are not adapted for use in acute settings.

65.2.2 Other Scales for Acute Consciousness Disorders Assessment

Since the publication of the Glasgow coma scale, several other scales have been proposed. In 1981, Salcman et al. published the **Scale of coma of Maryland** [55], as compared to the Glasgow coma scale this scale had the advantage to include indicators for the brainstem assessment; it however never convinced the medical community. The **Edinburgh-2 coma scale** [56] proposed by Sugiura et al. (1983) is a one-dimensional scale (Table 65.1) varying from zero to nine in a way inversely proportional to deterioration of the state conscience. This scale is simpler than the scale of Glasgow yet it never took a real rise.

Among the imperfections of this scale, one could mention the fact that it cannot be validly applied to individuals that are unable to give a verbal answer – such as intubated patients – and the fact that, in this single dimension scale is based on various neurological characteristics take place. The **Clinical Neurologic Assessment** scale (CNA), published in 1989 by Crosby et al. [57], is a 21 items instrument evaluating not only the verbal answer and the capacity to answer simple orders but also neurological aspects such as the muscular tone, the position of the body, movements, chewing or yawn. Although it offers subtle assessment possibilities than the Glasgow coma scale, this tool remained unexploited. In 1991, Benzer et al. published the **Innsbruck coma scale** [58]. In its principle, this scale is rather similar to the Glasgow coma scale; with various components scored separately then aggregated into a total score varying from 0 to 23 points. The Innsbruck coma scale however differs from the Glasgow coma scale by its number of components – eight instead of three – and by their nature: if eye opening and motor response are similar components, there is not in this scale an assessment of verbal activity but instead items assessing reaction to acoustic stimuli, body posture, pupils size and response to light, position and movement of the eyeballs and oral automatisms. Although this scale has potential advantages as compared to the Glasgow coma scale, it is cited in very few

Stimulation (maximal)	Response (best)	Score
Two sets of questions :	Answers correctly to both	0
1. Month?	Answers correctly to either	1
2. Age?	Incorrect for both	2
Two sets of commands:	Obeys correctly to both	3
1. Close and open hands	Obeys correctly to either	4
2. Close and open eyes	Neither correct	5
Strong pain	Localizing	6
	Flexion	7
	Extension	8
	None	9

Table 65.1. Edinburgh-2 coma scale [56].

Clinical descriptor	Responsiveness	Score
Alert	No delay in response, responsive without simulation	1
Drowsy or confused	Responsive to light stimulation	2
Very drowsy or confused	Responsive to strong stimulation	3
Unconscious	Localizes but does not ward of pain	4
Unconscious	Withdrawing movements on pain stimulation	5
Unconscious	Stereotyped flexion movements on pain stimulation	6
Unconscious	Stereotyped extension movements on pain stimulation	7
Unconscious	No response on pain stimulation	8

Table 65.2. The Reaction Level Scale (RLS85).

publications and its clinical use is limited. A Swedish scale, the **Reaction Level Scale** (RLS85), was proposed by Starmark et al. [59]. This tool is a simple ordinal scale varying from 1 to 8 combining verbal and motor responses (Table 65.2). This scale correlates with the scale of Glasgow, moreover it has a better inter-observers agreement than the latter [60]. However the use of this instrument remains primarily limited to Sweden.

65.2.3 The Full Outline off UnResponsiveness Score (FOUR score)

The **Full Outline off UnResponsiveness score** (FOUR) published by Wijdicks et al. in 2005 [61] is certainly a very interesting alternative on a Glasgow scale represents. This acronym reflects the number of components tested (eye response, motor response, brainstem reflexes and respiratory function) and the maximum score assigned to each of these (E4, M4, B4 and R4) (Table 65.3). The sum of the points attributed to each component can thus vary from 0 to 16. With all FOUR categories graded zero, the scale alerts to consider brain death or standard apnoea (oxygen-diffusion) testing. The main characteristic of the FOUR score are described below.

Eye Response

The FOUR score specifically evaluates ocular movements or the eye blinking on command, this implies to open the eyes manually if the patient does not open them spontaneously. This assessment facilitates the early diagnosis of locked-in syndrome which represents a considerable improvement since recent studies show that, at the initial phase, the clinicians miss this diagnosis in up to 50% of the cases [62].The FOUR score also evaluates eye tracking which is known as being this is the first sign heralding the transition from a vegetative to a minimally conscious state [63]. This distinction is not only a matter of semantics since patients in minimal state of consciousness have a more favorable outcome than patients in vegetative state [51]. The others items of the FOUR's eye score are similar to those of the scale of Glasgow.

Motor Response

With regard to the motor response, the most innovative item of the FOUR score is the hand position test, in which patients are asked to make thumbs-up, fist, or peace signs. This is a smart alternative to the V-score of the Glasgow coma scale and remains testable in intubated patients. The rest of the M-score is taken from the Glasgow coma scale, with the exception that no difference is made between abnormal stereotyped flexion and normal flexion to pain (similar to the early version of the Glasgow coma scale [30]). This difference may be difficult for inexperienced observers to appreciate but might lead

to lower prognostic power of the FOUR scale. Generalized myoclonic status epilepticus, which is a sign of poor prognosis in anoxic coma, is scored the same as absent motor response to pain.

Brainstem Reflexes

Amending the Glasgow coma scale's lack of brainstem-reflexes assessment, FOUR tests pupil, cornea, and cough reflexes and separately scores respiration. For untrained users, evaluation of the brainstem component is probably the most complex because it proposes different combinations of the presence or absence of each of its three reflexes. Unilateral fixed midriasis, alerting uncal herniation, has a separate score. To avoid corneal trauma by repeated testing, it is cleverly proposed to instil some drops of saline on the cornea.

Respiration

The last category of FOUR scores respiration as spontaneous regular, irregular, Cheyne-Stokes, ventilator-assessed patient-generated breaths, or absent. Whether pulmonary disease and respiratory settings will bias the assessment and how reliably inexperienced users can separate Cheyne-Stokes from irregular respiration are unknown.

In the past 30 years, many coma scales have been proposed as an alternative to the Glasgow coma scale, but none with success. The FOUR score has not been widely validated yet. To date only one study validated the score and assessed the inter-rater agreement [64]. The validity of this new scale needs to be corroborated when used in a general ICU setting by examiners other than neuroscience professionals. By virtue of its simplicity, and despite its drawbacks, the Glasgow coma scale became the most universally used and validated consciousness scale worldwide. Albeit convinced of the valuable improvement of the FOUR score, the Glasgow coma scale will not be dethroned effortlessly.

E	Eye response
4	Eye tracking (at least 3 times), or eyelids blinking to command (at least 2 of 3). Open eyes and assess tracking (horizontally and vertically) if necessary
3	Eyelids open but not tracking
2	Eyelids closed but open to loud voice
1	Eyelids closed but open to pain*
0	Eyelids remain closed with pain*
M	**Motor response**
4	Thumbs-up, fist, or peace sign (at least one of these)
3	Localizing to pain*
2	Flexion response (normal or stereotyped) to pain*
1	Extension response to pain*
0	No response to pain or generalized myoclonus status
B	**Brainstem reflexes**
4	Pupil and corneal reflexes present°
3	One pupil wide and fixed
2	Pupil OR corneal reflexes absent
1	Pupil AND corneal reflexes absent
0	Absent pupil AND corneal, AND cough reflex**
R	**Respiration**
4	Not intubated, regular breathing pattern
3	Not intubated, Cheyne-Stokes breathing pattern
2	Not intubated, irregular breathing
1	Breathes above ventilator rate^
0	Breathes at ventilator rate OR apnea§

Table 65.3. **The Full Outline UnResponsiveness (FOUR) score Adapted from [Wijdicks, 2005]. Instructions for the assessment of the individual categories of the FOUR score: Grade the best possible response.**

* Temporo-mandibular joint or supra-orbital nerve nociceptive stimulation

° Corneal reflexes are tested by instilling two to three drops sterile saline on the cornea from a distance of 10-15 cm (this minimizes corneal trauma from repeated examinations)

** The cough reflex to tracheal suctioning is tested only when both pupil and corneal reflexes are absent

^ No adjustments are made to the ventilator while the patient is graded, but grading is done preferably with $PaCO_2$ within normal limits

§ A standard apnea (oxygen-diffusion) test may be needed when patient breathes at ventilator rate (R0)

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66 Glycemic Control During Acute Cerebral Injury

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66.1 Introduction

The French physiologist Claude Bernard was the first to describe an association between high blood glucose levels and brain damage in 1849 [1]. Since then, hyperglycemia has been frequently recognized and associated with increased morbidity and mortality in neuroinjury scenarios including ischemic stroke [2-10], subarachnoid hemorrhage [11,12], severe traumatic brain injury [13-17], and spontaneous intracerebral hemorrhage [18-21], with or without diabetes mellitus.

There are multiple mechanisms involved in the exacerbation and/or production of hyperglycemia-induced brain injury, however, there is no consensus on whether hyperglycemia *per se* is a causal mechanism or merely an epiphenomenon accompanying cerebral damage [2,5,8,10]. Moreover, experimental animal studies have shown that besides reducing serum glucose concentrations, insulin has other beneficial pleiotropic neuroprotective effects [10]. In this context, recent studies have shown very positive results obtained with intensive insulin therapy (IIT), particularly in critically ill surgical patients [22,23]. The reason for the improved outcomes remains unknown, although the therapy's effectiveness could be largely due to the reduction of sepsis and multiorgan dysfunction by preventing mitochondrial and cell overloading and glucose toxicity [22-24].

The brain uses glucose in an insulin-independent way, ensuring an adequate amount of substrate (if available) especially during injuries, yet it is highly susceptible to damage caused by hypoglycemia, a potential complication during an IIT regimen [25-27]. Moreover, microdialysis studies have shown that in several conditions of acute brain injury an IIT regimen is often associated with overt brain extracellular glucopenia, which is potentially dangerous because it compromises glucose metabolism, triggering the so called "energy crisis" and further cell damage [28-31]. What remains to be determined is whether the positive effect of IIT observed in other populations of critically ill patients can be extrapolated to acute brain injury victims.

In this chapter, we will review the aspects related to the detrimental role of Hyperglycemia on the injured brain, and we will analyze the available evidence on glycemic control in neurocritically ill patients.

66.2 Cerebral Glucose Metabolism

The brain is unique in its high energy demand; together with spinal cord and retina, it needs a continuous and adequate supply of oxygen and glucose [25-27,32]. Although it weighs about 1500 g, accounting for only 2% of body weight, it receives 15% of cardiac output, 20% of the oxygen and 25% of the total glucose consumed by the entire organ-

ism. The brain has a high metabolic cost. The obligatory energy substrate for the brain is glucose, which is almost entirely oxidized to carbon dioxide (CO_2) and H_2O. The energy sources are supplied by the blood.

Cerebral blood flow averages 50 ml/100 g of tissue/min. As one might expect of an organ with highly specialized functions, the brain has a significant spare capacity because it only removes slightly over one third (33%) of the available oxygen and only 10% of the glucose. Cerebral oxygen consumption averages about 50 ml/min and CO_2 production is almost identical; hence, the cerebral respiratory quotient (RQ) is close to 1, indicating that carbohydrates are the main substrate for oxidative metabolism. Given a theoretical stoichiometry of 6 µmol of oxygen consumed for each µmole of glucose, glucose utilization by the brain should in theory be 26.6 µmol/100 g/min. However, the measured glucose utilization is 31 µmol/100 g/min, indicating that an excess of 4.4 µmol/100 g/min of glucose follows other metabolic fates.

Glucose can produce metabolic intermediates, such as lactate and pyruvate, which do not necessarily enter the tricarboxylic acid cycle but rather can be released and removed by the circulation. Furthermore, glucose can be incorporated into lipids, proteins, and glycogen, and it is also the precursor of certain neurotransmitters such as γ-aminobutyric acid (GABA), glutamate, and acetylcholine [33]. The cerebral metabolic consumption of glucose is 5 mg/100 g of brain parenchyma/min, which is equivalent to 140 grams per day. The amount of cerebral glucose linearly depends on blood glucose levels; it is typically 30% of the latter, being subject to variations according to blood levels (Figure 66.1). The range of brain glucose fluctuation is much smaller than that of blood glucose during euglycemia [34]. In rats, an increase of 50 mg/dl in blood glucose level from baseline only caused a 10 mg/dl increase in brain glucose level [35]. The brain microenvironment is isolated from the plasma by the blood brain barrier formed by tight junctions between vascular endothelial cells, where tightness excludes free diffusion of polar, hydrophilic molecules such as glucose resulting in a constant and significant glucose concentration gradient from blood to brain (Barros et al. 2007).

Because glucose cannot freely enter the brain, it requires a transport system to cross the endothelial cells of the blood-brain barrier and the membranes of neurons and astrocytes. There are several glucose carrier isoforms present in the brain (Figure 66.2). The predominant glucose transporter (GLUT) proteins involved in cerebral glucose utilization are GLUT-1 and GLUT-3, with GLUT-1 present in all brain cells including the endothelial cells of the capillaries (with very low neuronal expression in vivo), and GLUT-3 which is almost completely restricted to neurons (reviewed in [36]).

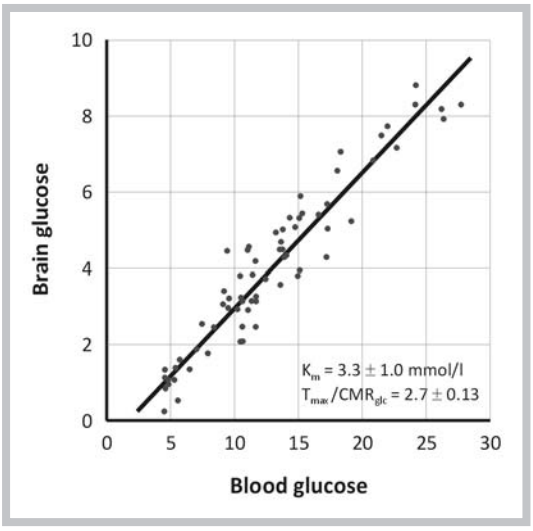

Figure 66.1. **Direct relationship between brain and blood glucose levels.**

Both carrier proteins are facilitative glucose transporters that allow glucose to enter cells independently of insulin and are activated by cytokines released via inflammatory responses. They are also upregulated during periods of increased brain activity in order to optimize glucose transport according to demand.

Repressive adaptation of GLUT across the blood-brain barrier occurs in response to chronic hyperglycemia to prevent a rise in brain glucose content [37]. This glucose

accumulation is avoided by bi-directional flux, which is influenced by the glucose concentration gradient (Figure 66.2) [36]. The different uptake kinetics according to the Michaelis-Menten equation (K_M) guarantees glucose uptake even at low blood glucose levels, which is essential for neurons especially during hypoglycemia (GLUT3: 2.8 mM, GLUT1: 8 mM) [36]. Cerebral glucose consumption depends directly on metabolic activity and on a continuous systemic supply because the brain has no glucose reserves: the low glycogen stores available mainly in astrocytes are rapidly depleted within 2 minutes.

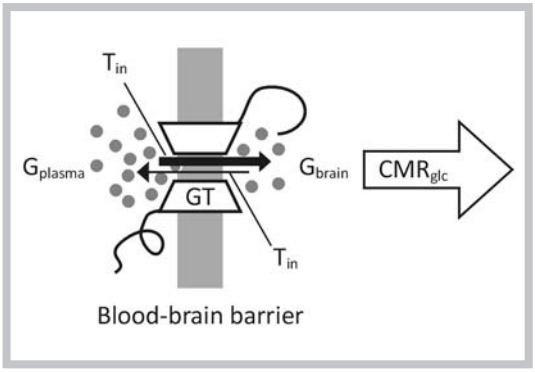

Figure 66.2. **Unidirectional model of glucose transport.**

The central nervous system cells need a sufficient availability of substrate so they can generate energy to develop and maintain their functions. This is achieved at the expense of consuming glucose to generate ATP as well as CO_2 and H_2O.

The pathway that glucose must follow in order to produce energy is a multisequential and finely regulated process. It starts with glycolysis, a metabolic pathway by which glucose is converted into pyruvate or lactate, with the net production of 2 moles of ATP per mole of glucose. The generated pyruvate can then enter the tricarboxylic acid cycle or Krebs cycle: through this cycle and another process known as oxidative phosphorylation,

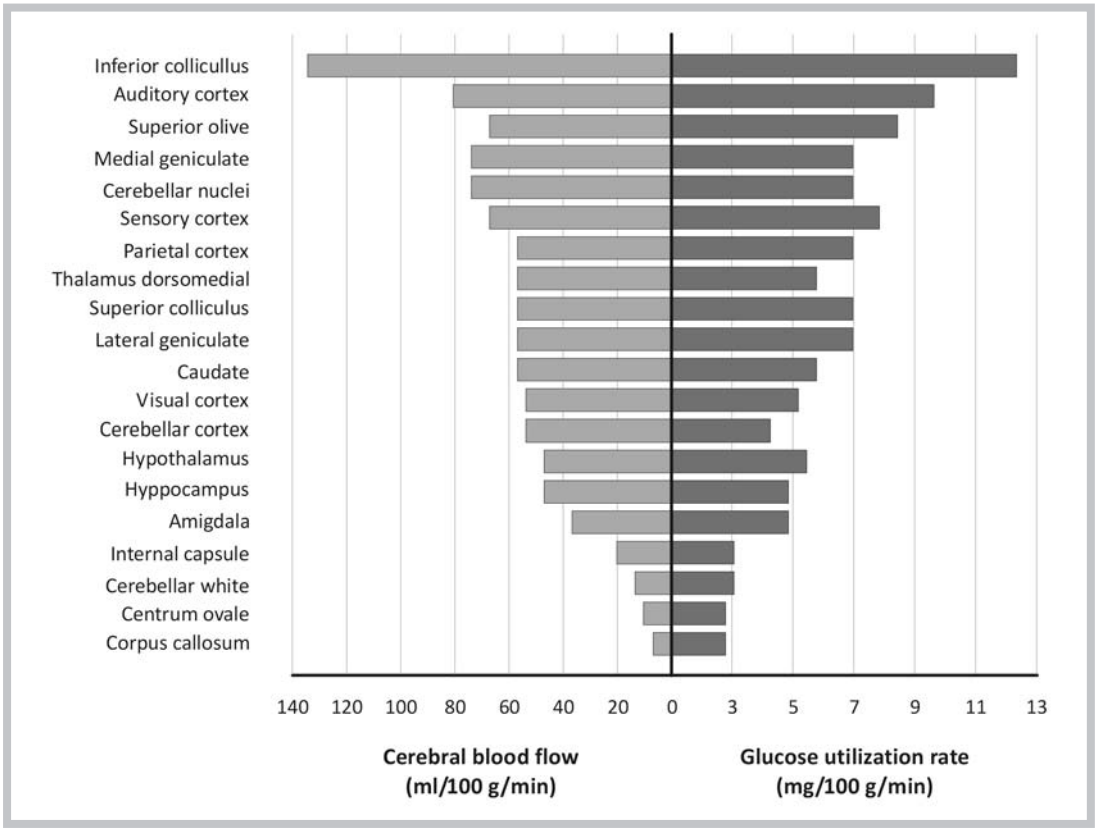

Figure 66.3. **Regional differences in cerebral and glucose consumption.**

30 moles of ATP are produced per mole of glucose metabolized, making this metabolic pathway the most efficient one for producing energy.

The control of brain glucose concentration is very important for humans. Very low glucose concentrations can immediately induce seizures, loss of consciousness, and death, while chronic hyperglycemia induces changes in hippocampal gene expression and function [38].

As mentioned, glucose can originate intermediates such as lactate and pyruvate, metabolites which in certain circumstances can maintain neuronal activity. However, neither molecule crosses the blood-brain barrier freely, and because neither of the two have specific carriers they cannot replace glucose as a cerebral energy substrate in physiological conditions. Numerous studies have investigated molecules that could substitute glucose as an alternative substrate for brain energy metabolism. Among the vast array of molecules tested, mannose is the only one that can sustain normal brain function in the absence of glucose. Mannose crosses the blood-brain barrier and is converted to fructose-6-phosphate, a physiological intermediate of the glycolytic pathway, via enzymatic steps.

However, mannose is not normally present in the blood and therefore cannot be considered a physiological substrate for brain energy metabolism. Lactate and pyruvate can sustain synaptic activity in vitro [39,40]. Because of their limited permeability across the blood–brain barrier, they cannot substitute for plasma glucose to maintain brain function [41,42]. When formed inside the brain parenchyma, however, they are useful metabolic substrates for neural cells [41,42].

In certain pathological conditions such as fasting, malnutrition, diabetes, and ketonic states, acetoacetate and D-3-hydroxybutyrate are markedly elevated because they may be used by the brain as metabolic substrates. As a corollary to these studies, steady-state arterial-venous (A-V) differences provide indirect evidence that a substance can either be used as a substrate by the brain (a positive A-V difference) or produced by the brain (a negative A-V difference) from a particular substrate such as glucose. Thus, in ketotic states, positive A-V differences have been measured for acetoacetate and D-3-hydroxybutyrate, indicating net utilization under these particular conditions. A net release of lactate and pyruvate (a negative A-V difference) is occasionally found in normal individuals and more frequently in aged subjects or during convulsions.

This makes it clear that glucose is the brain energy plant and that it participates in various processes fundamental to brain cell activity. Glucose allows the proper functioning of ion channels, which are essential to maintain transmembrane transport; it enters the production of nucleic acids, amino acids and lipid and the synthesis of hormones and neurotransmitters such as glutamate, acetylcholine and GABA.

Brain energy metabolism can be measured by two techniques: the method of 2-deoxyglucose (2-DG) and positron emission tomography (PET). The 2-DG method developed by Sokoloff and colleagues afforded a sensitive means to measure local rates of glucose utilization (LCMRglu) with a spatial resolution of approximately 50 to 100 μm [43]. With this method, LCRMglu has been determined in virtually all structurally and functionally defined brain structures in various physiological and pathological states, including sleep, seizures, and dehydration, and following a variety of pharmacological treatments [43]. Furthermore, an increase in glucose utilization following the activation of pathways subserving specific modalities, such as visual, auditory, olfactory, or somatosensory stimulation, as well as during motor activity, has been found in the pertinent brain structures [43]. Similarly, local oxygen consumption and changes in blood flow can be studied in humans by means of PET using $^{15}O_2$ and $H_2{}^{15}O$ and by means of local glucose utilization with 2-(^{18}F)fluoro-2-deoxyglucose [44]. Both have revealed the characteristic features of glucose metabolism: regional heterogeneity and relationship with the developed activity

(Figure 66.3). Glucose utilization by the gray matter varies between 5 and 15 mg per 100 g of tissue per minute. This variation depends on the brain region analyzed and that area's specific function. The average rate of glucose consumed by the white matter is 1.5-2 mg/100 g/min. Physiological activation of specific pathways results in a 1.5 to 3-fold increase in LCMRglc, as determined by the 2-DG technique.

Another interesting aspect of the two techniques is the simultaneous study of cerebral consumption of glucose and oxygen, together with blood flow, which has enabled and enhanced our understanding of phenomena occurring not only during functional activation but perhaps more importantly during situations of injury, clearly establishing a relationship between functional activity and energy metabolism.

Most current information on brain energy metabolism comes from studies of purified cell cultures enriched with astrocytes, neurons and endothelial cells. However, caution is warranted when extrapolating results obtained in vitro to in vivo situations. It is generally accepted, however, that insights may be gained from these cellularly homogeneous preparations. The results have allowed to review classic assumptions which considered neurons as the only metabolically active cell group and to properly reflect on what happens in the whole brain.

Although there are anatomical and structural differences between species, the neuronal population contributes up to 50% of the cerebral cortical volume. In addition, there are strong arguments for attributing astrocytes a key role in brain energy metabolism. Structurally speaking, there are 10 astrocytes per neuron, a relationship found in all brain regions studied.

Astrocytes are star-shaped cells strategically located around synapses; they possess receptors for a variety of neurotransmitters and reuptake sites mainly for glutamate. They differ from other cell types by having multiple extensions called "end-feet" in close contact with the wall of the capillaries where glucose transporters such as GLUT1 are expressed (Figure 66.2). Glutamate, the major excitatory amino acid, after exercising its function is taken up by astrocytes in the postsynaptic terminals and converted to glutamine, which is then released and taken up by neurons to maintain the neurotransmitter pool. This process results in the stimulation of aerobic glycolysis (requiring a sufficient amount of oxygen) and lactate production through a mechanism that involves activation of the sodium/potassium pump ATPase. Recent magnetic resonance spectroscopy studies in humans have shown that for every molecule of glutamate released from active synaptic terminals and captured by astrocytes one glucose molecule can be metabolized to lactate.

As noted earlier, in circumstances such as stimulation or vigorous activity, lactate can be used as an energy source by neurons although it doesn't cross the blood-brain barrier: the situation is different when it is generated within the brain parenchyma. In summary, during neuronal activation lactate is released into the perisynaptic space, the astrocyte detects it and stimulates glucose uptake from the bloodstream. Glucose is metabolized to lactate, which is released and taken up by neurons to produce ATP via the Krebs cycle and oxidative phosphorylation.

Astrocytes have two well-established functions: 1) to maintain extracellular potassium homeostasis; and 2) to ensure neurotransmitter reuptake (mainly glutamate). They can also be involved in water regulation and exchange by activating aquaporins (AQP4), which are densely grouped on the extensions around the capillaries. Their shape and location suggest they play a key role in the transit of glucose from the bloodstream and in the coupling of energy metabolism to synaptic activity.

Earlier we mentioned that when the cells of the nervous system are active and energy-hungry, their main mechanism of energy supply is the increase in cerebral blood flow (CBF) to provide sufficient amounts of oxygen and glucose. This is accomplished by dif-

ferent types of signals: either metabolites such as lactate, adenosine, K^+, H^+, or neurotransmitters (vasoactive intestinal peptide, noradrenalin, acetylcholine) or nitric oxide. In this way, there is a "physiological coupling between CBF and energy metabolism" which is not always maintained, especially during injury.

66.3 Glucose Metabolism and Acute Brain Injury

During brain injury, whether of traumatic, hemorrhagic or ischemic origin, profound changes in brain energy metabolism occur [45-52]. The brain enters a state of energy dysfunction, called a "metabolic crisis" by some authors. Studies using microdialysis and PET techniques have discovered that this state of crisis may take several days to resolve and that it differs from cerebral ischemia. Energy dysfunction is characterized by its heterogeneity (not all brain areas are affected in the same way), and a marked decrease in oxidative metabolism and alterations in glucose metabolism. Immediately after primary brain damage, glucose use dramatically increases to ensure the supply of enough energy to meet the increased metabolic demands, thereby maintaining ion gradients and cell membrane function intact. This defence mechanism against injury has been called hyperglycolysis. It is short-lasting and followed by a period of decline in glucose utilization. During this phase, secondary events such as seizures, intracranial hypertension, and hypoglycemia increase the demands on a tissue already working at diminished capacity, further compromising the limited energy reserves available to mitigate catastrophe.
Importantly, in pathological situations where the energy production is reduced and the cells cannot metabolize lactate aerobically, utilizing glucose acquires enormous significance. The main source of glucose derives from the extracellular space which, in turn, depends on an adequate supply and transport of glucose from the bloodstream. In these conditions, adequate glucose supplies to the brain might only be sustained when the concentration of systemic glucose is sufficient. Glucose can produce metabolic intermediates, such as lactate and pyruvate, which do not necessarily enter the tricarboxylic acid cycle but rather can be released and removed by the circulation. In this context, astrocytes play a role in glucose uptake by neurons by processing glucose through a glycolytic pathway and subsequently releasing lactate as a metabolic neuronal substrate [53]. Glucose metabolism in neurons is directed mainly to the pentose phosphate pathway, leading to the regeneration of reduced glutathione. Neurons die rapidly following the inhibition of mitochondrial respiration, whereas astrocytes utilize glycolytically generated ATP to increase their mitochondrial membrane potential, thus becoming more resistant to pro-apoptotic stimuli [53].
The increase in glucose utilization, together with a higher cerebral metabolic rate in the immediate hours following acute brain injury, lead to an increase in the capillary density of GLUT1, facilitating the transport of glucose from the blood to the brain interstitium [54]. The significant increase in GLUT3 and significant decrease of GLUT1 in neurons [55] suggest a mechanism of autoprotection against hypoglycemia due to the increased expression of high-affinity GLUT3 transporters (Km 2.8 mM) [55]. However, the lack of activity of the 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase, isoform 3 (PFKFB3), leads to a state of sustained brain energy dysfunction in both animals and humans and may eventually contribute to poor outcome [56,57]. Furthermore, transport of glucose at the blood-brain barrier and the neuronal plasma membrane may become inadequate to satisfy brain cellular metabolism.
The initial phase characterized by compensatory hyperglycemic glycolysis is typically followed by a regionally heterogeneous reduction in energy consumption, with a reduction

in cerebral metabolic oxidative metabolism and alterations in glucose metabolism [58]. Rapid-sampling microdialysis studies in patients with acute brain injury including ischemic stroke, subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and intracerebral hemorrhage [59] showed an inverse relationship between the rate of depolarization and the changes in tissue glucose, the highest rate being found in patients with the greatest falls in brain glucose levels. These results indicate a potential for a deficiency in the availability of extracellular glucose after severe brain injury which, in turn, is associated with worse neurological outcome.

Due to their expression of NMDA and non-NMDA receptors, neurons and oligodendrocytes are exquisitely sensitive to excitotoxicity by glutamate, which reaches high extracellular concentrations in brain injury for several reasons, including failing astrocyte uptake [53]. Excitotoxicity kills brain cells by energetic exhaustion (due to Na^+ extrusion after channel-mediated entry) combined with mitochondrial Ca^{2+}-mediated injury and the formation of reactive oxygen species.

Many but not all astrocytes survive energy deprivation for extended periods, but after returning to aerated conditions they are vulnerable to mitochondrial damage by cytoplasmic/mitochondrial Ca^{2+} overload and to nicotinamide adenine dinucleotide (NAD^+) deficiency. Ca^{2+} overload is established by reversal of Na^+/Ca^{2+} exchangers following Na^+ accumulation during Na^+-K^+-Cl^- co-transporter stimulation or pH regulation, compensating for excessive acid production [53]. NAD^+ deficiency inhibits glycolysis and eventually oxidative metabolism secondary to poly(ADP-ribose)polymerase (PARP) activity following DNA damage. This results in reduced pyruvate levels due to insufficiently replenished NAD+ and increased lactate levels due to metabolic short-cutting because pyruvate is metabolized to lactate by lactate dehydrogenase and cannot enter the citric acid cycle. Maintaining adequate intracerebral glucose levels can be beneficial for neurons, whereas excessive hyperglycemia increases astrocyte death due to enhanced acidosis.

66.4 Hypoglycemia-induced Brain Damage

Although there is no unanimous agreement, hypoglycemia in adults is defined as a decrease in serum glucose levels <50 mg/ dl (<2.8 millimol/l), regardless of the presence or absence of symptoms. The severity of a hypoglycemic episode is determined by the plasma glucose concentration together with the appearance of symptoms and changes in brain electrical activity [32,60-72]. The changes evidenced on the electroencephalogram (EEG) cover a wide spectrum from cortical slowing with predominantly theta and delta waves to silence or flat EEG through the suppression of wave patterns (“burst suppression”) and/or seizure activity. Glycemic thresholds that trigger symptoms or EEG impairment vary widely from individual to individual, even among non-diabetics and diabetics; indeed, fluctuations are noted among the latter regardless of whether glucose levels are under control or not.

However, several authors have underscored a key concept to bear in mind: hypoglycemia-induced brain injury occurs most often in patients in whom a strict control of blood glucose with insulin is attempted.

Hypoglycemia-induced brain damage is characterized by its depth or severity and duration. Brain energy metabolism is altered when one or both characteristics are present. This concept is important to emphasize because cerebral oxygen consumption remains unchanged during episodes of hypoglycemia, thus suggesting that alternative metabolic substrates are being utilized to ensure the production of ATP needed to maintain cellular functions.

From the physiological concepts described above it is clear that the work and survival of cells that make up the CNS is highly dependent on a continuous supply of glucose. The brain has a limited ability to adapt to situations of marked decrease in glucose intake. There are three compensatory mechanisms that counteract brain glucopenia: response to stress; increase in CBF; use of alternative reservoirs and substrates.

The systemic response to hypoglycemia is predominately via the release of counterregulatory hormones. Numbering among these hormones are catecholamines, glucagon, cortisol, and others. All favour the release of glucose into the bloodstream (hyperglycemia) in the attempt to preserve CNS cell function. Although several working groups have shown a marked increase in CBF during episodes of hypoglycemia, its pathophysiological mechanisms are not entirely clear. The extent of the increase in CBF depends on the severity of hypoglycemia. In addition, the cerebral blood vessels lose their ability to regulate their diameter in response to changes in perfusion pressure, i.e., the ability to self-regulate CBF. The astrocyte glycogen stores are depleted within 5 minutes. However, recent studies suggest that glycogen can be used longer, particularly when the supply of glucose to the brain is insufficient or when hypoglycemia is repeated.

Other endogenous substrates of energy utilized by the CNS cells both in vivo and in vitro are amino acids and fatty acids such as arachidonic acid, both of which are insufficient, inefficient and dangerous, since they induce the accumulation of products (e.g., oxygen free radicals, calcium) which are potentially toxic and lethal for neurons. Profound metabolic disorders ensue when the ability to cope with hypoglycemic insult fails or is depleted. Since glucose, besides being the brain's ultimate energy source, is involved in other vital processes, its lack or absence prevents amino acid metabolism, protein synthesis, neurotransmitter release, alters the local pH, and damages the cell membranes when ion channels don't work correctly.

As mentioned, the more profound and prolonged the hypoglycemia, the greater the likelihood of severe and irreversible damage. Multiple mechanisms are involved in neuronal death, including glutamate and adenosine toxicity, apoptosis, oxidative damage by oxygen free radicals, zinc and nitric oxide, and the accumulation of intracellular calcium. Not all brain regions show the same susceptibility to damage induced by hypoglycemia. The cerebral cortex, striatum and hippocampus are among the most vulnerable areas, while the hypothalamus, cerebellum and brain stem are highly resistant to hypoglycemic injury. Autopsy studies in humans have revealed scattered petechiae, congestion and edema of nerve cells, mainly located in axons and dendrites, which undergo a series of degenerative changes and subsequently disappear. Many areas of glial reaction, demyelination, and encephalomalacia can be found.

66.5 Hyperglycemia as a Prognostic Factor

When defining hyperglycemia in the context of serious illness in general and in patients with neurological/neurosurgical emergency in particular, the lack of a uniform definition in different series studied should be taken into account.

The values used to define it widely vary and were taken arbitrarily [1-21]. Nevertheless, it is estimated that the incidence of hyperglycemia in the neurocritical patient ranges between 28 and 68% [7,10,73]. Hyperglycemia is also an independent risk factor of mortality and poor functional outcomes in several situations of neurological injury such as ischemic stroke treated or not treated with thrombolysis [2-10,73-81], spontaneous intracerebral [18-21,82,83] and subarachnoid [11,12,84-87] hemorrhage, malignant brain tumors [88], severe head injury [13-17], and spinal cord injury [89-93].

Multiple studies have demonstrated the negative impact of hyperglycemia in the ischemic brain. Williams [6] showed a close association between hyperglycemia and mortality at 30 days, 1 year and 6 years after ischemic stroke. Capes et al. [5] in their meta-analysis showed that the risk of death after ischemic stroke was 3 times higher if blood glucose levels at hospital admission were between 110 and 126 mg/dl.

In a recent study, Stead et al. reported results similar to those above, because patients with cerebrovascular disease and hyperglycemia are 2.3 times more likely to die at 90 days compared to patients with normoglycemia [84]. The multicenter, prospective observational GLIAS study [81] established as its main objective to detect the glucose threshold with the greatest predictive power of poor outcome in the acute phase of ischemic stroke. The optimal cut-off point that most accuracy predicted poor outcome 3 months after the event is 155 mg/dl. This value is correlated with a 2.7-fold increase in the probability of poor outcomes after adjusting for variables such as age, presence of diabetes, glucose level at admission, infarct volume and stroke severity, while the risk of death is 3 times greater (hazard ratio [HR] 3.80, 95% confidence interval [CI], 1.79-8.10) [81].

Hyperglycemia is a common finding in patients with spontaneous intracerebral hemorrhage [18-21,82-83] and has a detrimental prognostic effect in the short term according to some studies (odds ratio [OR], 1.52; 95% CI 1.28-1.82; p <0.0001) [21].

Our working group investigated the relationship between early mortality, i.e., within 30 days after intracerebral hemorrhage, and elevated levels of blood glucose [21]. Patients who died had high blood glucose levels for 72 hours after the stroke (p <0.001). It is noteworthy that for each 18 mg/dl increase in glucose levels >90 mg/dl, the probability of experiencing a fatal event increases by 33%. The cut-off point in which the greatest predictive power is obtained is >164 mg/dl. All the above findings apply equally to diabetic and non diabetics patients [21].

Elevated glucose levels have been identified as independent predictors of final outcome after SAH [12,85-87]. A study by Frontera demonstrated a close association between hyperglycemia and the onset of complications such as heart and respiratory failure, pneumonia and brain herniation (p <0.05). Also, a close link was demonstrated between hyperglycemia and poor outcomes defined as either severe disability or death (OR 1.17; 95% CI 1.07-1.28; p <0.001) [12].

The Dutch group led by Kruyt [85] evidenced, after multivariate adjustment of baseline characteristics of non-diabetic patients with aneurysmal SAH, that the average levels of fasting glucose during the first week following initial bleeding predicts poor outcomes (OR 2.5; 95% CI 1.4-4.6) better than blood glucose at admission (OR 6.1; 95% CI 0.9-2.7) [85].

The deleterious effects of hyperglycemia on the injured brain in neurotrauma are well known. It is a factor of secondary damage to be avoided. However, currently available evidence is scarce and controversial at best, so we cannot definitively say whether high blood glucose levels are an independent risk factor of poor outcome after severe head trauma.

The few available studies show that patients with blood glucose >170 mg/dl have worse long-term results compared to subjects with normal blood glucose levels [13,16,17,89].

Salim et al. retrospectively analyzed a series of patients with severe TBI. Persistent hyperglycemia was defined as ≥150 mg/dl during the first week post-trauma was prevalent in older patients with a greater severity of head and systemic trauma, and on multivariate analysis independently predicted mortality (OR 4.91; 95% CI 2.88-8.56; p <0.0001) [90].

The degree of hyperglycemia seems to be important in prognosis [16]. Some predictive models have included hyperglycemia as a prognostic factor thus improving the prediction of outcomes [91-93].

Experimental models of spinal cord ischemic injury have shown that high blood glucose levels adversely affect neurological function [94-96]. In Only one retrospective study

concluded that after traumatic spinal cord injury hyperglycemia accompanies the most severe contusions, while hyperglycemia induced after spinal cord ischemia does not affect the final outcome [97].

66.6 Pathophysiology of Hyperglycemia in the Acute Phase of Brain Injury

The genesis of hyperglycemia after brain damage is not due to a single cause; instead, various multifactorial [10] mechanisms are involved [73] (Table 66.1). One hypothesis is that hyperglycemia is nothing more than an indicator of pre-existing and/or undiagnosed diabetes (intolerance to glucose); however, this hypothesis has not garnered much acceptance as many studies have shown that hyperglycemia in the absence of diabetes is by itself a risk factor of poor outcome in several neuroinjury scenarios [5-10,12-17,19-21,98,99].

Perhaps the most widely accepted explanation is that hyperglycemia during the early phase of neuroinjury is due to a non-specific reaction or response to "stress" situations [2,10,100-103]. This programmed, coordinated and adaptive response is of paramount importance for survival.

It has 3 main components: 1) Activation of the immune-neuroendocrine hypothalamus-pituitary-adrenal axis, with the subsequent release of counterregulatory and hyperglycemic hormones, such as catecholamines, cortisol, etc.; 2) Autonomic nervous system stimulation; 3) Modification of individual behaviour.

Each component to a different degree and in a different way contributes to the development of hyperglycemia, so that the greater the damage, the greater the response. Thus, hyperglycemia may be a marker of injury severity rather than a phenomenon that can worsen or trigger it. As mentioned, however, the prevalence of hyperglycemia is high, and independent of the type and severity of the neuroinjury [7,10,73,103]. Furthermore, studies which have reported a causal and unequivocal relationship between stress hormones and stroke are inconsistent [104].

Neuroendocrine dysregulation secondary to anatomic lesion of the insular cortex is one of the mechanisms thought to explain hyperglycemia [105,106] but evidence has not been sufficiently confirmed by other authors [107].

Inflammation triggered by CNS injury is another potential cause of hyperglycemia [100,108-116]. When brain damage of whatever origin occurs, a wide range of mediators including cytokines is immediately released mainly by astrocytes and microglia. Cytokines can, in turn, trigger hyperglycemia through the induction of insulin resistance in the liver and muscle.

The resulting hyperglycemia, coupled with the increased generation of glucose by the liver secondary to the above-mentioned metabolic response to stress, leads to glucose overload that perpetuates the inflammation and triggers the injury of endothelial cells [100,108-116]. In practical terms, we must take iatrogenic causes into account, since many drugs in routine neurointensive care (e.g., dopamine,

- Nonspecific response to tissue injury (autonomic, hormonal and metabolic alterations)
- Insulin resistance
- Drugs (catecholamines, steroids, tiazides, etc.)
- Hypothalamic dysfunction
- Irritation of central glucose regulation centers (hypothalamus, brainstem)
- Excessive glucose administration
- Unknown diabetes
- Latent diabetes

Table 66.1. **Pathophysiology of hyperglycemia in acute brain injury.**

norepinephrine, steroids, thiazides, dextrose-containing solutions, among others) can potentially trigger hyperglycemia [106,117-119]. In this context, adequate nutritional support is essential, given the multiple physiological changes triggering the injury. Among the less convincing hypotheses, or rather those not sufficiently backed in the literature, are those that seek to explain direct hypothalamic damage or irritation of the centres regulating blood glucose after neuroinjury [10].

66.7 Temporal Profile

Technological advances and the development of new monitoring techniques have greatly improved our understanding of the various phenomena occurring after brain damage, many of which can establish, perpetuate and worsen the initial injury. Hyperglycemia is one such factor. Although there is no a uniform and unanimous definition of hyperglycemia in the context of neuroinjury, cut-offs used to define it vary from study to study and most were obtained in an arbitrary manner from the analysis of retrospective series [2-21,70-87]. There are several forms of monitoring and all of them determine glucose levels by an enzymatic or electrochemical method based on the reaction of glucose oxidase. Blood glucose values can be obtained in the following ways: intravenous or arterial; capillary, "pricking" the fingertips; subcutaneous using a sensor inserted into the abdominal wall to record interstitial glucose values [76,120].

The units of expression of blood glucose values are standardized: 1) milligrams per decilitre (mg/dl) or 2) millimoles per litre (mmol/l), as expressed by most European studies. Hospital admission is the moment most authors select when analyzing the prognostic role of elevated blood glucose values during CNS injury [2-21,73-84].

Like other biological variables, however, blood glucose is characterized by its dynamic fluctuating nature because it is subject to variations induced by: nutrition, stress situations (pain, trauma, surgery), drugs, and other factors. Therefore, it is logical to think that the deleterious effects of hyperglycemia persist beyond the first few hours after injury, making serial monitoring of blood glucose levels during brain damage of paramount importance.

Few studies have elucidated the behaviour over time of blood glucose values. Baird [76] in a small series of patients reported that 35% had hyperglycemia at admission, in 43% of which high levels persisted over the study period (72 h post-ischemic stroke), whereas 46% with normal values at the admission in hospital developed hyperglycemia.

Hyperglycemia is strongly associated with infarct expansion ($r \geq 0.60$, $p < 0.01$) and poor functional outcome on the National Institutes of Health Stroke Scale ([NIHSS] $r \geq 0.53$, $p < 0.02$) or the modified Rankin scale ([mRS] $r \geq 0.53$, $p = 0.02$) [76].

Allport et al. [120] described two phases of occurrence of hyperglycemia in a series of 59 patients suffering from ischemic stroke: an early stage occurring in all diabetic patients and 50% of non-diabetic patients within 8 hours after the stroke, and a late phase (48-88 hours post-stroke) in 27% of non-diabetic and 78% of diabetic patients.

The recently published GLIAS study [81] highlights that hyperglycemia occurring within the initial 48 hours post-ischemic stroke is most important factor in determining the final results, regardless of the presence of known and widely validated predictors such as age, presence of diabetes mellitus, infarct volume and stroke severity.

In turn, Godoy et al. [21] identified four evolutionary patterns in a series of nearly 300 patients with spontaneous intracerebral hemorrhage; but perhaps most important was the relationship between different groups and mortality: the mortality was 8.6% among patients with normal blood glucose values and 79.5% for those with persistent hyperglycemia during the study period ($p < 0.0001$).

The main conclusions highlight that hyperglycemia is common, of long duration and with different evolutionary profiles in neurocritical patients. Additionally, it is strongly associated with death and poor functional outcomes.

66.8 Mechanisms of Hyperglycemia-induced Brain Injury

The body's cells naturally protect themselves against the potential toxicity of hyperglycemia by regulating glucose transporters [24,121]. Some cell groups, including neurons, astrocytes, hepatocytes, epithelial and endothelial cells, and the cells of the immune system, receive glucose (without using insulin) from transporter proteins GLUT 1, 2 and 3, which are responsible for facilitating the entry of this energy source into the cell [24,121].

During injury, local hypoxia and the release of mediators (e.g., cytokines, angiotensin II, endothelins) stimulate GLUT expression and localization on the cell membranes, thus deranging the cell's the defence system, ensuing in a glucose overload in the cellular microenvironment [24,122-126].

Although the precise mechanism of hyperglycemia-induced neuronal damage is not known, multiple factors, either together or isolated, interact to trigger, perpetuate or exacerbate the injury. In two elegant papers, Garg [10] and Tomlinson [127] reviewed the potential mechanisms involved. Briefly:

66.8.1 Reduced Cerebral Blood Flow (CBF)

A decrease of up to 25% has been shown in experimental animals [128,129]. Nitric oxide seems to play a key role: neutralizing it or inhibiting its production by the vascular endothelium produces an imbalance in cerebral vascular tone where vasoconstriction predominates. The trend towards microthrombosis of cerebral capillaries triggered by inflammatory mediators such as tissue factor is associated with this mechanism. In occlusion-ischemia models it has been observed that the decrease in flow also involves the penumbra area, showing that the initial area of infarction can be increased when hyperglycemia is present.

66.8.2 Metabolic Dysfunction

Kushner's study with PET and 2-deoxyglucose technique described a profound metabolic depression in the ischemic brain in patients with an average blood glucose level >155 mg/dl [130]. The hypometabolism may be due to impaired mitochondrial function secondary to the toxic effects of glucose overload or to the local lactic acidosis generated during hyperglycemia [10,130].

66.8.3 Toxicity Due to Excitatory Amino Acids and Calcium

Hyperglycemic states increase the availability of extracellular glutamate which activates postsynaptic NMDA receptors to open ion channels, thus allowing the massive entry of calcium into the cells, with consequent mitochondrial dysfunction and neuronal death [10,131]. Hyperglycemia also prevents the reuptake of calcium into the cell after reperfusion in cerebral ischemia models; therefore, it becomes a threat or impediment to the recovery of damaged tissue in such situations [132].

66.8.4 Inflammation

The injury-induced hyperglycemia and tissue damage trigger a complex series of events, among which inflammation and oxidative stress, resulting in the released of mediators such as cytokines, chemokines, oxygen free radicals which, in turn, aggravate the injury through several and varied mechanisms [10,119]. It is well known that the oxygen free radicals cause peroxidation of cell membrane lipids, carboxylation of proteins vital to cell function, and denaturation of DNA. Moreover, they also inhibit the endothelial production of nitric oxide or block its action [10,119,133].

Cytokines perpetuate the inflammatory activity [134] and induce the production and/or transcription of extracellular matrix metalloproteinases (MMPs) which will play a major role in damaging the blood-brain barrier and causing cerebral edema [135,136]. Also, hyperglycemia compromises cerebral microcirculation by altering the balance between thrombotic and fibrinolytic factors [10].

As a corollary, we can deduce that the mechanism of injury analyzed in isolation or together with other phenomena clearly explains the development of certain compli-

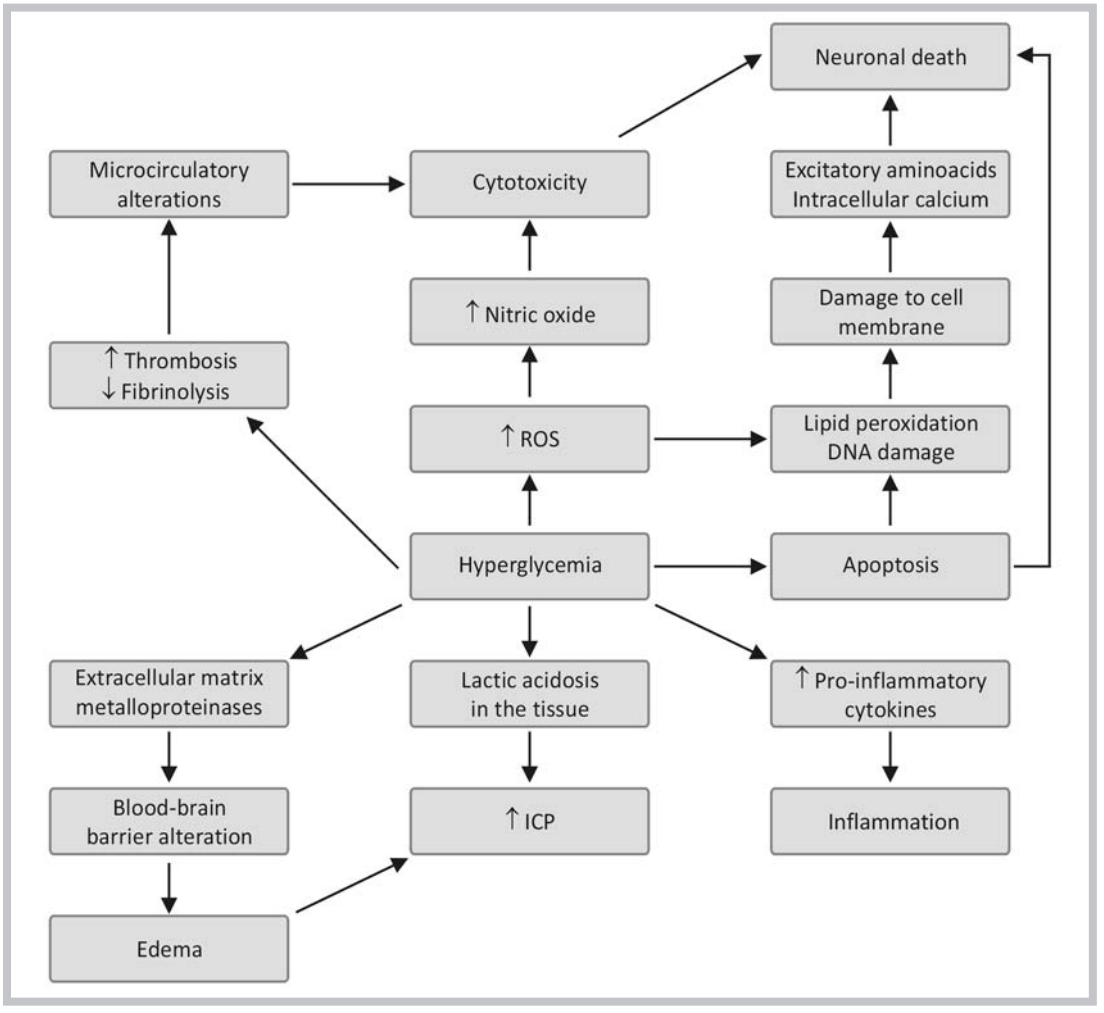

Figure 66.4. **Mechanism of brain damage during hyperglycemia.**
ICP = intracranial pressure
ROS = reactive oxygen species

cations in neurocritical diseases: hemorrhagic transformation [4,77,79] and/or expansion of cerebral infarction [76] or spontaneous enlargement of intracerebral hematoma [136], and vasospasm after subarachnoid hemorrhage [11,12,137].

66.9 Insulin: Neuroprotector?

Insulin, a key hormone in the control of intermediate metabolism, was isolated from the pancreas by Benting and Best in 1922 [138]. It has a profound effect on the metabolism of carbohydrates, lipids and a significant influence on protein metabolism. It plays a major role in mineral metabolism and energy storage.

Unlike other body tissues, the cells of the human CNS are highly permeable to glucose: they capture and utilize without requiring the action of insulin, i.e., cerebral glucose consumption and metabolism depends almost exclusively on the contribution and availability of glucose in the blood, its main vehicle of transport [24,121,139-141].

Evidence from experimental cerebral ischemia models has shown that, besides its physiological actions on blood glucose levels, insulin possesses certain neuroprotective properties by significantly reducing neuronal necrosis [10,73,142-145].

Insulin has recently been shown to exert a potent anti-inflammatory action in vivo and *in vitro* by blocking the production of pro-inflammatory agents, the generation of oxygen free radicals and the synthesis of MMPs [146-152]. As a result, this action of insulin increases the release of nitric oxide from endothelial cells, astrocytes and neurons, which would favour the maintenance of adequate blood flow [153-156].

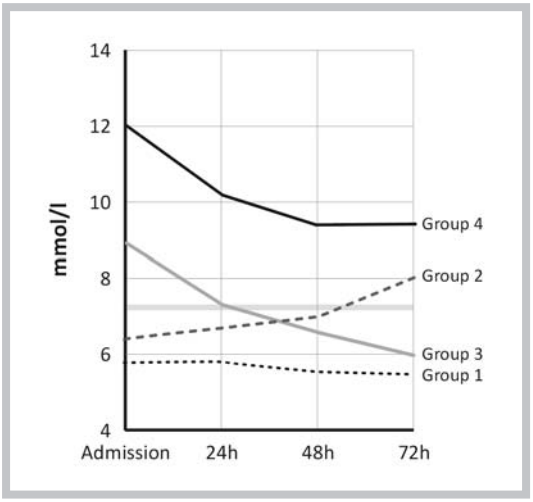

Figure 66.5. **Changes in blood glucose levels during initial 72 hours after spontaneous intracerebral hemorrhage in 295 patients. Different patterns were observed: persistently normal (group 1), increasing (group 2), decreasing (group 3), and persistent elevation (group 4).**

Insulin decreases the expression, transcription and synthesis of MMPs, so that tissue damage is limited by keeping the blood-brain barrier intact [152]. Additionally, insulin has antiplatelet, anticoagulant and profibrinolytic effects [10,73,156-159]. These mechanisms enhance insulin's anti-inflammatory action and hypothetically may improve cerebral microcirculation.

Other benefits of insulin derive from its physiological action. Since it is an anabolic hormone, it promotes protein synthesis, thereby stimulating neuronal repair and regeneration [10,73,156].

66.10 Management of Glycemia in the Neurocritical Patient According to Clinical Practice Guidelines

The term "evidence-based medicine" (EBM) was first used in the 1980s to describe a new learning strategy used at McMaster Medical School, Canada, which stressed the

Organization	Year	Cutoff to start treatment (mg/dl)	Evidence level
Severe traumatic brain injury			
BTF	2000	NS	-
BTF	2007	NS	-
Spontaneous intracerebral hemorrhage			
AHA	1999	NS	-
EUSI	2006	>300	IV
AHA	2007	>185	IIa C
Subarachnoid hemorrhage			
AHA	1994	NS	-
AHA	2009	NS	-
Ischemic stroke			
AHA	1994	NS	III-IV C
AHA	2003	>300	C
EUSI	2003	>180	IV
AHA	2007	140-185	IIa C
EUSI	2008	>180	IV
Ischemic stroke with thrombolytics			
AHA	1996	>400	-

Table 66.2. **Recommendations for hyperglycemia management during acute cerebral injuries according to current guidelines.**

AHA = American Heart Association
BTF = Brain Trauma Foundation
EUSI = European Stroke Initiative
NS = not specified

importance of reviewing evidence from investigation, and cautious interpretation of the clinical information derived from non-systematic observations [160].
According to the definition by Sackett in 1996 [161], "Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients".
Next, we will review past and present guidelines for the management of glycemia in different situations of acute brain injury.

66.10.1 Ischemic Stroke (IS)

All current recommendations have a common denominator when dealing with early detection, prevention and rapid correction of hypoglycemia since its deleterious role is well known in situations of acute brain injury (Class I, Level of Evidence Grade C) [162-167].
In the management of elevated blood glucose levels, according to then available evidence, the expert committee of the Stroke Council of the American Heart Association (AHA) stated in 1994 that the association between hyperglycemia and poor outcomes is uncertain and controversial. Nevertheless, it suggested treating hyperglycemia, without specifying guidelines or thresholds (Level of Evidence III-IV, Grade C) [162].
Later, in 1996, the AMA issued guidelines for thrombolytic therapy in ischemic stroke which advised keeping blood glucose values between 50 and 400 mg/dl [163]. A decade later, the AHA recognized the harm of hyperglycemia in the context of ischemic stroke, suggesting a cautious approach to hyperglycemia control, i.e., to keep levels <300 mg/dl (Level of Evidence Grade C) [164-165].

At the same time, the working group of cerebrovascular diseases in the European Stroke Initiative (EUSI) emphasized how frequent and dangerous hyperglycemia is during the acute phase of ischemic stroke, recommending the control of blood glucose values >180 mg/dl (Level of Evidence IV) [166].
Recently, the AHA and EUSI updated their guidelines in which hyperglycemia is recognized as a common phenomenon accompanying ischemic stroke in both diabetic and non-diabetic patients, highlighting its role in triggering and/or maintaining secondary injury, associated with such complications as expansion or hemorrhagic transformation of infarcts and poor outcome.
The AHA now recommends keeping blood glucose levels <185 mg/dl, suggesting also a possible, hypothetical additional benefit obtained by treating values >140 mg/dl (Class IIa, Level C) [167]. In contrast, the 2003 EUSI guidelines (Level of Evidence IV, GCP, remain unchanged [168].

66.10.2 Severe Traumatic Brain Injury (sTBI)

In 1995 and 1997, respectively, the Brain Trauma Foundation [169] and the European Brain Injury Consortium (EBIC) [170], presented the first recommendations for the management of TBI patients. The recommendations were updated in 2000 [171] and again in 2007 [172].
In the section on nutrition, all versions of the document stress that hyperglycemia is a contributing factor to secondary injury and that its presence worsens the prognosis. But there is no mention of cut-off points up- or downwards at which treatment for altered glucose levels should be initiated.

66.10.3 Aneurysmal Subarachnoid Hemorrhage (SAH)

The Stroke Council of the American Heart Association in 1994 [173], and again in 2009 [174], published clinical practice guidelines for the management of SAH following the rupture of a cerebral aneurysm. Similarly to the recommendations for the management of TBI, they only highlight that hyperglycemia should be avoided owing to its detrimental role in the pathophysiology of brain damage but without specifying how or when this should be done.

66.10.4 Spontaneous Intracerebral Hemorrhage (sICH)

In 2007, the AHA updated their guidelines for the treatment of acute phase of sICH. In contrast to the first edition [175], hyperglycemia is recognized as a component of the body's response to brain injury, its presence is identified as a marker of the severity of damage, and is associated with poor outcomes in the short and long term. Additionally and more importantly, they establish (Level of Evidence IIa, level C),

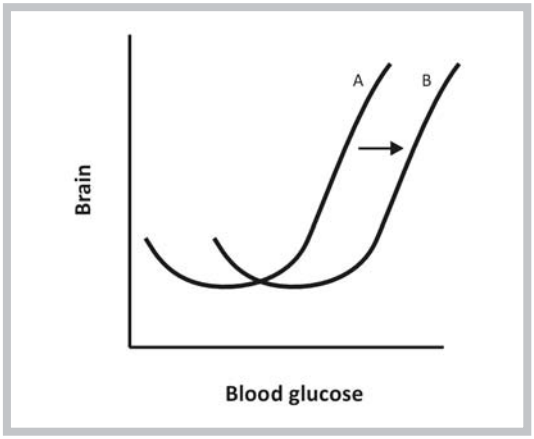

Figure 66.6. Hypo- or hyperglycemia increases the possibility of brain damage (A). During injury there is a shift of the curve towards B, showing an increased need for glucose by the brain, as well as increased susceptibility to glycogenesis in such situations.

the threshold for initiation of insulin therapy [176] starting at 185 mg/dl (possibly >140 mg/dl). In turn, the European Initiative (low level of evidence), suggested keeping blood glucose levels <300 mg/dl [177].

66.11 Intensive Insulin Therapy

There are two treatment options to decrease blood glucose levels in diabetic patients: insulin and oral hypoglycemic agents (OHAs). The latter have no place in the treatment of hyperglycemia in critical illnesses owing to circumstances that can alter their pharmacokinetics and pharmacodynamics.

The effects of many drugs commonly used in intensive care are enhanced or antagonized by OHAs. In addition, in critically ill patients a drug's bioavailability, volume of distribution and metabolism are all altered due to increased capillary permeability, hepatic and renal dysfunction [178].

Another important aspect to consider is the mechanism of action of OHAs. These drugs act by promoting insulin secretion and action by augmenting its receptor function. In contrast, in the critically ill patient, due to the metabolic response to stress-induced injury, the ability to release insulin is reduced and insulin resistance is increased [100,108-116].

Finally, one of the most feared side effects of OHAs is hypoglycemia, which is often very severe, prolonged and life-threatening, especially in neurocritical patients [60-72,178].

There are several routes and forms to administer insulin. The intravenous (IV) route is the one most frequently used in critically ill patients. Administration regimens vary. Some working groups prefer to correct the blood glucose levels in a phased manner and according to monitoring: this scheme is called "reactive". Instead, others estimate the requirements, trying to keep blood glucose levels within a preset range, and this regimen is known as "proactive". Both regimens have their pros and cons, but none has shown superiority or advantage over the other [73].

On the basis of the available evidence for the detrimental role of hyperglycemia, in 2001 van den Berghe published the results of a new therapeutic modality called intensive insulin therapy which aimed at maintaining blood glucose levels within a narrow range, i.e., between 80 and 110 mg/dl [22].

This prospective, randomized single-centre study included postoperative patients on mechanical ventilation, two thirds of which had undergone cardiac surgery. When compared with the group in which blood glucose levels were maintained between 180 and 200 mg/dl, a significant decrease in mortality is observed (8% vs. 4.6%; $p < 0.04$) especially in the patients who remained in critical care for more than 5 days, had proven septic focus, and developed multiple organ dysfunction (20.2% vs. 10.6% for those treated with conventional and intensive regimen, respectively; $p < 0.006$).

Additional benefits obtained from IIT were a lower incidence of infection, days on mechanical ventilation, hospital mortality, development of polyneuropathy of critical ill patients, and need for blood transfusions or dialysis in patients with acute renal failure.

The authors could not replicate the previous data in a series of patients with non-surgical pathology, except in a small subpopulation requiring critical care stay for more than 3 days [179].

Years later, the results of other multicenter studies that questioned the findings of the Belgian group were disclosed [180-184]. Brunkhorst in Germany applied prospectively and randomly IIT to septic patients. Not only was there no difference in mortality between the study groups but also the trial had to be aborted, upon the suggestion of the safety committee, because of the high rate of severe hypoglycemia [180].

Similar data were reported in diabetic and non diabetic patients, victims of acute myocardial infarction [182,183], and in a heterogeneous population of critically ill patients [184].
The prospective, randomized multicenter NICE-SUGAR study involving critically ill patients with different medical and surgical pathologies compared two goals in glycemic control. In one group, IIT was aimed at maintaining blood glucose between 81 and 108 mg/dl (intensive), while in the other one the objective to achieve slightly higher levels between 144 and 180 mg/dl (conventional).
At 90 days after admission to the ICU, the mortality in the intensive group was significantly higher (27.5% vs. 24.9%; OR 1.14; p=0.02), as was the incidence of severe hypoglycemia (6.8% vs. 0.5%; p <0.001), whereas there were no differences between the two therapeutic arms when comparing number of days on mechanical ventilation, length of ICU or hospital stay, or need for dialysis [185].
Therefore, to date, no accurate conclusions can be drawn as even the available meta-analysis of IIT come to different conclusions [186,187].

66.12 Can or Should the Data Obtained in Critically Ill Patients in General Be Extrapolated to Patients With Acute Brain Injury?

This patient subpopulation deserves special consideration. Some authors have approached the subject partially and from different perspectives [73,80,188,189]. While there is unanimous agreement that elevated serum glucose levels or hypoglycemia contribute to secondary damage and worsen the prognosis of these patients, there is no consensus on delineating the levels at which glucose should be maintained.
Although there are no studies specifically addressed to hypoglycemia, the body of available evidence says that there is no doubt that it must be avoided and/or treated in an urgent and aggressive way [60-71,162-177,190].
The debate about hyperglycemia is more complex and focuses on two unsolved questions:

- When or at what level should therapy be initiated?
- In what range or interval should it be maintained?

66.13 Effects of Intensive Insulin Therapy on Cerebral Metabolism

Under physiological conditions, glucose is the major metabolic substrate for the brain, so the possibility to measure or objectify interstitial concentrations of glucose in the brain parenchyma is interesting and fascinating [25-27,32,138] One technique that has furthered our understanding of the brain's energy metabolism is microdialysis [191-193]. This monitoring mode provides us with direct metabolic data, though local, on the fundamental brain energy substrate, glucose, and the production of metabolites and neurotransmitters.
Some of the metabolites usually analyzed in the clinical setting inform us about energy metabolism (glucose, lactate, pyruvate), while others indicate tissue damage (glutamate, glycerol) [191-193].

Another possibility offered by microdialysis is the evaluation of IIT on cerebral metabolism. The brain does not produce insulin or does so only in an insignificant way. Insulin enters the CNS by receptor-mediated transport [194-195]. There are insulin receptors distributed throughout the whole brain, with functions appreciably different from peripheral receptors [139-141,196,197].

Experimental studies suggest that insulin has other physiological functions to stimulate and maintain neuronal survival, without participating in the cerebral metabolic pathways for glucose utilization [25-27,32,139-141,192,194-197].

Therefore, brain interstitial glucose represents the balance between available and consumed glucose [192,193]. There are multiple mechanisms that can lead to neuroglycopenia, including:

- Decreased availability in the blood (hypoglycemia, insulin therapy).
- Impaired cerebral blood flow (severe hypotension, intracranial hypertension).
- Altered transport across the blood-brain barrier (inflammation).
- Increased glucose consumption (seizures, fever).

Two studies showed that low brain extracellular glucose levels are closely associated with poor outcome after SAH [198] or severe head trauma [33].

Vespa [30] conducted pioneer work in determining the effects of IIT on metabolism and the interstitial concentration of cerebral glucose in severe traumatic injury. Patients with severe TBI (GCS ≤8) or moderate (GCS ≤12) with space-occupying lesions on computed tomography (CT) were monitored by mean of microdialysis, xenon 133 and PET for commonly used variables (intracerebral pressure, jugular oxygen saturation) and cerebral blood flow, oxygen consumption rate, glucose, metabolic markers.

Continuous insulin infusion was used to maintain plasma glucose levels between 90-120 mg/dl (intensive) in one group and compared with another in which blood glucose was maintained in the range 120-150 mg/dl (conventional) but with a regimen of subcutaneous administration of insulin adjusted according to monitoring values.

In the whole population, enteral feeding was initiated within 12 hours postinjury. While IIT did not alter overall glucose metabolism, there was a significant decrease in the extracellular concentration of glucose in the brain parenchyma, associated with increases in oxygen and glutamate extraction, and in the lactate/pyruvate ratio, markers of cellular energy dysfunction. Although not designed for this purpose, the study showed no additional benefits in terms of mortality or functional outcomes [30].

Similar results were reported by Oddo [31] and Schlenk [199] in individuals after severe head trauma or SAH, respectively. Both reached the same conclusion, agreeing that IIT generates a decrease in interstitial glucose accompanied by an increase in markers of cellular distress despite the achievement and maintenance of normal glycemia.

In Switzerland, Holbein et al. retrospectively analyzed the effect that four intervals of different glycemic controls in severe head trauma victims have on cerebral metabolism. Glucose ranges varied widely from 72 to 163 mg/dl. Metabolic parameters were obtained indirectly through formulas derived from arteriojugular differences of the variable to be measured. Despite the limitations of the study, the authors concluded that brain metabolism is more “stable” when blood glucose levels are kept between 109 and 145 mg/dl [200].

66.14 Clinical Trials

Building on original work [22], van der Berghe discussed the effects of IIT on the central and peripheral nervous system [190] in a subpopulation with prolonged ICU stay

(≥7 days). In all, 405 patients took part in the follow-up assessment with weekly electromyograms (EMG) for detecting polyneuropathy (PNP). In the patients treated with IIT to maintain a strict control of blood glucose levels (range, 80 to 110 mg/dl), the risk of developing polyneuropathy was reduced by 49% (p <0.0001), with a lower risk of prolonged mechanical ventilation (OR 3.75; 95% CI 1.49-9.39; p=0.005).
It should be noted here that the number of patients so diagnosed varied greatly because only one or two EMGs were performed, which may question the criteria used to define polyneuropathy. No conclusions can be drawn regarding the 63 patients included in the "isolated brain injury" subset because of the small, heterogeneous and not well characterized sample [190].
We will next consider the available evidence for IIT in various neurocritical diseases.

66.14.1 Ischemic Stroke

As discussed above, there is a close association between hyperglycemia and poor outcomes in ischemic stroke [2-10,73-81,84,191]; however, the available evidence for the effects of increased blood glucose control in this group of patients is very limited. In ischemic thromboembolic stroke, Gentile et al. [201] in their retrospective study involving 960 patients once again reaffirmed the prognostic value of hyperglycemia at admission. Hyperglycemia was defined as ≥130 mg/dl. No defined treatment protocol was designed to control high blood glucose levels. Insulin, OHAs or a combination thereof were used interchangeably. The authors concluded that patients whose initial values had fallen within 48 hours post-stroke showed a mortality similar to those who had euglycemia during the same period of time, opening a research path aimed at controlling hyperglycemia in the acute phase of stroke [201].
In two subsequent pilot studies the primary endpoint was to determine the possibility of intensively controlling blood glucose levels with IV insulin infusion. Although the goals and treatment protocols differed, both arrived at similar conclusions: IIT is possible, well tolerated and has an acceptable safety profile [202-203].
In the United Kingdom, a prospective, randomized controlled phase 3 study was conducted to determine in patients with acute ischemic stroke whether the IIT designed to keep blood sugar levels in the range 72 to 127 mg/dl reduced mortality at 3 months from the event [204]. The intensive treatment regimen included continuous infusion of dextrose 10% together with potassium and human recombinant insulin (GKI) during the initial 24 hours. The study was terminated prematurely because of slow recruitment, however, the material from 933 patients was employed in the analysis.
Although GKI infusion significantly reduced and controlled serum levels of glucose, it also decreased blood pressure (average decrease, 9 mmHg; p <0.0001), and no difference was observed in mortality or in the secondary endpoints in outcomes such as prevalence of severe disabling sequelae [204].
Currently, the University of Virginia in collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) is conducting a prospective, multicenter randomized open-label study to determine whether strict glycemic control provides benefits in the acute phase of ischemic stroke.
Within 24 hours from the onset of symptoms, patients are randomized to one of three treatment arms:

- Control group where blood glucose levels are kept <300 mg/dl and a>70 mg/dl.
- Intensive treatment group with levels maintained between 70 and 110 mg/dl.
- More elastic control group which allows values between 70 and 200 mg/dl.

Insulin is administered by IV infusion in combination with dextrose and potassium and feeding is allowed. Outcome measures are mainly intended to obtain a safety profile of

treatment by analyzing the hypoglycemia event rate. The trial called GRASP (Glucose Regulation in Acute Stroke Patients) completed the enrolment, but the data have not yet been released [205].

66.14.2 Neurosurgical Patients

Two small retrospective studies conducted in Brasil [206] and Australia [207], two completely dissimilar countries in economic, social and cultural context, even with methodological problems such as use of historical controls at the time of comparing heterogeneous populations and different therapeutic ranges among others, drew a similar conclusion: IIT is associated with an increased probability of hypoglycemia without altering mortality or functional neurological status [206,207].
In turn, Bilotta et al. [208], in a randomized, prospective controlled trial, analyzed the safety profile and effectiveness of a protocol of aggressive blood glucose control with continuous infusion of insulin for achieving values between 80-110 mg/dl, versus conventional management aimed at maintaining blood glucose levels >180 and <216 mg/dl, in a series of individuals undergoing neurosurgery. Enteral or parenteral feeding was initiated early with standardized regimens.
The treatment protocol was maintained until discharge from the ICU and/or to the second week after surgery. While the length of intensive care stay and the rate of infection were lower in the intensive treatment group, the risk of hypoglycemia was higher, with no observed difference in mortality or functional outcomes at 6 months postoperatively [209].

66.14.3 Aneurysmal Subarachnoid Hemorrhage

The effects of intensive insulin therapy on patients with aneurysmal SAH secondary to rupture of a cerebral aneurysm were evaluated prospectively by an Italian working group [209]. The analysis included 78 patients who underwent clipping for exclusion of the aneurysm. After the patients were stratified according to their neurological status, they were randomized to receive insulin infusion to maintain blood glucose between 80 and 220 mg/dl or intensive treatment to maintain plasma glucose levels in the range of 80-120 mg/dl. Enteral and/or parenteral feeding was initiated after the first 24 hours. The protocol was extended until discharge from the ICU or until the second week after surgery.
The group that received IIT developed significantly fewer infections than the conventionally treated group (27% vs. 42%; $p < 0.001$), but no benefit was obtained in the prevalence of postoperative vasospasm, mortality and functional outcomes [209]. Latorre recently released the results of a retrospective series in two different time periods [210]. For patients admitted before 2003, the blood glucose values were corrected without a specific protocol only if the levels were >200 mg/dl, while after 2003 glycemia was treated more aggressively with a protocol designed to maintain blood glucose between 80 and 140 mg/dl. There were no differences in the final results between the two groups, showing only a trend for improvement in those patients treated intensively in whom the therapeutic goal or good glycemic control was achieved.

66.14.4 Severe Head Trauma

A very recent study involved 97 patients with severe head trauma (Glasgow Coma Scale [GCS] score ≤8), 60% of whom had space-occupying lesions. The management

of blood glucose was consecutively randomized. Continuous intravenous insulin infusion was regulated with the target set on achieving blood glucose levels 80-220 g/dl (conventional management) versus intensive therapy aimed at maintaining blood glucose 80-120 mg/dl.

The patients undergoing IIT obtained as the only benefit a shorter ICU stay (7.3 vs. 10 days; $p < 0.05$) and double the number of episodes of hypoglycemia recorded for the conventional group in ($p < 0.0001$). Moreover, the infection and mortality rates and functional results during the 6 months follow-up after the event were similar in both treatment arms [211].

Meier et al. [212] retrospectively analyzed 228 severe head-injured patients over two different periods. The effects of IIT were compared in two groups with different goals in terms of blood glucose levels to achieve: the strict control group (63-118 mg/dl) vs. the permissive one (90-145 g/dl). They studied the impact that both treatment modalities had on the number of episodes of hypoglycemia, and the incidence of infections and mortality. Additionally, they analyzed the effect of IIT on intracranial pressure (ICP), ICU stay, and presence of inflammatory markers.

Extensive data are reported that make their interpretation complex. In establishing a cut-off point in the first week post-trauma, during the week itself, the incidence of hypoglycemia, increased ICP and infection rates were higher in the group under strict glycemic control, while during the second week there was a trend to a more efficient management of ICP values. Moreover, there was a trend towards increased mortality during the first 2 weeks in patients undergoing aggressive blood glucose control. The authors concluded that in general IIT with strict goals yields no benefits in this patient population [212].

66.15 Conclusions

Glucose is essential for brain activity as it is the ultimate energy substrate. Because the brain has no energy reservoirs, brain interstitial glucose available for metabolism comes almost entirely from the bloodstream. There is a close relationship between blood and extracellular glucose.

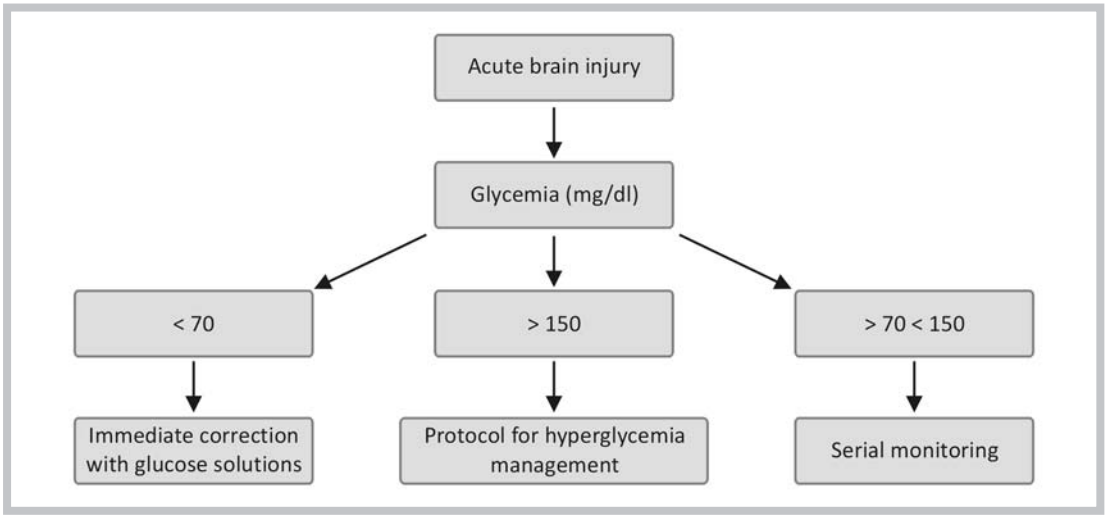

Figure 66.7. Management of acute brain injury.

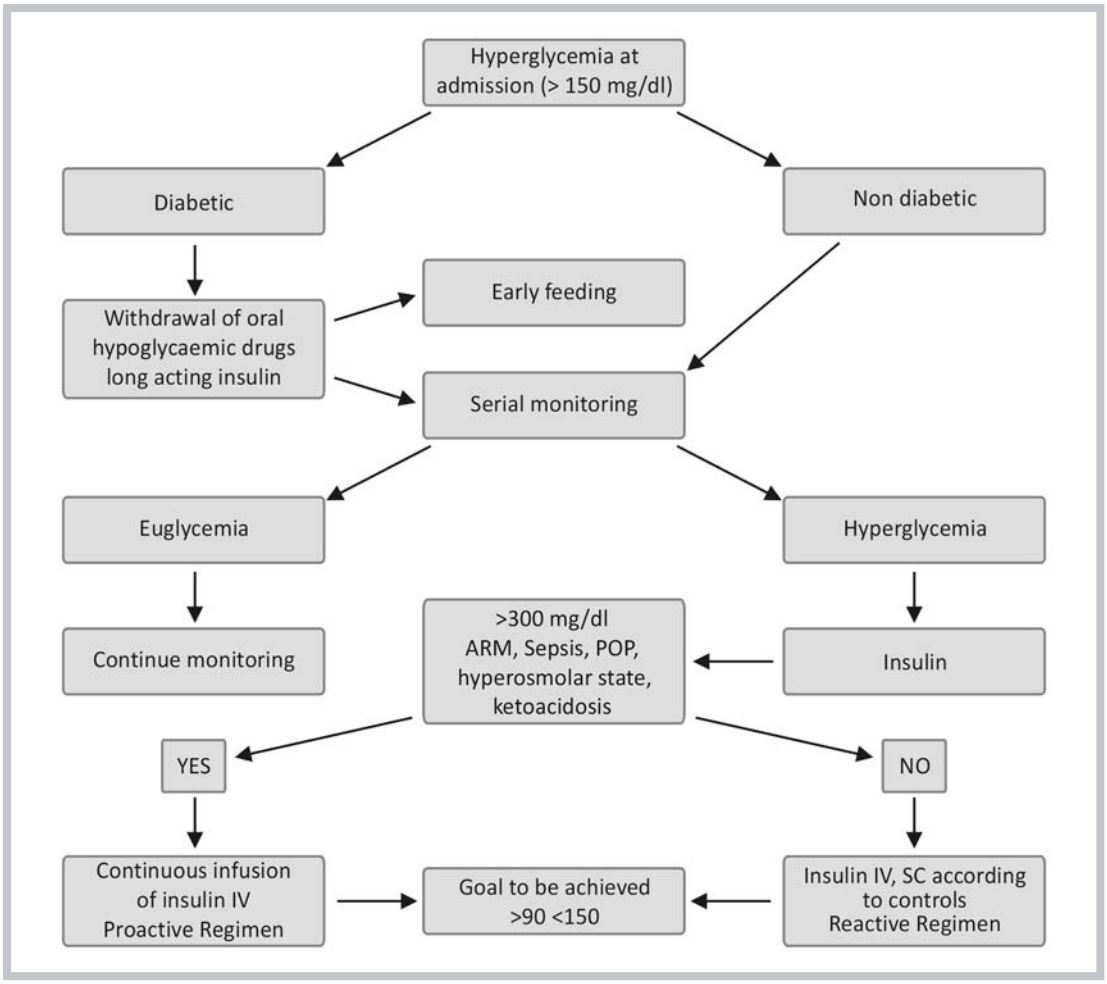

Figure 66.8. **Management of patients with hyperglycemia at admission.**

Physiologically, the brain has the ability to protect and adapt to extreme fluctuations in blood glucose levels. The glucose in the brain parenchyma depends on the balance between the supply and consumption by the cells. By contrast, glucose metabolism and need both increase after injury. The brain becomes more vulnerable to insufficient glucose supply; hence, the decrease in glucose intake is potentially dangerous.

Although available evidence suggests that elevated serum glucose levels or hypoglycemia contribute to secondary damage and worsen prognosis, there is no consensus on delineating the maximum and minimum levels at which blood glucose should be maintained. Treatment to intensively monitor serum glucose levels offers no advantage because it increases the likelihood of hypoglycemia and significantly decreased the concentration of glucose in the extracellular space despite euglycemia, increasing markers of energetic-metabolic dysfunction.

What the available data do suggest is that 150 mg/dl is the threshold at which hyperglycemia must begin to be treated [21,30,81]. In contrast, the lowest safe range has not been clearly defined. Perhaps, it might be broadly set, according to Vespa, as the serum glucose value that does not elicit metabolic disturbances in the brain [213].

Having determined this point, efforts should be directed to determine which method is most appropriate to keep blood glucose within the desired range and whether this is

better than moderate hyperglycemia. Pending the results of specific trials, we cannot recommend aggressive control of blood glucose levels in neurocritically ill patients regardless of the nature of the injury. Figures 66.7 and 66.8 summarize the management.

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67 Practical Guidelines for Analgesia, Sedation, Muscular Relaxation, and Delirium Management in Neurocritical Patient

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67.1 Analgesia, Sedation, Muscular Relaxation

Dosis sola venenum facit
[The dose alone makes the poison]
Paracelsus (Swiss alchemist and physician, 1493-1541)

The rapid broad-based development of intensive care medicine now allows the treatment and recovery of patients who some decades ago would have been considered hopeless. At the basis of this achievement lies not only a better understanding of pathophysiological mechanisms or the introduction of new drugs but also the implementation of invasive diagnostic, therapeutic and monitoring techniques. The critically ill patient often faces several potential sources of pain as well as physical and psychological stressors. The relief of pain and suffering is one of our priorities within this setting. The establishment of adequate analgosedation contributes to this goal and influences the prognosis and stay of patients in the the intensive care unit (ICU). Hence, health care professionals need to be familiar with the use of specific groups of drugs and have a proper knowledge of their various pharmacological aspects.

67.1.1 Terminology

Analgesia. A deadening or absence of the sense of pain without loss of consciousness.
Sedation. A drug-induced depression of central nervous system (CNS) activity; its intensity may be minimal (anxiolysis), moderate or deep (Table 67.1). In practical terms, sedation is the process of establishing a state of calm.
"Sedation", analgosedation or sedoanalgesia. Terms used indistinctly in anesthesiology and intensive care medicine to define therapeutic interventions performed to relief pain or provide sedation to reduce the signs and symptoms of pain, anxiety/stress, agitation, and delirium. Additionally, these procedures may include the use of amnesic drugs to prevent the "memory" and subsequent recall of unpleasant experiences or particularly stressful episodes.
General anesthesia refers to a pharmacologically induced and reversible state of unconsciousness (hypnosis) and lack of sensation, with the eventual addition or coexistence of analgesia, muscle relaxation, depression of the autonomic nervous system activity (decreased stress response) and amnesia.

Few seconds following the intravenous (IV) administration of a hypnotic dose of a general anesthetic, the patient loses consciousness and stops breathing. At the same time, airway reflexes are suppressed or impaired (risk of aspiration). Under such circumstances, positive pressure ventilation should be established (i.e., with a face mask, laryngeal mask or tracheal intubation). A properly anesthetized patient cannot be aroused even by means of intense painful stimulation.

Artificial coma, **pharmacological or barbiturate coma** refer to deep sedation or general anesthesia established to help patients recover from injury, serious life-threatening conditions in the ICU, or to protect the brain during or after certain major neurosurgical procedures. Pharmacological coma can be induced by means of different general anesthetic agents; barbiturate coma, for instance, may be used to lower elevated intracranial pressure (ICP) in patients with severe traumatic brain injury (TBI). Other uses include the treatment of refractory status epilepticus, cerebral vasospasm after subarachnoid hemorrhage (SAH), comatose survivors of cardiac arrest, and patients with cerebral edema and elevated ICP of any etiology other than TBI.

Anesthetics. Like narcotics (from the Greek word *narcosis* meaning stupor), anesthetics is a broad term under which the most commonly used drugs in anesthesia are grouped, i.e., opioids, hypnotics and muscle relaxants. Many anesthesiologists prefer to reserve this term for hypnotic or inducing agents, which can be subdivided into two categories: those given intravenously (propofol, midazolam, thiopental, ketamine, etomidate, etc.) and those inhaled (sevoflurane, desflurane, etc.).

Opiates and opioids are two other terms used interchangeably. Opiates are naturally occurring substances derived from opium obtained from the poppy plant (morphine, codeine, thebaine, papaverine, noscapine). The term opioids refers strictly to endogenous (endorphins, encephalin, dynorphins) or exogenous (synthetic agents distantly related chemically to opium's alkaloids) compounds with an intrinsic activity, either agonist or antagonist. Exogenous opioids are subdivided into semi-synthetic (heroin, oxycodone, tramadol, etc.) or synthetic (methadone, fentanyl, sufentanil, remifentanil, meperidine, etc.).

Minimal sedation	• Normal response to verbal stimuli • Cognitive function and coordination may be impaired. • Airway protective reflexes (±) and patency are preserved • Ventilatory and cardiovascular functions are unaffected
Moderate sedation/analgesia (conscious sedation)	• A drug-induced depression of consciousness during which the patient responds purposefully* to verbal command either alone or accompanied by light tactile stimulation • No interventions are necessary to maintain a patent airway** • Spontaneous ventilation is adequate** • Cardiovascular function is usually maintained
Deep sedation	• A drug-induced depression of consciousness during which the patient cannot be easily aroused, but responds purposefully* following repeated or painful stimulation • Independent ventilatory function may be impaired • Patient may require assistance to maintain a patent airway • Spontaneous ventilation may be inadequate • Cardiovascular function is usually maintained

Table 67.1. **Sedation levels according to the American Society of Anesthesiologists (ASA).**
(±) Swallow and gag
* Reflex withdrawal from a painful stimulus is NOT considered a purposeful response
** Patients with restrictive or chronic obstructive pulmonary disease, sleep apnoea, pregnant women, elderly or obese individuals may develop respiratory failure and arterial oxygen desaturation during moderate sedation

In the United States, the term **narcotics** are generally associated with opioids or opiates. The concept of narcotics includes any psychoactive compound with sleep-inducing properties which can also hinder the transmission of pain signals. Unfortunately, there is no anesthetic that fulfils these two requirements. It is true that the isolated administration of high doses of certain opioids can produce unconsciousness in humans. However, their effects are unpredictable and inconsistent. Furthermore, most currently available anesthetics (except ketamine) are simply hypnotics without an analgesic effect. Therefore, from a pharmacological standpoint, "narcotics" it is not an accurate term.
Muscle relaxation or neuromuscular blockade is the reversible paralysis of somatic striated muscle induced by the administration of pharmacological agents that interrupt the transmission of nerve impulses at the level of neuromuscular junction.

67.1.2 Analgesia in the Neurological ICU

Indications: to manage postoperative pain, traumatic injury, subacute or chronic pain, to facilitate tolerance to invasive diagnostic and therapeutic procedures, and to provide care and mobilization of patient by nursing and rehabilitation staff.

Monitoring of Pain

Pain intensity can be recorded on a variety of scales. Rating pain intensity allows the evaluation of the effect of analgesic regimens in individual patients. The numerical rating scale (NRS) is a good option when a patient preserves verbal communication. With this numerical scale, the user has the option to verbally rate the pain on a scale from 0 to 10 (where 0 indicates the absence of pain and 10 the worst pain possible). If verbal communication is not possible (i.e., due to tracheal intubation, speech or language disturbances), a 10 cm line with two end points (representing "no pain" and "worst pain imaginable", respectively), can be drawn on paper (visual analogue scale [VAS]). Patients are asked to rate their pain by indicating or placing a mark on the line corresponding to their current level of pain. The VAS score is determined by measuring in centimetres from the left end of the line ("no pain") to the point that the patient marks. A numerical score ≤3 on the NRS or VAS can be used as evidence of effective analgesia. The use of surrogate signs of pain such as physiological parameters (e.g., blood pressure or heart rate) or elicited behaviors (e.g., facial expression, lacrimation) is an unproven and probably inappropriate practice.

Opiates	• Morphine
Opioids	• Fentanyl • Sufentanil • Remifentanil • Piritramide • Oxycodone • Meperidine • Tramadol • Tilidine

Nonsteroidal anti-inflammatory drugs (NSAIDs)	• Nonselective COX inhibitors:
	  ▪ Metamizol
	  ▪ Ketorolac
	  ▪ Ibuprofen
	  ▪ Dexketropofen
	• Selective cyclo-oxygenase (COX-2) inhibitors:
	  ▪ Parecoxib

General anesthetics	Ketamine
Other drugs	α-2 agonists: • Clonidine • Dexmedetomidine • Radolmidine
Steroids	
Antidepressants	
Anticonvulsants	

Table 67.2. **Pharmacologic options options for analgesia in the neurological ICU.**

In unconscious or paralyzed patients, such signs may include: a transient increase in blood pressure or heart rate; grimaces or running tears; tachypnea when spontaneous respiration is preserved; pupil size changes; or increased muscle tone when the patient is not paralyzed. Practitioners should have a high level of suspicion in front of severe critically ill patients. Routine administration of analgesics is not always a synonym of an effective analgesia. In fact, about 50% of patients discharged from the ICU remember pain as their worst experience while in the ICU.

Pharmacological and Nonpharmacological Options

Pharmacological options are summarized in Table 67.2.

On the other hand, regional anaesthesia techniques encompass: continuous epidural anaesthesia (epidural catheter), plexus block, and peripheral nerve blocks. Other methods such: transcutaneous nerve stimulation, neuromodulation or neurostimulation, intrathecal pump implantation and other surgical procedures (i.e., rhizotomy) may eventually be considered.

Considerations and Precautions

The list of drugs included in the section on pharmacological options is partial. There are many others which for practical reasons will not be covered in this chapter. The availability and preferences for some of these drugs varies according to the country, institution, or personal experience. Similarly, the primary morbid nature of the disorder or the presence of certain accompanying conditions (renal failure, peptic ulcer, etc.) determine their selection and dosage.

- With few exceptions, opiates/opioids administration in hospitalized patients do not cause drug addiction. However, their withdrawal after prolonged administration may trigger rebound hyperalgesia.
- The effective dose of an opioid should be determined by patient response and not by a predetermined notion of what an effective dose should be (Table 67.3).
- Potent opioids induce severe respiratory and cardiovascular depression (Table 67.4).
- Chest wall rigidity, although rare, is another adverse reaction which can be triggered upon opioid administration.
- Potent opioids should administered by personnel familiar with these drugs and in an environment where all conditions for securing the airway and mechanically ventilate be readily available. .

Drug	Initial dose*	Peak effect upon IV administration**	Duration of operative analgesia [$]	Total analgesic effect [#]
Morphine	5-10 mg	15-30 min	(–)	3-5 h
Fentanyl	1-4 μg/kg	4-5 min	20-30 min	1-2 h
Sufentanil	0.1-0.2 μg/kg	2-3 min	30 min	Approx. 2 h
Remifentanil	0.5-0.75 μg/kg	1-1.5 min	5-10 min	Approx. 20 min
Piritramide	0 1 mg/kg	5-15 min	(–)	4-6 h
Meperidine	25 mg	15 min	(–)	2-3 h

Table 67.3. **Initial dose and duration of analgesic effect of some opioids used in anesthesia and intensive care medicine.**

* Required dose (in association with an hypnotic) to blunt the responses to airway stimulation (laryngoskopy, tracheal intubation)

** Time required to exert maximum effect

[$] Duration of maximal analgesia

[#] SIncludes time of maximal analgesia plus residual effect

(–) Not currently used during perioperative analgesia (anesthesia)

Drug	Comparative potency	Administration route	Half-life	Respiratory depression	Peculiarities
Morphine	1	IV, IM, SC, PO, epidural, intrathecal, rectal	114 min	+/++	Gold standard opiate in paliative care. Increases ICP. Its metabolite (morphine-3-glucoronide) may cause myoclonus and seizures
Fentanyl	100-300	IV, epidural, transdermal, intranasal	185-219 min	++++	Increases ICP. High doses rarely cause seizure activity; it is prone to accumulate. It does not cause histamine release
Sufentanil	1000	IV, epidural	148-164 min	+++	Most powerful opioid for use in humans. Chest wall rigidity after IV administration is rare
Remifentanil	200	IV	4-14 min	+++	Higher risk of chest wall rigidity than fentanyl when given by bolus; ultra-short half-life, it does not accumulate
Piritramide	0.7	IV, IM, SC	3-12 h	+/++	Does not induce histamine release; may be administered by bolus every 5-10 min. Good choice for PCA
Meperidine	0.1-0.2	IV, IM, PO, rectal	3.2-4.4 h	−/+	Is the first choice therapy for the treatment of post-anesthetic shivering. Its active metabolite (normeperidine) can accumulate and may trigger seizures, agitation, delirium, myoclonus and tremor
Oxycodone	1.5-2 (oral)	IV, IM, SC, PO, rectal; transdermal, intranasal	4-6 h	−/+	Second-line alternative to oral morphine for palliative cares; risk of addiction. Can trigger migraine. It has a cough suppressant effect. May accumulate in patients with renal or hepatic failure. May be effective in treating neuropathic pain
Tramadol	0.1	IV, IM, PO, rectal	6 h	−/+	Very weak opioid, wich induces serotonin release, and inhibits the reuptake of norepinephrine (eventual antidepressand and sedative effect). May be useful in treating restless legs syndrome. Not recommended in patients with history of seizures. Risk of addiction
Tilidine	0-0.2	IV, IM, SC, PO, rectal	4-6 h	−/+	Weak opioid, which may produce welfare state or euphoria (risk of addiction). Can be used to treat restless legs syndrome

Table 67.4. **Summary of pharmacological aspects of various opioid analgesics.**

- Use of background opioid infusion increases the risk of respiratory depression, especially when combined with sedative drugs.
- While pain antagonizes opioid-induced respiratory depression, sleep can intensify the depressant effects of opioids.
- Respiratory depression secondary to opioid use promotes the retention of carbon dioxide (CO_2).
- Hypercarbia related to respiratory depression may lead to cerebral vasodilatation increasing intracranial pressure (ICP) and thus impairing the condition in patients with poor intracranial compliance, or an acute brain catastrophe.
- When opioids are given intravenously, patients should be closely monitored (respiratory rate, pulse oximetry [SpO_2], ECG, blood pressure). Patients with severe hypercapnia may become somnolent (risk of CO_2 narcosis with respiratory acidosis and possible silent death consecutive to cardiac arrest).
- Caution: patients with respiratory depression and severe hypercarbia may show normal SpO_2 values!
- Fear of respiratory depression, however realistic or exaggerated, represents a major barrier to the most effective use of opioids in management of pain. Although serious complications or deaths from opioid-induced respiratory depression are rare, the risk is not zero, and a death or neurologic injury for a patient with an otherwise treatable illness is a great tragedy.
- Miosis is another side effect associated with opioids and an important sign to be taken into account during neurological examination.
- The anticholinergic effect of opioids, as well as several general anaesthetics, may cause delirium in some patients (see section on agitation and delirium).
- Opioid analgesics may disturb gastrointestinal motility; paralytic ileus can result when these agents are given continuously and in high doses.
- The appearance of tolerance (e.g. tachyphylaxis) is another problem associated with prolonged administration of some of these drugs, in such cases higher doses are needed to achieve the desired therapeutic effect. Dose increments may interfere at the time to perform the neurological examination, and ultimately trigger toxicity phenomena.
- The long-term administration of NSAIDs (mainly non-selective COX inhibitors) is often associated with a risk of bleeding dyscrasias or gastrointestinal bleeding (a relative contraindication in critically ill patients). Platelet aggregation disorders secondary to NSAIDs administration are an unwanted effect in patients with Intracranial bleeding.
- The use of selective COX-2 inhibitors occasionally provides significant pain relief in situations where other NSAIDs and even low-potency opioids are ineffective. This "superior" effect may be related to the particular mechanism of action inherent only to these specific drugs (see section on main drugs).
- Usually, NSAIDs provide good analgesia in neurosurgical patients; the rational use of these compounds can reduce opioid requirements or obviate the need for opioids altogether.
- An effective analgesia contributes to the maintenance of the sleep-wake cycle; pain and sleep deprivation are precipitating of delirium (see section on agitation and delirium).
- Analgesia is not only the act of blunting pain with drugs, but also through proper positioning of the patient, stabilising fractures and minimising harmful physical stimulation. For instance, proper patient positioning and frequent position changes help to prevent or decrease pain in the extremities or in support areas (i.e. back, sacrum, heels). Conscious patients, while intubated and paralyzed (i.e., Guillain-

Barré syndrome), may be experiencing unbearable pains undetected by medical personnel.

- Although regional anaesthetic techniques are an important complement to the analgesia regimen in some critically ill patients, they may be not taken into consideration if the medical staff are not familiar with them.
- The quality and duration of analgesia provided by regional anaesthesia techniques is superior to that offered by opioids or NSAIDs. Epidural analgesia allows the earlier return of bowel function. In addition, regional anesthesia may facilitate mobilization and physiotherapy and often it does not require complementary sedation. Under the effects of regional anaesthesia (i.e., thoracic epidural anaesthesia) both early mobilization of patient and normal thoracic excursions are guaranteed. Facilitating early mobilization and normal respiratory function allows early rehabilitation treatments and helps to reduce the incidence of complications such as atelectasis, pneumonia and thromboembolic events consecutive to deep vein thrombosis.

67.1.3 Sedation in the Neurological ICU

Anxiety, agitation and delirium represent diagnostic and therapeutic problems (see section on agitation and delirium). Increased physical activity during episodes of agitation increases oxygen consumption (VO_2) and the risk of self-harm (extubation, catheter dislocation, etc.). Moreover, sedation can interfere with the neurological examination. Talking to patients and making adjustments in the ICU environment should be the first steps to calm an anxious patient. However, in this setting drugs are often needed to calm patients. Anxiety and pain may be interrelated: pain is a major source of anxiety, and anxiety may lower the threshold for pain per¬ception. Sedation should only be performed by a qualified medical professional experienced in working with sedatives and who understands their potential side effects.

Chronic obstructive pulmonary disease patients or patient with obstructive sleep apnea are particularly prone to hypoxia during sedation treatments.

Patients with intracranial haemorrhage who preserve consciousness and may still rebleed need to be sedated. Sedation in these cases is aimed to ensure patient comfort but also to attenuate sympathetic activity. This simple measure can help to prevent unwanted events like tachycardia, sustained hypertension or systolic peaks. Similarly, patients at risk for secondary brain injury from cerebral edema and intracranial hypertension may benefit from sedation

Sedation in the neuro-ICU or general ICU as premedication is also an important

- Anxiety
- To induce amnesia
- To manage experiences after adverse life events (serious injury, mutilation, loss of loved ones, etc.)
- Mechanical ventilation
- Agitation with:
  - Risk of self-harm or harm to others
  - Risk of self-extubation, removal of catheters, venous lines, invasive monitoring devices, etc.
- Intracranial hemorrhage with risk of rebleeding
- Withdrawal syndrome (illicit drugs abuse, alcohol, etc.)
- Intracranial hypertension
- Refractory hypertension or sympathetic hyperactivity
- Recurrent seizures or status epilepticus
- Premedication before surgery
- Deep sedation during the immediate postoperative period in some patients with the aim to:
  - Reduce cerebral oxygen consumption to prevent the extension of injury or to ensure a faster recovery of central nervous system (CNS) function
  - Prevent certain complications such as rebleeding, sudden increases in ICP or blood pressure, seizures, etc.

Table 67.5. **Indications for sedation in the neurological ICU.**

component of the preoperative management for patients undergoing surgical procedures. Premedication should be reduced or withheld in the elderly, chronic obstructive pulmonary disease patients, or patients with obstructive sleep apnea, severe neurologic deterioration, or those candidates for awake or fiberoptic-assisted tracheal intubation e.g., cervical trauma, narrowed oral aperture (dermatomyositis, scleroderma, etc.). Indications for sedation are summarized in Table 67.5.

Monitoring

There is a wide variety of scoring systems to monitor sedation (Tables 67.7 and 67.8). These scores provide information about the grade of sedation but not about its quality, in addition, scoring indexes carry the potential for variability in measurements. Sedation scores are not intended for patients who are unconscious or receiving neuromuscular blocking agents.

In principle, most of these scores (see section on agitation and delirium) were created to evaluate patients admitted into general ICU, therefore, the inclusion of several important aspects of neurological evaluation were not included during their designs. These limitations should not be ignored considering how crucial neurological examination is to assess the effectiveness of treatment and the outcome of patients admitted to the neuro-ICU.

The bispectral index (BIS) is another alternative to monitor the depth of sedation. BIS monitors are noninvasive devices that reflect -into a single number- a signal-processed electroencephalogram (EEG). This technology was first developed as an adjunctive method of monitoring anesthesia states during surgery. Basically, it compares the patient's frontal EEG to processed data set from over 5000 volunteer EEG samples to scale the output of the measured EEG to between 0 and 100. A "fully awake state" is scored 100, whereas 0 is an isoelectric EEG reading; a score < 60 rates a high probability of unconsciousness. The aim during intraoperative monitoring is to achieve a score between 40 and 60, while sedation targets are typified by ranges of 60-75. Whether the use of BIS reduces drug doses, costs, length of mechanical ventilation or the length of ICU stay is controversial. Its main disadvantage is that it is best used when administering a short acting anesthetic (i.e., thiopental, propofol) on which the processed EEG algorithm is based. Agents such benzodiazepines, opioids or other classes of sedatives differentially influence the EEG and BIS is not programmed to interpret such changes. The Narcotrend index is other monitoring tool based on EEG pattern recognition during anesthesia or sedation. This technology has been developed in Germany and at present it is being use to assess the depth of sedation in several ICUs.

67.1.4 Pharmacological and Non-pharmacological Options

Pharmacological options are summarized in Table 67.6.

Non pharmacological options include: psychotherapy, background music, establishing effective communication with patients, and allowing flexible visiting hours, etc.

Considerations and Precautions

- When possible, sedation treatments that may interfere with neurological examination should be avoided. The goal of sedation in the ICU is a patient who is calm but easily arousable. Non-pharmacological options decrease sedative and analgesic requirements.
- A prolonged amnesia is not desirable, since it may interfere with long-term neuropsychological recovery.

- With few exceptions (e.g. morphine, tramadol) , opioids are not first-line sedation drugs because their sedative effect is usually achieved at higher doses than those required to produce analgesia. Agitation secondary to pain justifies the use of these drugs as sedatives (caution: consider side effects).
- Unlike opioids, therapeutic doses of benzodiazepines do not cause respiratory depression in healthy subjects, but this effect can occur in select ICU patients (Table 67.1).
- Airway protection often becomes insufficient after deep sedation.
- Paradoxical effects may occur upon administration of benzodiazepines (see chapter on agitation and delirium).
- Consider that all major antidepressant drugs, except trimipramine, mirtazapine and nefazodone suppress rapid eye movement (REM) sleep.

Benzodiazepines	• Midazolam • Lorazepam • Diazepam
Non-benzodiazepine GABA-A agonists	• Zopiclone • Zolpidem
Neuroleptics	• Haloperidol • Droperidol • Levomepromazine
Anesthetics	• Propofol • Thiopental
Barbiturates	• Thiopental • Pentobarbital • Phenobarbital
α_2 agonists	• Clonidine • Dexmedetomidine
Opiates or opioids	• Morphine • Fentanyl • Sufentanil • Remifentanil • Piritramide • Tramadol
Antidepressants	
Antihistamines	• Diphenhydramine • Hydroxyzine

Table 67.6. **Sedation: pharmacological options.**

67.1.5 Analgosedation

Pain and anxiety are frequently concurrent in critically ill patients. Analgosedation (or "sedation") is an essential therapy in the ICU where patients may be sedated for many hours and even days, largely because of their dependence on mechanical ventilation but also because of their poor general condition, post surgical or traumatic injuries, high treatment and monitoring invasiveness, nursing maneuvers, sleep deprivation, etc. The relief of pain and anxiety is not only a humanitarian gesture but also serves to attenuate the stress response (tachycardia, hypertension, increase of VO_2), which may be poorly tolerated by some patients. Increased VO_2 can have deleterious effects on patients with ischemic stroke, ischemic heart disease, anaemia, or acute respiratory distress syndrome (ARDS). Furthermore, there is some evidence that optimising analgesia may prevent wound infection, by improving the subcutaneous oxygenation.

However, sedation poses many problems since it is difficult to titrate. Inadequate, light sedation may lead to hypertension, tachycardia, and poor ventilator synchrony, producing stressful experiences, which sometimes are responsible for long-term psychological effects and the so called "post-traumatic stress disorder".

On the other hand, providing adequate and appropriate sedation for patients in prolonged or long-term mechanical ventilation is often a difficult task . Over-sedation, side effects, tolerance, ceiling effect and withdrawal symptoms are among the problems to be faced in this setting. Therefore, the medical personnel involved in this task should be aware to detect and treat such unwanted effects early.

When weaning neurological ICU patients from the ventilator and approaching extubation it has to be acknowledged that conventional ICU criteria for weaning and extubation can only have an orienting character and that dysphagia is much more frequent in these patients.

67.1.6 Peculiarities in Neurocritically Ill Patients

- In the setting of sedation, serious neurological events may be occurring and go undetected and untreated. For instance, in a neuro-ICU setting, the rates of nonconvulsive status epilepticus are as high as 35%.
- Certain specific aspects of brain-injured patients should be taken into account. These include interactions of drugs with intracranial pressure, disturbed autoregulation, a higher frequency of seizures and an increased risk of delirium.
- Patients with acute brain insult are mostly intubated, ventilated and sedated; neurological examination may be difficult, and the insult severity can be over-estimated.
- The lesions responsible for brain damage can evolve during the initial hours and, unfortunately, continuous sedation can mask important changes that can only be identified by clinical examination. For these reasons, the strategy of repeated wake up tests (WUt) is often used for reliable assessment.
- Patients with preexistent neurologic impairment are more sensitive to the sedative effects of multiple medications and may take a prolonged time to awaken from sedation or general anesthesia.
- When weaning neurological ICU patients from the ventilator and approaching extubation it has to be acknowledged that conventional ICU criteria for weaning and extubation can only have an orienting character and that dysphagia is much more frequent in these patients.

67.1.7 Key Points of Analgosedation

- Analgosedation is a combination therapy: a strong opioid analgesic plus a sedative, with the eventual addition of supportive drugs (e.g. clonidine). Drug combinations provide analgesia and anxyolisis, and reduce hypnotic dose requirements.
- Combine drugs according to patient's disease and expected sedoanalgesia duration (see SeSAM).
- The administration of drugs must be individualized based on the patient's response.
- Consider periodic dose adjustments: administer as much as is necessary, and as little as possible.
- Total pain suppression is not always desirable, since changes in pain intensity may be an indicator of illness course. A numerical score of 3 or less on the NRS or VAS can be considered as effective analgesia.
- Inadequate sedation complicates daily ICU tasks and management of ventilation; excessive sedation promotes difficulties in weaning and may delay enteral feeding.
- Whenever possible, etiological diagnosis should be addressed in case of pain and agitation. Does pain led to agitation, or does agitation obey to another disorder?
- Ideally, drug doses should be titrated to the minimum required to maintain patient comfort, and to allow a normal sleep pattern; promoting daily interruption of sedatives significantly improve clinical outcomes and reduce ICU stay. Nevertheless, it should be considered that, daily sedation holds (i.e., WUt) are not possible or appropriate in all patients.
- Avoid neuromuscular blocking agents whenever possible. However, neuromuscular relaxants may be required to treat certain conditions (e.g., refractory intracranial hypertension), or when IV sedatives and analgesics have proven ineffective in facilitating mechanical ventilation.
- Neuromuscular blocking agents do not produce analgesia or sedation and, because paralysis is an extremely frightening and even painful experience, it is imperative to establish the desired levels of sedation and analgesia before initiating drug-induced paralysis.

- Consider, some patients may require higher doses of sedatives and analgesics (e.g., alcoholics, drug addicts, smokers, patients undergoing hemofiltration). Conversely, opioid analgesic and sedative requirements can be less in elderly, renal failure or due to the synergism with other drugs.
- The potential for opioid, benzodiazepine, and propofol withdrawal should considered after high doses or more than seven days of continuous therapy. Doses should be tapered systematically to prevent withdrawal symptoms, e.g., 10-15% medication reduction every 6-8 h when sedation treatment lasted less than seven days, or 10-15% dose reduction per day by long-term sedation treatments (>10days).
- Consider, antidepressants may be required at the weaning time.
- According to a recent study, previous antidepressant use is associated with higher mortality in critically ill patients; however, the findings do not suggest the drugs cause deaths.

Sequential Analgosedation Management (SeSAM)

Category I (SeSAM I)

Sedation up to 24 h: e.g., short-term intubated patients including: drug overdose patients, short-term postoperative ventilation, etc. Drugs: 2% propofol (or midazolam IV by bolus), with a low potency opioid (i.e., piritramide 7.5 mg every 4-6 h), and the eventual addition of NSAIDs.

Category II (SeSAM II)

Sedation for 24-72 h (original concept), currently up to 7 days: e.g., patients who have not totally recovered within the first 24 hours; patients with multiple or serious underlying disease undergoing major surgery; patients in whom immediate weaning is unlikely (e.g., patients with extensive lung damage, patients undergoing brainstem surgery, etc.). Drugs: 2% propofol with sufentanil (separated infusion pumps). Regional anaesthetic techniques or clonidine may be added.

Category III (SeSAM III, stage 1 and 2)

Sedation for a period longer than 7 days.

Stage 1: e.g., for critically ill patients (severe TBI or polytrauma , sepsis, ARDS, etc.) in whom ventilation and sedation are essential components of treatment. During stage 1, patients undergo deep sedation (Ramsay Score 4-5). Drugs: midazolam and sufentanil IV (separated infusion pumps); ketamine/ketamine-S and sufentanil is an¬other alternative.
Stage 2: After stabilizing the patient, and when weaning is intended (Ramsay Score 2 during the day). Use drugs recommended for SeSAM II (propofol/sufentanil/clonidine).

Category IV (SeSAM IV)

Brief sedation (2-5 h): deep sedation (Ramsay Score 4-5) for few hours, striving to early spontaneous breathing. Drugs: e.g., propofol and remifentanil IV (separated infusion pumps).

Score	Clinical description	Assessment of sedation
0	Awake and fully oriented	Awake
1	Anxious and agitated or restless, or both	Insufficient
2	Cooperative, oriented and tranquil; e.g., tolerates mechanical ventilation	Optimal
3	Sedated, responds to commands	Suitable
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus	Suitable
5	Asleep, exhibits a sluggish response to light glabellar tap or loud auditory stimulus	Deep
6	Asleep, exhibits no response	Too deep

Table 67.7. **Ramsay Scale (1974) with sedation assessment (modified).**

Agitation	1. Unresponsive to command or physical stimulation 2. Appropriate response to physical stimuli, state of calm 3. Mild anxiety, delirium, agitation (patient calms down easily) 4. Moderate anxiety, delirium, agitation 5. Severe anxiety, delirium, agitation
Alertness	1. Difficult to arouse, eyes remain closed 2. Mostly sleeping, eyes closed 3. Dozing intermittently, arouses easily 4. Awake, calm 5. Wide awake, hyper-alert
Respiration	1. Intubated, no spontaneous effort 2. Respirations even, synchronized with ventilator 3. Mild dyspnea/tachypnea, occasional asynchrony 4. Frequent dyspnea/tachypnea, ventilator asynchrony 5. Sustained, severe dyspnea/tachypnea
Patient classification (sedation goal)	Acutely ill (weaning not a goal) (5-9)
	Ventilated patient being weaned (7-10)
	Chronic ventilated patient (weaning not a goal) (6-9)
	Nonventilated patient (7-9)

Table 67.8. **AVRIPAS Scale (2001). Modified from [Avripas, 2001].**

Sedation Using Inhalational Anesthetics

The ideal IV sedative does not exist. Inhalational anesthetics are a feasible alternative, which have often shown better performance when compared to IV drugs. Unfortunately, most ICU-settings do not have the proper devices or facilities to administer inhalational anesthetics, and in many cases, the ICU staff is not familiar with the pharmacology, physiologic effects, and handling of volatile anesthetics.

Volatile anesthetics, for instance, have usually a quick onset of action, and their emergence time are shorter and more predictable than IV sedation. Inhalational anesthetics accumulate very little, and elimination via the lungs is independent of liver and kidney function. Volatile anesthetics act primarily on the cerebral cortex, and even at low concentrations may completely depress consciousness while leaving many autonomic functions undisturbed (e.g., breathing, temperature control, and blood pressure regulation). These characteristics, and others like a cardiovascular protective effect, make inhalational anesthetics an almost ideal sedative in general ICU-settings. However, regarding neurocritically ill patients, it has to be taken into account that volatile anesthetics increase ICP, and may trigger malignant hyperthermia in the setting of myopathy. Therefore, studies have to be performed in order to evaluate the impact of this attractive sedation modality in neuro-ICU settings.

67.1.8 Muscular Relaxation in the Neuro-ICU

Optimal administration of analgesics and sedatives, as well as the application of certain modalities of mechanical ventilation (i.e., biphasic positive airway pressure [BiPAP]) have led to a substantial reduction in the use of muscle relaxants in the ICU settings. Currently, less than 10% of ICU patients receive neuromuscular blocking agents. These drugs are not devoid of side effects. Their long-term administration has been associated with the development of a group of neuromuscular disorders (i.e. critical illness myopathy, cachectic myopathy, or necrotizing myopathy, among others). The relationship between these my¬opathies and the administration of muscle relaxants and high-dose cor-

ticoesteroids remains controversial. At present, certain metabolic derangements like hyperglycemia are being considered as a major risk factor for ICU-acquired neuromuscular disorders. Indications are summarized in Table 67.9.

- Facilitation of tracheal intubation
- Brief bedside invasive or surgical procedures
- Severe refractory intracranial hypertension
- Transport, facilitation of diagnostic procedures
- Eventually in the management of refractory status epilepticus
- Severe pulmonary disease with inability to mechanically ventilate
- Reversion or reduction of lung hyperinflation (air trapping, auto-PEEP, etc.)
- Nonconventional ventilation modes: high frequency ventilation, prone positioning, etc.
- Treatment of muscle spasms related to drug overdose or tetanus
- Eventually in the treatment of shivering, therapeutic hypothermia
- Extreme agitation in sedated and ventilated patients
- Management of chest wall rigidity secondary to opioid administration
- Preservation of delicate reconstructive surgery

Table 67.9. **Indications for muscular relaxation in the neurological ICU.**

Monitoring

Monitoring of neuromuscular function after the administration of neuromuscular blocking agents is extremely important for appropriately dosing these agents and to better guarantee patient safety. The depth of neuromuscular blockade, as well as residual neuromuscular blockade may be monitored by performing clinical manoeuvres or by using peripheral nerve stimulators.

Clinical manoeuvres include the head lift (at least 5 seconds with patient supine at 180°), the handgrip, or the assessment of inspiratory force (at least 40 cmH2O), among others. Examination of these signs usually takes place before extubation.

On the other hand, the peripheral nerve stimulator allows another group of tests, which encompass the single twitch, the train of four (TOF), the double burst stimulation, and the tetany. These monitoring techniques are simple and can be performed at the bedside. TOF is very likely the standard method of monitoring drug-induced neuromuscular blockade (Figure 67.1).

Figure 67.1. **Peripheral nerve stimulation. TOF test in the forearm. The electrodes are placed on the ulnar nerve and the thumb is extended for better test execution; an intensity of 40 mA is sufficient for correct stimulation. Other site options for electrode placement include posterior tibial, and facial.**

It denotes four successive stimuli in 2 seconds (2Hz). The twitches in a TOF pattern progressively fade as relaxation increases. Disappearance of the fourth twitch represents a 75% block; the third and the fourth twitches an 80% block; and the second, the third and the fourth twitches a 90% block. Clinical relaxation usually requires 75-95% neuromuscular blockade, in other words: the desired goal is 1 or 2 perceptible twitches, and the drug administration is adjusted to achieve that end-point; total absence of thumb adduction is evidence of excessive block (overdose), peripheral nerve stimulator malfunction, or improper electrodes positioning. Cautions: microshock from nerve stimulators may pose a risk to patients with implanted cardiac defibrillators (ICDs); electrical stimulation of these tests can be very uncomfortable in the awake patient; severe edema may prevent proper nerve stimulation.

At the time of extubation it should be taken into consideration that clinical observations and the use of peripheral nerve stimulator provide useful but not necessarily infallible information: an individual can lift his head for 5 seconds or longer, even when 50% of their muscle fibbers are relaxed. Similarly, the four twitches of TOF may manifest even with 70% block. Pharmacologic options for muscular paralysis are shown in Table 67.10.

Depolarizing muscle relaxants	• Succinylcholine
Nondepolarizing muscle relaxants	• Rocuronium • Cisatracurium • Mivacurium • Pancuronium

Table 67.10. **Pharmacological options for muscular relaxation.**

Considerations and Precautions

- Use neuromuscular blocking agents only when indicated. Administer the lowest effective dose, and for the shortest time necessary.
- Neuromuscular blocking agents can be avoided in most critically ill patients, when analgosedation regimens are sufficient. Airway maintenance is mandatory in patients under pharmacologic paralysis.
- The selection of neuromuscular blocking agents is based on certain criteria, i.e., reasons for its use, expected duration of paralysis, characteristics of primary disorder, personal medical history (underlying conditions e.g., renal failure, myopathies, etc.).
- The absence of coughing during paralysis impairs the clearance of respiratory secretions; pooling of secretions can lead to atelectasis and ventilator associated pneumonia.
- Succinylcholine increases ICP and intraocular pressure (unwanted effects in TBI, brain tumor, intracranial hemorrhage, glaucoma and open eye trauma).
- Loss of the milking action of muscle contraction on the venous return from the legs predisposes to venous thrombosis during neuromuscular paralysis; prophylaxis for venous thrombosis is mandatory under these circumstances.
- Other complications of continuous muscle relaxant use include increased incidence of skin pressure ulceration, and the possibility that a patient may be aware and/or in pain, but unable to express discomfort because of the paralysis.
- Neuromuscular paralysis makes neurological examination unreliable.
- Following situations should be avoided in paralyzed and ventilated patients: malfunction or accidental disconnection from ventilator; paralysis without sedation; accumulation of tracheobronchial secretions; corneal injury; overdose or unnecessary long lasting muscle relaxant administration with accumulation; adverse drug interactions (e.g., with aminoglycosides, steroids, furosemide, etc.).
- Tolerance can develop with prolonged administration.
- The effect of non-depolarizing muscle relaxants can be antagonized (i.e., neostigmine + atropine), the reversal should be attempted when at least 2 twitches of the TOF are present.
- Prolonged paralysis may be observed after a single dose of succinylcholine or mivacurium. This phenomenon is mostly related to a congenital enzyme (pseudocholinesterase) deficiency.
- Neuromuscular blocking drugs can be associated with prolonged periods of muscle weakness after the drugs are discontinued. Consider residual drug effect, or underlying conditions that may predispose to neuromuscular weakness (e.g., critical illness polyneuropathy).

Main Drugs for Analgesia, Sedation, and Muscular Relaxation

Morphine (Analgosedation in Ventilated Patients)

Dose: 1-3-5 mg IV bolus; e.g. 3-10 mg/h

Morphine is the "gold standard" opiate analgesic in palliative care. However, its use for long-term analgosedation in ICU settings in Germany is uncommon.

Tips for infusion pump preparation (50 ml syringe): 1st option, morphine ampoule 10 mg/1 ml; 50 mg morphine (5 ampoules) plus 20 ml NaCl, infusion rate 2-3 ml/h. 2nd option, morphine ampoule 10 mg/1 ml; 100 mg morphine (10 ampoules) plus 40 ml NaCl, Infusion rate 2-3 ml/h. 3rd option, morphine ampoule 100 mg/10 ml; 100 mg morphine (1 ampoule) plus 40 ml NaCl, Infusion rate 2-3 ml/h.

Cautions: do not use in patients with head trauma, since it moderately increases ICP (unknown mechanism, not related to hypercapnia). Risk of hypotension (not recommended in patients with hemodynamic instability) and bronchospasm due to histamine release. Its use in the ICU has been associated with a high incidence of delirium. One metabolite (morphine-3-glucoronide) can produce myoclonus and seizures. Risk of accumulation in patients with renal failure. Immunosuppressive effect.

Fentanyl (Analgosedation in Ventilated Patients)

Tips for infusion pump preparation (50 ml syringe): fentanyl ampoule 0.5 mg/10 ml; 1.5 mg fentanyl (3 ampoules) plus 20 ml NaCl 0.9% (= 30 μg/ml). Dosage: 1-3.5 μg/kg/h = 2-12 ml/h = 60-360 μg/h.

Dose adjustments are not need in renal failure. Fentanyl is preferred to other opioids for patients with hemodynamic compromise; it does not cause direct histamine release.

Cautions: like morphine, fentanyl also moderately increases ICP. Fentanyl is not easily controllable since it causes prolonged drug effects as a result of drug accumulation in fatty tissue when using continuous infusion; it may also trigger chest wall rigidity or skeletal muscular rigidity when given by bolus. High doses of fentanyl rarely cause seizure activity. Fentanyl exert a powerful respiratory depressant effect (Table 67.4).

Sufentanil (Analgosedation in Ventilated Patients)

Sufentanil is very likely at present, the most common used opioid for analgosedation in ICU settings.

Tips for infusion pump preparation (50 ml syringe): 1st option, sufentanil ampoule 0.25 mg/5 ml; 0.5 mg sufentanil (2 ampoules) plus 40 ml 0.9% NaCl (= 10 μg/ml). Dose: 0.5 to 1.5 μg/kg/h = 2-10 ml/h = 20-100 μg/h.

2nd option, sufentanil ampoule 1 mg/20 ml; 1 mg sufentanil plus 20 ml 0.9% NaCl (=25μg/ml). Dosage 0.5 to 1.5 μg/kg/h = 0.8-4 ml/h = 20-100 μg/h.

Sufentanil is the most powerful opioid currently available for use in humans (about 1000 times the efficacy of morphine) (Table 67.4). **Carfentanil**, another analogue of fentanyl with a potency 10,000 times greater than morphine, is intended for large animal use only (e.g. bears) as its extreme potency make it inappropriate for use in humans.

Remifentanil (Short-term Analgosedation in Ventilated Patients)

Tips for infusion pump preparation (50 ml syringe): remifentanil 1 mg lyophilized vial, 1 mg of remifentanil in 50 ml NaCl 0.9% (= 20 μg/ml). Remifentanil is also supplied as 2 mg and 5 mg lyophilized powder vials.

Dosage: 0.04 -0.1 μg/kg/min = 2.5 to 6 μg/kg/h = 0.1-0.3 ml/kg/h.

Remifentanil is an ultra-short acting opioid (Table 67.4). Interruption of its infusion lead to rapid offset of effect. Rapid clearance and lack of drug accumulation result in rapid dissipation of analgesic effect, therefore, an alternative analgesic therapy should be anticipated and administered in a timely fashion prior to discontinuation of remifentanil (e.g. piritramide).

Caution: rapid bolus doses of remifentanil should not be given, specially in awake patients, since they may trigger unpleasant and unwanted side effects like respiratory depression and chest wall or skeletal muscle rigidity (a neuromuscular blocking agent or a μ-opioid antagonist may be required to facilitate assisted or controlled respiration).

Piritramide

It's a synthetic opioid mostly used for post-surgery pain in several European countries. Its potency is about 0.7 times that of morphine (Table 67.4). Piritramide is a long-lasting drug, what allows intermittent bolus administration. After a single IV or IM injection of 15 mg, pain can be relieved for 4-6 h. Its effect is similar to morphine, although with greater sedative effect and lower likelihood of hypotension; nausea and vomiting are among the side effects observed in some patients.

Figure 67.2. **Patient-controlled analgesia (PCA) system. The dose by bolus, the dose intervals, and the maximum total dose are preset before allowing the patient to self-regulate analgesia; in this way, accidental overdosing or abuse of the medication by the patient is prevented.**

In our environment, 3 mg IV bolus doses are given to adults every 15 minutes up to a maximum of 30 mg in 4 hours; in some cases the first bolus may consist in a loading dose of 7.5 mg of piritramide or higher. Piritramide is also a good choice for "patient-controlled analgesia" (PCA). This method is only suitable for patients who are awake and capable of drug self-administration (Figure 67.2).

Meperidine

Was the first synthetic opioid synthesized in 1932. At present, this drug is no more effective in managing pain than other opioid analgesics (Table 67.4), and its use is associated with a variety of severe side effects (i.e. neurotoxics e.g., seizures, delirium, dysphoria, tremor). These features led to decline in the use of this opioid as analgesic. Although not advised as an analgesic in the ICU, meperidine is still the first choice therapy for the treatment of post-anaesthetic shivering (PAS). Dosage: 25 mg meperidine IV every 4-6 h. Caution: meperidine may trigger tachycardia; one of its metabolites (normeperidine/norpethidine) can accumulate with repeated doses, and this accumulation is more pronounced when renal function is impaired. Normeperidine is toxic and has convulsant and hallucinogenic effects. These toxic effects cannot be countered with opioid receptor antagonists (e.g. naloxone); meperidine should not be administered to patients under concurrent antidepressant therapy with selective serotonin reuptake inhibitors or monoamine oxidase inhibitors.

Parecoxib

Is a selective cyclooxygenase-2 (COX-2) inhibitor for parenteral administration, approved in the European Union for the short-term treatment of post-operative pain in adults. This NSAID is an attractive alternative in the treatment of postoperative pain because of the potential for fewer gastrointestinal events. Parecoxib is supplied in 20 mg or 40 mg powder vial and solvent for solution for injection.

Dosage and administration: 40 mg by IM or IV injection, followed every 6 to 12 hours by 20 mg or 40 mg as required to a maximun of 80 mg per day.

Some years ago, certain selective COX-2 inhibitors (i.e., Rofecoxib® or Vioxx®) were taken off the market because of concerns about increased risk of heart attack and stroke

associated with long-term high-dosage use. However, further studies have also shown that some nonselective COX inhibitors are not entirely devoid of similar adverse effects. Selective COX-2 inhibitors (or "coxibs") may be regaining interest since it recently has been shown, they exert an analgesic effect not only by inhibiting prostaglandin synthesis, but also by increasing the availability of endocannabinoids in the CNS (i.e. spinal cord) and thus hampering the central sensitization process . The latter mechanism could explain the eventual superiority of coxibs over nonselective NSAIDs and low potency opioids. However, these observations have yet to be tested.

Ketamine (Analgosedation in Ventilated Patients)

Tips for infusion pump preparation (50 ml syringe): ketamine ampoule 500 mg/10 ml; 1.5 g ketamine (3 ampoules) plus 20 ml NaCl 0.9% (= 30 mg/ml)

Dosage: 0.5-4.5 mg/kg/h = 2-10 ml/h = 60-300 mg/h

Ketamine is different from most other anesthetics in that it has significant analgesic effect. It does not usually depress the cardiovascular and respiratory system. However, with the use of adjuvant sedatives or anesthetic drugs, respiratory depression can develop. Ketamine is also bronchial smooth muscle relaxant (good choice for acute asthma exacerbations), but it does possess some worrisome adverse effects. For instance, ketamine has a propensity to cause hypertension and tachycardia (increasing myocardial oxygen consumption) specially when given by bolus. Thus, ketamine is contraindicated in patients with ischemic heart disease. Likewise, it is unwise to give ketamine to patients with vascular aneurysms because of the possible sudden change in arterial pressure. The potential of ketamine to induce delirium has also to be taken into account, although this can be prevented by the concomitant administration of low doses of benzodiazepines. Other sides effects include hypersalivation, increased production of tracheal secretions, nystagmus, laryngospasm and increase in pulmonary resistance.

Ketamine has been suggested as an adjunctive treatment for refractory status epilepticus. In addition, to antiepileptic effects ketamine may induce neuroprotection.

Traditionally, ketamine has been avoided in the management of patients with TBI owing to concerns that it may increase intracranial pressure. However, several recent studies have refuted the original findings and showed no statistically significant rise in ICP in brain injured patients who are sedated with ketamine. Thus, ketamine is a safe and effective sedative agent to use in patients with TBI. Unlike opioids, ketamine does not alter gastrointestinal motility, which is of great benefit in critically ill patients.

Synergy between ketamine and opioids reduces dose requirements. Additionally, ketamine as an NMDA antagonist prevents the risk of developing secondary opioid withdrawal hyperalgesia during weaning; the addition of magnesium (0.08 g/kg/day adjusted according to renal function) makes ketamine more efficient in synergy.

Caution: ketamine produces undesirable psychological reactions (e.g. illusions, disturbing dreams, extracorporeal experiences, etc.). Therefore, it should not be given as monotherapy for analgosedation; its combination with other drugs (e.g. benzodiazepines) is recommended.

Propofol (Sedation in Ventilated Patients)

Propofol is an ultra short acting anesthetic with no analgesic activity. Due to its short duration of action, propofol should be given as continuous infusion for sedation.

Caveat: propofol for ICU sedation should be restricted to patients over 16 years of age, for up to 7 days, and to a maximum dose of 4 to 5 mg/kg/h (see bellow).

Tips for infusion pump preparation (50 ml syringe): 2% propofol vial (20 mg/ml); pure.

Dosage: 0.8 to 3 mg/kg/h (0.01-0.05 mg/kg/min) ≈3-10 ml/h = 60-200 mg/h

Propofol is dosed based on ideal rather than actual body weight, and no dose adjustment is required for moderate hepatic insufficiency; propofol's metabolites may accu-

mulate during acute renal failure. In elderly patients and sicker patients, the infusion rates that are necessary are markedly reduced. Since propofol provides no analgesia, concurrent analgesics are needed for pain. Propofol may cause hypotension, especially when given by bolus; a fall in mean arterial blood pressure (MAP) may reduce the cerebral perfusion pressure (CPP) if this is not mitigated with adequate fluid resuscitation and vasopressors. Hemorrhagic shock greatly enhances the hypotensive effects of propofol, even after resuscitation with IV fluids. Other side effects include hypertriglyceridemia (usually after 3 days continuous infusion), immunosuppressive effects, and life-threatening brady-arrhythmias, especially in the patient with intracranial hypertension. Propofol-related lipid loads must be considered when calculating calorie intake and prescribing tube feeds. The lipid emulsion of propofol promotes bacterial growth, good sterile technique must be observed in preparation and handling.

On the other hand, propofol decreases ICP in patients with either normal or increased ICP. Propofol also reduce the cerebral metabolic rate (CMR), and the consequent decrease cerebral oxygen uptake might prevent ischemic damage in regions with low perfusion. Propofol appears to have predominately anticonvulsant properties (i.e. burst suppression), it has been successfully used to terminate status epilepticus, and may be safely administered to epileptic patients. Propofol has been shown to be useful as therapy for delirium tremens, not only as adjuvant therapy, but also in treating delirium tremens refractory to benzodiazepines.

There is increasing awareness in the literature of the central role of mitochondrial dysfunction and cerebral cell death in areas of the brain with high oxidative stress. Propofol may act as a neuroprotective agent through limitation of oxidative stress.

When compared with midazolam for maintenance of sedation, propofol provides equal or better control and more rapid recovery. Propofol does not trigger malignant hyperthermia, and can safely be used in patients with porphyria. Tachyphylaxis may occur after prolonged administration.

Caution: a rare but potentially life-threatening complication associated with excessively high doses of propofol is known at the “Propofol Infusion Syndrome”. This syndrome is characterized by metabolic acidosis, bradycardia, hyperlipidemia, dysrhythmias, rhabdomyolysis, renal failure and cardiac arrest. The triad of bradycardia, hyperlipidemia, and rhabdomyolysis are unique features that help to distinguish this syndrome from septic shock. While originally reported in pediatric patients, it has subsequently been reported in adult as well. Treatment involves prompt discontinuation of the drug, supportive care, and cardiac pacing when needed. The mortality is high (>80%) despite therapeutic efforts. Maintaining propofol infusions below a rate of 4 mg/kg/h may reduce the risk of this deadly condition.

Midazolam (Sedation in Ventilated Patients and Procedural Sedation)

Tips for infusion pump preparation (50 ml syringe): 1st option, midazolam ampoule 15 mg/3 ml; 90 mg midazolam (6 ampoules = 18 ml) plus 32 ml of NaCl 0.9% (= 1.8 mg/ml).

Adult Dosage: 2-5 µg/kg/min → 0.1-0.3 mg/kg/h = 4 -12 ml/h = 7-22 mg/h.

2nd option, dosage 0.05-0.2 mg/kg/h: midazolam ampoule 50 mg/10 ml; 240 mg/48 ml → 5 mg/ml, infusion rate 1-3 ml/h = 5-15 mg/h.

To reduce the risk for oversedation, the infusion rate of midazolam should be determined using ideal body weight rather than total body weight. Analgosedation regimens with midazolam in neurocritically ill patients can be started at an infusion rate of 0.02 mg/kg/h after a loading dose of 0.2 mg/kg.

Midazolam is a short-acting benzodiazepine, which possesses profoundly potent anxiolytic, sedative, amnestic, hypnotic, anticonvulsant, and “centrally acting” skeletal muscle relaxant properties. Midazolam is more lipid soluble than lorazepam; thus it has a more

brisk onset and offset, making it the benzodiazepine of choice for rapid or temporary sedation. Its elimination half-life (1.8-6.4 hours, mean approx. 3 hours) is the shortest of all benzodiazepines, but it can be prolonged in obesity, elderly, congestive heart failure, alcoholic patients, and in renal failure.

Because of its short duration of action, midazolam is commonly given by continuous infusion. However, midazolam can also be given by bolus (adult: 1-2 mg q 5-10 min., as required) for procedural sedation (e.g., bronchoscopy, cardioversion). Infusions of midazolam lasting more than a few hours can produce prolonged sedation after the drug infusion is stopped. This effect is the result of multiple factors (e.g., drug accumulation in the CNS, accumulation of a active metabolite, especially in renal failure, decreased metabolism, etc.). Tachyphylaxis can occur with prolonged use, particularly after 3 or more days; ceiling effect is also observed with midazolam.

Cautions: abrupt discontinuation following prolonged benzodiazepine administration can produce a withdrawal syndrome consisting of anxiety, agitation, disorientation, hypertension, tachycardia, hallucinations, and seizures. Midazolam, like other benzodiazepines, requires special precaution when used in the elderly (risk of oversedation, respiratory depression, and paradoxical reactions). α-hydroxymidazolam, an active metabolite, may accumulate in renal failure. The overdose of midazolam can be treated with flumazenil. However, flumazenil can trigger seizures in mixed overdoses and in benzodiazepine-dependent individuals. Flumazenil is contraindicated in patients with tricyclic antidepressant overdose and patients receiving benzodiazepines for control seizures or elevated ICP. Like other benzodiazepines, midazolam should not be administered to patients with myasthenia gravis. Other relative contraindications include, sleep apnoea, chronic obstructive lung disease, and glaucoma.

Lorazepam

Unlike midazolam and diazepam, lorazepam has poor lipid solubility. Thus, it crosses the blood-brain barrier more slowly, which results in a delayed onset of action. In addition, its high degree of protein binding (85-90%) means its volume of distribution is mainly the vascular compartment, causing relatively prolonged peak effects. After single IV dose administration, the duration of action of lorazepam is 4 to 6 hours compared with 5-20 min of midazolam or diazepam (depending on the dose). Therefore, lorazepam is preferred for long-term sedation. Lorazepam has a high relative potency (1-2 mg of lorazepam is equal in effect to 10 to 20 mg of diazepam), and its elimination half-life is 10-20 h. Its metabolism does not led to the formation of active metabolites.

Lorazepam is usually given by bolus, although it can also be given by continuous infusion (caveat: risk of toxicity). As pointed out above, lorazepam is preferred for prolonged sedation due to its pharmacokinetics and because of lower cost, more consistent efficacy, fewer drug interactions, and less dependence on hepatic metabolism. However, lorazepam is not a suitable drug when rapid awakening is required (e.g., for neurological assessment). Lorazepam has strong sedative/hypnotic effects, and the duration of clinical effects from a single dose makes it an appropriate choice for the short-term treatment of insomnia, in particular in the presence of severe anxiety. The dose of lorazepam should be tailored according to the patient's needs. Withdrawal symptoms, including rebound insomnia and rebound anxiety, may occur after only seven days' administration of lorazepam. Lorazepam's anticonvulsant and CNS depressant properties are useful for the treatment and prevention of alcohol withdrawal syndrome. In this setting, impaired liver function is not a hazard with lorazepam, since lorazepam does not require oxidation, hepatic or otherwise, for its metabolism.

Dose-adult: 1-4 mg (0.02-0.06 mg/kg) IV bolus every 4 to 8 h. Patients with withdrawal syndrome may require higher doses.

Cautions: accidental intra-arterial injection can cause severe vasoconstriction with gangrene. Propylene glycol is the solvent vehicle used to deliver lorazepam and diazepam IV; large-dose lorazepam infusion may led to propylene glycol toxicity (metabolic acidosis, hyperosmolality, renal dysfunction, seizures, etc.). Lorazepam impairs body balance and standing steadiness and is associated with falls and hip fractures in the elderly.

Diazepam

It's a highly lipophilic benzodiazepine drug, which results in rapid distribution into the brain as well a relatively short duration of action upon redistribution into peripheral tissues. The use of diazepam for sedation in ICU-setting is rather limited because of its short duration of action, and the risk for oversedation due to accumulation. Like midazolam, diazepam can be given for procedural sedation. Diazepam is metabolised in the liver, and it has several pharmacologically active metabolites. Because of these active metabolites, the serum values of diazepam alone are not useful in predicting the effects of the drug. Diazepam has a biphasic half-life of 22 to 50 hours, and two to seven days for the active metabolite desmethyldiazepam. The elimination half-life of diazepam and also the active metabolite desmethyldiazepam increases significantly in the elderly, which may result in prolonged action, as well as accumulation of the drug during repeated administration.

Dose-adult: 0.03-0.2 mg/kg bolus IV every 2-4 h as required.

Clonidine (Analgosedation in Ventilated Patients)

Tips for infusion pump preparation (50 ml syringe): clonidine ampoule 0.15 mg/1 ml; 2.25 mg of clonidine (15 ampoules) plus 35 ml 0.9% NaCl (= 45 µg/ml).

Dosage: 0.3-1.2 µg/kg/h = 0.5-4 ml/h → 22-(90)-180 µg/h; eventually with a loading dose of 150-450 µg over 10-15 minutes; rapid administration of the loading dose is not recommended, since it may cause transient hypertension due to α-1 receptors stimulation.

Clonidine has been prescribed as an antihypertensive drug since the 1950s; however, some of its side effects led to a gradual decrease in clinicians enthusiasm for this drug. Interestingly, few of these side effects like sedation, dry mouth, and eventually bradycardia are welcome during anesthesia. Thus, clonidine has become one of the most important adjuvant or supportive drugs in anesthesia.

Clonidine is a central α-2 adrenoreceptor agonist that stimulate post-synaptic α-2 adrenergic receptors in the vasomotor center in the brainstem, leading to enhanced activity of inhibitory neurons and subsequent decreased sympathetic outflow. It also acts peripherally on α-1 receptors to cause a pressor response that is usually overshadowed by its central effect. Clonidine also binds to specific I-1 imidazoline receptors in the rostral ventrolateral medulla, leading to hypotension. Its sedative effect is mediated by the activation of α-2 adrenergic receptor at the locus coeruleus in the brainstem, while its analgesic effect (spinal and supraspinal) is attributed to the inhibition on the release of nociceptive neurotransmitters like substance P, and the enhancement of the analgesic effect of opioids through the stimulation of α-2 receptors.

The respiratory depression produced by clonidine is clinically irrelevant. Unlike benzodiazepines, clonidine does not increase the respiratory depression associated with opioids use.

Clonidine is useful as premedication for alcoholic patients undergoing surgery, and as alternative therapy for the treatment of PAS. In the ICU-setting, clonidine may be used to ease withdrawal symptoms associated with the long-term use of opioids, alcohol and nicotine.

Dexmedetomidine (Analgosedation in Ventilated Patients)

The broad spectrum of action of clonidine aroused interest in synthesizing more selective drugs, leading to the introduction of dexmedetomidine in 1999. Dexmedetomidine

is a drug with 8 times higher affinity for the α2-adrenoreceptor than clonidine, which causes it to be a much more effective sedative and analgesic agent than clonidine. In addition, dexmedetomidine has less cardiovascular effects than clonidine and causes minimal or none respiratory depression. The absence of respiratory depression makes dexmedetomidine an appealing sedative for patients who are prone to drug-induced respiratory depression (e.g., patients with sleep apnea or chronic obstructive lung disease), especially when these patients are weaning from mechanical ventilation.

Patients who receive dexmedetomidine in the ICU remain sedated when undisturbed but arouse readily with stimulation. Dexmedetomidine has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and postextubation.

Dosage and administration: the doses should be titrated to the desired clinical effect. Dexmedetomidine must be diluted in 0.9% saline for solution. For adult patients, dexmedetomidine is usually initiated with a loading infusion of 1μg/kg over 10 minutes, followed by a maintenance infusion of 0.2-1.0 μg/kg/h. The bolus doses is not used as it can cause paradoxical increases in blood pressure.

Cautions: mild hypertension in response to the loading dose is observed in 15% of patients, this effect is usually transient, and it can minimized by giving the loading dose over 20 minutes. Drug infusions were initially recommended for not longer than 24 hours; however, recent studies have shown that the safety and efficacy of dexmedetomidine persist beyond 24 hours, without the emergence of rebound effects after discontinuation. Hypotension and bradycardia may occur during ongoing therapy. Dexmedetomidine should be used cautiously in patients with pre-existent severe bradycardia and conduction problems, in patients with reduced ventricular functions (ejection fraction <30%), and in patients who are hypovolemic or hypotensive. Dexmedetomidine dose should be reduced in patients with severe liver dysfunction. All effects of dexmedetomidine can be antagonized by administering atipamezole (Antisedan®).

Zopiclone and Zolpidem

Are nonbenzodiazepine hypnotics ("Z-drugs") used for the short-term treatment of insomnia. Long-term use of Z-drugs is not recommended as tolerance, dependence, addiction may eventually occur with prolonged use.

Nonbenzodiazepine hypnotics appears to offer significant advantages over benzodiazepines due to its lower incidence of adverse side effects.

Zolpidem (2.5 h half-life time) has not proven effective in maintaining sleep and is more used for sleep initiation problems. This drug has less residual effect on sleepiness and psychomotor function the next morning, although morning-after anterograde amnesia may occur. Zopiclone has longer duration of effects (3.5-6.5 h half-life time) and it is indicated for the treatment of insomnia where sleep initiation or sleep maintenance are prominent symptoms (dosage: 5 to 7.5 mg at bedtime). Zolpidem does not significantly alter sleep architecture at recommended doses (10 mg immediately before bedtime, 5 mg in the elderly); however, zopiclone reduces the total amount of time spent in REM sleep as well as delaying its onset. Zolpidem showed no significant incidence of respiratory depression in healthy adults although reductions in lowest oxygen saturations were reported in one study of mild to moderate sleep apnea patients given 10 milligrams of zolpidem.

At present, it is unknown whether non-benzodiazepine agents will help prevent the development of post-traumatic stress disorder in ICU patients.

Cautions: combinations of zolpidem with antidepressants have resulted in increased incidences of hallucinations in patients. Zopiclone may cause delirium. Nonbenzodiazepine hypnotics causes impairments in body balance and standing steadiness in individ-

uals who wake up at night or the next morning, geriatric patients may be more likely to experience accidental events, or falls with hip fractures while taking these drugs (i.e. zopiclone).

Caveat: critically ill patients do not suffer from reduced total sleep time, but have increased sleep fragmentation and reduced restful sleep. Pharmacological treatment of sleep disorders in the ICU should first involve a review of all current medication, as well as the detection of delirium or other trigger factors for insomnia. Any drug prescription for acute sleep disturbances in the ICU should be only a short course of therapy.

Succinylcholine

It's the only approved depolarizing neuromuscular blocker. This ultra-short-acting agent (6-8 min) with a rapid onset time (30-60 sec) is mostly used to induce muscle relaxation and short-term paralysis, usually to facilitate tracheal intubation.

Succinylcholine is often considered as the most dangerous drug used in anaesthesia and intensive care medicine since it can trigger life-threatening reactions. In fact, succinylcholine is a relatively safe drug when its contraindications are known, and assuming that its many potential complications are understood and avoided. Succinylcholine is contraindicated in the routine management of children and adolescents because of the risk of rhabdomyolysis, hyperkalemia, and cardiac arrest in children with undiagnosed myopathies. In certain high-risk patients, succinylcholine should be also avoided due to the potential for exaggerated K+ release and subsequent hyperkalemia-induced cardiac arrest. Therefore, do not use succinylcholine in patients with severe burns, massive trauma (crush injuries), personal or family history of muscle disease or malignant hyperthermia, acidosis, severe intra-abdominal infection, renal failure with pre-existing hyperkalemia, stroke, Guillain-Barré syndrome, tetanus, closed TBI or spinal cord injury with muscle weakness and atrophy.

Despite the potential complications mentioned above, succinylcholine remains the muscle relaxant of choice for rapid sequence induction or intubation (RSI) in adults (i.e., emergency intubation in patients with suspected or confirmed "full stomach", ileus, acute abdomen, etc.). Endotracheal intubation in critically ill patients is a high risk procedure containing the danger of hypoxia and cardiovascular collapse; therefore, RSI is also the method of choice for emergency intubation in the ICU setting.

Caution: succinylcholine is also contraindicated in patients with increased ICP, penetrating eye trauma, and Glaucoma. The duration of action of succinylcholine may be prolonged in case of pseudocholinesterase deficiency.

Dose: 1-1.5 mg/kg.

Rocuronium

Introduced in 1994, rocuronium is a non-depolarizing neuromuscular blocking agent with a rapid to intermediate onset of action (1.5-2-[3] min), depending on dose, and with an intermediate duration of action (30-40 min). Usually, it is administered by IV bolus and is devoid of significant cardiovascular side effects. Due to its rapid onset of block, rocuronium has become the second-line choice agent for RSI when succinylcholine is contraindicated or not desired. Rocuronium undergoes no metabolism and is eliminated mostly by the liver (~70%) and slightly by the kidneys (~30%).

Caution: Rocuronium can produce a prolonged duration of action in elderly patients; the maintenance dosage must be reduced in liver failure.

Initial dose: 0.5 to 0.6 mg/kg; use higher dose (twice the normal dose) for RSI (0.9-1.2 mg/kg). Maintenance dose: 0.1 mg/kg. Continuous infusion: ≈ 0.5 to 0.7 mg/kg/h (9-12 µg/kg/min).

Cisatracurium

Is a muscle relaxant with an intermediate duration of action (40-50 min) and with an onset time of 2-3 min. It can be administered by IV bolus, however, for sustained muscu-

lar relaxation it is better to consider a continuous infusion since it is rapidly degraded in the plasma. Like atracurium, cisatracurium spontaneously degrades at physiological pH via Hofmann elimination (a temperature and plasma pH dependant process), this feature favors the use of this neuromuscular blocking agent as suitable choice for patients with renal failure. Cisatracurium does not cause histamine release, does not cause cardiac depression, and it generates less laudanosine (a metabolite that may cause neuroexcitation) than atracurium.
Initial dose: 0.1 mg/kg. Maintenance: 0.02 mg/kg.
Continuous infusion: ≈ 0.05-0.1 mg/kg/h (1-2 µg/kg/min).

Pancuronium

Is a long acting (90-120 min) non-depolarizing neuromuscular blocking agent with an onset time of 45 to 90 seconds and a maximum block effect reached within 2 to 5 minutes. Muscle relaxation suitable for intubation sets in about 90–120 seconds after administration of the drug. Although pancuronium can be given by continuous infusion, it is usually given as intermittent IV bolus doses to decrease the risk of drug accumulation. About 80% of pancuronium is excreted through the kidneys and the remainder is metabolised in the liver and excreted in the bile. When hepatic and renal function are intact, pancuronium is the preferred neuromuscular blocking agent in the ICU.
Caution: tendency to accumulate with prolonged use. Pancuronium should be given carefully to patients in whom an increased heart rate would be detrimental, since it usually produce tachycardia and hypertension (vagolytic effect). In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of pancuronium bromide may have profound effects.
Initial dose: 0.07 to 0.1 mg/kg, maintenance: 0.015 to 0.02 mg/kg.

67.2 Agitation and Delirium in the Intensive Care Unit

When in a continued fever occur difficulty of breathing
and paraphrosyne (delirium), it is a fatal sign
Hippocrates (460-377)

The set of symptoms and signs that characterize the syndrome which we now call delirium, was described at least three millennia ago. However, the definition, study, and diagnosis of this disorder is still difficult due to its nature, fluctuating course, and presentation. The terms agitation and delirium are often indistinctly used in clinical practice. Even when these conditions might be related, not all delirium is manifest with agitation, nor do all agitated patients have delirium.
Delirium is the most common mental dysfunction in critically ill patients, occurring in up to 87% of the sickest intensive care unit (ICU) populations (i.e. ventilated patients). The disorder is reported to be also present in 10 to 30 % of all hospital admissions, representing a frequent mental disorder among elderly patients, and the most frequent postoperative complication in this group. Critically ill patients suffering delirium have a three times increased risk of death. Delayed treatment of delirium, longer periods of mechanical ventilation, and increased complications among other factors, contribute to a bad outcome. The occurrence of this disorder in the ICU increases length of stay, hospital costs, and at the same time represents a challenge for the medical staff. Attempts to deliver high quality care to patients with disruptive or combative behaviours compromise more time and effort, and may cause the interruption or shortening of care tasks required for other patients.

67.2.1 Terminology

The word "delirium" was first used in medical writing by Celsus in the first century AD, it derives from the Latin *deliro-delirare*: *de-lira*, to go out of the furrow, hence, to deviate from a straight line. Even though Celsus used this term to describe (either as a symptom or as a syndrome) mental disorders during fever or head trauma, it should be pointed out that it was Hippocrates in 500 B.C., who previously coined the terms *phrenitis*, *paraphrosyne*, *leros* (incoherent language) and *mania* among others, to encompass mental abnormalities caused by fever, poisoning or head trauma.

Synonyms: acute confusional state, acute cerebral failure (or dysfunction), ICU's psychosis, postoperative psychosis, ICU's syndrome, organic brain syndrome, acute brain syndrome, pseudodementia, etc.

Definition of delirium according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV: disturbance of consciousness and attention; change in cognition (including memory deficit, disorientation or language disturbance); development of perceptual disturbance that is not better accounted for by a pre-existing or evolving dementia. The disorder develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition, substance intoxication or substance withdrawal.

Diagnosis of delirium according to the International Classification of Diseases-10th edition (ICD 10): impairment of consciousness and attention; global disturbance of cognition (including illusions, hallucinations, delusions and disorientation); psychomotor disturbances; disturbance of the sleep-wake cycle; emotional disturbances.

Other definitions of delirium: acute disturbance of mental status in the context of illness, stress, or drug intoxication (Meagher et al. 2008); Delirium is a symptom which indicates the transition of a purely somatic disease into a mental disorder (von Feuchtersleben 1845); "Delirium are the Dreams of waking Persons" (Quincy 1719); Delirium is an acute, fluctuating, transient and reversible condition caused by physical illness. Once the acute episode has remitted, the premorbid level of functioning is reached again, with personality reappearing intact (Adamis 2007).

Regarding this last definition, Adamis clarifies that experience and research shows that, not all cases survive this condition nor experience a full recovery of mental function. Delirium is often irreversible, especially in the elderly and those with pre-existing dementia, only 15% of patients with delirium return to their baseline level of functioning at the time of discharge, and less than 45% of the cases show a complete recovery at 6 months of leaving the hospital. Neither the existing DSM-IV and ICD-10 definitions of delirium describe this disorder in terms of evolution. In addition, it is considered that the ICD-10 criteria lack sensitivity and exclude many patients that would be classified as delirious by DSM systems and which have similar clinical profiles and prognosis as delirium. On the other hand, the DSM-IV definition does not cover characteristic features such as disturbances of sleep-wake cycle and motor activity. It is clear that a fully satisfactory definition of this disorder has not been yet achieved, however, the publication of ICD-11 may offer the possibility for an improved definition of delirium.

Central anticholinergic syndrome (CAS): this disorder, described by Longo in 1966, encompass the symptomatic complex of a psychosis induced by substances or medications with a central anticholinergic effect. In anesthetic practice, this syndrome arises during or immediately upon the emergence from general anesthesia. The definition of this disorder also includes the paradoxical reaction to certain psychotropic drugs (ie. benzodiazepines), or psychosis triggered by the consumption of psychoactive substances. The inci-

dence of SAC in anesthetic practice can be up to 10%. In the ICU however, its incidence is much lower (4.2%). Two variants of this syndrome are described: one with agitation and another comatose. The symptoms of both clinical forms respond well to intravenous administration of physostigmine. *Caveat*: clinical manifestations may recur several minutes after a first treatment with physostigmine. Seldom, as part of the symptomatic components of the syndrome, some patients manifest transitory respiratory depression or even breathing suppression after awakening.

Postoperative Cognitive Dysfunction (POCD): This term includes a wide spectrum of abnormalities of mental function, ranging from inconspicuous changes in memory and personality, to a complete loss of the skills needed for independent living.

The incidence of POCD increases with age, affecting up to 25% of subjects over the age of 90. Open heart surgery (e.g., cardiopulmonary bypass) and orthopedic surgery increase the frequency of occurrence of this disorder. Its manifestations are usually transient in young adults, disappearing at 3 months in the 40 to 59 years of age group. In elderly patients, symptoms can persist for long periods of time, or even be irreversible. It remains unclear whether this disorder is the result of the use of anesthetic drugs, or if it is an effect of surgery itself, or just the combination of both. According to a recent study, individuals carrying the apolipoprotein E-epsilon 4 (APOE4) are at high risk of developing POCD. Cerebrovascular disease or pre-existing dementia may also be contributing factors. In cases of cardiac surgery other pathophysiological mechanisms have been proposed, such as loss of pulsatile perfusion (cardiopulmonary bypass), altered cerebral autoregulation, and microembolisms. The use of neuraxial anesthesia procedures (spinal, epidural) does not reduce the incidence of POCD.

The availability of new anesthetics has substantially reduced the recovery time after general anesthesia. Today anesthetic recovery is usually reached in a period of time ranging from 30 to 240 minutes maximum. The diagnosis of POCD is usually considered when mental function abnormalities persist for more than 4 hours. Clinical manifestations can be subtle and only detected by the family. Often it tends to take from several days to up to 2 weeks until a deficiency is detected, whereas in another group of patients, the cognitive deficit is frankly obvious from the immediate postoperative period.

Postoperative delirium: this condition is independent from POCD and it affects between 10 and 60% of surgical patients 65 years of age or older. Postoperative delirium and POCD may coexist. As with POCD, the incidence of postoperative delirium is especially high in patients undergoing orthopedic surgery (e.g., hip fracture, knee replacement recipients, etc.) and open heart surgery. Currently it is doubtful that this variant of delirium is associated with hypoxia and hypotension intra-and/or postoperative, as previously accepted. Unlike the CAS, postoperative delirium may take several minutes or hours to develop after anesthesia recovery.

Abstinence syndrome: This disorder, also known as withdrawal syndrome, includes a set of signs and symptoms that occur upon the abrupt discontinuation/separation or a decrease in dosage of the intake of medications, recreational drugs, and alcohol. The group of symptoms of a withdrawal syndrome varies in intensity and form according to the type and amount of drug or substance used; the deprivation of certain substances such as alcohol, MAO inhibitors, hypnotics, amphetamines, etc., can lead to the development of genuine delirium if deprivation evolves for longer time..

Delirium tremens: is the most severe manifestation of alcohol withdrawal in individuals with a history of heavy alcohol use. While the symptoms of alcohol withdrawal usually appear between 4 to 12 h after the last drink, delirium usually occurs 3-10 days following the last alcohol consumption.

Psychomotor agitation: is a kind of restlessness or increased muscular activity associated with emotional distress. Agitation may vary in intensity, i.e., from slight restless-

↑ Cephalic Caudal ↓	Intracranial lesions	• Head trauma • Subdural or epidural hematoma • Traumatic subarachnoid hemorrhage • Intracerebral hemorrhage (i.e. non dominant temporal lobe) • Encephalitis/limbic encephalitis (paraneoplastic syndromes) • Meningitis/cerebral abscess • Neoplasms • Cerebral vasculitis (i.e. granulomatous, lupus)
	Encephalopathies	• Septic encephalopathy • Anoxic or ischemic-hypoxic encephalopathy (i.e. post cardiac arrest) • Hypertensive encephalopathy • Hepatic encephalopathy • Uremic encephalopathy • Wernicke encephalopathy • Pancreatic encephalopathy
	Endocrinopathies	• Pituitary dysfunction • Thyroid dysfunction • Parathyroid tumors • Adrenal dysfunction
	Intoxications	• Inhalant: ether gasoline, glue • Others: illicit drugs, CO, insecticides organophosphates, metals, etc. • Vitamins: A and D
	Drugs (medication)	• With direct anticholinergic effect: atropine, scopolamine, ipratropium bromide, disopyramide, neuroleptics, tri-cyclic antidepressants, antiparkinson drugs, H2-receptor blockers, other antihistaminics, etc. • With indirect anticholinergic effect: opiates/opioids, NSAIDs, benzodiazepines, inhaled anesthetics, propofol, ketamine, alcohol, local anesthetics • Others: theophylline, some antibiotics and antiarrhythmic agents, methyldopa, corticoesteroids, etc.
	Miscellaneous	• Sepsis • Postconvulsive delirium • Postoperative and postconcussive states • Sleep deprivation • Withdrawal syndromes (alcohol, sedatives, anti-psychotics, etc.) • Dehydration or hydric intoxication • Heat stroke • Hyper or hypothermia • Electrocution • Radiation • Extensive burns • Poisoning
	Respiratory disorders	• Hypoxemia/hypercapnia • Pneumonia • Pulmonary embolism • Acute respiratory distress syndrome
	Cardiovascular disorders	• Heart failure • Subacute endocarditis • Hypertension or hypotension
	Hepatic disorders	• Biliary sepsis • Hepatic insufficiency
	Metabolic and nutritional disorders	• Hyperglycemia/hypoglycemia • Electrolytes and acid-base disturbances • Porphyrias • Vitamin deficiencies: vitamin B1, B12, niacin, folic acid • Renal disorders • Urinary tract infections • Renal failure • Long bones, soft tissue trauma and burns • Fat embolism

Table 67.11. Some causes of delirium.

ness to vigorous uncoordinated movements. Motor activity tend to be purposeless, repetitive, and may also be accompanied by a sympathetic overdrive (autonomic hyperactivity). Agitated patients in the ICU exhibit continual motions like constant fidgeting, moving from side to side; pulling at dressings, bed sheets, and restraints; attempting to remove catheters or other tubes; overbreathing the ventilator; and evincing asynchrony with the current ventilator settings. In more severe cases, the motions may become harmful to the individual or to others. The agitated patient remains disoriented in one of several spheres. Depending on the degree of agitation and the ability of the patient to listen or communicate, commands may or may not be successfully followed.

67.2.2 Risk Factors and Causes of Delirium

Delirium is a multi-etiological disorder (Table 67.11), whose exact pathophysiologic mechanisms are still unknown. In addition, the pathophysiology of different subtypes of delirium may be different. Delirium is theorized to be a neurobehavioral manifestation of imbalances in the synthesis, release, and inactivation of neurotransmitters (acetylcholine, dopamine, GABA, serotonin, endorphins, and glutamate) that normally control cognitive function, behaviour, and mood.

Other hypotheses suggest: 1) an impairment of cerebral oxidative metabolism; 2) an excess of availability of some amino acids (i.e. tryptophan, phenylalanine) into the brain; and 3) the cerebral effect of certain mediators (for example IL-1, IL-6, tumor necrosis factor α, and other cytokines) released during an acute inflammatory response (i.e. sepsis, head trauma).

More useful in understanding delirium is the stress-diathesis model, which posits an interaction between the underlying constitutional or pre-existing factors (degree of susceptibility or diathesis) and the stressful nature of the insult (precipitating factors). For example, in an already vulnerable individual such as someone with established dementia, a minor factor, such as the prescription of a hypnotic, could trigger delirium, while in a healthy individual it would need a massive insult such as a major surgery to do so.

Risk factors for delirium can be categorized into two main groups: predisposing factors and precipitating factors (Table 67.12).

Predisposing factors	Precipitating factors (critical illness)	Precipitating factors (iatrogenic)
• Age (>65 years) • Male sex • Alcoholism • Smoking • Illicit drug use • APOE 4 polymorphism • Previous history of delirium • Cognitive impairment/dementia • Depression • Transfer from nursing home • Hypertension • Vision/hearing impairment • History of stroke • History of congestive heart failure	• Acidosis • Anemia • Fever/infection/sepsis • Hypotension • Metabolic disturbances • Respiratory disease • High severity of illness	• Immobilization (catheters, restraints) • Medications (for example, anesthetics, opioids, benzodiazepines) • Abrupt discontinuation of long-term treatments • Sleep disturbances

Table 67.12. **Risk factors for delirium in ICU patients.**

Predisposing risk factors encompass features existing before hospital or ICU admission, which can signify a patient's baseline vulnerability. Precipitating factors arise as a consequence of noxious insults or hospital-related issues.

67.2.3 Diagnosis of Delirium in the ICU

The Society of Critical Care Medicine (SCCM) recommends the systematic and simultaneous monitoring of the level of sedation and the possible presence of delirium for all critically ill patients. This has led to the development and validation of a number of delirium assessment tools in an effort to endorse and facilitate systematic screening for delirium. The Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for the ICU (CAM-ICU) allow nonpsychiatric physicians and other ICU personnel to diagnose delirium in ICU patients rapidly and reliably, even when the patient cannot speak because of endotracheal intubation

Using the ICSDC, or Bergeron's scale (Table 67.13), the patient is assigned a score from 0 to 8; a cut-off score of 4 has a sensitivity of 99% and specificity of 64% for identifying delirium.

The CAM-ICU, adapted from the conventional Confusion Assessment Method (Table 67.14), was designed for use in intubated patients. It has a high sensitivity (93% to 100%) and specificity (89% to 100%), but its main problem lies in its inability to distinguish between alterations of consciousness due to delirium from those caused by the effect of sedative medication. Using the CAM-ICU, delirium is diagnosed in two steps (Figure 67.3).

Level of consciousness is first assessed using a standardized sedation scale, while the content of consciousness is assessed using the CAM-ICU. One example, the Richmond Agitation-Sedation Scale (RASS), is a 10-point scale ranging from +4 to -5, with a RASS score of 0 denoting a calm and alert patient. By convention, RASS scores of -4 or -5 identify coma; a comatose patient cannot be assessed for delirium. All other patients, whether moderately sedated (RASS score -3) or more alert, should be evaluated for

Checklist item		Description
Altered level of consciousness*	A	No response
	B	Response to intense and repeated stimulation
	C	Response to mild or moderate stimulation
	D	Normal wakefulness
	E	Exaggerated response to normal stimulation
Inattentiveness		Difficulty following instructions or easily distracted
Disorientation		To time, place, or person
Hallucination-delusion-psychosis		Clinical manifestation or suggestive behavior
Psychomotor agitation or retardation		Agitation requiring use of drugs or restraints, or slowing
Inappropriate speech or mood		Related to events or situation, or incoherent speech
Sleep/wake cycle disturbance		Sleeping <4 hours/day, waking at night, sleeping all day
Symptom fluctuation		Symptoms above occurring intermittently
Total score		**0 to 8**

Table 67.13. **The Intensive Care Delirium Screening Checklist (ICSDC)**
* If A or B, then no other items are assessed that day. The ICDSC consists of eight items (rated present=1, or absent=0), and each patient is given a score from 0 to 8; 4 or greater is considered diagnostic of delirium.

delirium. The CAM-ICU assesses patients for four features of delirium (acute changes or fluctuations in mental status, inattention, disorganized thinking, and altered level of consciousness); three out of four features are required for a diagnosis of delirium (Figure 67.3).

Feature		Score	Check here if present
1. Acute onset or fluctuating course	Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?	Either question yes	☐
2. Inattention	**Letters Attention Test** Directions: Say to the patient, "I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand." Read letters from the following letter list in a normal tone 3 seconds apart. S A V E A H A A R T Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	Number of errors >2	☐
3. Altered level of consciousness	Present if the actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero	☐
4. Disorganized thinking	**Yes/No Questions** 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question.	Combined number of errors >1	☐
	Command Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If pt is unable to move both arms, for 2nd part of command ask patient to "Add one more finger". An error is counted if patient is unable to complete the entire command.		
Overall CAM-ICU Feature 1 plus 2 and either 3 or 4 present=CAM-ICU positive		Criteria met	☐ CAM-ICU Positive (Delirium Present)
		Criteria not met	☐ CAM-ICU Negative (No Delirium)

Table 67.14. Confusion Assessment Method for the ICU (CAM-ICU).
For more information: http://www.mc.vanderbilt.edu/icudelirium/docs/CAM_ICU_training.pdf

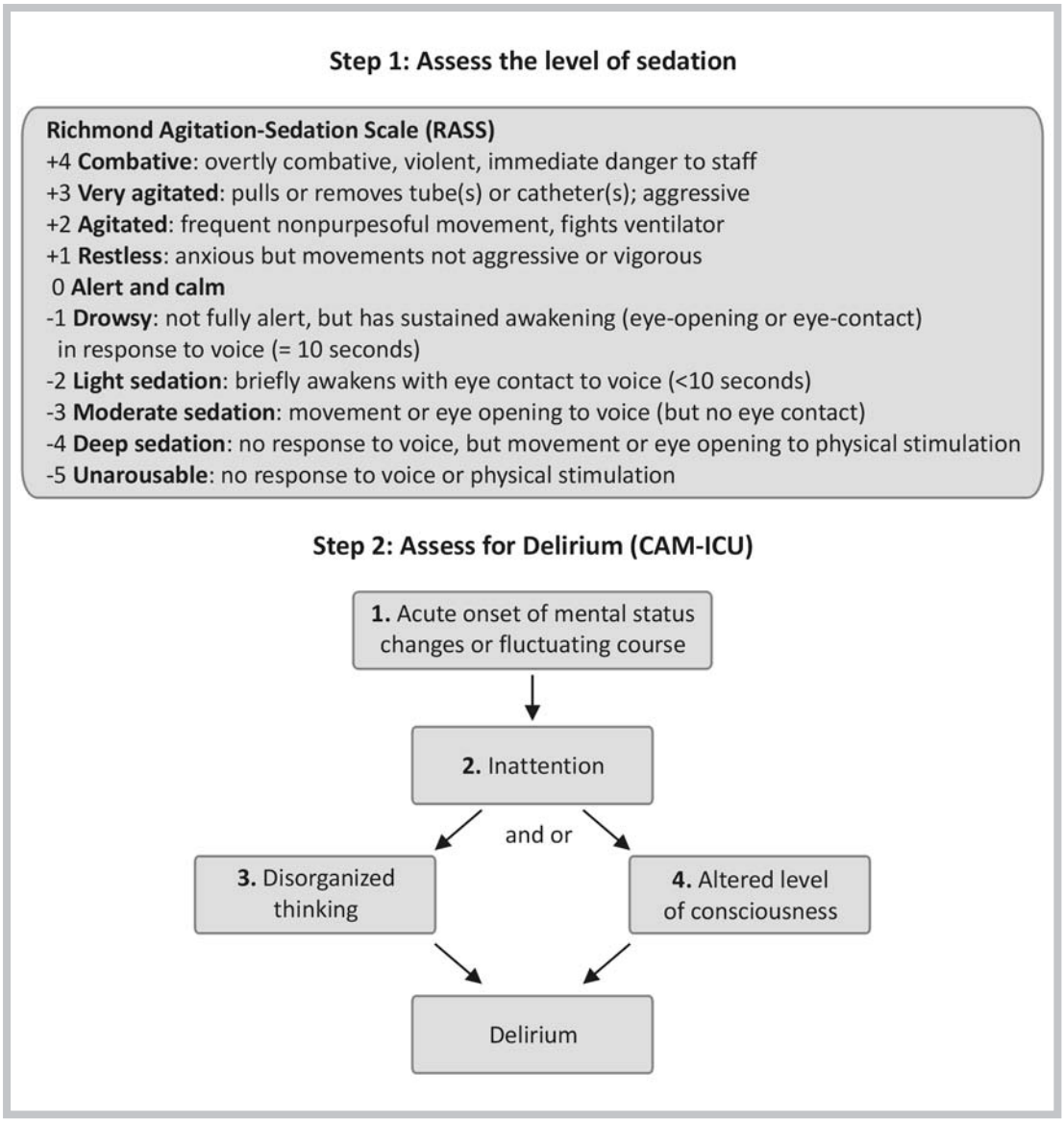

Figure 67.3. RASS and CAM-ICU for the Diagnosis of Delirium

67.2.4 Prevalence and Subtypes

The prevalence of delirium reported in medical and surgical ICU cohort studies has varied from 20% to 80%, depending upon severity of illness observed and diagnostic method used. Despite high prevalence rates in the ICU, delirium often goes unrecognized by clinicians or its symptoms are incorrectly attributed to dementia, or depression.
Delirium usually manifests as three subtypes; hyperactive, hypoactive, and mixed forms. However, there is a group of patients with subthreshhold symptoms or incomplete forms of the syndrome (subsyndromal delirium), whose symptoms do not fulfill the requirements of the DSM-IV or ICSDC defined criteria for delirium; subsyndromal delirium represents an intermediate state that is different from both clinical delirium and a normal

neurologic state, the mortality and ICU length of stay of these patients are significantly higher from those who have no symptoms of delirium.
Hyperactive delirium is characterized by restlessness, agitation, confusion, mood lability, psychotic symptoms, refusal of care and disruptive behaviours, whereas hypoactive delirium manifests with decreased responsiveness, lethargy, withdrawal, and apathy. Purely hyperactive delirium is rare (1.6%). Among non-ICU patient hyperactive delirium has been associated with a better prognosis than hypoactive delirium, but this relationship has not been evaluated thoroughly among ICU patients. In contrast, 43,5% of patients had purely hypoactive delirium, and 54,1% had mixed delirium. The hypoactive variant of delirium is less frequently recognized or is often dismissed as a transient, insignificant problem due to absence of disruptive, bizarre, and injurious behaviours. Hence, it represents a different challenge and requires greater skill in recognizing it because patients do not seemingly interrupt care delivery.

67.2.5 The Agitated Patient

Psychomotor agitation is a sign whose etiology should always be investigated. Agitation can result from psychiatric disorders (Table 67.15), as well as various organic disorders that may represent life threatening conditions. The exclusion of these organic causes is the first and crucial step in the evaluation on agitated patients; in all agitated patients the presence of delirium should be ruled out. In the ICU agitation is most commonly caused by delirium but may also result from fear, pain, patient-ventilator asynchrony, drug withdrawal or toxicity, hypoxia, CAS, or akathisia.
The agitated patient is usually a poor collaborator. The information provided by relatives or friends is very important in establishing the cause of agitation when a comprehensive history fails. It should be noted that in many cases drug-addicted or alcoholic patients deny or hide information about their addictions; a hospital stay of several days and hence restricted access to drugs or alcohol, often result in the emergence of unexpected withdrawal syndrome or delirium.
Motor and autonomic hyperactivity, anxiety and improper behaviours are usually the presenting symptoms of psychomotor agitation. Psychomotor agitation is not necessarily a synonym for violence. In most cases the agitated patient is not aggressive, however, disorganized and purposeless movements carry some potential risk of injury to both the patient and medical staff.
Akathisia ("inability to sit") is a syndrome characterized by unpleasant sensations of restlessness that manifests itself with an inability to sit still or remain motionless (i.e.

Non-psychiatric agitation	Psychiatric agitation

• Delirium
• Withdrawal syndromes
	• Psychotic disorders not associated with delirium:
	  ▪ Acute schizophrenia (at onset of disease, during treatment interruption or exacerbation)
	  ▪ Manic episode (bipolar disorder)
	  ▪ Delusional disorder (paranoia)
	• Others:
	  ▪ Personality disorders
	  ▪ Anguish crisis or panic attacks
	  ▪ Dissociative disorders
	  ▪ Phobias and adjustment disorder after life altering events

Table 67.15. Etiology of psychomotor agitation.

the patient paces the floor or jiggles the legs constantly). First noted in patients with Parkinson disease and senile dementia, akathisia is now observed most often in patients receiving neuroleptic drugs (e.g. haloperidol), or in some unmedicated patients with Parkinson disease; it can be also induced in normal individuals by the administration of L-dopa, or metoclopramide. Akathisia can be misinterpreted as anxiety, when in fact the causal relationship is inverse (the patient is nervous because he perceives that he can not stop moving). Akathisia should also be distinguished from agitation, otherwise antipsychotic administration may result in worsening symptoms; restless leg syndrome or depression with agitation are other differential diagnoses to keep in mind.

67.2.6 Prevention and Treatment of Delirium

The treatment of delirium begins with its prevention. Primary prevention is preferred; however, some degree of delirium is inevitable in the ICU. The prevention of delirium is essential in trying to reduce the morbidity, complications, and adverse outcomes caused by this condition. As delirium is most frequently multifactorial, successful preventive strategies are multi-component and aimed at reducing risk factors. However, it must be pointed out that, interventions aimed at preventing delirium have not been adequately studied in critically ill patients, on the other hand, a higher rate of incident delirium in critically ill patients (delirium present upon admission to the ICU or upon recovery from coma) compared with that observed in hospitalized patients without critical illness may indicate that preventive strategies that are effective in non-ICU patients may be less likely to prevent delirium in the ICU. The nature and number of delirium risk factors in ICU patients are different from those observed among other inpatients. Preventive interventions, therefore must address those risk factors that are most common in the ICU, including hypoxia, hypercapnia, hypoglycemia, shock, electrolyte abnormalities, infection, and exposure to sedative and analgesic medications.

67.2.7 General Preventive Measures

- Identify patients at high risk of delirium (predisposing/precipitating factors).
- Identify and correct sensory impairments: ensure patients have their glasses, hearing aid and dentures.
- Avoid prolonged immobility.
- Avoid physical restraints, if possible, as they often increase agitation. If restraint is unavoidable, observe appropriate guidelines.
- Encourage early mobilization.
- Timely removal of catheters and physical restrains.
- Early correction of dehydration.
- Avoid constipation.
- Detection and treatment of sleep disorders.
- Arrange treatments to allow for maximum periods of uninterrupted sleep.
- Quiet environment especially at rest times – noise reduction strategies (e.g.: use of vibrating pagers rather than call bells).
- Avoid psychoactive drugs; use them judiciously when needed (in the smallest effective dose and for the shortest time necessary).
- Avoid or minimize the use of medications with anticholinergic effect, or that trigger delirium.

- Manage discomfort and ensure adequate pain control.
- Provide environmental and personal orientation (communicate clearly and concisely: give repeated verbal reminders of the day, time and location, and identify key individuals, such as members of the treatment team and relatives).
- Provide clear signposts to patient's location, including clock, calendar (reorientation).
- Have familiar objects from the patient's home in the room (i.e., family photos).
- Involve family and caregivers to encourage feelings of security and orientation.
- Use a television or radio for relaxation and to help the patient maintain contact with the outside world.
- Explain the disease and all procedures and interventions that will take place.
- Encourage self care and participation in treatment (for example have the patient give feedback on pain).

67.2.8 Preventive Measures for Critically Ill Patients

- Adequate sedation (avoid over-sedation, promoting daily interruption of sedatives and analgesics or intermittent boluses rather than continuous infusions).
- Repositioning the patient.
- Reassurance (for fear, anxiety).
- Repositioning endotracheal tube (>2 cm from carina).
- Providing the patient with a writing board if unable to communicate.
- Early tracheostomy (reduces sedative use, and improves communication and patient mobility).
- Optimize pain control (both, inadequate analgesia and excessive opioids administration provide risks for developing delirium).
- Early diagnosis, prophylaxis and treatment of withdrawal's syndromes.

Pharmacological treatment for postoperative delirium prevention is currently under investigation. Reports from some studies demonstrated that the preoperative premedication with haloperidol or gabapentin either reduces the severity or the incidence of postoperative delirium; other drugs such cholinesterase's inhibitors (e.g., donepezil) have been also used for this purpose, but results did not reach statistical significance.

Analgesic medication play a vital role in maintaining patient comfort, and adequate pain control is likely to reduce risk for delirium, however, practitioners must strive to avoid over sedation by administering the drugs only as necessary. In fact, sedation protocols that use validated sedation scales, emphasizing intermittent boluses rather than continuous infusions, and promoting daily interruption of sedatives and analgesics significantly improve multiple clinical outcomes. Halting sedative infusions and allowing patients to "wake up" on a daily basis reduces the risks of accumulation of longer acting agents, duration of mechanical ventilation and length of stay. Nevertheless, daily sedation holds are not appropriate in all patients and are not a substitute, but an adjunct to appropriate sedation monitoring and sedative dose titration. Sedative drug choice is also important; for instance, a comparison of patients sedated with dexmedetomidine versus lorazepam demonstrated an increase in coma-free days and trend towards delirium-free days in the dexmedetomidine group. Furthermore, preliminary data from a multicenter randomized controlled trial reported that dexmedetomidine significantly decreased the incidence and duration of delirium in ICU patients compared with midazolam. The effect of these methods of sedation on delirium is the subject of ongoing investigations.

67.2.9 Managing the Agitated Patient

Agitation may be a distressing issue in ICU, since it is associated with potentially dangerous complications such as self-extubation, removal of arteria and venous catheters, increased systemic and myocardial oxygen consumption, and failure to participate in therapeutic interventions. An extremely agitated patient can hamper the workflow in the ward. Managing the disruptive behaviours is often demanding of time and attention and has been highlighted as a cause of stopping or abbreviating care delivery to another patient. Under these circumstances, the newcomer physician may feel urged to quickly end the agitation episode. However, medications only become necessary when other interventions are ineffective in controlling agitation, or to prevent patients endangering themselves or others. Whenever possible, an accurate and fast diagnosis of the cause of agitation should be performed before implementing any pharmacological treatment ("look around" before searching for a syringe).

The behavior of an agitated patient is impossible to predict, therefore, there are not rigid guidelines for the management of these cases. Usually, the risks of patient's behaviour are assessed at first in order to ensure his safety. Verbal containment, if possible, should precede the use of any other therapeutic procedure. In this phase, the first line of intervention is to develop dialogue with the patient, a companion or family members may also contribute. The attitude toward the agitated patient should be reassuring, and nonjudgmental, they should be approached with a soft and calm voice, while showing interest in their problems and making it clear that the intentions are to help them.

When the patient's agitated behavior poses a real danger to himself or others, and verbal containment does not seem to work, physical restraints are necessary; the control of an extremely agitated patient may require the efforts of 4 or more individuals. Once this point has been reached, we should explain that restriction is not a punishment, but a procedure for his safety, because he is unable to control his behavior.

67.2.10 Pharmacological Treatment

The treatment of delirium requires addressing the underlying causes; pharmacological treatment would be incomplete, or even ineffective, when the treatment of the underlying cause has not been initiated. The use of psychotropic drugs complicates the ongoing mental state assessment, and can also impair the patient's ability to understand and therefore cooperate with treatment. Thus, drug treatment should be reserved for 1) patients whose symptoms of delirium would threaten their own safety or the safety of others, 2) to relieve distress in a highly agitated or hallucinating patient, or 3) in order to carry out essential medical treatment or investigations.

Haloperidol (0.5-2 mg PO or IV every 4-6 hours as needed) remains the first-line treatment in many clinical guidelines for ICU-acquired or postoperative delirium. It has been proven to be useful in the treatment of both hyperactive or hypoactive subtypes. Clinical effects are observed within 30-60 min. after iv administration and last for as long as 4-8 hrs. The SCCM guidelines suggest that patients with hyperactive delirium should be treated with 2 mg intravenously, followed by repeated doses (doubling the previous dose) every 15 to 20 minutes while agitation persists. Once the agitation subsides, scheduled doses (every 4 to 6 hours) should be continued for a few days, followed by tapered doses for several days (up to 7 or 10 days upon symptoms fully resolve). Common doses for ICU patients range from 4 to 20 mg/day, but higher doses are frequently used for the treatment of acute agitation. It is important to bear in mind that, usually, the elderly population needs lower doses.

Haloperidol does not cause major respiratory depression, but may induce hypotension. Generally, intravenous use of haloperidol is associated with lower incidence of extrapiramydal adverse effects but a higher risk of developing Torsades de pointes. Therefore, patients receiving intravenous haloperidol should have ECG monitoring. A QTc interval >500 ms would suggest a need to stop haloperidol and eventually a referral to a cardiologist. Neuroleptic malignant syndrome (NMS) is a rare but a life- threatening neurological disorder most often caused by an adverse reaction to neuroleptic or antipsychotic drugs; NMS develops slowly over 24-72 hrs. and can last for up 10 days after discontinuation of the drug. Individuals using haloperidol and chlorpromazine are at risk of developing NMS. The use of haloperidol should also be avoided in case of hepatic failure, anticholinergic toxicity, and patients with Lewy body dementia.

The administration of haloperidol in delirium tremens is somewhat controversial since it reduces the threshold to seizures. However, some clinicians use it as adjunctive therapy with benzodiazepines to control psychiatric symptoms associated with this delirium such as anxiousness, hallucinations, and combativeness.

Droperidol, **chlorpromazine**, **levomepromazine** and **pimozide** have all been used in the treatment of hyperactive delirium. Levomepromazine and chlorpromazine have been used for very agitated delirious patients, largely because these drugs are more sedative compared to haloperidol, however, these two drugs are not recommended in hypoactive delirium because they cause excessive sedation; on the other hand, chlorpromazine causes local irritation, an effect to take into consideration at the time of peripheral intravenous administration.

Benzodiazepines are the treatment of choice for delirium tremens and alcohol withdrawal. So far, there is no evidence to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalized patients, conversely, when benzodiazepines are used to treat agitation associated with delirium from other causes, they often make it worse, particularly in patients with dementia.

There are not studies showing one benzodiazepine to be more effective than another in treating delirium tremens. Selection of a benzodiazepines is dependent on several factors including route of administration, onset and duration of action, hepatic and renal function; lorazepam, for instance, does not have active metabolites, making it an attractive choice for patients with decreased hepatic or renal function. Doses of benzodiazepines used during delirium tremens may exceed that which is considered to be normal; genetic differences in patients may contribute to the variable response seen with these drugs.

Clonidine (an α-2 receptor agonist) does not stop the delirium or seizures associated with the withdrawal process, however, it is a good adjunctive therapy to treat the symptoms of autonomic hyperactivity (i.e., increased blood pressure and tachycardia).

Clomethiazole (Distraneurin®) is also an effective drug in the management of delirium tremens; however, its use in the ICU has been declining due to some unwanted side effects such as hypotension, severe respiratory depression, and increased bronchial secretions.

Atypical antipsychotics (for instance, **risperidone**, **quetiapine**, **olanzapine**, and **ziprazidone**), may also be helpful in the treatment of non-alcohol withdrawal related delirium, but only preliminary data exist supporting their use in the ICU. Comparative studies of haloperidol and atypical antipsychotics have failed to identify evidence of any advantage in terms of clinical efficacy. In a non-randomized trial that enrolled 73 medical and surgical ICU patients, olanzapine was compared to haloperidol; the authors reported that resolution of delirium symptoms was similar in both treatment groups, but more side effects were observed in patients treated with haloperidol. It has also been suggested that, few of these new anti-psychotic drugs have a faster onset of action than haloperidol. Unfortunately, many of these new anti-psychotics are only available as oral formulations.

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68 Acute Hypertensive Response and Stroke

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68.1 Introduction

Chronic arterial hypertension is the premier manageable risk factor for both hemorrhagic and ischemic stroke [1]. There is a direct and indirect association between chronic arterial hypertension and ischemic stroke. Hypertension is the most common risk factor for small subcortical infarct associated with small vessel disease in the brain [2]. Moreover, hypertension is a known risk factor that predispose for atherosclerosis in the large cervical and intracranial vessels, which constitute the most common etiology of acute ischemic stroke [3]. On the other hand, hypertension is the most important risk factor for spontaneous intracerebral hemorrhage and it has been associated with about 50% of all the intracerebral hemorrhages [4].

Elevated blood pressure is quite common in acute phase of ischemic or hemorrhagic stroke. This phenomenon, known as acute hypertensive response, is the elevation of blood pressure (BP) above normal and premorbid values that initially occurs within the first 24 hours of symptom onset in patients with stroke [5]. Management of acute hypertensive response in acute stroke involves physicians from different disciplines including but not limited to emergency physicians, intensivists, primary care physicians, neurologists, neurosurgeons, and cardiologists. In this chapter we will emphasize the importance of the elevation in blood pressure after ischemic and hemorrhagic stroke and we will discuss its epidemiology, pathophysiology, and current evidence of blood pressure management.

68.2 Definition

Acute hypertensive response is the elevation of blood pressure (BP) above normal; premorbid values that initially occurs within the first 24 hours of symptom onset in patients with stroke. The 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement [6] and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) define hypertension on the basis of the presence of consistent BP >140/90 mmHg (multiple readings on separate days) [7]. This definition of hypertension is a threshold for the use of long-term antihypertensive treatment that is supported by evidence derived from randomized trials and clinic population-based data that demonstrate reduction in cardiovascular events with this threshold for treatment. The same definition cannot be applied in the case of acute hypertensive response, because the above-mentioned ascertainment criteria and rationale are not valid. The executive summary of the ISH statement on management of BP in acute stroke stated that high BP (>140/90 mmHg) is very common early after ischemic stroke (occurring in ≈75% of cases) and intracerebral hem-

orrhage (ICH >80%) and is independently associated with a poor functional outcome [8]. To maintain consistency with the ISH statement, acute hypertensive response is defined as «systolic BP >140 mmHg or diastolic BP of >90 mmHg demonstrated on 2 recordings taken 5 minutes apart within 24 hours of symptom onset.» This definition predominantly serves to provide a uniform standard for measuring prevalence and not for setting treatment thresholds for antihypertensive treatment, which may vary depending on stroke subtype and other considerations.

68.3 Epidemiology

Acute hypertensive response is reported in more than 60% of patients presenting with stroke in a nationally represented study from United States [9]. With approximately 15 million patients experiencing stroke worldwide each year, the acute hypertensive response may be expected in approximately 10 million patients per year [10]. In a systematic review of 18 studies, 52% of patients with stroke were reported to have high blood pressure at the time of the admission. The criteria used to define high BP varied considerably: systolic BP ranged from 150 to 200 mmHg and diastolic BP criteria from 90 to 115 mmHg [11]. In one of the largest studies in United States using the National Hospital Ambulatory Medical Care Survey, systolic BP >140 mmHg was observed in 63% of the 567, 704 adults with acute stroke, diastolic BP >90 mmHg in 28%, and mean arterial pressure (MAP) >107 mmHg in 38% of the patients [9]. In the same study, the subgroup analysis showed that 67% of the patients with ischemic stroke presented with elevated blood pressure compared to 75% and 100% of the patients with intracranial hemorrhage and subarachnoid hemorrhage, respectively.
Elevated blood pressure is common after stroke, particularly after intracerebral hemorrhage (ICH). It has been reported that up to one third of the patients presenting with acute stroke have elevated blood pressure and there is tendency to normalization within ten days with spontaneous reduction without any antihypertensive treatment [12]. Marked elevation of the blood pressure has been associated with poor clinical outcomes including death and disability in a retrospective study of 87 patients with ICH. In the same study the marked elevated blood pressure (systolic blood pressure >145 mmHg) during the admission and persistent inadequate blood pressure control were both associated with poor clinical outcome [11].

68.4 Pathophysiology

The brain requires constant influx of oxygen and is very susceptible to ischemic changes after even short time of oxygen deprivation. The regional cerebral blood flow (rCBF) needs to be kept steady in order to ensure a constant delivery of oxygen. Approximately 20% of the cardiac output is delivered to the brain. The rCBF is approximately 55 ml/100 g of tissue/minute, ranging from 20 ml/100 g of tissue/minute in the white matter to 70 ml/100 g of tissue/minute in the gray matter [13]. In the brain, the rCBFcan be maintained constant in spite of a significant variation in the cerebral perfusion pressure, which is mainly determined by the mean arterial pressure [14].
Under normal circumstances, changes in precapillary arteriolar diameter (<400 μm) maintain constant cerebral blood flow in the capillary bed between MAP of 60 and 150 mmHg [15]. A fast dynamic response to changes in pressure pulsations is followed

by a slow static response that restore rCBF after the initial dynamic response has settled by myogenic [16] (mechanogenic) and metabolic (chemogenic) mechanisms [17].
In chronic arterial hypertension, the lower end of the autoregulation curve is shifted toward high pressure, presumably because vessel wall thickening and luminal narrowing limit the capacity of the resistance vessels for dilation [18]. In acute stroke, autoregulation may be impaired in regions surrounding an acute lesion and even in the contralateral hemisphere due to dilation of cerebral resistance vessels in an attempt to increase rCBF in response to tissue ischemia and acidosis [19]. More recently, it has been shown that autoregulation is impaired for rapid changes (dynamic autoregulation) in systemic BP even when it is preserved for controlled changes [20]. Other conditions, such as cerebral vasospasm in subarachnoid hemorrhage, also cause arteriolar constriction, which shifts the autoregulatory range toward higher values [21]. In these circumstances (chronic hypertension and vasospasm) there is a clear shift of the autoregulatory curve towards the right. Thus, there is a potential risk of ischemic brain injury with sudden decrease in the cerebral perfusion pressure below the lower limit of the autoregulation [22]. In the presence of elevated intracranial pressure, MAP >60 mmHg may not be adequate to maintain constant cerebral blood flow in the capillary bed. The cerebral perfusion pressure measured as the difference between the mean arterial pressure and the intracranial pressure can underestimate the localized increased pressure and perfusion changes in focal stroke or localized ICH. In absence of a more sensitive method to evaluate the peristroke perfusion changes, the measure of the global perfusion pressure remains still useful. A perfusion pressure of 70 mmHg or higher has been used as a treatment threshold, mainly based on the extrapolation from head trauma patient's management [23].
The underlying reason for high blood pressure in the setting of acute stroke is not known. In part, could be just the reflection of inadequately treated or undetected chronic hypertension [24]. However, the tendency to spontaneous reduction in the subacute phase of the stroke supports the role of other transient and stroke-specific related mechanisms [25]. Stroke involves transient or permanent damage to the areas affected in the brain regulation of cardiovascular functioning, including BP. The parasympathetic and sympathetic nervous systems are lateralized to the left and right cerebral hemispheres, respectively [26]. Prefrontal and insular cortices provide inhibitory and excitatory input, respectively, through pathways that connect to the nuclei in the brainstem, particularly in nucleus tractus solitarius and ventrolateral medulla [27,28]. Further modulation is provided by cingulated cortex, amygdala, and hypothalamus. Because of the widespread distribution of these areas, most stroke lesions involve these areas to a varied extent.
Increased sympathoadrenal tone [29] with subsequent release of renin and vasoconstriction of arterioles results from: 1) direct injury to inhibitory or modulatory brain regions, or 2) indirect effects of reduced parasympathetic activity [30], which leads to impaired cardiac baroreceptor sensitivity in patients with stroke [31]. Although direct injury is the most likely explanation, an indirect effect of muscle paralysis or the release of neurotransmitters such as nitric oxide during ischemia may be contributing factors to altered activity of these nuclei [32,33]. Other stress responses to hospitalization, headache, urinary retention, or concomitant infection [34] may lead to abnormal autonomic activity and raised levels of circulating catecholamines [35] and inflammatory cytokines [36], and subsequently may contribute to the hypertensive response. Presumably, these abnormal autonomic responses normalize over a few hours secondary to spontaneous or therapeutic recanalization and resolution of the ischemia and perhaps because of other neural compensatory mechanisms [37]. The aforementioned mechanisms suggest that the primary cause of the acute hypertension response is damage or compression of specific regions of the brain that mediate autonomic control.

68.5 Management of Acute Hypertensive Response in Stroke Patients

Acute hypertensive response can be observed in all type of acute stroke subtypes. However, differences in underlying mechanism mandate different management strategies. Intravascular volume depletion has been identified in patient with acute stroke which may result in a natural hypertensive or hypotensive response as well as on an exaggerated hypotensive response to antihypertensive medication [38-40]. An acute hypertensive response after stroke usually follows one of the four most common courses: 1) spontaneous decline without antihypertensive medication; 2) no clear decline, or even an elevation; 3) modest decline with antihypertensive medication (approximately 10 to 15% reduction for the baseline value); or 4) an intense decline with antihypertensive medication (more than 20% from the baseline value).

68.6 Acute Hypertensive Response in Patients With Intracerebral Hemorrhage

Non traumatic ICH results from rupture of blood vessel in the brain. It is a major public health problem with an annual incidence of 10 to 30 per 100.000 inhabitants [41,42]. Long term uncontrolled arterial hypertension constitute the common cause of non traumatic ICH in adults [4]. Most bleeding in hypertension- related ICH occurs at the or near the bifurcation of the small penetrating arteries that originate from the basilar, middle cerebral, anterior and posterior cerebral arteries [43]. The most common sites of ICH are basal ganglia, thalamus, pons, cerebellum, and deep cerebral white matter. Intracerebral hematoma induces injury of the neurons and glial cells by mechanic disruption, causing oligemia, neurotransmitter release and final mitochondrial dysfunction with membrane depolarization [44-46]. Ultimately, depending on the degree of mitochondrial dysfunction the perihematoma region can suffer from temporary metabolic suppression (hibernation) [47] to cellular edema and necrosis.

Three phases have been described for cerebral blood flow and metabolic changes in the peri-hematoma region based on recent laboratory and clinical studies [48]. A hibernation phase is seen during the first 48 hours. This phase is described by a reduction in rCBF and metabolism, in both ipsilateral and contralateral hemispheres. This has also been proven by using PET scan, demonstrating decrease rCBF and oxygen extraction flow (OEF) [49]. A reperfusion phase is seen between 48 hours and 14 days. This consists of a heterogeneous pattern, including areas of normal, hypo- and hyper-cerebral perfusion. The normalization phase is observed after 14 days and consists of normal blood flow except in non-viable tissue. Based on this assumption, blood pressure reduction in the period of hibernation should be relatively safe. Hemostasis is initiated by local activation of hemostatic pathways and mechanical tamponade. There is evidence that products of the coagulation, particularly thrombin and hemoglobin breakdown products that can trigger activation of the microglia with a secondary cascade of injury inducing edema around the hematoma [50-53]. One third of subjects presenting with ICHs continue to demonstrate hematoma expansion (with subsequent deterioration and death) in the first few hours after onset [54]. An initial systolic BP more than 200 mmHg is associated with hematoma expansion [55] and increased mortality [56] among patients with ICH. Persistently higher systolic BP is also associated with perihematoma brain edema formation [57]. Reducing BP may reduce the rate of hematoma expansion, although conclu-

sive evidences are not available. Recent studies suggest that reduction of BP may be tolerated because of reduced metabolism (hibernation) [58] and preserved autoregulation in the perihematoma region [59].

A multicenter prospective observational study reported the use of intravenous labetalol, hydralazine, and/or nitroprusside for maintaining blood pressure more than 160/90 mmHg within 24 hours of symptom onset among patients with ICH [60]. Low rates of neurological deterioration and hematoma expansion were observed in treated patients. Patients treated within 6 hours of symptom onset were more likely to be functionally independent at 1 month than patients who were treated between 6 and 24 hours. Another study evaluated the tolerability and safety of intravenous nicardipine infusion within 24 hours of symptom onset to reduce and maintain MAP equal or less than 130 mmHg, consistent with previous American Heart Association/American Stroke Association Stroke Council guidelines (ASA) [61]. The primary outcome of tolerability was achieved in 86% of the patients. Low rates of neurological deterioration and hematoma expansion were observed among treated patients. Indirect comparisons suggest that intermittent intravenous bolus regimens of antihypertensive agents have greater variability in BP control than continuous infusion regimens.

The current ASA Stroke Council guidelines recommend [62] that «until ongoing clinical trials of blood pressure intervention for intracerebral hemorrhage are completed, physicians must manage blood pressure on the basis of the present incomplete evidence» by maintaining systolic blood pressure less than 180 mmHg in the acute period with short half-life intravenous antihypertensive drugs. The European Stroke Initiative guidelines [63] recommend lowering the blood pressure in patients with intracerebral hemorrhage to maintain a systolic blood pressure below 180 mmHg. Both guidelines consider more aggressive systolic blood-pressure lowering in the absence of clinical signs of high intracranial pressure or chronic hypertension. Recent data suggest a greater therapeutic benefit with more aggressive lowering of blood pressure [64]. In one observational study, hematomas enlarged in 9% of patients with systolic blood pressure maintained below 150 mmHg and in 30% of those with systolic blood pressure maintained at less than 160 mmHg or a higher threshold. The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial [65] and the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) trial [66]reported that aggressive reduction of blood pressure to less than 140 mmHg probably decreases the rate of substantial hematoma enlargement without increasing adverse events. In subgroup analyses from INTERACT, patients recruited within 3 hours and those with an initial systolic blood pressure of 181 mmHg or more seemed to have the greatest benefit with aggressive lowering of blood pressure. No difference in rates of death and disability at 3 months were seen between patients treated with aggressive and conservative lowering of blood pressure in ATACH or INTERACT studies, although the analyses were limited by small sample sizes. Because the effect on clinical outcome has not been fully assessed, the more conservative targets set in the ASA Stroke Council and the EUSI guidelines should be followed. Great caution is advised about lowering blood pressure too aggressively without concomitant management of cerebral perfusion pressure.

68.7 Acute Hypertensive Response in Patients With Ischemic Stroke

Ischemic stroke results from occlusion of an artery with subsequent reduction in rCBF, demarcated into regions of severe reduction (core) and moderate reduction (penum-

bra) [67]. The penumbra remains viable for hours because some degree of blood flow is sustained through collateral supply; however, it is theoretically vulnerable to further ischemic injury with systemic BP reduction because of impaired regional autoregulation, particularly during rapid BP reduction [68]. Conversely, in an experimental model of focal cerebral ischemia and reperfusion, BP reduction reduced infarct size and deficits [69]. Therefore, a period of vulnerability to progression of ischemic deficits may exist after which there may be benefit from BP reduction. A higher rate of death or dependency was observed in patients with initially high or low systolic BP (U-shaped relationship) among 17,398 ischemic stroke patients randomized in the International Stroke Trial [70]. The relationship appeared to be mediated in part by increased rates of early recurrence and death that resulted from presumed cerebral edema in patients with high BP and increased coronary heart disease events in those with low BP. Recent data suggest that wide fluctuations (not initial values) of BP in the first few hours in patients with acute ischemic stroke may be associated with an increased risk of death at 90 days [25,71].

The management of high BP in acute ischemic stroke is highly controversial because of a lack of reliable evidence from randomized, controlled trials. There are three major studies looking into the management of the high blood pressure after acute ischemic stroke. The Low Dose Beta Blockade in Acute Ischemic stroke (BEST) study [72], revealed a greater mortality among patients in whom a beta blocker therapy was started in the first 48 hours after symptoms onset. The Intravenous Nimodipine West European Stroke Trial (INWEST) found a significant correlation between diastolic blood pressure reductions with nimodipine and worsening of the neurological status (within 24 hours of symptoms onset) [73]. Patient with a diastolic blood pressure reduction of more than 20% or diastolic blood pressure of less than 60% have a higher risk of dependency and death at 21 days. A meta-analysis evaluating the use of oral versus intravenous calcium channel blocker initiated six hours to five days after symptom onset in acute ischemic stroke patients found that intravenous administration, higher doses, and administration within 12 hours of symptom onset were associated with an increased risk of poor outcomes [74].

The Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) trial [75] treated patient with acute ischemic stroke and systolic blood pressure higher than 200 mmHg and diastolic blood pressure higher than 100 mmHg within 6 to 24 hours or systolic blood pressure higher than 180 mmHg and diastolic blood pressure higher than 105 mmHg within 24 to 36 hours with the angiotensin receptor antagonist candesartan or placebo. The primary outcome was disability at three months measured by the Barthel index. Patients that were found to have hypertension (daytime systolic blood pressure >135/85 mmHg) at seven days after the qualifying event were started on cardesartan (placebo treated patients), the doses of candesartan was increased or a second antihypertensive medication was added. The twelve months cumulative mortality (2.9% versus 7.2%) and the incidence of new vascular events (9.8% versus 18.7%) were less in the candesartan treated group. Unfortunately, there was no difference in the primary outcome.

The post hoc analysis of hypertensive patients in the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen (rtPA) trial [76] who received antihypertensive therapy (intravenous labetalol and/or nitroprusside in selected patients) but no rtPA therapy within 24 hours of randomization showed no difference in rates of deterioration or death at 24 hours or in rates of favorable outcome at 3 months compared with hypertensive patients who received neither antihypertensive medication nor rtPA.

The results from various studies suggest somewhat contradictory consequences of antihypertensive treatment in acute ischemic stroke: INWEST showed a detrimental effect;

ACCESS, a favorable effect; and post hoc analysis of NINDS rtPA study showed no effect. The current recommendations regarding BP management in acute ischemic stroke are based on 2 observations [77]. BP reduction is associated with an increased risk of neurological deterioration and worse outcome in patients with ischemic stroke in some studies, although a causal relationship has not been demonstrated conclusively [78,79]. The benefit of acute BP lowering (unlike chronic treatment) in patients with ischemic stroke remains unclear. There may be a reduction of cardiovascular events with early institution of angiotensin receptor antagonists; however, the benefit is not conclusively related to BP reduction [75]. Therefore, in the absence of definitive benefit, both the ASA and the European Stroke Initiative are consistent in not recommending routine lowering of BP unless it is repeatedly exceeds 200 to 220 mmHg systolic or 120 mmHg diastolic in the acute period [77,80].

68.8 Acute Hypertensive Response in Patients With Ischemic Stroke Receiving Thrombolytics

The acute hypertensive response among patients with acute ischemic stroke receiving thrombolysis is frequently transient [81] and tends to resolve with vessel recanalization [82]. Uncontrolled hypertension in patients with acute ischemic strokes before receiving intravenous rtPA has been associated with increased risk of ICH [83]. In a large audit of practices and outcomes in 29 hospitals in the Cleveland (Ohio) metropolitan area, BP parameters recommended by the NINDS rtPA trial were not followed in 52% of the 70 patients treated with intravenous thrombolysis. The result was a 16% rate of symptomatic ICHs [84]. A quality improvement program in 9 of these hospitals decreased the rate of noncompliance to BP recommendations to 6% in 47 patients subsequently treated with rtPA [85]. The rate of symptomatic ICH dropped to 6%, which indirectly supports the beneficial value of BP control in reducing rtPA-related ICHs. Both the ASA and European Stroke Initiative guidelines recommend the reduction of BP according to the eligibility thresholds for inclusion in the NINDS rtPA efficacy trial before thrombolytics are administered. In the NINDS rtPA efficacy trial, patients were not eligible if they required aggressive antihypertensive therapy, defined as use of intravenous nitroprusside or repeated intravenous infusions of other medications. A post hoc analysis reported the frequency, course, and treatment of hypertension (more than 185/110 mmHg before randomization or 180/105 mmHg within the first 24 hours after randomization). Antihypertensive treatment before and after treatment with rtPA was used in 9% and 24%, respectively, of the patients treated with rtPA [76]. Prethrombolysis use of antihypertensive treatment did not adversely affect the rate of favorable outcomes at 3 months. Post-thrombolysis hypertension and use of antihypertensive treatment correlated with a lower rate of favorable outcome at 3 months. It remains unclear whether this adverse effect was related to more severe ischemic injury, persistent vascular occlusion, or pronounced reduction in BP. Patients treated with thrombolytics and antihypertensive therapy were more likely to have an abrupt decline in BP than those who were not treated. The higher susceptibility to hypotension associated with antihypertensive treatment after thrombolytic use (not seen in the placebo group) may be related to recanalization or reperfusion; however, the rate of ICH among patients with acute hypertension with appropriate control was similar to that observed in nonhypertensive patients. Early blood pressure reduction with rapid acting antihypertensive agents appears to be appropriate for a safe and beneficial thrombolysis in acute ischemic patients.

68.9 Chronic Arterial Hypertension and Stroke

Chronic hypertension is the most important risk factor for stroke [1]. Chronic hypertension predisposes to stroke by: 1) accelerating atherosclerosis of the aortic arch and large cervico-cranial arteries, 2) causing structural alteration in the small-diameter penetrating cerebral arterioles, and 3) promoting cardiac disease that may be complicated with stroke. Moreover, uncontrolled hypertension is an independent risk factor associated with intracerebral hemorrhage associated with use of oral anticoagulant for prevention of stroke in patients with atrial fibrillation [86,87]. In atrial fibrillation patients, routine blood pressure lowering is likely to provide protection against major vascular events additional to that conferred by anticoagulation [88]. Epidemiologic observations have been showed that treating hypertension dramatically decreases the incidence of intracerebral hemorrhage and can substantially reduce the incidence of the ischemic stroke [89]. In the randomized Perindopril Protection Against Recurrent Stroke Study, in 6,105 participants with prior stroke or TIA, intracerebral hemorrhage was reduced by 76% (95% CI 55-87) by lowering blood pressure 12/5 mmHg using perindopril and indapamide [90]. In 611 participants with hemorrhagic stroke as their qualifying event, a blood pressure reduction of 11/4 mmHg reduced subsequent strokes (most hemorrhagic) by 49%. The large effect of blood pressure lowering on hemorrhagic stroke was also seen in a primary prevention trial using different antihypertensive agents (Systolic Hypertension in the Elderly Program) [91].

Long term arterial hypertension produces a constellation of cerebral parenchymal lesions due to chronic arteriolar disease also known as small vessel cerebral disease or microangiopathy. Chronic hypertension induces structural changes in cerebral arterioles between 50 and 400 μm [92]. The so called “end arteries”, including the long penetrating arteries (lenticulostriatral arteries) and penetrating arteries arising from a large medium size arteries, have no collateral vessel anastomosis. These arteries that supply the basal ganglia, thalamus, hemispheric deep white matter and pons are more directly exposed to the high pressure than the arterioles of similar caliber in the cerebral cortex, which are protected by a gradual stepdown in the caliber. Approximately half of the total vascular resistance in the brain can be traced to the small intraparenchymal arteries [93]. In chronic arterial hypertension, the resistance in these vessels increases in order to protect arterioles and capillaries and keep the cerebral blood flow within normal limits [94]. The cerebral microcirculation is directly or indirectly involved in chronic arterial hypertension. The endothelial cells became functional and structurally abnormal permeating circulating macromolecules by enhanced transcytosis, opening of endothelial junctional sites, and loss of the net negative charge of the endothelium allowing the tunica media to interact with vasoconstrictors released from the platelets such as thromboxane and serotonin. The endothelial dysfunction is expressed as an imbalance in the production of EDRF (endothelium-derived relaxing factors) and EDCF (endothelium-derived constricting factors) in arteries and arterioles of the brain favoring vasoconstriction. These functional changes translate in structural abnormalities in the small brain blood vessels also known as cerebral hypertensive microangiopathy or small vessel disease.

The most common pathological findings of the hypertensive microangiopathy are: microatheroma, lipohyalinosis, fibrinoid necrosis, and microaneurysm. These vascular lesions are the subtract for the most common parenchymal brain lesions found in patient with long standing arterial hypertension: lacunar infarcts [95], subcortical leukoencephalopathy [96], leukoaraiosis [97], and small deep intraparenchymal hemorrhage. The cumulative long term consequences of these lesions in the brain are mainly related to

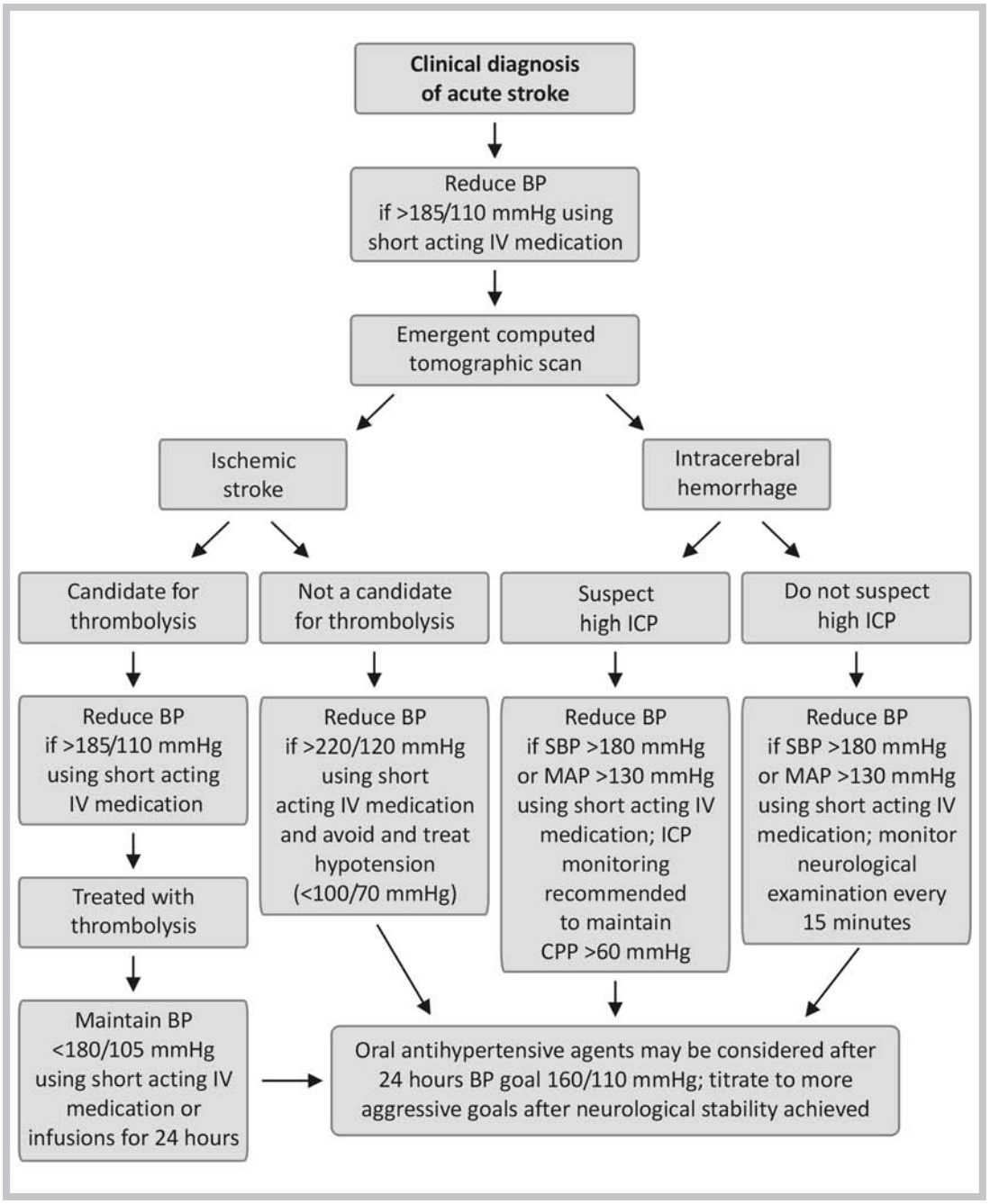

Figure 68.1. **Algorithm for treatment of acute hypertensive response among patients with stroke and stroke subtypes. Based on the NINDS rtPA prethrombolytic protocol for patients with acute ischemic stroke, for short-term BP management by Emergency Medical Services without delaying early diagnosis and differentiation. The Emergency Medical Services BP management practices vary considerably in the absence of distinction between ischemic stroke and ICH. Based on recommendations of the ASA, Stroke Council, and/or European Stroke Initiative. The recommended BP treatment threshold is similar to the existing ASA and European Stroke Initiative recommendations for patients with ICH. Based on recommendations of JNC 7 and the ACCESS protocol.**

IV = intravenous
SBP = systolic blood pressure
DBP = diastolic blood pressure
CPP = cerebral perfusion pressure

a stepwise cognitive decline defined as subcortical vascular dementia. Adequate treatment of the arterial hypertension can diminish these devastating cerebral complications. In a patient with chronic hypertension who suffers from an acute ischemic stroke, it is recommended the cautious use of antihypertensive medication in order to prevent hypotension with consequently worsening of the ischemic penumbra. The decision to continue or discontinue antihypertensive agents must be made on a case-by-case basis with the intent to avoid hypotension, excessive hypertension, and myocardial ischemia. Reduction of the dose of the current agent or a change to a short-acting intravenous antihypertensive agent may be considered. Another issue is the timing of initiation or aggressive titration of oral antihypertensive treatment in patients with stroke who have chronic hypertension or undetected hypertension. In the California Acute Stroke Prototype Registry, great variability in practices between hospitals and considerable room for improvement was noted among two thirds of patients with acute ischemic cerebrovascular events discharged from the hospital that were given 1 or more antihypertensive medications [98]. The heterogeneity in practice despite the definitive benefit demonstrated in clinical trials is concerning [99-101].

Theoretically, oral hypertensive agents can be initiated at 24 to 48 hours after symptom onset, because most of the acute processes, such as ischemic penumbra and hematoma expansion, are uncommon after the first 24 hours. In the ACCESS trial treatment was started with daily candesartan or placebo on day 1. On day 2, the dosage was increased 2- or 4-fold if BP was higher than 160/100 mmHg. If patients in the candesartan group showed a hypertensive profile on day 7 (mean daytime BP equal or higher than 135/85 mmHg), candesartan was increased or an additional antihypertensive drug was added [75]. The results support early initiation of antihypertensive treatment with gradual titration to more aggressive BP treatment targets. The JNC 7 report recommends that BP is maintained at intermediate levels (around 160/100 mmHg) until neurological stability is achieved. Special circumstances such as elevated ICP, progressive cerebral edema, ongoing cerebral ischemia due to occlusive vessel disease or symptomatic cerebral vasospasm, and postoperative cerebral changes require individualized management.

After the first week, or when neurological stability is achieved, a more aggressive treatment can be initiated for secondary prevention of recurrent stroke [7]. The ASA recommends that antihypertensive therapy be considered for all patients with ischemic stroke or transient ischemic attack, because benefit is seen in persons with and without a history of hypertension. Special consideration may be necessary for patients with bilateral severe carotid stenosis, who may bear a high risk of stroke with aggressive BP lowering until carotid revascularization is performed [102,103]. Figure 68.1 shows the algorithm for treatment of acute hypertensive response among patients with stroke and stroke subtypes.

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69 The Anticoagulated Patient in the Acute Phase of Intracerebral Hemorrhage

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69.1 Introduction

Intracranial hemorrhage is the most serious and feared complication of warfarin anticoagulation. As evidence for the benefit of warfarin for stroke prevention in atrial fibrillation has mounted in the past two decades, the use of long-term warfarin anticoagulation has increased dramatically. Concurrently, the incidence of anticoagulant-associated intracerebral hemorrhage (ICH) has increased. It has been estimated that anticoagulants may be associated with as many as 17% of ICH cases, up from 5% twenty years ago [1]. Furthermore, oral anticoagulant use with vitamin K antagonists such as warfarin increases the risk of hematoma expansion in the setting of acute intracranial hemorrhage and through this mechanism increases the risk of death or serious disability [2]. While non-coagulopathic ICH has a high 30-day mortality rate of around 40% in most clinical series, the mortality in coagulopathic patients is nearly doubled. Additionally, while it is now recognized that hematomas frequently expand in non-coagulopathic ICH in the first few hours after onset, coagulopathic patients continue to bleed more often and for a longer duration [2]. Thus, reversal of coagulopathy is of the highest priority in the acute ICH patient presenting while being treated with warfarin or other anticoagulants.

While the focus of this chapter is on reversal of coagulopathy in patients who develop acute non-traumatic ICH while on oral anticoagulants, the principles of risk of hematoma expansion and need for urgent coagulopathy reversal apply to those patients with other conditions (such as acute head trauma) or those who are coagulopathic for other reasons (such as unfractionated heparin, low-molecular weight heparin, thrombolytic therapy for myocardial infarction or stroke, or underlying liver failure). Several basic principles apply to the acute management of patients who present with intracranial hemorrhage and coagulopathy. These relate to the timing, efficacy, and utility of clinical and neuroimaging assessments and help determine the best current approach for these patients.

The first principle is the absolute necessity for reversal of the coagulopathy as soon as possible. Because bleeding is ongoing in many cases of ICH, and likely most cases of anticoagulant-associated ICH, then every minute means that there is increased risk of continuing bleeding, and therefore worsened patient outcome. It must be emphasized that treating the coagulopathy does nothing to treat the initial underlying cause of intracranial hemorrhage. Thus, cessation of intracranial bleeding can be viewed as hyperacute preventive therapy in order to preserve the current status of a patient and allow treatment of the underlying condition (such as hypertensive ICH or head trauma). Second is the understanding that small hemorrhage size or good clinical status does not mean that

coagulopathy reversal is less urgent or necessary. In fact, patients with smaller hemorrhages and with a favorable neurological examination have the most to lose from hematoma expansion. Unfortunately, paradoxically many times these patients receive less urgent care than lose who are already moribund because of the mistaken reliance on their current clinical status. Finally, many patients with oral anticoagulant-associated hemorrhage present with a therapeutic INR (usually between 2.0 and 3.0), not necessarily a supratherapeutic INR. While very high INR levels further increase the risk of continued bleeding, all INR elevations in this setting should be corrected to normal. These and other basic principles of acute care for anticoagulant-associated ICH help to clarify optimal characteristics for warfarin-reversal algorithms (Table 69.1).

- Normalize INR (and other coagulation parameters) as soon as possible
- All patients should have immediate coagulopathy reversal, even if hemorrhage is small and clinical condition is good
- Level of INR elevation does not influence timing of reversal. All levels of INR elevation (modest <2.0, therapeutic 2.0-3.0, supratherapeutic >3.0) require urgent correction
- Initial correction must include longer acting agents (e.g. vitamin K) to avoid rebound INR elevation later

Table 69.1. **Principles of coagulopathy reversal in anticoagulant-associated ICH.**

69.2 Options for Warfarin Reversal

Warfarin is a vitamin K antagonist and therefore acts to inhibit γ-carboxylation of coagulation factors II, VII, IX and X as well as the inhibitors protein C and S [3]. Warfarin reversal can be achieved through three different pathways:

- Direct competition by administering vitamin K.
- Replacement of native coagulation factors using (fresh frozen) plasma or a prothrombin complex concentrate (PCC).
- Bypassing the central part of the coagulation cascade through the use of recombinant factor VIIa (rFVIIa) [3].

The different pharmacological and blood product options which are available target these different mechanisms and each has specific characteristics related to ease of administration, timing and duration of effect, and cost which may potentially influence the choice of their use. Agents used are summarized in Table 69.2.

Agent	Pro	Con	Usefulness for urgent reversal
Vitamin K	Inexpensive; directly reverses warfarin effect	Slow onset of action	Poor
Fresh frozen plasma	Contains all coagulation factors	Large volumes usually needed; requires cross-matching and thawing	Fair
Prothrombin complex concentrate	Rapid onset; small volume	Expensive; variable factor concentrations in different preparations	Good
Recombinant Factor VIIa	Rapid onset; small volume; thrombin burst	Very expensive; acts directly on only a single factor; INR correction may be “lab artifact”	Good

Table 69.2. **Options for urgent warfarin reversal.**

69.2.1 Vitamin K

Administration of vitamin K is a central part of any warfarin reversal strategy. However, its slow onset of action makes it a poor choice as a single agent. It usually takes at least 2 to 6 hours, and frequently 12 to 24 hours, for vitamin K to effectively reverse the effect of warfarin [3,4]. Vitamin K is inexpensive with a 10 mg dose costing $6.82 at San Francisco General Hospital in 2012. While the most efficacious route of administration is still debated, the effect of vitamin K is more rapid when given intravenously. Anaphylaxis from intravenous administration has been a previous concern but is likely extremely rare (3 per 10,000 doses in one study) [4]. Because of the short half-life and duration of action of the other warfarin-reversal options, vitamin K should be administered in all patients in order to avoid a rebound in coagulopathy after initial correction. Subcutaneous administration does not carry the same rare anaphylaxis risk as the intravenous route, but the onset of action is not as rapid or reliable.

69.2.2 Fresh Frozen Plasma

Fresh frozen plasma (FFP) is a blood product which contains all the coagulation factors in an unconcentrated form. Because of this, the volume of FFP required to reverse a high INR to below 1.5 is often 800-3500 ml. Given that each unit may be about 200 ml in volume, the often-used clinical practice of giving two units of FFP and rechecking the INR is insufficient for urgent warfarin reversal. Furthermore, the actual levels of vitamin K dependent clotting factors in each unit of FFP are not standardized and may vary widely. FFP requires compatibility testing and thawing prior to administration, thus there is an inherent delay in initiating FFP transfusion. Cost is moderate with a unit of FFP at $75 in 2012 at San Francisco General Hospital. However, for a patient requiring 2000 ml, this would translate roughly to $750. As a blood product, there is risk of blood-borne infection and transfusion-associated lung injury. Additionally, the rapid transfusion rate and large volume of FFP often required for urgent warfarin reversal could lead to intravascular volume overload. Therefore, even though FFP is often considered the standard current treatment, it remains a poor overall choice for acute warfarin reversal because of inherent time delays in administration and large volumes usually required.

69.2.3 Prothrombin Complex Concentrates

Prothrombin complex concentrate (PCC) is a generic term for many different products which are derived from plasma and contain factors II, VII, IX, and X in varying concentrations. Originally designed as factor IX concentrates, there are at least ten different PCC products which are available in different parts of the world and which contain varying levels of factors II, X, and especially VII [5]. For example, a PCC product available in the United States, Bebulin®, contains low levels of factor VII, while Beriplex®, a PCC product available in other parts of the world, contains all four factors as well as protein C and S [3,5]. PCCs are available as a concentrate which can be reconstituted to a total volume of about 50-150 ml in about 15 minutes and delivered in 10-30 minutes depending on volume and rate of infusion. For each IU (international unit) of PCC per kg body weight, the plasma concentration of factor IX increases by 1% [3]. Optimal PCC dosing (INR-based versus standardized fixed dose) remains somewhat controversial, although individualized dosing may ensure INR correction more rapidly. For example, in order to correct an INR of 4.5 (~10% of factor IX concentration) to an INR of 1.4 (~40% factor IX), would require a dose of at least 30 IU/kg. The corresponding dose of FFP would be 30 ml/kg

(2100 ml for a 70 kg patient). PCCs work very rapidly and can correct the INR within minutes. Thus, they are very good agents for acute warfarin reversal because of the small volume, range of coagulation factors provided, and rapid onset of action. PCCs are significantly more expensive than vitamin K and FFP, with a 3500 IU dose (50 IU/kg for a 70 kg person) costing $3150 in 2012 at San Francisco General Hospital. Concern for thrombotic complications exists with acute PCC administration but this has not been systematically studied. Because of the potentially short duration of action of PCC, vitamin K should always be concurrently administered to avoid rebound coagulopathy. When using PCC preparations with low amounts of factor VII, co-administration of one to two units of FFP may also be considered.

69.2.4 Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa) is an approved medication for the treatment of hemophilia, has been tested in clinical trials for non-coagulopathic ICH, and used off-label for warfarin-related ICH as well as traumatic hemorrhage. rFVIIa leads to a burst of thrombin activity and interacts with tissue factor. Because even low doses of rFVIIa correct the INR, the INR cannot be used as a reliable indicator of cessation of bleeding in patients who have received rFVIIa. It is not known whether other emerging coagulation tests such as thromboelastography might be better measures. Because of this, optimal dosing is not known. rFVIIa is administered as a single one-time bolus over 2-5 minutes and 80-90 μg/kg is a commonly used dose. Onset of action is very rapid and this makes it a potentially very good agent for acute warfarin reversal. In clinical trials involving non-coagulpathic ICH patients, rVIIa was associated with a small increase in arterial thrombotic events [6]. Of all the current warfarin-reversal options, rFVIIa is the most expensive, with a 5600 μg dose (80 μg/kg for a 70 kg person) costing $8375 at San Francisco General Hospital in 2012. Vitamin K should always be administered concurrently to avoid rebound coagulopathy.

Convert INR to % of estimated circulating functional prothrombin complex (PC)	• >5=5% • 4.0-4.9=10% • 2.6-3.2=15% • 2.2-2.5=20% • 1.9-2.1=25% • 1.7-1.8=30% • 1.4-1.6=40% • 1.0=100%
Calculated dose	• Target in %PC – current estimated %PC x kg=IU of PCC or ml of FFP needed
Example	• Present INR 4.5 • Target INR 1.4 • Body weight 70 kg • (40-10) x 70=2100 IU of PCC or 2800 ml of FFP needed

Table 69.3. **INR-based dosing for PCC and FFP for warfarin reversal [15]. From University of California, San Francisco Neurovascular Service.**

69.3 Current Studies: Benefits, Evidence, and Challenges

As of this writing, there are no prospective, randomized, controlled clinical trials comparing the various warfarin-reversal strategies. Specifically, there are no controlled trials assessing whether PCC or rFVIIa are clearly superior to a strategy of FFP and vitamin K, or comparing PCC and rFVIIa against each other regarding clinical outcome. However, there have been several small retrospective and prospective studies evaluating the effectiveness of INR reversal between the various agents.

In a retrospective study of 69 patients with anticoagulation-associated intracerebral hemorrhage treated with FFP alone or in conjunction with vitamin K, 17% of patients

did not have correction of the INR to <1.4 even at 24 hours after emergency department arrival. Earlier time to initiation of FFP transfusion was significantly associated with INR reversal [7]. This study and others suggest that a significant proportion of patients treated with FFP alone (with or without vitamin K) will not be adequately reversed and that adequate reversal using FFP takes many hours.

Another retrospective study compared 55 patients who were treated with either PCC (with or without FFP and vitamin K), FFP (alone or with vitamin K), and vitamin K monotherapy. Patients treated with PCC were less likely to have hematoma expansion. However, when including only patients who had reversal of the INR to <1.4 within 2 hours, there was no difference in hematoma expansion [8]. This suggests that it is the speed of reversal rather than the agent itself that is most important. However, achieving full reversal within 2 hours with FFP is difficult for the reasons noted previously. Outcome was generally poor, with 77% of patients having a modified Rankin Scale score of 4 to 6. In a different retrospective review performed in Sweden, there was no difference in mortality irregardless of treatment with FFP, PCC, or vitamin K [9].

Several small case series have found that rFVIIa effectively and rapidly reduces the INR in patients with anticoagulant-associated ICH and may limit hematoma expansion [10]. While INR correction has generally been interpreted in these reports as demonstrating effective warfarin reversal, given the fact that even low doses of rFVIIa correct the INR, the true efficacy of this treatment approach remains unclear.

Thus, there is limited evidence to support a specific treatment regimen for warfarin-related ICH. Randomized trials using patient mortality and neurological function as outcome have been proposed. However, these are challenging to design due to the large sample size required, frequent poor outcome of anticoagulant-associated ICH patients, and variability in available products in different areas of the world. Thus, current approaches derive more from consensus-based guidelines driven from concern for rapid and safe coagulopathy correction.

69.4 Other Anticoagulants

Spontaneous (or traumatic) intracranial hemorrhage in patients receiving unfractionated heparin (UFH) or low molecular weight heparin (LMWH) is less common than with warfarin and usually occurs in-hospital or in the context of treatment of another condition such as myocardial infarction or stroke. Protamine directly reverses the effect of UFH with 1 mg of protamine reversing approximately 100 units of UFH. Thus, the dose in a bleeding patient who had just received a 10,000 unit bolus of UFH would be 100 mg. There is no definitely effective reversal agent for LMWH. Protamine may be partially effective and there are case reports of the use of rFVIIa. At present, there have been no randomized studies of intervention for thrombolysis-associated intracranial hemorrhage and optimal treatment remains unknown for this relatively uncommon complication. Current recommended therapy includes the administration of platelets (6-8 U) and cryoprecipitate containing Factor VIII [11].

69.5 Treatment Algorithms and Guidelines

Despite the lack of evidence from randomized clinical trials for an optimal treatment regimen for anticoagulant-associated ICH, there are numerous consensus-based inter-

national guidelines which address this issue and provide a general framework. In general, these guidelines come from larger recommendations on overall use of antithrombotic agents [12-14], but at least one guideline is specific to ICH [11]. Overall, these guidelines emphasize the high morbidity associated with warfarin-related intracranial hemorrhage and the urgency of rapid reversal. Several of these guidelines make the distinction between patients with an elevated INR who are not bleeding, have no significant bleeding, or who have life-threatening bleeding. Given the high risk of ongoing hemorrhage and the high rate of death and disability from anticoagulant-associated intracranial hemorrhage, we believe that it is most appropriate to consider any intracranial bleeding in a patient with an elevated INR due to warfarin use as life-threatening regardless of hematoma size or the patient's clinical condition at first evaluation.

The 2007 American Heart Association ICH management guidelines state that PCC, factor IX complex concentrate, and rFVIIa all lower the INR very rapidly, but have a risk of thromboembolism. FFP is considered another choice but is associated with greater volumes and longer infusion times. This evidence is considered as class IIb (usefulness/efficacy is less well established by evidence or opinion) [11]. It should be noted that these guidelines also recommend that intravenous vitamin K should be given in patients with warfarin-related ICH and consider this as class I evidence (conditions for which there is evidence for and/or general agreement that the treatment is useful and effective).

The American College of Chest Physicians 8th edition of Evidence-based Clinical Practice Guidelines state that warfarin should be stopped and that PCC, rFVIIa, or FFP should be given, supplemented by vitamin K (10 mg by slow intravenous infusion) [12]. Guidelines from the UK recommend discontinuation of warfarin, vitamin K (5 mg intravenous or oral), and administration of PCC (50 U/kg fixed dose) or FFP (15 ml/kg fixed volume) [14]. Finally, guidelines from the Australasian Society of Thrombosis and Hemostasis are somewhat more complex and provide several different tiered options based on availability of different compounds. In these guidelines, all patients should have warfarin discontinued and receive vitamin K 5-10 mg intravenously. They then recommend giving Prothrombinex-HT (a PCC compound) in a dose of 25-50 IU/kg and FFP 150-300 ml total. If either FFP or Promthrombinex-HT are not available then just the available agent (PCC or FFP) should be given with vitamin K.

Thus, all current guidelines emphasize the importance of rapid reversal of coagulopathy and all recommend the use of vitamin K (usually intravenously). However, none provide a specific target INR indicating adequate reversal. Additionally, all make mention of the use of PCC (or rFVIIa) given the rapid onset of action of these agents and the shortcomings of FFP alone. However, the lack of clear evidence limits the ability to make stringent recommendations regarding agent and dose. Figure 69.1 provides and example of enlargement of hematoma due to warfarin anticoagulation, while Figure 69.2 shows the proposed algorithm for hyperacute warfarin reversal.

69.6 Conclusions

Anticoagulant-associated intracranial hemorrhage is increasing in incidence. Because it is associated with high risk of ongoing bleeding, death, or disability, urgent reversal of coagulopathy is of the highest priority. Several agents are available, all with various positive and negative attributes. All protocols for warfarin-related intracranial hemorrhage emphasize immediate cessation of the anticoagulant medication and immediate administration of vitamin K (usually intravenously). The use of PCC or rFVIIa may reverse coagulopathy more rapidly than FFP alone, but randomized trials testing this have yet to be performed. Furthermore, cost and availability of these agents may limit their widespread use.

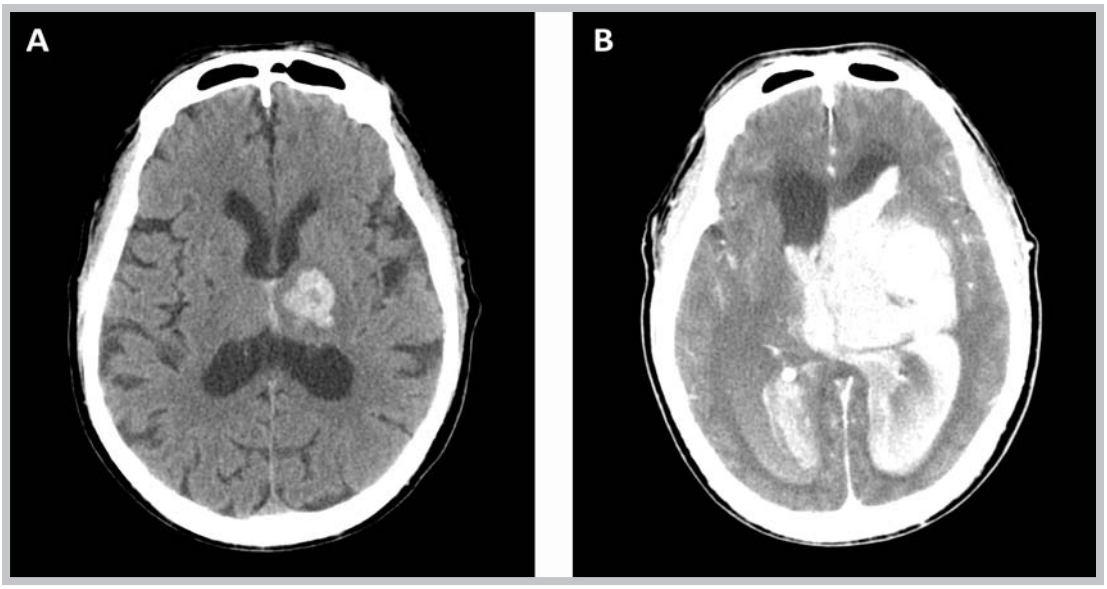

Figure 69.1. **Enlargement of hematoma due to warfarin anticoagulation. 64 year old woman with hypertension and atrial fibrillation, receiving long-term warfarin oral anticoagulation for cardioembolic stroke prevention. Initial INR 4.5. Panel A demonstrates the non-contrast head CT scan at initial presentation, which likely represents a hypertensive ICH occurring while the patient was being treated with warfarin. At this time she was alert, with normal language, and a mild right hemiparesis. Fresh frozen plasma was ordered, cross-matched, thawed and intravenous administration begun. 10 hours later the patient deteriorated due to massive hematoma expansion (Panel B) and later died.**

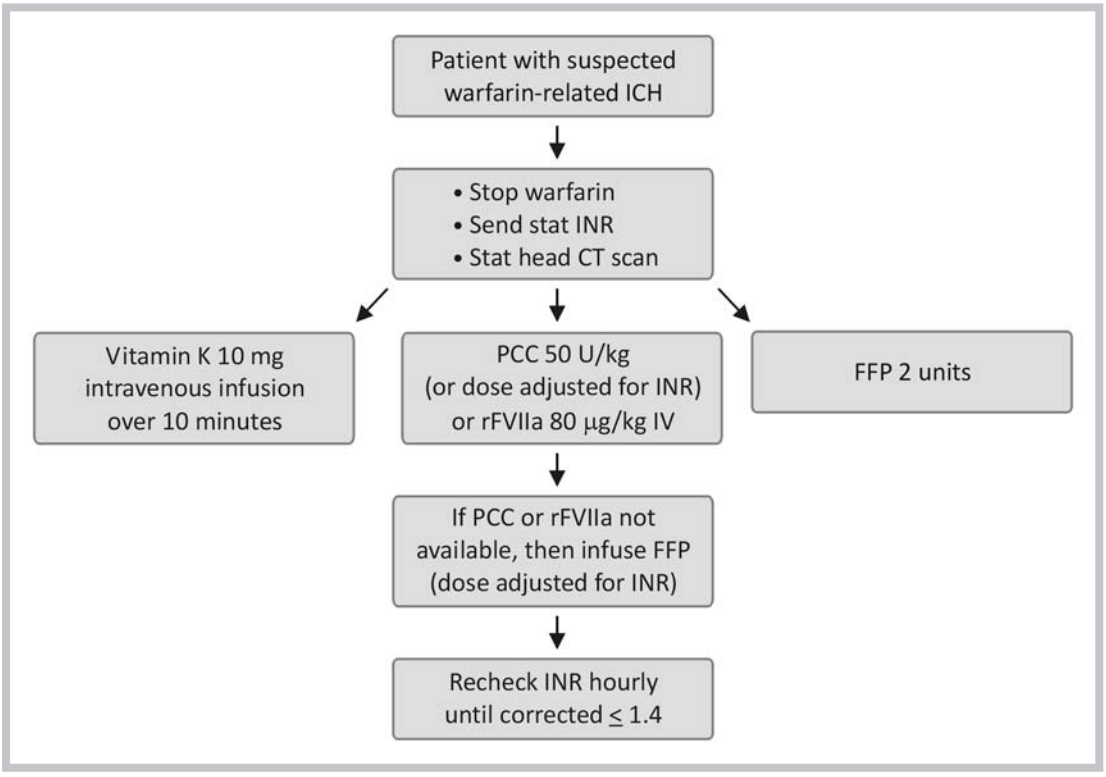

Figure 69.2. **Proposed algorithm for hyperacute warfarin reversal.**

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70 What is the Optimal Level of Hemoglobin in Neurocritical Care Patients?

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70.1 Introduction

In red blood cells, hemoglobin is a carrier for oxygen and delivers oxygen to the tissues. Red blood cell transfusion is a potentially life-saving therapy in order to replace losses in hemoglobin to maintain oxygen delivery to vital organs. The main objective of red blood cell transfusion is to increase tissue oxygenation and thereby reduce oxygen debt. After red blood cell transfusion, an increase in hemoglobin concentration is readily measured, but the effect of red blood cell transfusion on utilization of oxygen in peripheral tissue is rarely measured. Clinical studies attempting to determine the effects of red blood cell transfusion on oxygen kinetics have not provided definitive answers.

Transfused red blood cells may increase tissue oxygenation not only as an oxygen carrier but also as an oxygen sensor with the capacity to regulate microvascular blood flow by release of vasodilators, such as nitric oxide (NO).

Transfusion of red blood cells, may, however be associated with negative effects. The delivery of oxygen to the tissue can be lower than expected, and the transfused red

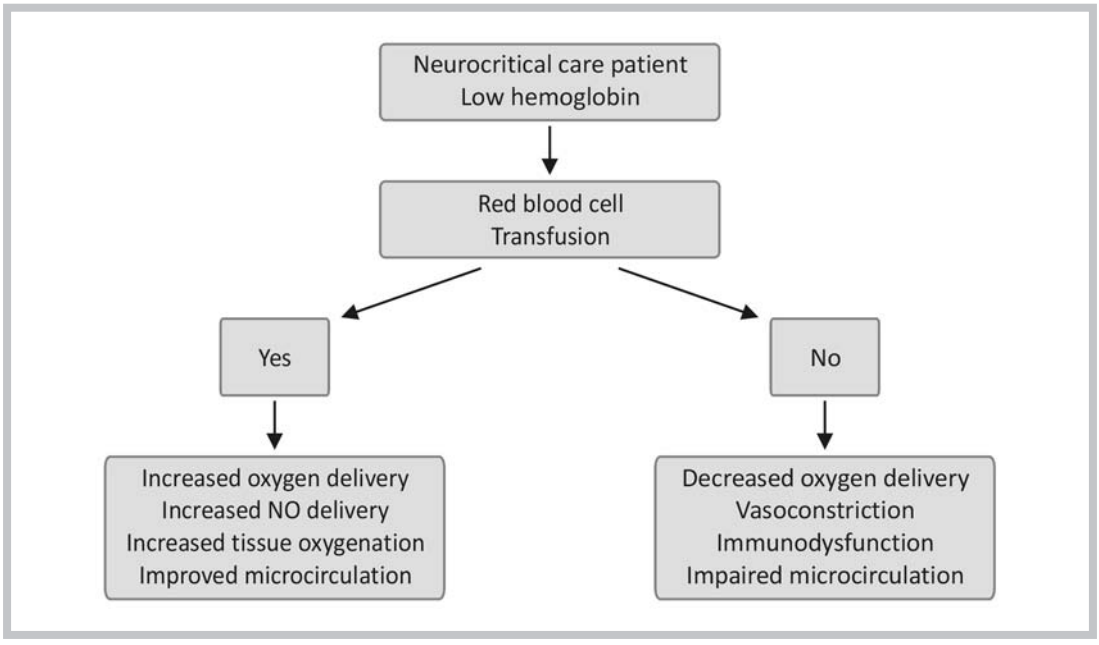

Figure 70.1. Pro-con red blood cell transfusion.

blood cells units can enhance an inflammatory response with possible impairment of microcirculation.
Clinical studies have demonstrated an association between red blood cell transfusion and increased mortality and morbidity in general critical care patients. These results cannot be directly transferred to the neurocritical care patient. For the neurocritical care patient, we still lack convincing studies of effects on outcome of red blood cell transfusion.
This chapter will discuss:

- The normal physiology concerning red blood cells and hemoglobin.
- The beneficial and harmful effects of red blood cell transfusion.
- The target levels of hemoglobin in patients with neurological/neurosurgical acute injury such as traumatic brain injury, subarachnoid hemorrhage and ischemic stroke.

70.2 Red Blood Cells and Hemoglobin

Red blood cells are biconcave discs with a diameter of about 7.5 µm. The capillary diameter is 3-8 µm, which implies that the red blood cells must possess the ability of deformation to pass the capillary network and deliver oxygen to the tissues. The red blood cells carry hemoglobin, and hemoglobin has four important functions: 1) to facilitate O_2 transport; 2) to facilitate CO_2 transport; 3) to act as a buffer; 4) to transport NO.

70.2.1 Oxygen (O_2) Transport

The total sum of the oxygen delivered to the whole body or to specific organs, is the product of blood flow and arterial oxygen content. The arterial oxygen content is mainly dependent on the hemoglobin level. More than 99% of the oxygen is transported by hemoglobin. Oxygen delivery must be sufficient for the metabolic demand of the tissues. Oxygen is not stored in tissues and must be delivered continuously in adequate amounts for avoidance of anaerobic metabolism and production of lactate. The cerebral metabolic rate in the human brain is on average 3.5 ml/100 g brain/minute. This represents approximately 20% of the total body resting oxygen consumption. Aerobic metabolism is the primary energy source for the brain and the brain is dependent on a continuous delivery of substrate, including glucose and oxygen. The brain is thus extremely sensitive to decreased delivery of oxygen.
The affinity for oxygen to hemoglobin is an important factor for oxygen delivery to the tissues. Increased affinity means that less oxygen is liberated in the tissues.
Important factors affecting the affinity for oxygen in hemoglobin are: pH, temperature, and concentration of 2,3-diphosphoglycerate (2,3-DPG).
2,3-diphosphoglycerate is plentiful in red blood cells and it enhances the ability of red blood cells to release oxygen in tissues. For example, high altitude triggers a rise in 2,3-diphosphoglycerate concentration in red blood cells, which subsequently increases the release and availability of oxygen in tissues.

Factor	Effect
Decrease in pH	Decrease in oxygen affinity
Increase in temperature	Decrease in oxygen affinity
Decrease in 2,3-diphosphoglycerate	Increase in oxygen affinity

Table 70.1. Factors affecting the affinity for oxygen in hemoglobin.

The uptake of oxygen in the tissue is less in the alcalotic than in the acidotic patient.
A fall in 2,3-diphosphoglycerate is associated with an increased hemoglobin affinity for oxygen, resulting in less oxygen liberated to the tissues. In stored red blood cells 2,3-diphosphoglycerate is decreased within 48 hours of storage.
The delivery of oxygen to a tissue increases with raised hematocrit up to a certain level. Above that level there is a net reduction in oxygen delivery most likely due to the simultaneous increase in blood viscosity. While a normal hematocrit of 35-45% is optimal in healthy individuals, it may vary in critically ill patients due to different pathophysiological conditions depending on type of illness and quality of the blood transfused (see below).
In summary, the brain is dependent on a continuous delivery of oxygen in order to survive. Hemoglobin carries more than 99% of the oxygen. The optimal hematocrit may vary in patients with different pathophysiological conditions.

70.2.2 Carbon Dioxide (CO_2) Transport

CO_2 is the major end product of oxidative metabolism. Since CO_2 is able to convert into carbonic acid when hydrated, and accumulation of carbonic acid, H_2CO_3, can produce problems in the tissue, an effective elimination of CO_2 from the tissue is essential. The focal point of CO_2 transport is the hydration reaction; $CO_2 + H_2O = H_2CO_3$. The rate of this reaction is fastest in the red blood cell by the help of carbonic anhydrase. In the red blood cell, H_2CO_3, dissolves into hydrogen ion, H^+ and bicarbonate, HCO_3^-. The H^+ generated in the red blood cell is buffered by hemoglobin and HCO_3^-, is pumped back into plasma in exchange for chloride. In summary, hemoglobin plays a major role in the elimination of carbon dioxide (CO_2) from the tissue.

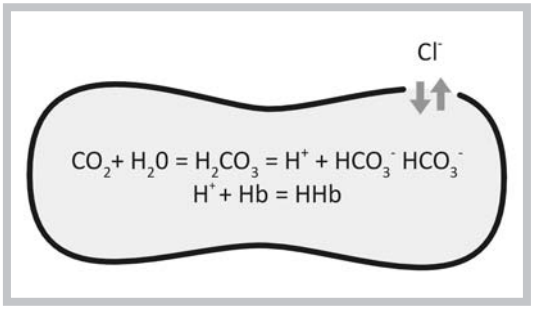

Figure 70.2. **Transport and reactions of CO_2 in the red blood cell. In the red blood cell, the reaction, $CO_2 + H_20 = H_2CO_3$, is facilitated by carbonic anhydrase. Carbonic anhydrase is only present in the red blood cell. Carbonic acid, H_2CO_3, dissociates into hydrogen, H^+, and bicarbonate, HCO_3^-. The hydrogen ion is buffered by hemoglobin, Hb, and forms HHb. A large fraction of the bicarbonate produced is pumped back into plasma in exchange for chloride, Cl^-.**

70.2.3 Hemoglobin as a Buffer

Hemoglobin has an important role in $CO_{2\ transport}$. By transporting CO_2, hemoglobin acts as an important buffer for the hydrogen ions produced by the hydration of CO_2 (see above, CO_2 transport). Hemoglobin in blood has six times the buffering capacity of the plasma proteins.

70.2.4 Transport of Nitric Oxide by Hemoglobin

Nitric oxide is a potent vasodilator that is produced in endothelial cells and acts more or less exclusively at its site of synthesis. New evidence suggests that red blood cells distribute nitric oxide (NO), thereby matching blood flow to tissue oxygen demand. This mechanism could provide an explanation for physiological matching of blood flow to tissue oxygen levels, by mediating dilatation of blood vessels under low oxygen conditions, and constriction of blood vessels when oxygen levels are high.

In summary, nitric oxide can be transported by hemoglobin. Hemoglobin can thus be an important factor for physiological matching of blood flow to metabolic demands.

70.2.5 Red Blood Cells and Blood Volume

The red blood cells comprise about 40% of normal blood volume. The red blood cells are, therefore, of importance to maintain normovolemia. In a pathophysiological situation with increased transcapillary leakage it will, therefore, be more difficult to maintain normovolemia at a low than at a normal hematocrit. In summary, the red blood cells contribute to maintenance of normovolemia.

70.3 Transfused Red Blood Cells

A main goal of red blood cell transfusion is to increase the hemoglobin concentration, and thereby improve O_2 delivery to tissues.
The efficacy of stored red blood cells to maintain the biological activity of red blood cells has been questioned. Transfusion of large amounts of stored red blood cells can possibly lead to adverse clinical consequences. Transfused red blood cells may be ineffective transporters of oxygen, especially in compromised critically ill patients who have microcirculatory abnormalities from a number of pathologic processes and the content of leukocytes (see below) and other inflammatory components can trigger inflammation in a compromised host.

70.3.1 Red Blood Cells and Storage

During storage, red blood cells undergo changes in morphology, associated with biochemical and biomechanical changes, collectively referred to as storage lesions. There is strong laboratory evidence suggesting that prolonged red blood cell storage may be deleterious and clinical studies have reported an association between prolonged storage and adverse clinical outcome. Storage lesions ultimately include loss of deformability. Loss of deformability in combination with increased interactions with vascular endothelium compromise microvascular flow. The unloading of oxygen to the tissues will be impaired by the well-documented depletion of 2,3-DPG in red blood cells that occur after storage for more than 48 hours.

70.3.2 Transfused Red Blood Cells and Immunodysfunction

Perhaps the most negative characteristic of transfused red blood cells units is the content of white blood cells. The immunomodulating effects of red blood cell transfusion

Characteristic	Effect
Compromised deformability	Microvascular obstruction
Depletion of 2,3-diphosphoglycerate	Increased affinity for O_2, reduced ability to unload O_2
Pro-inflammatory effects	Immunodysfunction
Depletion of NO	Vasoconstriction

Table 70.2. **Possible negative characteristics of stored transfused red blood cells.**

have mainly been attributed to leukocytes and inflammatory mediators in the supernatant liquid, denoted as transfusion related immunomodulation (TRIM). TRIM is supposed to be mediated by white blood cells in the transfused red blood cell unit. The donated white blood cells may either down-regulate the immune function of the recipient or trigger TRIM effects by soluble mediators released in the red blood cell unit during storage. Randomized controlled trials comparing the risk of postoperative infection or short-term (three months) mortality between non-leukocyte depleted versus leukocyte depleted red blood cell transfusions have reported conflicting results.
A clinical situation where randomized controlled trials clearly have revealed that the use of leukocyte depleted red blood cell transfusion reduces short-term mortality is in cardiac surgery patients. Many blood transfusion services have added universal leukocyte depletion to the routine processing of all blood components and the majority of red blood cell transfusions in Western Europe and North America are today depleted of white blood cells. Noteworthy, the published studies on harmful effects of red blood cell transfusion in critical ill patients have used mainly non-leukocyte depleted blood.
In summary, storage of red blood cells can alter the biological effects negatively. Content of leukocytes in transfused red blood cells units can induce immunodysfunction.

70.4 Red Blood Cell Transfusion in Neurocritical Care Patients

There are studies in critically ill patients indicating that a liberal transfusion policy is ineffective and even potentially harmful. Interestingly, a well-known and world wide accepted treatment approach in severe sepsis and septic shock, i.e. the early goal directed therapy, contains a recommendation of red blood cells transfusion to achieve a hematocrit of at least 30%, if the central venous saturation is under 70%. In the treatment group 68% of the patients received red blood cell transfusion compared to 45% in the control group. The inhospital mortality in the treatment group was 31% versus 47% in the control group. This indicates that critically ill patients with severe sepsis had a lower mortality if transfused to a hematocrit of at least 30% in the presence of hypoxemia.
The applicability of a restricted transfusion policy to neurocritical care patients has been questioned, given that impaired oxygen delivery is an important cause of secondary brain injury. The brain is more than any other organ depending on a continuous supply of oxygen and only moderate reductions in oxygen delivery to an injured brain could lead to cerebral hypoxia.
Most of the studies concerning the level of hemoglobin and outcome after neurocritical care are prospective or retrospective cohort studies and therefore despite multivariate analysis, the relationship between red blood cell transfusion and increased adverse events may still be a result of confounding factors. There are studies that have reported an association between red blood cell transfusion and increased mortality, but it has to be taken into consideration that the amount of blood transfused may reflect injury severity rather than the blood transfusion per se.
No evidence based optimal hemoglobin level exists for patients receiving neurocritical care. Randomized controlled studies regarding the optimal hemoglobin concentration in neurocritical care patients are lacking.

70.4.1 Traumatic Brain Injury

Patients with traumatic brain injury have been thought to be particularly susceptible to injury from anemia, due to the well-documented association of increased mortality and

worsening functional outcome in the presence of hypotension and hypoxia. Few studies have investigated the effects of anemia in patients with traumatic brain injury. Retrospective studies have revealed that any period of anemia in traumatic brain injury is associated with a significant increase in morbidity and mortality, but also that red blood cell transfusion in traumatic brain injury patients, whether or not anemia is present, is an independent risk factor for complications and mortality. The Transfusions Requirements in Critical Care, TRICC, trial was a randomized controlled clinic trial investigating liberal (hemoglobin level 10.0 g/dl to 12.0 g/dl) versus restrictive (hemoglobin level 7.0 g/dl to 9.0 g/dl) transfusion policy in critically ill patients. The results from the trial were published in *New England Journal of Medicine* in 1999. Primary outcome in the TRICC trial was mortality at 30 days. Although overall results from the original TRICC trial suggested that a restrictive red blood cell transfusion strategy was safe, it was suggested that subgroups of patients may exist, who are especially vulnerable to effects of anemia. A subgroup analysis from the TRICC trial in patients with traumatic brain injury was published in 2006, and even though no significant difference in mortality between a restrictive and a more liberal transfusion strategy could be detected, the mortality rate at 30 days was 13% in the liberal transfusion group and 17% in the restrictive transfusion group. Thus, the liberal transfusions strategy seemed to be at least as safe as the more restrictive transfusion policy. The subanalysis of the TRICC trial concerning patients with traumatic brain injury could not recommend a specific transfusion trigger level in those patients, but the authors concluded that the brain could be an organ that is especially vulnerable to adverse effects of anemia.

It may also be of importance that during the TRICC trial, red blood cells units were not universally leukocyte depleted. Perhaps physiological indications of the need for red blood cell transfusion other than the hemoglobin level could be triggers for transfusion of red blood cells in the future. Recent studies have documented that red blood cell transfusion increases brain oxygenation, measured by brain tissue partial pressure of oxygen ($PtiO_2$) catheters, in most patients with traumatic brain injury and subarachnoid hemorrhage. A limitation of these studies is that $PtiO_2$ might not be an accurate tool to demonstrate the effect of transfusion on oxygen uptake by the tissues.

Normalization of the hemoglobin level would theoretically improve the oxygen transport capacity to injured areas of the traumatized brain, in spite of limitations in this capacity in stored red blood cells. Arguments can be given that patients with a traumatic brain injury would benefit from keeping a normal hemoglobin level in order to optimize oxygen delivery to the traumatized brain. This approach has been adopted in the Lund-concept for treatment of severe traumatic brain injury, the outcome data presented with this approach is good, even though of course this can not be attributed only to the hemoglobin level.

More prospective investigations are required to determine the effects of anemia and the potential benefits and optimal indications for red blood cell transfusion in patients with traumatic brain injury. The hemoglobin threshold may not be identified as the treatment goal, rather more sophisticated methods of neuromonitoring may be necessary to guide the need for red blood cell transfusion.

In summary, no evidence based hemoglobin level can be recommended for patients with traumatic brain injury, but the existing data taken together support a hemoglobin level near normal, that is, a target hemoglobin value around 110 g/l.

70.4.2 Subarachnoid Hemorrhage

Patients with subarachnoid hemorrhage, especially those with a manifest cerebral vasospasm, are vulnerable to hypoxic episodes. Limited oxygen delivery due to anemia,

could have deleterious effects. The optimal transfusion threshold for patients suffering from non-traumatic subarachnoid hemorrhage is debatable. Current practice most often uses a liberal approach. Anemia after subarachnoid hemorrhage has been identified as an independent predictor of infarction, death and dependency. Retrospective studies have reported that subarachnoid hemorrhage patients with higher initial and mean hemoglobin value had improved outcome. Anemia seems to be a predictor of adverse outcome in subarachnoid hemorrhage patients, even when baseline differences in clinical and radiographic severity are taken into account. However, data suggesting an association between red blood cell transfusion and adverse outcome after subarachnoid hemorrhage have also been reported. The triple-H (hypervolemia, hypertension, hemodilution) therapy, used for treatment of cerebral vasospasm, could be one reason for anemia in patients with subarachnoid hemorrhage.
It remains unclear whether anemia after subarachnoid hemorrhage reflects general illness severity or whether the treatment for anemia, red blood cell transfusion, directly contributes to poor outcome. Randomized trials that compare liberal and restrictive transfusion strategies in patients with subarachnoid hemorrhage are needed.
In summary, no evidence based hemoglobin level can be recommended for patients with non-traumatic subarachnoid hemorrhage, but the existing data supports a near normal hemoglobin level. In patients with non-traumatic subarachnoid hemorrhage, the target hemoglobin value could be 100-110 g/l.

70.4.3 Ischemic Stroke

Patients with ischemic stroke have an injured brain that theoretically would benefit from a constant and normal delivery of oxygen. The effect of red blood cell transfusion on outcome in patients with ischemic stroke has been scarcely investigated. Elevated hematocrit has been associated with greater infarct size, early mortality and major disability in patients with ischemic stroke. Elevated hematocrit could be caused by decreased fluid intake and hypovolemia. Hemodilution on the other side has not been proven to improve survival or functional outcome after ischemic stroke. A too low hematocrit may decrease oxygen transport to the injured brain and a too high hematocrit may increase blood viscosity and thus impair microcirculation.
In summary, no evidence based hemoglobin level can be recommended for patients with ischemic stroke. Theoretically normovolemia and a near normal hemoglobin level would be of value for avoiding secondary insults in the injured brain.

70.5 Conclusion

Red blood cell transfusion is a potentially life-saving therapy in order to maintain oxygen delivery to an injured brain. Transfused red blood cells may not only increase oxygen delivery but also possibly influence tissue oxygenation by the capacity to regulate microvascular blood flow. The efficacy of stored red blood cells to maintain their biological activity has been questioned, due to storage damages.
Patients with **traumatic brain injury** may, based on the data presented, benefit from hemoglobin levels near normal. In patients with traumatic brain injury, the target hemoglobin value could be around 110 g/l.
Anemia has been identified as an independent risk factor for unfavourable outcome after **subarachnoid hemorrhage**. The existing data support a near normal hemoglobin lev-

el. In patients with non-traumatic subarachnoid hemorrhage, the target hemoglobin value could be 100-110 g/l.
The optimal hemoglobin level in patients with **ischemic stroke** is barely investigated. Theoretically would normovolemia and a near normal hemoglobin level be of value for avoiding secondary insults in the injured brain.

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71 Optimizing Cerebral Perfusion Pressure in Acute Brain Injury

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71.1 Introduction

The management of cerebral perfusion pressure (CPP) is an integral part of hemodynamic resuscitation of brain injured patients. CPP, the difference between mean arterial pressure (MAP) and intracranial pressure (ICP), plays a major role in defining blood flow to the injured brain. The clinician's main task at the bedside is to ensure adequate delivery of oxygen and nutrients to match neuronal metabolic demands and avoid secondary brain injury. Since delivery is dependent on cerebral blood flow (CBF), finding the optimal CPP is crucial to limit secondary injury and improve outcomes.
The objective of this chapter is to discuss how to define and achieve optimal CPP goals based on individual patient profiles and different clinical situations.

71.2 Multimodal Monitoring

A comprehensive approach to goal-directed interventions requires that organ function is assessed to indicate the need and evaluate the response to specific treatments. The ideal monitoring tools in the ICU should be continuous, noninvasive and accurate measurements of the end-organ function of interest. In order to monitor cerebral function parameters there are no good substitutes to intracranial probes that measure intracranial pressure, brain tissue oxygen tension and aerobic metabolic activity. Our approach to multimodal monitoring focuses on systemic and cerebral parameters and the interrelation between them, as shown in Table 71.1.
Hemodynamic monitoring is a cornerstone of the management of critically ill neurological patients. We use either Vigileo™ or PICCO™ devices to monitor mean arterial pressure and pulse-contour analysis of the arterial waveform to generate continuous cardiac output [1-5]. Both technologies also offer continuous measurement of stroke volume variation (SVV) which is used as an estimate of fluid responsiveness in mechanically ventilated patients. The PICCO™ further calculates extravascular lung water (EVLW) and global end-diastolic volumes based on a transpulmonary thermodilution curve [5]. Through a central venous line, preferably on the subclavian site, central venous pressure (CVP) and oxygen saturation are continuously monitored. Arterial lactate and arterial-venous delta CO_2 (a-v ΔCO_2) allow estimation of tissue hypoperfusion and inadequate systemic CO_2 washout, an indication of inappropriate cardiac output [6-10].
Multimodal monitoring parameters of brain function are shown in Table 71.1. It is composed of intracranial measurements of ICP, partial pressure of brain tissue oxygen ($PbtO_2$), microdialysis, brain tissue perfusion (Hemedex™) and cortical depth continuous electroencephalography (cEEG) [11,12]. In addition to the intracranial monitoring, surface cEEG and jugular bulb oxymetry complete the armamentarium of tool avail-

Modality	Purpose and general goals	Description and comments
Systemic		
Continuous cardiac index (CI)	Above 2.5 l/min/m^2	BSA indexed cardiac output based on pulse contour analysis of arterial waveform
Mean arterial pressure (MAP)	Above 70 mmHg	Invasive MAP through radial or femoral artery
Stroke volume variation (SVV)	Below 10%	Ventilation induced variability of stroke volume
Global end diastolic volume index (GEDI)	Above 600 ml/m^2	Estimated maximal volume of 4 heart chambers based on transpulmonary thermodilution curve
Central venous oxygen saturation (scO_2)	Above 70%	Blood oximetry measured by central venous catheter located at right atrium or superior vena cava
Central venous pressure (CVP)	Above 5 mmHg	Intravascular pressure measured by central venous catheter located at right atrium or superior vena cava
Extravascular lung water index (ELWI)	Below 10 ml/kg	Estimate of the intra-thoracic volume of water outside the blood vessels base on transpulmonary thermodilution
Cerebral		
Continuous eletroencephalography (cEEG)	Seizure and ischemia detection	Surface continuous EEG with quantitative parameters
Intracranial pressure (ICP)	Below 20 mmHg	Intracranial parenchymal or ventricular pressure
Cerebral perfusion pressure (CPP)	Above 60 mmHg	MAP-ICP
Brain tissue oxygen tension ($PbtO_2$)	Above 15 mmHg	Partial pressure of oxygen measured at brain tissue level
Cerebral microdialysis	Lactate/pyruvate ratio <40 and glucose >0.7 mmol/l	Lactate, pyruvate and glucose measured at brain tissue level
Brain tissue perfusion (rCBF)	Above 20 ml/100 g/min	Regional brain tissue perfusion based on thermodilution method
Depth continuous EEG	Seizure and ischemia detection	Subcortical continuous EEG
Jugular venous bulb oximetry (sjO_2)	Above 65%	Blood oximetry measured at jugular venous bulb

Table 71.1. Multimodal monitoring. Systemic and cerebral parameters.

able. The intracranial modalities are usually used as a bundle, inserted into a multi-lumen bolt and/or tunneled in, as necessary. $PbtO_2$ is a measure of tissue oxygen tension and is believed to reflect the balance between delivery, consumption and tissue diffusion of oxygen [13-16]. Microdialysis allows measurement of glucose, lactate and pyruvate in a small volume of tissue around the catheter. High lactate/pyruvate (L/P) ratios indicate anaerobic metabolism and if associated with low brain glucose, suggest tissue metabolic crisis [17,18]. Tissue perfusion around the area of the probe is estimated through a thermodilution method between two thermistors along the probe (Hemedex™) [12,19].

71.3 Goal Directed Systemic Resuscitation

Systemic hemodynamic resuscitation should always precede brain targeted interventions. Comatose patients with severe brain injury are likely to be mechanically ventilated and should be monitored with an invasive arterial line, a central venous catheter and an intracranial pressure probe. Semi-invasive continuous monitoring of cardiac output and stroke volume variation are possible through pulse contour analysis of the arterial waveform. GEDVi is used as a volumetric static measure of preload and extra-vascular lung water measurements as an indicator of pulmonary edema. Central venous pressure and central venous oxygen saturation ($scvO_2$) complement this comprehensive list of hemodynamic monitoring parameters.

Markers of end organ hypoperfusion, such as high lactate and low central venous oxygen saturation, indicate inadequate oxygen delivery and should prompt interventions in order to achieve optimal mean arterial pressure and cardiac output [9,10,20]. Assessment of fluid responsiveness should follow based on GEDV and stroke volume variation (SVV). SVV greater than 10% and GEDVi less the 600 ml/m^2 generally indicate that the patient will respond to a fluid challenge with either 500 ml of crystalloid or 250 ml of colloid [21]. An increase in cardiac output confirms the response to the fluid challenge.

After optimal preload is achieved, MAP should be maintained above 70 mmHg with norepinephrine and cardiac index kept above 2.5 l/min/m^2 with dobutamine or milrinone, if necessary. After hemodynamic stabilization, end organ perfusion parameters should be reassessed. Urine output >0.5 ml/kg/h, clearance of arterial lactate, $scvO_2$ >70% and delta a-v ΔCO_2 <6 are good indicators of effective systemic resuscitation.

71.4 Multimodal Monitoring and Goal Directed Cerebral Resuscitation

The goal of advanced neuromonitoring in patients with severe brain injury is to allow early detection of complications and ensure adequate delivery of oxygen and nutrients to the brain in order to avoid permanent damage. After the primary event, a number of processes can lead to secondary brain injury. Nonconvulsive seizures after traumatic brain injury, vasospasm after subarachnoid hemorrhage, expansion of the hematoma after intracerebral hemorrhage and increased ICP after cardiac arrest are examples of detectable complications that progress in the ICU and can be captured by comprehensive monitoring of brain function [22-31]. Early detection and prompt intervention can potentially prevent irreversible damage.

Continuous multimodality neuromonitoring includes ICP, $PbtO_2$, microdialysis, continuous EEG (surface and depth) and tissue perfusion. These probes are introduced at the bedside through a multi lumen bolt and/or tunneled in subcutaneously. All the data is stored and continuously displayed at the bedside along with systemic monitoring parameters.

An integrative approach to brain oxygenation, metabolism, electrical activity and perfusion allows the clinician to understand the pathophysiology of events and to individualize clinical therapy. Small elevations in ICP below traditional thresholds may compromise perfusion and lead to brain tissue hypoxia and metabolic crisis. Early treatment to optimize perfusion may reverse these alterations and avoid a vasodilatory cascade that leads to refractory intracranial hypertension [32]. Similarly, a reduction in regional blood flow to ischemic levels may cause reduced alpha/delta ratios, elevated lactate/pyruvate

ratios and low $PbtO_2$ [14,18,33]. Early CPP optimization and balloon angioplasty may also reverse ischemia and avoid permanent deficits.

CPP is the primary determinant of cerebral blood flow and oxygen delivery to the brain [34-36]. It is thus a powerful and practical tool at the bedside to achieve adequate balance between oxygen and nutrient delivery and the brain's metabolic demand. Instead of relying on arbitrary thresholds to target CPP, functional assessment of the brain permits goal directed management of cerebral hemodynamics and individualized targets of optimal CPP.

The main goals when optimizing CPP are to maintain $PbtO_2$ >15 mmHg, sjO_2 >65%, L/P ratio <40 and regional perfusion >20 ml/100 g/min [18,37]. The first step is usually to optimize cardiac preload with fluids in patients who are fluid responsive. Once adequate preload and an SVV<10% are achieved, MAP and cardiac output can be improved with vasopressors and inotropes, respectively. We initially keep cardiac index above 2.5 and CPP above 60 mmHg.

CPP and cardiac output, though critically important, are only 2 pieces of the homeostatic puzzle where factors such as blood rheology, serum osmotic pressure, glucose and arterial pO_2 influence ongoing neuronal injury. Taking into account the complexity and interactions between these variables, efforts are undertaken to adjust sedation, serum osmolarity, blood glucose control and exclude surgical complications through neuroimaging while hemodynamic is optimized.

When brain physiological targets are not yet achieved, further efforts to increment CPP and cardiac output are undertaken. Supranormal levels are defined as optimal if they correlate with improvements in the cerebral oxygenation and metabolic profile.

71.5 Specific Situations

71.5.1 Subarachnoid Hemorrhage (SAH)

Patients with aneurysmal SAH are at increased risk for rebleeding, hydrocephalus and vasospasm. The highest rates of rebleeding occur in the first 3 days after SAH and surgical clipping or endovascular coiling of the ruptured aneurysm should be pursued as soon as possible after admission. While the aneurysm is unsecure, systemic hypertension should be avoided but hemodynamic stability is crucial to avoid cerebral hypoperfusion, acute ictal infarcts and cerebral circulatory arrest [38].

Liberal fluid resuscitation with crystalloids is commonly necessary in poor grade SAH patients before securing the aneurysm. Although frequently hypertensive, patients are admitted with relative intravascular volume depletion – due to natriuresis and systemic inflammatory response – and 2 l of normal saline are acutely administered to maintain organ perfusion. If a MAP goal of 70 mmHg is not achieved, norepinephrine is initiated. If, instead, the MAP is higher than 130 mmHg or systolic blood pressure is above 180 mmHg, continuous infusion of nicardipine is started to avoid unsafe blood pressure levels.

Comatose patients with suspected hydrocephalus should emergently have an extraventricular drain (EVD) placed and ICP monitored [38]. Once the aneurysm is treated and multimodality monitoring data is available, optimal CPP should be pursued as described previously.

Vasospasm is a major concern after SAH, especially between days 4 and 14 after the initial hemorrhage. Up to 50% of patients will develop symptomatic vasospasm after SAH. Especially those who present with diffuse and thick cisternal blood are at increased risk

for delayed infarcts due to vasospasm. There is increasing evidence that multimodality monitoring allows detection of cerebral ischemia due to vasospasm before clinical signs develop [14,15,18,27,33]. Integrating electrical activity monitoring through quantitative EEG, oxygenation with $PbtO_2$ and oxidative metabolism measured by microdialysis may create a window of opportunity for intervention before clinical signs appear and permanent deficits take place. Recent evidence suggests this window may vary from hours to a few days [17,39].

Dynamic changes in alpha/delta ratio, a relative reduction in $PbtO_2$ or elevation in lactate/pyruvate ratio should alert the bedside nurse or clinician of potential ongoing ischemia. Repeated clinical and transcranial Doppler examinations usually follow. If vasospasm is suspected, especially in a comatose or sedated patient, a perfusion CT scan is indicated to evaluate the extent of the perfusion deficit. At the same time a trial of increased CPP and cardiac output is undertaken with reversal of the altered parameter as the goal. A positive response to improved cerebral blood flow is seen within minutes for the continuously measured $PbtO_2$ and qEEG parameters and is reflected in the next 1 to 2 hours of microdialysis measured lactate and pyruvate. If a positive response is achieved, these supranormal levels of cardiac output and CPP are defined as optimal. Caution is advised in patients with stunned myocardium for excessive MAP and CPP may result in increased left ventricular afterload and lead to reduced cardiac output and pulmonary congestion [40]. Angiography and definite treatment with intra-arterial vasodilators and balloon angioplasty are often necessary for refractory symptomatic vasospasm [41].

71.5.2 Traumatic Brain Injury (TBI)

A recent update of the Brain Trauma Foundation Guidelines for the management of patients with severe TBI addresses the evidence available on CPP management, including the role of brain tissue oxygenation and metabolism [37]. It suggests there is a clinical threshold of CPP, between 50 and 60 mmHg, below which cerebral blood flow is compromised and poor outcome is more likely. Studies have shown that CPP values below 60 mmHg are associated with low $PbtO_2$ and jugular venous oxygen saturation and that these findings are related to poor outcome. Microdialysis studies have also suggested that ischemia, as measured by altered L/P ratios, is more frequent when CPP trends below 50 mmHg.

The guidelines' update also emphasizes recent evidence from a randomized clinical trial comparing treatment based on CPP and ICP goals. CPP was kept above 70 mmHg in one group while the other group was treated to maintain ICP below 20-25 mmHg and avoid CPP <50 mmHg. There was no difference in outcome between the 2 groups and the CPP-based management group had a five-fold increased incidence of acute respiratory distress syndrome (ARDS) [42].

Similar results were found in a retrospective analysis of a RCT where CPP-targeted therapy was associated with ARDS and this complication was strongly related to vasopressor administration [43].

The body of evidence available suggests that finding an optimal CPP is crucial to the management of patients with TBI [37]. The optimal level should be individualized after assessing cerebral autoregulation, oxygenation, metabolic and electrical profiles and their responses to changes in CPP. We assess autoregulation in the acute phase after severe TBI through the moving correlations between MAP and ICP (pressure reactivity index) [44,45] and CPP and $PbtO_2$ (oxygen reactivity index) [46]. Impaired autoregulation indicates that cerebral blood flow is dependent on CPP and that unnecessary high CPP

levels may lead to increased cerebral blood volume and intracranial pressure. Initially we avoid CPP levels below 60 mmHg. Intracranial pressure levels above 25 mmHg are treated with sedatives/analgesics and osmolar therapy followed by hypothermia and barbiturates in refractory cases [37]. Concomitantly, optimal CPP is pursued.

Cardiac preload assessment always precedes efforts to increase systemic vascular resistance with vasopressors and myocardial contractility with inotropes. The goal is to avoid CVP <5 mmHg, keep GEDVi >600 ml/m^{2}and maintain stroke volume or pulse pressure variation below 10%. Extreme caution to avoid unnecessary fluid overloading is warranted during the course of fluid resuscitation. We prefer using fluid boluses of crystalloid as needed instead of continuous infusion of large volumes of fluid. After every fluid challenge cardiac output improvement is reassessed. Ineffective fluid challenges will fail to increase cardiac output and thus cerebral blood flow, and contribute to pulmonary edema. Although we do not consider high extravascular lung water measurements as a contraindication to fluid administration, special caution is warranted in patients with values above 10 to 15 ml/kg [5,47].

Vasopressors and inotropes should be initiated for patients who fail to maintain minimum values of CPP (>60 mmHg) and cardiac output (>2.5 l/min/m^2) after fluid resuscitation. The next step is to titrate CPP and CI to meet individual needs based on physiological information from multimodality monitoring. In patients that present with reduced $PbtO_2$ and elevated L/P – less than 15 mmHg and above 40, respectively – despite hemodynamic stability, a trial of increased CPP and/or cardiac output is attempted [48,49]. Dynamic improvement of oxygenation and metabolism suggest that the supranormal values achieved are necessary to maintain brain homeostasis and avoid secondary injury.

71.5.3 Intracerebral Hemorrhage (ICH)

The presence and severity of acute hypertension may affect outcome after intracerebral hemorrhage (ICH). There is reasonable evidence that elevated admission BP is associated with increased risk of deterioration, death or dependency after ICH [22,29]. Though, the target BP to pursue and the drug of choice to achieve it are still a matter of debate. Recent guidelines suggest maintaining SBP below 160 mmHg and MAP below 110 mmHg in patients at risk for deterioration and high ICP during the acute phase after ICH [50]. We usually start a continuous infusion of nicardipine in all ICH patients with SBP greater than 160 mmHg or MAP greater than 110 mmHg.

Comatose patients with intracranial mass effect associated with the hematoma or perihematomal edema regularly undergo multimodal monitoring. The main objective is to achieve adequate BP control without compromising cerebral perfusion and metabolism. Some authors suggest there is a penumbra region around the area of the hematoma with impaired autoregulation and at risk for ischemia [51]. The monitoring probes are usually directed to the ipsilateral hemisphere in the perilesional region. This approach to probe placement may potentially detect regional hypopefusion and diagnose expansion of perihematomal edema.

Initial CPP is targeted between 60 mmHg and 80 mmHg and finer adjustments are made based on $PbtO_2$ and microdialysis values. If CPP levels of 60 to 70 mmHg are tolerated without evidence of brain tissue hypoxia or metabolic distress MAP is titrated to achieve this goal with either vasopressors such as norepinephrine or vasodilators such as nicardipine. Although the relationship between hematoma growth and hypertension is still controversial, CPP levels above 80 mmHg are usually avoided in the first 72 hours post ICH and, when deemed necessary, titrated with extreme caution.

71.5.4 Post Cardiopulmonary Resuscitation

There is little evidence on CPP management in patients that survived a cardiac arrest, especially after hypothermia was instituted as an evidenced-based treatment by the International Liaison Committee on Resuscitation (ILCOR) [52-54]. Furthermore there is negligible data and experience with intracranial multimodal monitoring of these patients [31].

Cardiac arrest causes a global ischemic injury to the brain followed, after return to spontaneous circulation (ROSC), by a potentially harmful reperfusion injury. Patients that survived cardiac arrest used to have devastating outcomes, especially those with delayed time to ROSC and non ventricular fibrillation rhythms [53,55]. Since hypothermia was incorporated to the armamentarium of treatment for these patients, improved outcomes have been consistently shown in clinical trials and real world case series, even for severely ill patients with cardiogenic shock and time to ROSC of up to 30 minutes [53].

Although hypothermia can potentially ameliorate the effects of a global hypoperfusion injury to the brain, we believe it should be part of a comprehensive approach to avoid secondary injury that includes systemic and cerebral hemodynamic management guided by multimodal monitoring. Continuous EEG and jugular bulb oxymetry monitoring have been shown to be associated with outcome after cardiopulmonary resuscitation [56-58]. Studies conducted before the hypothermia era suggest that the presence of non-convulsive status epilepticus (NCSE) and elevated jugular bulb saturation indicate poor prognosis. More extensive monitoring of cerebral function including intracranial pressure, tissue oxygenation, metabolism and perfusion may help titrate systemic drivers of cerebral blood flow such as CPP and cardiac output. All patients treated with hypothermia after cardiac arrest in our ICU undergo invasive arterial pressure, semi-invasive cardiac output and continuous EEG monitoring. Initial hemodynamic goals include euvolemia – optimized preload – with MAP above 80 mmHg and CI above 2.5. If post resuscitation myocardial stunning is present, patients may require vasopressor and inotropic support to achieve these goals and care should be taken not to overload the patient and cause impaired lung gas exchange. Once multimodal monitoring data is available hemodynamic variables are titrated to keep CPP >60 mmHg, ICP <20 mmHg, CBF >20 ml/100 g/min, $PbtO_2$ >15 mmHg and L/P ratios <40. These levels are derived from other scenarios of severe brain injury and need to be tested in prospective trials of patients after cardiopulmonary resuscitation.

With increasing numbers of patients undergoing hypothermia treatment in the post resuscitation phase and more comprehensive monitoring of cerebral function, the pathophysiology of the ischemia-reperfusion injury caused by cardiac arrest will be better understood. This can potentially lead to specific approaches that avoid secondary injury during the hypothermia, rewarming and post rewarming phases. We believe that better understanding and targeted treatment can further improve outcomes of cardiac arrest survivors.

71.6 Conclusions

CPP management after severe brain injury is part of a comprehensive approach that includes goal-directed systemic and cerebral hemodynamic management. The first step should always be to achieve optimal preload and adequate volemic status through targeted fluid resuscitation. Vasopressor and inotropic support may be necessary at this early resuscitation phase to guarantee systemic end-organ perfusion.

Optimal CPP is then pursued. In general, the goal of achieving optimal CPP is to guarantee adequate delivery to meet the brain's metabolic demands. CPP and cardiac output are major determinants of CBF. Thus, oxygen and nutrient delivery to the tissue are directly related to CPP and cardiac output. The purpose of multimodal monitoring is to allow goal-directed management of cardiac output and CPP guided by measures of brain tissue perfusion, oxygenation and metabolic function. This approach allows not only early detection of harmful complications but also guides treatment towards a healthier profile of brain function, potentially preventing secondary brain injury and improving patients' outcomes.

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72 Pathophysiology and Management of Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage

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72.1 Introduction

Subarachnoid hemorrhage (SAH) from spontaneous rupture of cerebral aneurysms of the base of the brain is the cause of 5-10% strokes annually in the United States [1]. Epidemiological studies suggest that the incidence rates vary substantially according to the geographic region with the highest rates seen in Japan and Finland [2,3]. The mortality after SAH has historically been high, ranging from 30-70% and about 10-20% of these patients experience severe long-term neurological disability. Approximately 12% of these patients will die before arriving to the hospital, 25% of patients will die within 24 hour before any medical or surgical intervention; and historically 40-60% will die within 30 days of admission [4]. The outcome after SAH depends on several factors, including age, the severity of the ictus, medical management strategies, and the incidence of medical complications [5].

One of the most important complications seen after SAH is cerebral vasospasm (CV), which occurs in up to 70% of the survivors. The incidence of CV correlates with a 1.5-3 fold increase in the baseline mortality [4]. The diagnosis of CV may be suspected on the basis of daily thorough neurological examinations, variations of transcranial Doppler (TCD) waveforms and results, and with cerebral angiography, which serves as the gold standard for its diagnosis. Most often, CV begins on the third day after SAH (index day 3), and reaches its acme on the 6th to 8th day after the ictus. The symptomatology is related to the vascular region of cerebral ischemia, and if CV is severe enough and remains untreated, cerebral infarction may occur. Aside from its effect on mortality, one of most important aspects of CV is its refractoriness to established medical interventions, thus emphasizing the need for additional research into the physiopathology of SAH-induced cerebrovascular dysfunction. Although it is well recognized that the volume of blood on computed tomography (CT) is the most reliable prognostic factor for developing vasospasm [6], the precise pathophysiology of CV remains poorly understood.

72.2 Pathophsyiology of Cerebral Vasospasm

Since the demonstration of arterial narrowing during CV by Ecker in 1951 and Weir in 1978 [7,8], it has been shown that SAH is associated with arterial narrowing, which in

turn may be related to cerebral ischemia, infarction, and increased morbidity and mortality. Important well studied variables associated with the development of CV include: hemoglobin products, entotelin-1 (ET-1), and decrease of nitric oxide.

72.2.1 Hemoglobin

When ferrous hemoglobin is released from the blood in the subarachnoid space, it leads to delayed arterial spasm by physiopathologic mechanisms that are poorly understood. According to Pluta et al. [9], explanations for this phenomenon include: neuronal apoptosis, scavenging or decreased production and levels of nitric oxide (NO), high ET-1 levels, direct oxidative stress on smooth muscle cells, free radical production and lipid peroxidation of cell membranes, modification of potassium and calcium channels, and differential gene upregulation. Oxidative stress in the subarachnoid space has also been reported to activate protein kinases. In this particular scenario, C and Rho kinase activation lead to smooth muscle cell constriction. Rho kinase in particular, initiates vascular contraction through protein kinase C-δ activity, which also induces proliferation and growth of vascular smooth muscle cells, a possible mechanism for the phenotypic change and remodeling of vascular smooth muscle seen in vasospasm [9]

72.2.2 Endothelin 1

After experimental isolation of a potent vasoconstricting peptide known as ET-1 from pig endothelial cells, elevated levels of this protein were also seen in the cerebrospinal fluid of patients and animals with CV. It appears that oxy-hemoglobin causes an increase in ET-1 synthesis from endothelial cells. Similarly, astrocytes may synthesize ET-1 in response to ischemia and leucocytes that have infiltrated the subarachnoid space after SAH may produce ET-1 as well. Furthermore, cerebral arteries may become sensitized to ET-11, leading to increased cerebrovascular tone even in the absence of an increase in ET-1 levels [9].

72.2.3 Nitric Oxide

Inhibition of smooth muscle relaxation can also cause or contribute to arterial narrowing because of the basic myogenic tone of the cerebral vasculture. Nitric oxide (NO) is a potent vasodilator produced by the endothelium, and plays an important role in the maintenance of cerebrvascular tone. According to Pluta et al, several mechanisms have implicated NO in the physiopathology of vasospasm after SAH: 1) the disappearance of neuronal NO synthase immunoreactivity from arteries in spasm, 2) endothelial NO synthase dysfunction in cerebral vessels after SAH, and 3) the affinity for NO of the heme moiety in hemoglobin [9]. New strategies for NO-based therapy against vasospasm include: gene therapy, pre-clinical and early clinical trials of NO donors administered intra-arterially, intrathecally, locally or intravenously [9].

72.3 Medical Treatment of Cerebral Vasospasm

Medical treatment in the Neurological Intensive Care Unit (NICU) is instituted in all SAH patients with adequate hemodynamic support, nutritional support, prevention of fever, hyperglycemia, and of medical complications.

72.3.1 Fluid Management and Normovolemia

Maintenance of normovolemia is key in the management of SAH patients (Diringer et al. 2011; Solomon et al. 1988), though the prophylactic use of the so called "triple – H therapy" (hypervolemic, hypertensive, hemodylution) is not indicated as initial management, it is occasionally instituted for those patients with confirmed vasospasm (Lennihan et al. 2000). The rationale of "Tiple-H" in the management of cerebral vasospasm is that the maintenance of high circulating blood volume may be associated with enhancement of CBF in the setting of vasospasm. This observation has recently been challenged by studies that have demonstrated that CBF is mainly dependent on the induced hypertension component rather than the volume component (Muench et al. 2007). Current guidelines for the management of SAH do not endorse the use of "Triple-H" therapy in the setting of cerebral vasospasm but on maintancence of euvolemia (Diringer et al. 2011).

72.3.2 Calcium Antagonists

Of the numerous types of calcium channel blockers, nimodipine is the most widely administered based on its relative selectivity for dilation of the cerebral arteries as compared to the systemic vasculature. While nimodipine does not appear to decrease angiographic vasospasm, multiple trials have shown it to improve outcomes by decreasing the incidence of cerebral ischemia [11,12]. A dose of 60 mg PO q4h in normotensive patients or 30 mg PO q4h in hypotensive patients can be administer up to index day 21.
Nicardipine is another dihydropyridine calcium antagonist that displays regional selectivity on vascular smooth muscle. Unlike nimodipine, nicardipine may be administered intravenously. Initial dose-escalation studies demonstrated that intravenous nicardipine results in angiographic and symptomatic improvement in patients with vasospasm, with higher doses being limited by medical complications such as hypotension, pulmonary edema, and renal failure [13]. Subsequent prospective, randomized controlled studies have demonstrated that while nicardipine significantly lowers the incidence of documented vasospasm, it confers no benefit in neurologic outcome [14-16].
Recent trials have tested the efficacy of local prolonged-release nicardipine-loaded polymers implanted at the time of aneurysm clipping into the basal cisterns close to the proximal cerebral arteries, with the medication being released over 14 days. The second work confirmed reductions in vasospasm (ARR 66%) and delayed ischemic lesions (ARR 33%) with significantly better outcomes [17,18]. This type of therapy is a promising alternative for the management of vasospasm but needs further study in randomized controlled setting.

72.4 Endovascular Treatment

Angioplasty and intra-arterial vasodilators, either alone or in combination, are the mainstay of therapy of vasospasm after SAH.

72.4.1 Balloon Angioplasty

Angioplasty commonly results in excellent, and nearly always permanent, angiographic reversal of vasospasm. By stretching the artery, balloon dilatation leads to an immediate and profound impairment in smooth muscle function, with in vitro and in vivo studies demonstrating both a functional and morphologic change in these fibers. Observations

indicate that earlier treatment with balloon angioplasty for patients with medically intractable vasospasm may result in better clinical outcomes. Rosenwasser et al. sought to define a time frame in which balloon angioplasty would be maximally effective and determined that early treatment within 2 hours was associated with better angiographic outcomes and clinical improvement [19].

72.4.2 Intra-arterial Vasodilators

The ability to reach distal vessels beyond the limits of balloon angioplasty makes intra-arterial administration of vasodilator an attractive approach to endovascular treatment of vasospasm. Papaverine, a non-specific smooth muscle relaxant, has been used in refractory vasospasm but recent reports concerning its plausible association with worsening focal cerebral edema and seizures have limited its use with newer agents such as verapamil and nicardipine being preferred in most centers despite the lack of head to head trials.

72.5 Novel and Experimental Treatment

72.5.1 Drainage of Clots and CSF Manipulation

Initial experience in Japan has demonstrated that CSF clearance by lumbar drainage provided protective effects against vasospasm (ARR 34%) [20]. Similarly, fenestration of lamina terminailis has shown to reduce the incidence of vasospasm in preliminary studies [21].

72.5.2 Statins

In a retrospective series, patients who received statin therapy for at least 1 month before SAH demonstrated an 11-fold decrease in the risk of developing symptomatic vasospasm after SAH and a recent prospective, double-blind, randomized placebo-controlled clinical trials of statins given for 14 days after SAH, the incidence of symptomatic cerebral vasospasm was significantly reduced in treated patients [22-24].

72.5.3 Clazosentan

There have been many clinical trials, but until the arrival of clazosentan, a selective endothelin 1A receptor antagonist, it has not been possible to reproducibly break the chain of vasospasm. Clazosentan did, however, effectively prevent and reverse arterial narrowing in one work, providing what was thought may at last be an effective treatment. However, the subsequent multicenter CONSCIOUS trial, despite significant reductions in angiographic vasospasm, failed to show any effect on long-term outcome [25].

72.5.4 Fasudil

Intra-arterial fasudil hydrochloride (a Rho-kinase inhibitor) is part of the multimodal therapy strategy after SAH in some centers in Japan, along with the use of cisternal urokinase injection, drainage of subarachnoid blood, and strict maintenance of conventional medical therapy. The results of this multimodality treatment strategy with fasudil when compared with patients without multimodal therapy was a decrease in incidence of vasospasm from 57% to 37% with subsequent reduced morbidity and mortality.

72.6 Conclusions

Cerebral vasospasm is as an important cause of poor outcome after an otherwise successful treatment of aneurysmatic subarachnoid hemorrhage (SAH). Current manage-

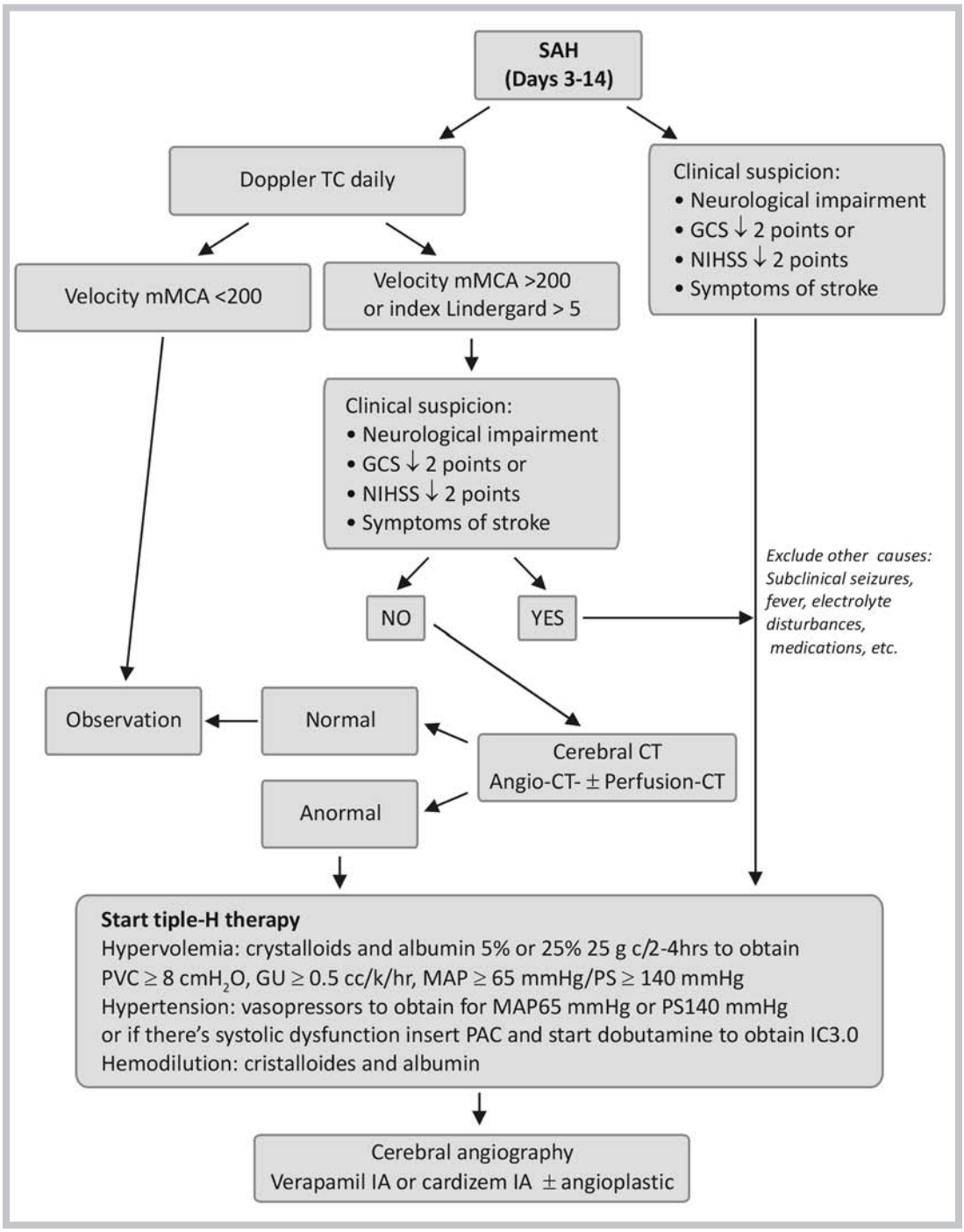

Figure 72.1 **Management of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Columbia University Protocol.**

ment of this condition includes maximal medical therapy with a regimen of euvolemia and induced hypertension, oral calcium channel antagonists, and with endovascular approaches. Novel and exciting alternatives are being studied and the development of promising alternatives will likely follow [26].

Figure 72.1 summarizes the management of cerebral vasospasm after aneurysmal subarachnoid hemorrhage according to Columbia University Protocol.

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73 Intensive Care Management of Poor-grade SAH Patients. An Overview

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73.1 Introduction

Subarachnoid hemorrhage (SAH) still poses a significant challenge to neurocritical care, as its cumulative morbidity and mortality remains persistently high, despite continuous research efforts. Diagnostics, monitoring and treatment are certainly a multidisciplinary effort, involving neurosurgeons, neurologists, neurointerventionalists and intensive care physicians alike.

Patients suffering a spontaneous, non-traumatic subarachnoid hemorrhage (incidence 10-15/100.000 per year) usually complain of a split-second onset of most severe headache. It is often accompanied by neck stiffness, and patients may demonstrate (transient) focal neurological deficits or even sudden loss of consciousness. Despite the characteristic symptomatology many patients are presented to a dedicated neurovascular center only in a delayed fashion. Cumulative mortality may amount up to 50%, with 10-15% of all patients with SAH not reaching a treatment facility in time.

The severity of SAH is commonly graded according to the initial neurological presentation: the Hunt and Hess grading (HH) [2] or the World Federation of Neurological Surgeons score (WNFS) [1]. Overall morbidity and mortality are clearly associated with the initial neurological deficit and increase dramatically with HH or WFNS grade (i.e. survival in HH IV-V as low as 20%). Patients with poor-grade SAH (HH IV-V) account for about 20-30% of all patients admitted with SAH, and they require the most intensive, highly specialized neurocritical observation and treatment. At the same time they may represent the group of patients who benefit the most, since 40% will achieve a favorable outcome with sophisticated treatment while 90% will die or become severely disabled if not treated adequately.

73.2 Diagnostics

Initial work-up includes cranial computed tomography (CT) to show characteristic hyperdense distribution of the extravasated blood within the subarachnoid space; sensitivity for SAH is 98% within the first 12 h, decreasing thereafter. If the initial CT is negative, but SAH is suspected, a lumbar puncture has to be performed to rule out recent hemorrhage. As acute SAH is caused by an intracranial aneurysm in 85% of cases, CT is then followed either by CT-angiography (CTA) or conventional digital subtraction angiography (DSA) and three-dimensional reconstruction, the choice of diagnostics means depending on the institution´s infrastructure. CTA being an inexpensive and less invasive diagnostic tool, it can be performed immediately after the initial CT scan. It is now gen-

erally considered to yield sufficient information about the source of bleeding to develop a treatment plan, in particular if DSA is not readily available. However, in up to 20% of cases, aneurysms smaller than 4 mm or particularly close to the skull base may be missed due to limitations in collimation or imaging artifacts. Depending upon the preference of the treating physician, an additional conventional angiography should be obtained, if the quality of CTA is limited or CTA is negative despite typical localization of subarachnoid blood.

73.3 Early Management

Upon completion of the initial work-up poor-grade SAH patients should be admitted to an ICU facility as soon as possible. Patients usually present hypertensive, and an arterial line for blood-pressure management is mandatory. Early re-rupture of an unsecured aneurysm is estimated to occur in 4% of cases within the first 12 hours, but this risk may increase to 20% in poor-grade SAH, and it increases overall mortality to over 70%. We generally advocate a target systolic blood pressure of 120-140 mmHg before the aneurysm is secured, also carefully avoiding critical hypoperfusion and infarction. Alpha- and beta-receptor antagonists such as labetalol are preferred over cerebral venodilators such as nipride and nitroglycerine. Other general monitoring parameters include continuous ECG and oxygen saturation, to detect detrimental arrhythmias or hypoxemia; ECG abnormalities are estimated to occur in 50 to over 90% of patients, though the significance in the acute phase is not clear. Intubation and central line access is required in all comatous or unstable patients. If the patient cannot be sufficiently assessed clinically (neuro checks to be performed hourly) or impending hydrocephalus is suspected (generally in about 20% of patients, but more frequent in poor-grade cases), an intracranial pressure monitoring should be put into place, preferably an external ventricular drain with the option of ICP treatment by drainage. Single-shot antibiotic prophylaxis before insertion is recommended while continuous use of antibiotics is not. While ventriculitis due to the indwelling catheter is a potential complication, the risk of infection may be reduced by tunneling the drain, but not by frequent exchange of the catheter. If an EVD or intraparenchymal pressure measuring device is in place, cerebral perfusion pressure (CPP) can be calculated and corrected to be above 60 mmHg. Patients should observe strict bed rest with the head and upper torso elevated around 30°; they should receive adequate analgesia and provocative actions such as Valsalva maneuvers (e.g. during defecation or vomiting) should be minimized through use of laxatives and antiemetics respectively. Any coagulation pathology should be corrected rapidly, antifibrinolytic agents should be avoided and coagulation factors, thrombocytes or vitamin K are substituted as needed.

73.4 Treatment of the Aneurysm

While there is general consensus that a ruptured aneurysm should be secured within the first 48-72hrs and as completely as possible in order to minimize the risk of recurrent hemorrhage, there is also persistent debate as to how these aneurysms should be treated. The ISAT study compared clipping of an aneurysm with coiling and found a 7% reduction in morbidity associated with interventional treatment [3]. However, only 4.4% of patients investigated presented with poor-grade SAH, and conclusions from this study have to be drawn cautiously when discussing treatment option for patients HH° IV-

V. Also, analysis of this data does not take into account neither the anatomical location, configuration or orientation of the aneurysm, nor the particular expertise and infrastructure available in the respective department. Therefore, no general recommendation can be derived from this study for patients with poor-grade SAH. The interdisciplinary decision has to be made on an individual basis of numerous considerations in each case, and complimentary use of both techniques may represent an additional option. While smaller aneurysms presenting with a high dome-to-neck ratio (usually greater than 1.5:1), particularly in the posterior circulation, may be amenable to interventional treatment, blister-like aneurysm with particularly fragile wall-composition, broad-based or partially thrombosed aneurysms or those involving several efferent vessels (such as many MCA aneurysms) may be better suited for open surgery and reconstruction, possibly with additional options such as revascularization through bypass-application; space-occupying lesions such as intracerebral hemorrhages or subdural hematomas may also advocate for an open approach with the chance of evacuation. Another advantage is the option of opening up Liliquist membrane or the lamina terminalis to potentially reduce the risk of hydrocephalus. It remains a matter of debate, whether the so-called "definite" treatment (clipping) may indeed be superior to a technique that shows compaction and re-perfusion in follow-up angiography in 50-70% of coiled aneurysms, particularly in larger aneurysms (greater than 8-10 mm). The clinical implications of these differences, for example in younger patients, are still unclear, as longer follow-ups of aneurysms with reperfusion characteristics are still lacking. In poor-grade patients often demonstrating brain swelling and intracranial hypertension, an interventional approach may be preferable, particularly if the patients is clinically unstable or in severely reduced physical condition (with a rate of favorable recovery of about 35%); securing the aneurysm can facilitate more aggressive medical treatment afterwards, despite a higher rate of neck remnants or reperfusion in this particular subgroup. An open operation, in many instances, poses a greater immediate, perioperative risk of complications in a critically ill patient. However, one has to also appreciate the duration of the treatment, and difficulties in coiling due to the location or a particularly complex anatomy of the aneurysm might also favor a direct and open approach. Recently, the surgical approach has been greatly facilitated by the introduction of intraoperative indocyanine-green videography, where complete occlusion of the aneurysm and perfusion of important perforators can be assessed immediately [4].

Morbidity and mortality remain high for both coiling and clipping in patients with poor-grade SAH, but some studies have shown considerably better outcome in patients HH IV (44%) vs. HH V (13%). Age is another strong predictor of poor outcome. If elderly and/or multimorbid patients present with a prolonged comatous state (HH V, GCS 3-4), severe SAH on imaging scan and/or an absence of improvement after successful ICP management, the initial decision can be deferred to first determine the chance for meaningful recovery. Despite the data supporting the early exclusion of an aneurysm from the circulation, in these rare cases, observation and conservative treatment might constitute a sensible alternative to aggressive early treatment, including surgery.

73.5 Late Management

Once the aneurysm is secured, restrictions in blood pressure can be lowered. Spontaneous blood pressure may be allowed, although a minimum CPP of 60 mmHg should always be maintained. As soon as intracranial pressure and hemodynamics as well as ventilation parameters are stable, sedation should be weaned to determine neurological

function. Depending on the initial severity of the hemorrhage (and possibly on the severity and duration of intracranial hypertension), recovery of function might be protracted. This holds true for those patients with higher HH grade in particular. The following parameters of metabolism and electrolyte balance have been shown to significantly improve outcome and recovery and should be adhered to strictly:

- Hemoglobin >10 g/dl.
- Normoglycemia.
- normocarbia; pO_2 >100 mmHg.
- Normotermia.
- Intravenous fluid management: 0.9% normal saline 140-150 ml/h with 20 mEq KCl/l; central venous pressure greater than 4 mmHg.
- Enteric nutrition with continuous infusion from day 2 onwards.

Additional neuroprotective measures such as hypothermia (33-34°C) may improve outcome, but they are employed only in some centers; hypothermia in particular requires an extensive infrastructure as well as a great expertise, as complications such as coagulopathy, arrhythmia and overwhelming infections are frequent. The use of prophylactic anticonvulsants is controversial, but is advocated by some centers but not all (peri/postoperative risk about 4%; load with IV phenytoin, if needed); use of steroids is not recommended. To avoid gastric stress ulcers, treatment with proton pump inhibitors is advocated. Cerebral salt wasting and SIADH are frequent complications after SAH, causing profound hyponatremia and worsening in outcome, therefore warranting tailored fluid treatment and/or the use of hydrocortisone. Other common complications after SAH include (neurogenic) pulmonary edema (23%) and arrhythmias (25-100%), as well as imbalances in hemostasis and electrolytes (28%), sepsis, meningitis and multi-organ failure; and again, patients in poor-grade SAH are at higher risk for developing these complications. Physical therapy is recommended early on to avoid development of contractures and thrombosis, the risk of the latter also being reduced by routine use of (sequential) compression devices or stockings.

73.6 Management of Elevated ICP

Elevated ICP on the basis of hydrocephalus is a frequent complication after SAH (incidence 20-25%, posterior > anterior circulation) and is more common in poor-grade SAH patients and in patients with intracerebral or intraventricular extension of the hemorrhage. While sometimes mechanical blockage of intraventricular foramina due to intraventricular blood clots prevents drainage into the spinal canal, most often a compromised re-absorption of CSF is assumed, a term phrased malresorptive hydrocephalus. This is believed to result from occlusion of the villi within the plexus/ependyma and is treated with placement of an intraventricular catheter. ICP in an awake patient should not exceed 25 mmHg (20 mmHg in sedated patients), however, transitory increases (possibly due to external manipulation, pulmonary complications or coughing) can be tolerated if recovery is prompt and does not exceed more than 10-15 minutes. In rare cases, patients may be awake and asymptomatic with an elevated intracranial pressure of more than 30 mmHg, and while this probably does not pose a significant risk for the patient, the relevance of these findings is still not completely clear. Technical problems have to be ruled out, but asymptomatic increase in ICP may also be the first symptom of hyperemia. In fact, elevated ICP might be caused by a variety of other reasons, the most serious being global parenchymal swelling, intraventricular/intraparenchymal hemorrhage or space-occupying ischemia. If ICP is not amena-

ble to immediate relieve via CSF drainage, the following actions should be considered in consecutive order:

- Exclude new pathology (urgent CT scan, check serum electrolytes).
- Deep sedation (with continuous EEG monitoring): morphine/benzodiazepines (may consider barbiturate coma).
- Moderate hyperventilation (pCO_2 of 32 mmHg, only in absence of severe vasospasm or eminent infarction).
- Mannitol IV 125 ml/q4h until effect is only short lasting.
- Consider placing a lumbar drain (only with well defined basal cisterns) and use as needed (check pupils for signs of herniation).

Hypertonic saline solution, repeat as necessary until critical sodium level.
Consider decompressive craniectomy in selected patients.
If the ICP is controlled for more than 48hrs without or decreasing amount of CSF drainage, test occlusion under neurological monitoring is advocated to determine the necessity of further CSF drainage. Slow weaning by way of increasing outflow resistance (elevating the draining valve successively higher) has been not proven to be more beneficial than abrupt closure of the drain. About 50% of poor-grade patients will require permanent drainage, i.e. a ventriculo-peritoneal/-atrial shunt.

73.7 Management of Delayed Vasospasm

Delayed vasospasm occurs angiographically in up to two-thirds of patients, while symptomatic ischemia is present in about 30% of patients. Outcome is affected adversely, and vasospasm is the most significant cause for morbidity and mortality of those patients reaching medical care in time. Monitoring poor-grade SAH patients is essential to detect neurological deterioration, since the incidence of vasospasm is highest in this group: HH I 22%, HH V 74%. Our department has developed a standardized approach for SAH patients to detect and treat vasospasm (Figure 73.1). First choice of monitoring always includes neurological assessment if the patient is rousable without focal neurological deficit. If a patient recovers after the initial insult and is awake for several days after the treatment of the aneurysm, neurological assessment in combination with transcranial doppler sonography (TCD) may be sufficient monitoring to exclude clinically relevant vasospasm. However, as most patients with poor-grade SAH do not recover sufficiently to be monitored clinically, discussion of most further treatment issues has to be focussed on intubated patients with impaired consciousness. Despite its limited sensitivity, TCD is an established bedside tool, where flow of the intracranial vessels can be assessed non-invasively. Usually, the flow velocity within the proximal MCA is measured for the ease of accessibility from the second day after hemorrhage. Not only absolute flow values are important in the management decision (norm ~55cm/s); while an increase of more than 50cm/s from one day to the other or an absolute flow exceeding 160cm/s may already raise suspicion as to the development of vasospasm, the Lindegaard index (ratio of flow velocity within the MCA/extracranial ICA) is more sensitive and specific. An index of greater than 3 is highly suspicious of ensuing vasospasm (which should prompt further diagnostics including conventional angiography), while increased flow velocities and an index of less than 3 may indicate hyperemia. If the latter scenario coincides with refractory elevation of ICP, a quantitative measurement of CBF, such as XeCT may help to frame a therapeutic decision, such as moderate hyperventilation to minimize the effects of hyperemia and/or lower ICP.

Conventional angiography, however, is still considered the gold standard in the diagnosis of vasospasm. It should be performed routinely on day 7-9 after SAH where the risk of vasospasm is highest. Imaging may also serve as a control for clip- and coil-positioning and determine the necessity of further follow-ups (conventional angiography versus CTA or MRA). If angiography demonstrates significant vasospasm, adequacy of cerebral perfusion is the main goal of future treatment. In selected cases, spontaneous upregulation of mean arterial blood pressure and tachycardia is observed, and this might suffice to prevent critical hypoperfusion. A new deficit in an awake patient (new focal deficit, confusion/lethargy, neglect) should always prompt rigorous assessment of hemodynamics and the need of further imaging. CT scanning can exclude hydrocephalus and subacute infarction. However, if CT scanning is normal, but hypoperfusion due to impending vasospasm is suspected, mean arterial blood pressure should be increased to levels above 90 mmHg empirically until diagnostics such as angiography can be performed.

If a patient cannot be assessed clinically, as is the case in most poor-grade SAH patients, the need for further means of monitoring arises. ICP measurement is mandatory in all unconscious patients, and elevation should be treated accordingly (see above). For the treatment of vasospasm, our department has implemented a modified approach to the widely-used concept of triple-H therapy (hypertension, hypervolemia, hemodilution), a therapy concept both moderately plausible but unproven at the same time. Since complications such as pulmonary edema, myocardial infarction and electrolyte imbalance are frequent (20-30%), the widely propagated hypervolemia has been omitted since its efficacy is not proven and reduction in regional cerebral blood flow has been observed [5]. Moderate hemodilution with a hematocrit around 30-35% is usually achieved automatically when keeping patients normovolemic after surgery. While sedation sometimes is required, depending on the severity of vasospasm a mean arterial blood pressure of at least 100 mmHg (or sometimes >120 mmHg) is mandated, usually requiring the use of vasopressors. The efficacy of hypertension has to be assessed either by way of intermittent global CBF measurements (such as XeCT, to some semiquantitative extent also perfusion CT or MRI), more practical, however, are continuous measurements. Various, validated intraparenchymal probes exist to indirectly measure CBF (thermal diffusion flowmetry=TDF probe; brain tissue oxygen tension=$p_{ti}O_2$ probe) or the change in local metabolism (microdialysis). As the area of parenchyma analyzed with these probes is spatially very restricted, the application of this technique to detect distant vasospasm may be limited as well, but their usefulness to estimate efficacy of treatment has been repeatedly demonstrated. Placement of the probe is essential and should be aimed at potential areas of misery perfusion. In most cases, placement may be guided by angiography, which identifies hypoperfused territories at greatest risk for infarction. It seems plausible to guide treatment according to the results obtained within these critical regions, since they are most vulnerable and are likely to turn ischemic. Even though pathophysiology may vary significantly throughout the brain, it is suspected that “healthy” territories are less susceptible to modulation and are more robust to changes in perfusion. Different ranges of critical values have been identified for most methods. The critical threshold for $p_{ti}O_2$ (usually advocated over holohemispheric measures such as jugular venous oxygen saturation=$S_{jv}O_2$) and the thermal probe is generally considered to be around 10-15 mmHg and 15 ml/100 g x min respectively, with values below indicating impending hypoxia or ischemia. For microdialysis, a variety of metabolic markers can be analyzed. Lactate, the calculated ratio of lactate and pyruvate as well as glutamate mirror the extent of change towards anaerobic metabolism, with an increase implying ischemia. However, it has to be stated critically, that these metabolic markers usually are only obtained after a relevant change in metabolism has already occurred and therapeutic relevance remains limited.

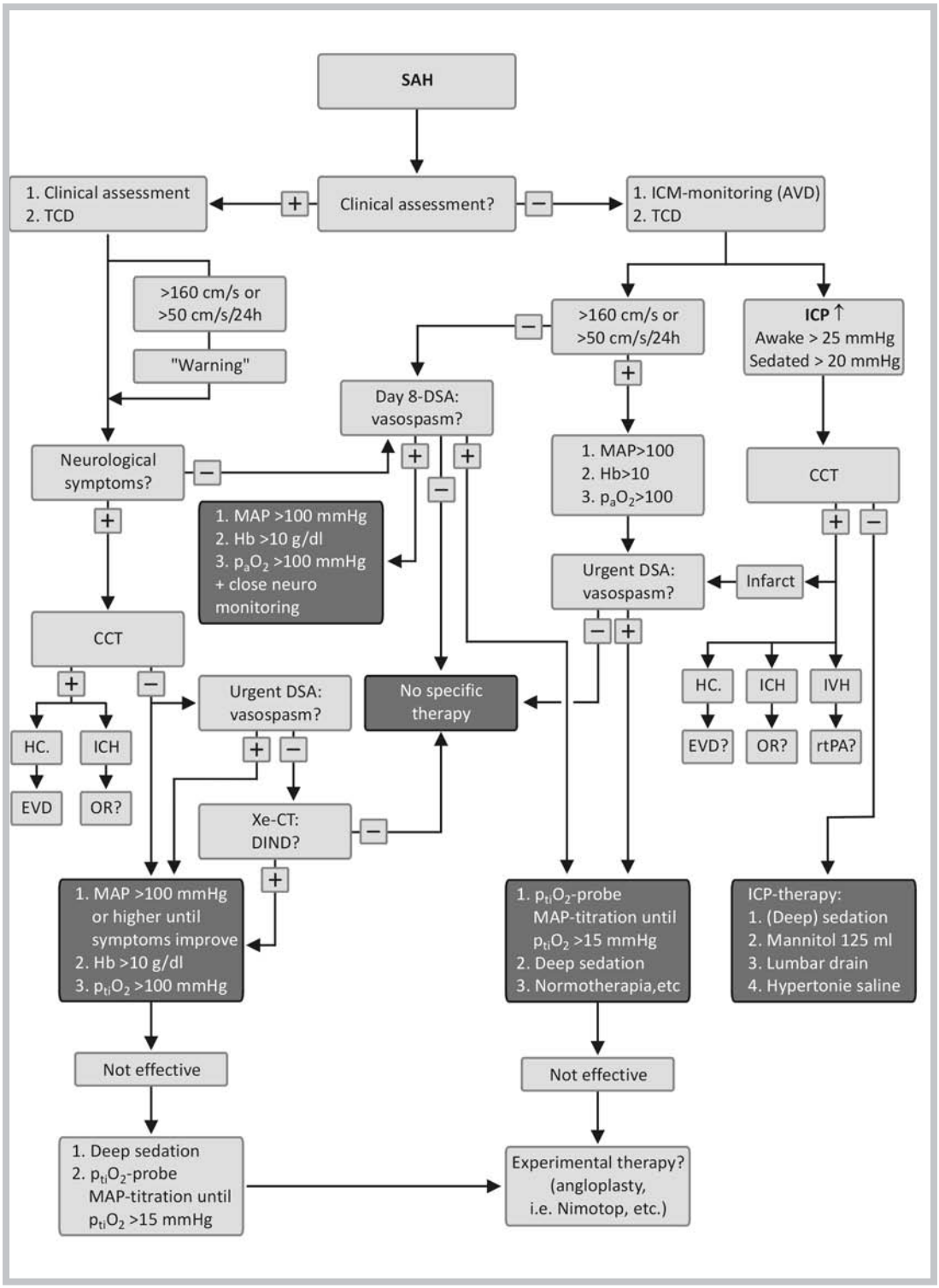

Figure 73.1. **An algorithm for decision-making in suspected vasospasm after SAH is provided.**

EVD = external ventricular drain
HC = hydrocephalus
ICH = intracerebral hemorrhage
IVH = intraventricular hemorrhage
MAP = mean arterial pressure

There is continuous effort to prevent the development of vasospasm, and an abundance of studies is available regarding its etiology and possible treatment options. Inflammation as well as scavenging of nitric oxide by oxyhemoglobine and liberation of ET-1 are only some of the major pathways currently open for discussion as to the development of vasospasm. At present, therapy mostly consists of minimizing the effects of vasoconstriction. One of the most widely used and most extensively studied prophylactic treatment involves calcium antagonists such as nimodipine, the only FDA approved medication. Interestingly, however, only oral nimodipine was found to effectively reduce neurological deficits and improve overall outcome (doses usually starting at 60 mg/q4h, than tapering after 8-14 days) [6] with no apparent effect on angiographic vasospasm; neuroprotective effects or improvement of collateral circulation are assumed. Contrarily, intravenous calcium antagonists are prone to cause hypotension due to their vasodilatatory function. The use of IV nimodipine in poor-grade patients who cannot take oral medications (crunched tablets have shown to have significantly lower efficacy) and have a high risk of impaired autoregulation, has to be viewed critically. Application of magnesium sulphate might be useful, as hypomagnesemia occurs in up to 50% of cases and is also associated with the occurrence of delayed ischemic deficits and poor outcome, convincing evidence, however, is lacking as well.

CPP-monitoring is essential to avoid the risk of critical hypoperfusion. Angiography followed by either mechanical dilatation (transluminal balloon angioplasty=TBA) or application of intraarterial vasoactive substances such as papaverine (usually 200-300 mg applied over 30 mins) or calcium antagonists are other treatment options at institutions where an experienced neurointerventionalist is available. Their effectiveness, however, is usually limited to cases with localized, preferably single-vessel narrowing, and a preceding CT scan without signs of infarction. In those selected cases, repetitive treatment may be necessary, and generalized or diffuse multi-vessel vasospasm is mostly less susceptible to this kind of intervention. TBA in poor-grade patients is associated with worsening in outcome. An ongoing multicenter investigation is looking into the benefits of emergency angiography followed by vasodilatatory measures versus conventional, conservative treatment in those patients who develop new focal deficits without signs of infarction on recent CT scan.

One recent study has analyzed the effect of clazosentan, an ET-A receptor antagonist that experimentally has been shown to ameliorate the deleterious effects of ET-1 in particular [7]. While angiographic vasospasm and incidence of ischemia was influenced favorably, overall clinical outcome did not change significantly. Other multicenter trials are concerned with the role of NO-donors, statins and magnesium sulfate in ameliorating cerebral vasospasm. The application of slow release pellets of nicardipine, deposited intraoperatively in close proximity of larger vessels has gained substantial interest as of late, as the occurrence of vasospasm and subsequent infarction is significantly lower in those patients [8]. It will be the aim of future investigations, if treatment with nicardipine pellets remains equally effective when applied intraventricularly only, a treatment option tailored specifically for patients treated interventionally, as is suggested in many poor-grade SAH patients.

73.8 Conclusion

The treatment of subarachnoid hemorrhage is particularly challenging in poor-grade SAH patients, as morbidity and mortality increase exponentially. After successful treatment of the offending aneurysm, close neurological and multimodal monitoring are es-

sential to anticipate potentially treatable complications such as refractory ICP elevation and delayed vasospasm in order to improve overall outcome.

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74 Paroxysmal Sympathetic Hyperactivity in the Neurocritical Care Unit: Definition, Clinical Picture, Etiology, Diagnosis and Management

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74.1 Introduction

Elevated physiological parameters are extremely common following severe acute neurological insult. For example, such features occur in between 62% [1] and 92% [2] of patients admitted to the intensive care unit (ICU) following traumatic brain injury (TBI). However, a smaller number of such patients develop excessive sympathetic responses that have the potential to produce additional morbidity. This latter group represents an ill defined and under-recognized disorder that is known by various names but termed paroxysmal sympathetic hyperactivity (PSH) in this article. Using PSH to describe this condition was suggested by Rabinstein in 2007 [3] and represents a more accurate clinical description of the syndrome than other frequently used terms such as dysautonomia, sympathetic storm and paroxysmal autonomic instability with dystonia (PAID) [4]. In particular, PSH is a more specific term than dysautonomia and identifies the dominant role of the paroxysmal sympathetic overactivity, while not limiting motor activity to dystonia as suggested by the term PAID. There are currently at least 5 sets of overlapping diagnostic criteria used to describe the syndrome, the first proposed in 1999 [5].

In the first weeks post injury, individuals with PSH show frequent, prolonged and intense episodes of sympathetic and motor overactivity, often occurring on a background of elevated heart rate (HR) and temperature. The paroxysmal sympathetic changes are variable in severity but include documented heart rates up to 190 beats per minute, respiratory rates of 60 breaths per minute, core temperatures up to 42°C, blood pressures of 170/120 mmHg and sweating severe enough to affect the patient's fluid balance [5]. This sympathetic hyperactivity is accompanied by assorted forms of motor overactivity such as decerebrate or decorticate posturing, dystonias, rigidity and spasticity. The pattern of posturing is most often asymmetrical and may not fit into classical decorticate or decerebrate postures [6].

The impact that PSH has on heart rate can be seen in Figure 74.1. This 24 hour Holter monitor data comes from an individual 28 days post TBI. Mean daily HR was 129 beats per minute (bpm), ranging from a minimum of around 70 to a maximum of 182. As can be seen, the subject had multiple paroxysmal episodes over the 24 hours, each lasting

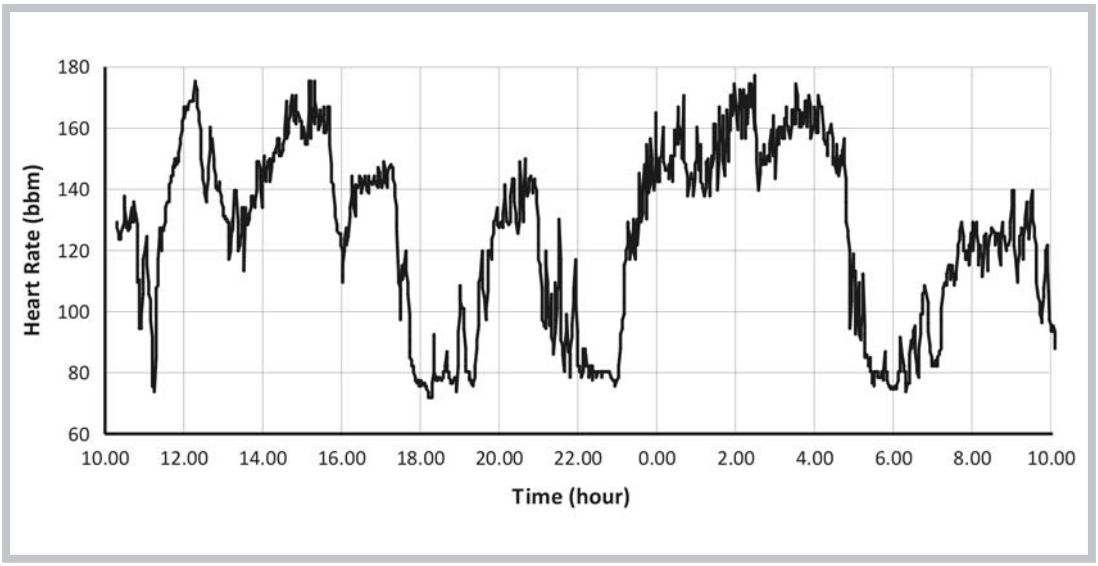

Figure 74.1. **Minutely Heart Rate in an untreated dysautonomic subject (heart rates are minutely values derived from a 24 hour Holter monitor recording).**

between 2 and 6 hours. While the subject had several episodes with heart rates below 80 bpm (amounting to 11% of the day), heart rates above 140 bpm totaled 39% of the day.

With increasing time post injury, paroxysms decrease in duration, frequency and magnitude. The reduction in severity of paroxysms usually coincides with an observable improvement in neurological status [5,7], although whether this is causative or an epiphenomena has not been identified. As subjects improve, paroxysms become rarer and resting blood pressure, respiratory rate, heart rate and temperature trend towards normal values.

While TBI accounts for an estimated 80% of published cases of PSH, many other neurological disorders have been reported to cause PSH. These include (in order of decreasing frequency) severe hypoxic brain injury, stroke (hemorrhagic stroke in particular), acute hydrocephalus and tumors. There are also isolated case reports of uncommon etiologies, such as PSH following infection [8] and hypoglycemic coma [9]. However, despite the wide range of etiologies associated with the disorder, the limited available data suggests that the syndrome itself is equivalent irrespective of the causative condition.

74.2 Pathophysiology

The earliest theories for PSH suggested that seizure activity was the likely etiology [10]. For this reason the syndrome was termed diencephalic epilepsy. However, multiple attempts to either identify or treat epilepsy in these patients have produced negative results (for example [7,11-14] The limited autopsy and pathophysiological data suggest the syndrome results from a relative disconnection of pathways at or around the level of the midbrain (reviewed in [15]).

Most disconnection theories suggest that paroxysms are driven by upper brainstem and diencephalon lesions, with clinical features arising from either excitatory or inhibitory centers in these areas. However, more recent evidence suggests that spinal cord pro-

cesses are instrumental in initiating the condition. Two studies have assessed the effect of standardized nociceptive stimuli in driving paroxysms. In the first study, endotracheal tube suctioning of severe TBI survivors on day 7 post injury found that PSH subjects had heart rate increases of twice the magnitude (16% vs. 8% averaged over 100 beats) and of longer duration when compared to non-PSH subjects [16]. In a separate study, subjects with PSH a mean of 5 years post injury (the majority of whom were no longer exhibiting paroxysms) showed disproportionately excessive sympathetic responses to the nociceptive stimulus of botulinum toxin A injections [17]. These studies provide empirical support to anecdotal reports dating back to 1954 [18] that multiple physical stimuli can provoke sympathetic paroxysms.

When considered as a whole, the literature suggests that PSH results from a combination of both cerebral and spinal cord changes. A theoretical model, the Excitatory/Inhibitory Ratio (EIR) model, has been proposed to promote testing of the interaction of spinal and cerebral influences on PSH [19]. This model highlights the previously noted physiological similarities of PSH and autonomic dysreflexia [20,21] (that is, sympathetic over-responsivity to stimuli resulting from the loss of supraspinal inputs) and combines them under a common pathophysiological process. This integrative model suggests that the causative brainstem centers are predominantly inhibitory in nature, and that damage to these structures predisposes the spinal cord to overreact to afferent stimuli in a manner akin to that which produces allodynia (where non-painful stimuli become perceived as nociceptive) [22].

74.3 The Clinical Relevance of PSH

In injury severity matched cohorts, prolonged PSH is associated with worse outcome following severe TBI [5,8]. Such individuals have been found to have prolonged swallowing abnormalities, longer duration of coma and post traumatic amnesia [5]. In addition, subjects with PSH often display features consistent with “locked-in” syndromes [2,23], a situation that can result in under-managed pain or a misdiagnosis of persistent vegetative state. Affected individuals show reduced capacity for voluntary movement, particularly during paroxysms, and may be exacerbated by under-managed spasticity and dystonia [5]. In addition, posturing subjects show increased metabolic rates [24,25] resulting in a highly catabolic state [26] and an estimated 25% loss of body weight in the first weeks post injury [2]. Affected individuals have also been found to be significantly more likely to develop heterotopic ossification [27]. These factors combine to place the individual at risk of developing critical illness or compression neuropathies, longer hospital admissions [2,5] and greater overall health care costs [2]. It has been argued that early identification of PSH may minimize unnecessary diagnostic testing [28], promote timely and appropriate intervention [29]. and minimize secondary morbidity [5,30].

As recovery continues, posturing patterns may change, revealing an underlying spastic tetraplegia or other focal neurological deficit. Most subjects are left with some permanent degree of dystonia and spasticity [2]. Sweating patterns change from whole body to upper trunk, head and neck, before ceasing entirely [31]. Three studies have reported changes in sweating in a longitudinal fashion. In two of these, paroxysmal diaphoresis resolved a mean of 2.5 months post injury in 35 subjects [5] and 5.9 months post-injury in 87 subjects [8]. In another study, 22 of 31 subject’s features had settled by 6 months post injury [32]. While the overt features of sympathetic hyperactivity settle over time, the tendency to display paroxysmal tachycardias remains evident for at least 14 months post injury [30].

74.4 Management

Despite the impressive nature of the symptomatology and the largely circumstantial evidence promoting the importance of early intervention, there is surprisingly little literature available to guide management [4,21]. As the diagnosis of PSH is currently one of exclusion, other primary disease processes such as acute hydrocephalus and sepsis need to be considered and treated. Various autonomic emergency syndromes with similar symptom complexes (for example, malignant hyperthermia and neuroleptic malignant syndrome) should be ruled out. A careful examination for evidence of triggering [16] and treatment of potential noxious stimuli (such as undiagnosed fractures, heterotopic ossification, pressure areas, painful spasticity or dystonias, infection, etc.) may decrease the frequency or severity of paroxysms [21,33]. In this context, one author has suggested pre-treatment of patients prior to nociceptive procedures being undertaken to reduce "triggering" of paroxysms [33].

In spite of these possible interventions, conservative measures alone are rarely sufficient to control the paroxysmal sympathetic overactivity in severe cases. Although a large number of medications have been used to treat the condition, information regarding their efficacy is largely restricted to anecdotal reports and has been reviewed elsewhere [3,4,21,34]. Accepting the limitations of current literature, a range of medications from many classes of neurologically active agents may be beneficial. In particular, these medications include alpha and beta antagonists, dopamine agonists, GABA A and B agonists, opioids and gabapentin.

The most effective intervention appears to be intrathecal baclofen (ITB), with anecdotal reports of a large reduction or cessation in paroxysmal sympathetic overactivity [29,35-38] However, deciding when to consider implementing ITB therapy can be difficult. Many subjects will exhibit paroxysmal overactivity lasting for only a few months [5,27], the procedure is invasive and has a relatively high complication rates (20-50% [39]). On the other hand, ITB is also effective for managing spasticity [40] and this may have long-term advantages in such patients. Intravenous morphine and midazolam are also effective, but their sedative effects limit their usefulness during rehabilitation [21].

Gabapentin has been reported to reduce the number and severity of sympathetic paroxysms [9,29] and allowed an overall reduction in other medications, including ITB, without a recurrence of symptoms [29]. However, the drug should be trialed at a low starting dose (e.g., 100 mg) to minimize the risk of marked bradypnea or sedation, presumed to result from a sudden loss of sympathetic drive [14].

Drugs with sympathetic activity have also been commonly used. Of the beta-blockers, propanolol has the largest literature base, with mixed reports between those where it has been useful and where it has been unable to control paroxysms [4]. Recent research suggests that beta-blockers improve survival post TBI [41] and propanolol has long been known to decrease catecholamine levels following TBI [42,43]. Labetalol has little literature available, evenly split between beneficial and unhelpful. Clonidine also reduces catecholamine levels [44], but has been reported to be useful in less than half of the cases in the literature [4]. It has been suggested that clonidine may control sympathetic crises but requires high doses (for example, 800 µg 2nd hourly) [45].

Several other pharmacological agents show a mixed picture in terms of efficacy. Dopamine agonists, predominantly bromocriptine, have a patchy literature of cases with at least partial efficacy versus where no effect was observed [4]. Benzodiazepines also present a mixed picture, with anecdotal reports favoring diazepam and midazolam [7]. Drugs that have been reported to be ineffective include methadone [7,11], metoprolol [13,29,33], oral baclofen [7,35], and phenytoin [11,28,46]. Oral dantrolene has been reported to be unhelpful in all but one patient [7,11,47].

It is readily apparent that there is insufficient available literature to provide a definitive protocol to guide management. However, in terms of minimizing the possibility of adverse drug reactions, it would appear appropriate to utilize morphine/midazolam, gabapentin and/or propanolol in the first instance. There are occasional reports of excellent efficacy with bromocriptine, suggesting it may have a secondary role. ITB is most useful in cases that are resistant to oral medication, are of greater severity or longer duration.

74.5 Current Controversies

Despite increasing research into PSH over the last decade, the current estimated incidence of the condition varies across a considerable range (between 8 and 33%) [4]. Also complicating the literature are the large number of synonyms used for the condition (around 33 in total), most of which have only been used once or twice in the literature. The more commonly used names include dysautonomia, autonomic dysfunction syndrome, paroxysmal sympathetic storms, paroxysmal autonomic instability with dystonia and so on [4]. Another difficulty with research into the condition is the 5 current sets of overlapping diagnostic criteria [5,27,34]. In addition, it has recently been suggested that the concept of "triggering" of paroxysms following minor stimuli has been proposed as a clinical sign that may help to differentiate individuals with and without the syndrome [16]. While moves to critically appraise these criteria have begun [48], there is insufficient research available to be able to establish consensus criteria at this time.

Linked in with the issue of the lack of diagnostic criteria, there has also been a lack of quantitative mechanisms to investigate the pharmacological management of dysautonomia. Dysautonomic subjects tend to show marked day to day variability in their presentation (as illustrated in Figure 74.1) and an appropriate research tool would need to accurately measure the frequency, severity and duration of paroxysms over time. Recently, a number of tools have been proposed to overcome this limitation including event related heart rate changes and heart rate variability paradigms, either over 5 minute intervals [16] or 24 hour time scales [9]. Research techniques such as these are required to raise awareness of the syndrome and to properly evaluate treatment efficacy.

74.6 Key Concepts

Research suggests that PSH is a distinct but under-recognized clinical syndrome that can result from numerous forms of acquired brain injury. While short duration sympathetic hyperactivity does not appear to be associated with worse outcome, clinical research suggests that prolonged dysautonomia places a considerable burden on both patient and health care services. There is potential for reducing this burden through timely recognition and intervention, however, the field is hampered by a lack of clinical awareness, a poor understanding of pathophysiology and anecdotal management protocols. Investigatory techniques are becoming available that will allow the development of evidence based treatment paradigms for the first time. However, due to the relatively low incidence of the condition, multicentre research using standardized nomenclature and diagnostic criteria will be required to achieve this aim. It is hoped that more effective treatment protocols will, in turn, result in improved outcomes for individuals affected by this condition.

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Section 9.
Conditions That Require Special Care

75 Acute Neuromuscular Disorders

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75.1 Introduction

At first glance, the term "neuromuscular weakness" may lead a reader's mind to consider the neuromuscular junction as the region of most interest; however, this couldn't be further from the truth. Neuromuscular weakness can result from insults to the spinal cord, motor neuron, root and nerve, neuromuscular junction or muscle. In general, and due to the diverse clinical settings in which neuromuscular weakness can present, some key points are universal to all. First, use a systematic approach to localizing the weakness to the brain, spinal cord, peripheral nerves, neuromuscular junction or muscle. Next, in importance is to review all data included in the medical chart. In addition, obtain a history from family members to establish the patient's baseline neurologic and mental function prior to admission. Common risk factors for acquired neuromuscular weakness to keep in mind include autoimmune disorders, steroid use, sepsis, the systemic inflammatory response syndrome (SIRS), multi-organ failure, and extended duration of intubation. Physical examination should be conducted with an emphasis on the distribution of weakness, reflexes and sensory exam. When it is time to complement the examination with objective testing, electrodiagnostic studies such as nerve conduction studies, electromyography, repetitive nerve stimulation (train of four), somatosensory evoked potentials (SSEP) and electroencephalogram are crucial. These studies help to place the lesion in the central versus the peripheral nervous system, establish if the patient is globally weak but cooperative versus encephalopathic and neuropathic versus myopathic. This chapter discusses diseases based upon their anatomical location and begins by describing the clinical presentation and exam. Next, diagnostic and management strategies key to patients are described.

75.2 Spinal Cord

75.2.1 Normal Spinal Vasculature

Spinal cord injury due to ischemia is not a common presentation (1-2%) with respect to vascular neurology; however, this group of diseases and their respective clinical syndromes require clinicians to act immediately. We begin by briefly describing the normal vascular supply to the entire adult spinal cord in a general manner to help provide a framework to understand spinal cord injury. Next, we will discuss the salient clinical features, exam findings, diagnostic and management principles of a few important causes of vascular myelopathy.

Three major arteries, two posterior spinal arteries and one anterior spinal artery, dominate the spinal cord vasculature. The two posterior spinal arteries begin as branches off of each vertebral artery, respectively. The anterior spinal artery is formed by one branch off each vertebral artery, which then joins to form the anterior spinal artery. Contributing to the anterior spinal artery blood volume in the cervical and high thoracic region is a group of radicular arteries originating from the vertebral artery, the deep cervical artery, and the ascending cervical artery. The mid-thoracic region (T3 to T7) is often considered a "watershed region" due to its lack of a substantive, major feeding artery to the anterior spinal artery blood volume. The next major contribution to the anterior spinal artery comes in the low thoracic high lumbar region called the arteria radicularis anterior magna (artery of Adamkiewicz). The artery of Adamkiewicz is a major feeding artery that contributes to the anterior spinal artery by supporting arterial blood supply to the spinal cord from T8 to the conus medullaris. The posterior and anterior spinal arteries communicate with each other through multiple small vessels at each spinal level.
The spinal cord venous system is similar to its arterial counterpart because of its anterior and posterior arrangement. Here, the venous system incorporates one large posterior spinal vein and one anterior spinal vein. When visualized, both the anterior and the posterior spinal vein run along the midline of the cord. Unlike the arterial system, the posterior one half of the spinal cord will drain into the posterior spinal venous system and the anterior one half will drain into the anterior venous system. The deep veins of the spinal cord parenchyma drain the right and left half of the cord, respectively, and anastomose with their respective central spinal vein. Each spinal cord segment is connected by a valveless external and internal venous plexus. These plexuses ultimately drain into multiple radicular veins located throughout the length of spinal cord.

75.2.2 Anterior Spinal Artery Syndrome

In general, the anterior spinal artery supplies the anterior two-thirds of the spinal cord. Within the anterior two thirds of the spinal cord itself are major tracts that carry ascending and descending information. The clinically relevant tracts are the corticospinal and the spinothalamic tracts which are responsible for motor and sensory (pain and temperature) modalities, respectively. Ischemia to the anterior spinal artery can occur due to:

- Occlusion secondary to external compression (bone fragment, herniated disk).
- Aortic dissection.
- Vasculitis.
- Atherosclerosis of the aorta.
- Postinvasive vascular or thoracoabdominal surgery.
- Fibrocartilaginous embolism.
- Systemic hypotension due to shock or cardiac arrest.
- Angiography.
- Vertebral artery dissection (often traumatic).
- Arterial embolic phenomena.
- Cocaine abuse.
- Hypercoagulable state.

At onset, symptoms tend to evolve over minutes. Initially, pain or paraethesias can be reported in a radicular/girdle-like distribution or ascending from the lower extremities. As soon as the pain is noticed, the patient may begin to sense motor dysfunction below the highest vascular level of ischemia. The most common motor presentation is paraplegia due to spinal shock; however, ischemia to the corticospinal tract above C7 can produce quadriplegia in selected patients. Development of peak motor symptoms can take

up to 12 hours; and, in addition to motor deficits, the key feature on clinical examination is a new separation of sensory modalities. A sensory level (loss of function) to pain and temperature can be demonstrated below the level of the lesion, while the patient's dorsal column function (preserved deep pressure sensation, joint position sense, two-point discrimination and vibration) remains intact. Furthermore, ischemia will also affect the autonomic pathways, resulting in the loss of bowel, bladder and sexual function. Vascular supply to the spinal cord has been oversimplified for the sake of our discussion, but the examiner must remember that a measurable degree of variability between persons exists and that some patients may present with a patchy distribution of symptoms. Initial examination of patients with anterior spinal artery ischemia should demonstrate areflexia, sensory level to pain/temperature and flaccid weakness below that level in the early stages. Over time, due to the destruction of the corticospinal tracts, the patient's initial flaccid paralysis will transition into upper motor neuron signs and spasticity in the neurological exam. Unless contraindicated, contrast-enhanced magnetic resonance imaging (MRI) is the initial imaging modality of choice for acute spinal cord injury due to ischemia; however, imaging within the first 24 hours after symptom onset may or may not demonstrate an abnormality. This said, MRI soon after the initial clinical examination is very helpful to rule out extrinsic causes of myelopathy and hemorrhage. After 24 hours, MRI in more than 50% of patients will demonstrate appreciable abnormalities on primary T_1 and T_2-weighted sequences. First, attention to the T_2 sequence may demonstrate a hyperintense, pencil-shaped lesion in the anterior aspect of the cord that studies suggest is seen in patients with anterior spinal artery syndrome. Fat saturation suppression sequence can help delineate if there is vertebral bony infarction as well, which is also associated with anterior spinal artery infarct. In addition, most authors agree that swelling of the spinal cord will be seen by the fifth day as a T_2-weighted hyperintensity and increase in spinal cord caliber. Diffusion weighted imaging (DWI) of the spinal cord is a potential tool, but current variability of image quality due to surrounding artifacts increases the false positive rate, making DWI not very reliable at this time. Angiography does play a role if T_2-weighted images reveal a "flow void" or dilated vessels on the surface of the spinal cord. Radiographic evidence of abnormal vessels, either extramedullary or intramedullary, may suggest that a spinal vascular malformation is present. Finally, the natural evolution of anterior spinal artery ischemia is visible with serial MRIs. T_1 contrast enhancement will demarcate the infarct, some hemorrhagic transformation (hyperintensity on T_1-weighted images) may be seen, and eventually cord atrophy will be the end result. Cerebrospinal fluid (CSF) evaluation does not help to rule out disease; and, unless spinal vascular malformation has been ruled out, lumbar puncture is a relative contraindication because it can create a pressure gradient that could lead to further spinal cord infarction. There are no clear management strategies for spinal cord ischemia. Acute placement of a lumbar drain has been performed with the goal of improving perfusion pressures. Further management principles should mirror those derived from cerebral stroke guidelines, which include permissive hypertension, fever control and avoidance of both hyperglycaemia and hyponatremia. Prognosis varies from case to case, but it should include aggressive physical rehabilitation. The only long-term complication that has been established as secondary to spinal cord ischemia is neuropathic pain which takes months to present and may or may not develop in all patients.

75.2.3 Spinal Vascular Malformations

Spinal cord vascular malformations are a group of rare and complicated vascular malformations that account for 15% of space-occupying lesions in the spinal canal. There are

several classifications based on various anatomical and radiographic features. For this chapter, we will discuss spinal arteriovenous malformations (S-AVMs) and dural arteriovenous fistulas (D-AVFs) separately.

Dural arteriovenous fistulas (D-AVFs) are the most common type (70%) of spinal vascular malformations. They are commonly found in the mid-thoracolumbar region and most often in men. Initial presentation is often after the fourth decade of life, and since they present later in life, they are thought to be acquired lesions. D-AVFs can be classified as being located intradural (most common) or epidural, and can be further distinguished based on one or multiple arterial feeders. Intradural D-AVFs are highly unlikely to rupture or enlarge enough to cause mass effect; instead, the most consistent course of the pathology is venous hypertension due to the transmission of arterial pressures without an intervening capillary bed. In addition to venous hypertension, the decreased arteriovenous perfusion gradient causes suboptimal drainage of the surrounding normal spinal veins, which results in spinal cord edema. Over time, this process leads to enlarged, engorged and tortuous veins. Both spinal cord edema and abnormal veins are often seen in tandem on MRI T_2-weighted sequences as central cord hyperintensity and "flow voids" on the surface of the spinal cord. These multiple pathologic processes work simultaneously and eventually result in progressive spinal cord ischemia and myelopathy.

Spinal arteriovenous malformations (S-AVMs) comprise a group of lesions of both acquired and hereditary origin. Multiple classifications are based on angiography, biological and genetic influences. S-AVMs are true AVMs of the spinal cord because they derive from both spinal arteries and spinal veins. If classification is based on the nidus located either intramedullary or extramedullary (perimedullary), 80% of spinal AVMs are located intramedullary and 20% extramedullary. For the purposes of this chapter, we have organized S-AVMs based on their anatomic location and features as described in Table 75.1.

Glomerular type S-AVMs are sometimes referred to as "nidus type" AVM because the nidus is quite compact and resembles those found in cerebral AVMs. The glomerular type nidus is located intramedullary, involves multiple anastomoses between the anterior and posterior spinal arterial system and is often found in the cervical or thoracic region. The term "juvenile type" is appropriate if the nidus diffusely infiltrates the spinal cord. The perimedullary type of S-AVM can be further distinguished based on the angiographically quantified volume of blood that is shunted with the amount of venous dilation present. In addition, another feature of perimedullary lesions is that they are often found near the conus medullaris. Other features of spinal AVMs that distinguish them from D-AVFs include aneurysm formation (20-40% of intramedullary S-AVMs), hemorrhage, development of a space-occupying lesion, and vascular steal phenomenon.

The initial presentation of spinal arteriovenous malformation varies widely and is based on the specific location and complexity of the malformation. Venous hypertension evolves in a chronic process; but due to the unpredictable nature of the pathology, D-AVF can present in many ways. These presentations are acute motor symptoms that can occur at any time, with slow insidious presentation over months due to a progressive myelopathy or with a relapsing remitting course. In addition, patients may also develop pain, bladder dysfunction, spasticity and sexual dysfunction. Unlike D-AVFs, S-AVMs most commonly present with hemorrhage by the third decade of life. The initial clinical presentation may be acute back pain with mixed motor and

Intramedullary	• Glomerular type – compact nidus • Juvenile type – diffuse nidus
Extramedullary (perimedullary) type	• Low shunting • Intermediate shunting • High shunting

Table 75.1. **S-AVMs classification based on their anatomic location and features.**

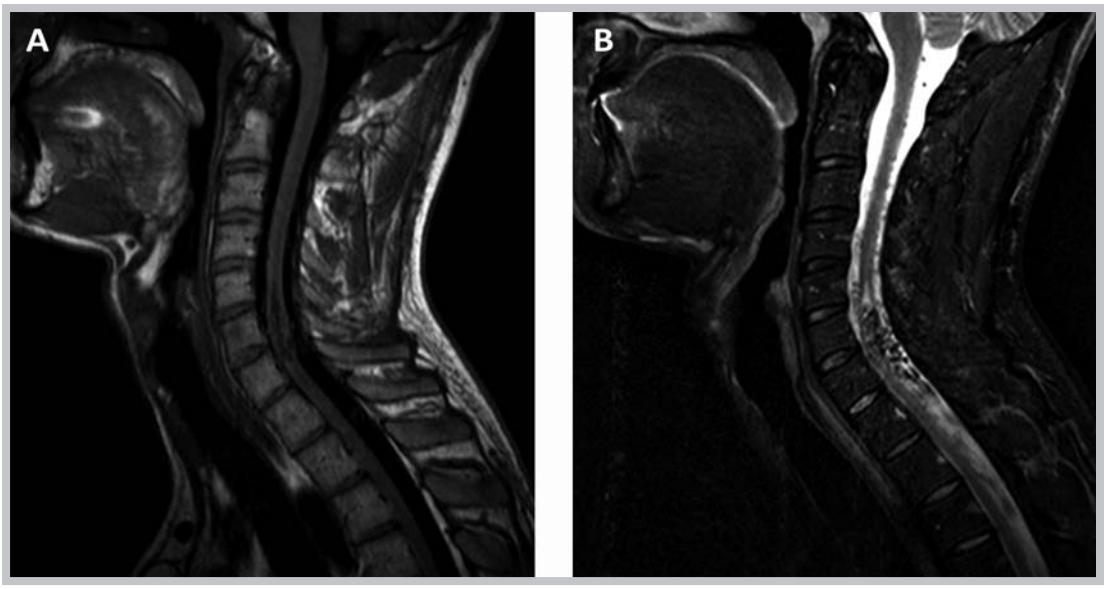

Figure 75.1. **(A). Sagittal T_1 sequence showing increased spinal cord diameter at C6-C7 and hypointense images within the cord suggesting the presence of vascular structures. (B). Sagittal T_2 sequence of the same patient showing abnormal vascular structures within the cervical spinal cord (intramedullary vascular malformation).**

sensory deficits. Since hemorrhage is not a uniform process; deficits on presentation are based on the level, location and extent of insult to the spinal cord.

Neurologic examination may demonstrate both upper and lower motor neuron signs. The initial exam should involve inspection of the skin, paraspinal muscles and bone. This can provide clues to the diagnosis in the genetic and hereditary forms of S-AVMs. For both D-AVFs and S-AVMs, the initial workup of choice is MRI with contrast material. This imaging modality has supplanted plain films, computed tomography (CT) and myelography, except when MRI is contraindicated. Even when using a combination of images generated from T_1, T_2 and T_1 postcontrast weighted images, MRI may not be able to visualize what type of spinal vascular malformation is present but should be able to visualize cord edema and "flow voids". In addition, where available, MR angiography (MRA) with contrast of the spinal arterial system has been shown to help identify the arterial feeder(s). Examples are shown in Figures 75.1, 75.2, 75.3 and 75.4. Ultimately, the goal standard for the management of any spinal vascular malformation via endovascular, surgical or a combination thereof remains catheter angiography. Initial management will be determined by the presentation, evidence gathered by imaging and in consultation with neurosurgery and interventional neuroradiology. Supportive care is the mainstay of treatment until a definitive treatment plan has been decided on.

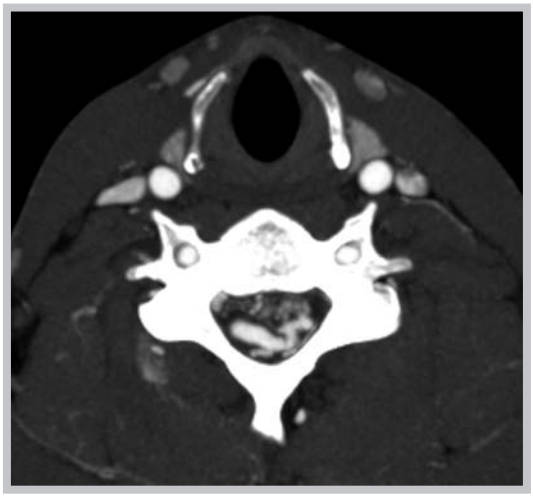

Figure 75.2. **CT-angiography (CTA) of the same patient as in Figure 75.1. At the cervical level, abnormal and dilated vascular structures are seen intra- and extramedullary, corresponding to a cervical arteriovenous malformation.**

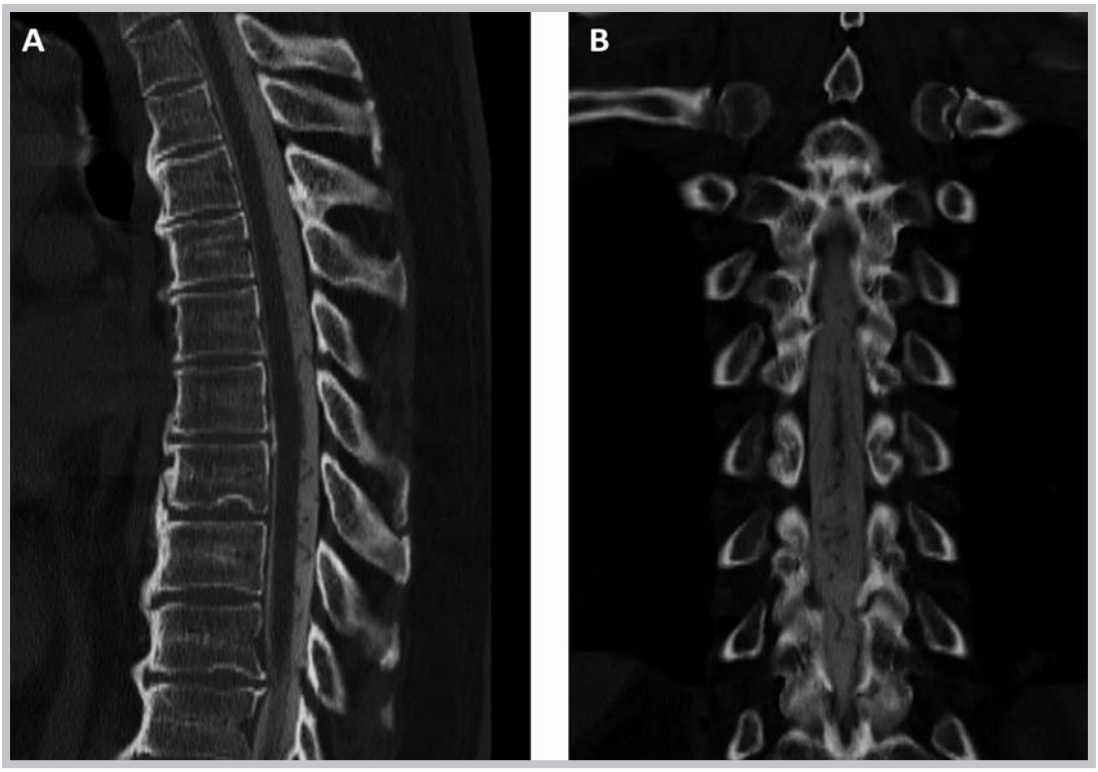

Figure 75.3. Tomographic myelogram showing serpiginous vascular structures in the extramedullary space corresponding to a dural arteriovenous fistula. (A). Sagittal reconstruction. (B). Coronal reconstruction.

75.2.4 Acute Transverse Myelitis

Figure 75.4. Digital angiography in a patient with an arteriovenous malformation (arrows) within the spinal canal at the levels of the chest and abdomen.

Acute transverse myelitis (ATM) is a syndrome of multiple neurologic deficits due to a focal inflammatory attack of the spinal cord. Although the name may imply the pathologic process was not present until symptoms arose, ATM is often the clinical presentation of a pathologic process that was previously unrecognized, subacute, acute or chronic or secondary to another disease. Although ATM can have vascular and structural aetiologies, our focus will be on pathologic processes where inflammatory activity leads to focal demyelination or destruction of the spinal cord. Publications often state that ATM has a bimodal distribution during the first and third decades of life. In reality, this is not absolute. As we improve in diagnosing patients with multiple sclerosis, Devic's disease (neuromyelitis optica) and autoimmune-associated transverse myelitis, we encounter patients who can develop spinal cord lesions at any point during their disease. As an acute attack evolves and maximal deficits

are reached, up to 50% of patients will develop motor paralysis and 80-95% will experience sensory disturbances below the level of the lesion. The diagnosis of ATM is often secondary to another disease or medical history:

- Multiple sclerosis.
- Devic's disease (neuromyelitis optica).
- Recent infection.
- History of radiation exposure.
- Post-vaccination.
- Autoimmune-associated systemic illness.
- Neoplastic (paraneoplastic disorder or neoplasm causing compressive myelopathy).
- Idiopathic.

Since the clinical presentation will depend on multiple factors, no pathognomic sign or syndrome exists. A patient may present with his or her own distinct constellation of symptoms. When gathering the initial history of symptom presentation, "the tempo" will help differentiate inflammatory from vascular aetiology. Maximal clinical deficits should rapidly occur with vascular lesions, whereas inflammatory lesions can take up to 7 days to peak. Acute transverse myelitis occurs mostly in the thoracic region but cervical and lumbar segments are also vulnerable. Inflammatory lesions are not confined by anatomical or vascular boundaries; therefore, patients can present with a mixture of deficits in motor, sensory and autonomic function due to the compact anatomical arrangement of the spinal cord. Inflammatory ATM is often the end result of another disease process or seen for the first time in a "previously healthy" patient; hence, the past medical history, review of systems, and family history should be explored in detail. The review of system should be directed towards episodes of transient weakness, sensory disturbance, episodes of visual changes, recent febrile illness or contact with an ill person, Uhthoff's sign (worsening of neurologic symptoms during exercise or excess body heat), dry mouth or dry eyes. The family history is important to look for associated demyelinating or autoimmune diseases that run in the family. Another important feature on exam is Lhermitte's sign (electrical sensation running down the spine with flexion of the neck). On clinical exam, most patients will have a sensory level and sensory disturbance below the level of the lesion. In addition to motor weakness and sensory disturbance, autonomic symptoms such as bowel or bladder incontinence, urinary urgency, inability to completely void the bladder and sexual dysfunction can be present.

Once a complete neurologic exam has been performed and a patient demonstrates myelopathic features, an MRI with contrast should be one of the first actions taken. If MRI is contraindicated, then a CT-myelogram of the spinal cord can help to rule out compressive lesions. The first question to answer with neuroimaging is to rule out a compressive structural or vascular lesion that correlates with clinical symptoms on exam. If MRI demonstrates a compressive or vascular lesion, a neurosurgical consultation should be obtained immediately. In ATM, sagittal T_2-weighted sequences demonstrate focal area(s) of hyperintensity often associated with an increase in the calibre of the spinal cord due to inflammation and edema. If focal, isointense areas of atrophy are noted; this may suggest previous episodes of transverse myelitis. To fully evaluate a focal hyperintensity, both the axial and sagittal T_2 image sequences should be scrutinized simultaneously. Inflammatory lesions usually affect both the gray and white matter of the cord, involving up to half the diameter of the cord, and are often eccentric. Hyperintense lesions specific to multiple sclerosis should only span roughly two vertebral bodies. Lesions spanning more than three vertebral bodies imply either systemic disease associated ATM or Devic's disease. In addition to neuroimaging of the spine, MRI with contrast of the brain is also useful to understand if the current acute illness is part of a larger process. Inflammatory lesions are a dynamic process; therefore, if the first MRI obtained is "non-diag-

nostic", a repeat MRI 7 days later should be performed (Figure 75.5). Finally, if both brain and spine MRI only demonstrate spinal cord lesions, visual evoked potential (VEP) is still valuable to detect occult central nervous system (CNS) demyelination.

Diagnosis and management of patients with ATM begin with basic serology, specialized serology and CSF analysis as listed below. Basic serology is meant to establish a baseline prior to immune-directed therapy and to rule out infection. In fact, in patients with a known history of demyelinating disease, an infection could have been the trigger for the ATM attack. Specialized serology is important for two groups of patients: first, for patients with known systemic autoimmune disease and, second, for patients with no significant past medical history. For example, in patients with known systemic lupus erythematosus (SLE) it is important to establish if their disease is active or dormant in relation to the attack. The second and most important group of patients are those considered "previously healthy" yet harbouring an occult disease. Swift pursuit of the underlying aetiology has both immediate and long-term implications when treating ATM. For example, in a small group of patients with Sjögren's syndrome-associated ATM, their SS-A and SS-B serum titers can be negative on initial presentation. These patients require salivary gland lip biopsy to establish the diagnosis; however, if the biopsy is taken after multiple days of corticosteroid therapy, the biopsy results may return non-diagnostic. Furthermore, if the ATM occurred in a setting of occult autoimmune disease, then long-term treatment should incorporate management of the new diagnosis. Basic CSF studies in patients with ATM should demonstrate high protein levels and very mild pleocytosis due to breakdown of the blood-brain barrier. The remaining panel of viral PCRs (polymerase chain reaction) should be considered as well. Tests that should be performed are summarized in Table 75.2.

Figure 75.5. **MRI, sagittal T_2 sequence. Patient with ATM: extensive hyperintense area (predominantly central) involving the medulla oblongata, the whole cervical spinal cord, and the first segment of the thoracic cord.**

All of these studies are aimed to help the clinician tailor a treatment regimen that will ultimately involve immunosuppression. Historically, when treating ATM, corticosteroid therapy has been the mainstay and should begin immediately once concurrent infection has been ruled out. The CBC, urinalysis, blood cultures and CXR help to rule out infection prior to corticosteroid treatment and establish a baseline prior to therapy. In addition, a baseline CBC helps to place eventual elevation of the white blood cell (WBC) count into context due to demargination and not infection. At our institution, we treat patients for 5 days with 1 g IV solumedrol per day for an initial attack of ATM. In addition to corticosteroid therapy, advances in immune-directed therapy have added an entirely new dimension to what is available for patients affected by ATM. Intravenous immunoglobulin (IVIg) and plasma exchange have been tested in randomized trials and proved to complement corticosteroid therapy, while chemotherapies and monoclonal antibodies are now being incorporated

Basic serology	• Complete blood count with differential (CBC)
	• Comprehensive metabolic panel (CMP):
	  · Includes basic metabolic profile and liver function tests
	  · Magnesium
	  · Phosphate
	• Coagulation profile
	• Urinalysis and culture
	• Blood culture, two sets
	• Chest x-ray (CXR)

Specialized serology	• Oligoclonal bands (both CSF and serum samples required)
	• Neuromyelitis optica (NMO) antibody
	• Systemic autoimmune panel:
	  · Antinuclear antibodies (ANA)
	  · Sjögren's syndrome (SS-A, SS-B
	  · Anti-double stranded DNA antibody
	  · Rheumatoid factor
	  · Anti-cardiolipin antibody
	  · Lupus anticoagulant
	  · Complement levels
	  · Angiotensin converting enzyme (ACE)
	• Human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV)
	• Mycoplasma titer
	• Lyme titer
	• Hepatitis panel
	• B12
	• Rapid plasma reagin (RPR)
	• Thyroid stimulating hormone (TSH)

CSF analysis	• Cell count with differential
	• Bacterial, viral and fungal culture
	• Acid-fast bacilli smear
	• Polymerase chain reaction (PCR):
	  · Herpes simplex virus I and II (VI to be considered in immunocompromised patients)
	  · Varicella-zoster virus (VZV)
	  · Cytomegalovirus (CMV)
	  · Epstein-Barr virus (EBV)
	  · Enterovirus
	  · West Nile virus
	• CSF ACE (if history of systemic sarcoidosis is present)
	• Paraneoplastic panel (patient with history of neoplasm)

Table 75.2. Serological tests.

into regimens for patients with refractory or recurrent attacks. With respect to ATM, plasma exchange versus IVIg has been a topic of debate and research; nonetheless, plasma exchange is superior to IVIg in this case for the following reasons. Plasma exchange in a setting of Guillain-Barré syndrome and myasthenia gravis has been shown to deliver immune induction slightly faster than IVIg, with a peak efficacy of IVIg 2-3 weeks after administration. Furthermore, in the author's opinion, ATM is often antibody mediated as evidenced by the long list of diseases associated with it. Moreover, our ability to identify antibodies is still limited and is demonstrated by the fact that up to one third of ATM is ultimately diagnosed as "idiopathic". Furthermore, plasma exchange offers a very effective means of initially treating patients with ATM without committing patients to long-term immunosuppression. Due to the risks associated with plasma exchange, most patients should be started on IV corticosteroid therapy, with the decision to add plasma exchange based upon the underlying aetiology, extent of neurologic deficits, and clinical judgment.

Management Principles for Plasma Exchange and IVIg

Here we will discuss some of the finer points of using plasma exchange and IVIg in clinical practice. The dosages and duration of treatment apply to ATM and the remaining diseases discussed in this chapter unless specifically stated otherwise.

Therapeutic plasma exchange was first used to treat myasthenia gravis; since then its application has been extended to treat many disease processes where antibody or suspected antibody-mediated disease occurs.

The actual procedure should be performed in consultation with the institution's blood bank. Current use of plasma exchange is based on North American and French trials, and although no "optimal" standard of care has been established, general practice still follows these studies. The goal of plasma exchange is to remove the offending IgG and IgM from the bloodstream. Studies have demonstrated that in total, 45% of IgG and 75% of IgM are located in the intravascular space. Plasma exchange every other day will rebalance the antibodies in the intravascular space, which then allows for their removal. Therefore, plasma exchange should involve 250 ml per kilogram of body weight (per exchange) every other day for a total of five exchanges. As a result, based on the kinetics (half-life) of autoantibody resynthesis (5-6 weeks for IgG and 5-6 days for IgM), therapeutic plasma exchange should offer a 1-month window to begin immune modulation if warranted. Plasma exchange itself is a very dynamic process. The fluid removed can be replaced with either albumin solutions or fresh frozen plasma (FFP). The preferred solution is 5% albumin (in saline), which significantly reduces the rate of adverse events but does not confer a therapeutic advantage; and FFP should be avoided unless required to treat a concurrent disease. Due to the need for large bore central venous access, plasma exchange requires special attention to the patient's baseline coagulation profile and platelet function.

The current and recent medications list should be screened for use of anticoagulants and antiplatelet agents such as Coumadin or Plavix, which may delay initiating plasma exchange. Due to the inherent movement of large volumes of blood during plasma exchange, anticoagulation is needed to prevent clotting. Citrate is the agent of choice and works by binding free ionized calcium from within the blood, preventing it from participating in coagulation. As a consequence, some patients may develop hypocalcaemia.

Patients should be informed that they might experience perioral and peripheral paraesthesias, which are transient and related to the plasma exchange. In addition, electrocardiographic changes including prolongation of the QT interval may also occur as a result of hypocalcaemia. A further consequence of citrate use in plasma exchange is the transient diuresis of electrolytes secondary to the renal excretion of this large cation. Another management point to consider when using plasma exchange is the fluid shifts that occur. As a result of the volume of whole blood removed from the body for exchange, hypotension can be the immediate consequence; and, once the blood is returned with 5% albumin, patients with cardiac or renal insufficiency may develop volume overload due to the oncotic pressure inherent to albumin.

Finally, due to the non-specific nature of exchanging serum plasma with 5% albumin in saline, fibrinogen and clotting factors themselves are lost in the process. This is another reason why plasma exchange occurs every 48 hours to allow for the resynthesis of fibrinogen and clotting factors. When treating a patient with plasma exchange, daily CBC, basic metabolic panel (BMP), coagulation profile and electrolyte levels (ionized calcium, magnesium and phosphate) should be performed and replacement given when needed. Once therapy is complete, removal of the central venous access should be delayed for 48 hrs until the international normalized ratio (INR) falls below 1.4.

IVIg is a pooled product derived from many patients' plasma; its mechanism of action is not fully understood. In the author's experience, the following ideas are useful to remember when treating patients with IVIg. When treating diseases discussed in this chapter, unless stated otherwise, utilize a total IVIg dose of 2 g/kg ideal body weight. This dose of 2 g/kg is given in divided doses of 0.4 g/kg per day over 5 days in order to minimize side effects in patients who have never received this medication. If future rounds of IVIg are required, in select patients the total dose of 2 g/kg can be divided over 3 days. When calculating the dosing for your patient, you may land on a dosage that is in between two vial sizes. We recommend to simply round up to the next highest dose. For example, if your calculation equals 32 g/day, round up to the nearest vial, such as a 35 g vial. Second, the clinician should be aware of common side effects (flulike symptoms, headache, hypotension, aseptic meningitis) and potential adverse events (myocardial infarction, stroke, renal failure, venous thrombosis, anaphylaxis) secondary to IVIg administration and discuss these with your patient prior to starting therapy. This will increase both adherence to the protracted time needed to infuse each dose and patient tolerance of side effects.

Subsequently, when ordering baseline serology, also include a serum IgA level to screen for patients with IgA deficiency who may be at risk for anaphylaxis. Many IVIg formulations are available. At our institution we attempt to minimize the risks by using only IgA depleted, sucrose-free IVIg. In addition, running the infusion overnight (6-8 h infusion time) minimizes patient discomfort and being bound to an IV pole. Between each infused dose of IVIg, we suggest continued IV hydration; daily basic serology (BMP, CBC, magnesium, phosphate) should be drawn with attention to changes in renal function, down trending WBC count and platelet levels or changes in electrolyte levels. Finally, 5 days of IVIg infusion and maintenance fluids may cause volume overload in some patients; therefore, concurrent use of diuretics may be warranted in those with cardiac and renal insufficiency.

75.3 Anterior Horn Cell to Neuromuscular Junction

We continue our discussion of neuromuscular weakness, transitioning from the spinal cord to anterior horn cell, peripheral nerve, neuromuscular junction. The topics discussed in this section do not represent all entities that can cause neuromuscular weakness along the peripheral nervous system (PNS); instead we have selected a few topics which are important to understand. It is essential to recognize that neuromuscular weakness in the PNS can present in multiple settings. The emergency room, after treatment of another disease, prolonged hospitalization or intensive care unit (ICU) stay, discovered postoperatively are all clinical settings in which neuromuscular weakness can clinically appear for the first time. Some examples of neuromuscular weakness due to disease of the PNS include:

- One third of patients treated for status asthmaticus.
- Prevalence of up to 46% of patients with a median duration of 7 days in the ICU who were admitted for sepsis, multiorgan failure or prolonged mechanical ventilation.
- Within the group of patients diagnosed with acquired neuromuscular weakness, the specific incidence was 34% for critical illness myopathy (CIM), 35% for critical illness sensorimotor polyneuropathy (CIP), and 30% for combined CIM/CIP in the same patient.
- The risk of acquired neuromuscular weakness is increased with elevated plasma glucose levels.

75.3.1 West Nile Virus

We begin our look at neuromuscular weakness by discussing a viral illness that can affect the anterior horn cell. West Nile Virus (WNV) was first isolated from a woman in Uganda in 1937 and the first case documented in the United States wasn't until 1999 in New York. Since then, the Centers for Disease Control (CDC) reported over 11,000 cases of this illness and over 1000 deaths as of 2007. WNV is an arthropod-borne and maintained Flavivirus which utilizes mosquitoes as vectors and birds to amplify. Based on data from 2002-2007, the peak incidence of human infection is the summer months of July through September. In addition, cases of West Nile transmission have been reported via organ transplant, blood transfusion, breast milk and transplacentally from mother to foetus. The mechanism of viral entry into the CNS is unknown, but histopathology studies demonstrate the virus has a predilection for neurons.

In the clinical arena, WNV infection leading to neurologic disease is actually quite rare. Data combined from both North America and Europe estimate that up to 70-80% of infections are asymptomatic, 20-30%, develop West Nile Fever (WNF), and only 1% demonstrate neurologic disease or West Nile neuroinvasive disease (WNND). WNF emerges after a 2-14 day incubation period with clinical signs and symptoms similar to the common flu such as headache, myalgias, weakness, fever, nausea and vomiting, diarrhoea and abdominal pain. Patients with WNF can experience lingering symptoms that last weeks to months, but usually recover without sequelae. The 1% who develop WNND can present in three different ways, or in combinations thereof. WNND can present as West Nile encephalitis (WNE), meningitis or flaccid paralysis. About 25-35% of patients will present with pure signs and symptoms of meningitis (fever, nuchal rigidity, photophobia and phonophobia) without encephalitis, whereas 60-75% patients with WNND will present with WNE. This group is characterized as having encephalitis with focal neurologic deficits such as tremor, myoclonus or Parkinsonian features (rigidity and bradykinesia). Furthermore, WNE carries a higher mortality rate of up to 20%, especially with increased age, when compared to WNF and the meningitic form. When the virus attacks motor neurons, the clinical presentation of WNV is an acute, asymmetric flaccid paralysis that begins in one or more limbs. Initially, patients may complain of pain in the limb(s) that subsequently become paralyzed. The weakness can ascend in 50% of cases to include bilateral facial muscles, but the infection should spare sensory modalities. In cases where flaccid paralysis resulted in respiratory neuromuscular weakness, the mortality increases to 50%.

Patients presenting with high fever and meningitis, encephalitis or paralysis should trigger a high index of suspicion for WNV if their history includes spent many hours outdoors during the summer months. CSF evaluation demonstrates pleocytosis, with <500 cells and often lymphocytic in predominance. Furthermore, CSF protein can be elevated and glucose should be normal. Diagnosis is confirmed by IgM antibody to WNV in the CSF if collected within 8 days of illness onset or from serum if collected within 8-14 days of illness onset. While PCR can diagnose diseases such as herpes encephalitis with great accuracy, WNV PCR is positive in only 50% of patients. What can also make arriving at a final diagnosis more difficult is that the serum test of WNV also cross-reacts with other known flavivirus infections such as Japanese encephalitis, St. Louis encephalitis, yellow fever and Dengue. As a result of WNND mimicking other diseases on initial presentation, neuroimaging and electrodiagnostic studies serve to rule out other diseases rather than rule in WNV. If WNND is suspected in the spinal cord, MRI may demonstrate T_2-weighted hyperintensity in the anterior (ventral horns) spinal cord. Ultimately, the diagnosis of WNV infection is made on the basis of strong clinical suspicion and diagnostic laboratory testing.

There is no specific treatment for any form of WNV infection and care is only supportive. Recovery from flaccid paralysis does occur, but can take many months and requires aggressive physical rehabilitation.

75.3.2 Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) affects one to four persons per 100,000 annually worldwide and two per 100,000 annually in the United States. Most patients who experience GBS ultimately recover; however, up to 20% have permanent disability. Respiratory failure is an initial presentation in 10% of patients with 30% of remaining patients eventually requiring mechanical ventilation. If intubated, the most common causes of morbidity in a GBS patient include systemic infection, venous thromboembolism and cardiac arrhythmia secondary to dysautonomia. Two-thirds of patients, 2 to 4 weeks prior to the onset of neurologic symptoms, will have suffered from an acute illness. Upper respiratory infection, *Campylobacter jejuni* infection, and CMV are the most common preceding illnesses associated with GBS. In addition, other diseases associated with developing GBS include hepatitis, HIV, herpes virus, influenza, mononucleosis, systemic lupus and lymphoma. Also, when GBS is suspected, inquiring as to any recent vaccinations is also important because epidemiological links have been reported.

Within the first 2 weeks of symptom onset, GBS has certain typical clinical features. Symptoms begin as a progressive ascending weakness from the legs, depressed or absent reflexes and distal extremity paraesthesias. On initial presentation, patients may recall experiencing difficulty with tasks dependant on proximal muscles such as rising from a chair or climbing steps and may complain of low back pain. Acutely, the incidence of weakness is 60%, paraesthesias is 80%, both at the same time is 30%, areflexia is 70% and hyporeflexia is 30%. With time, GBS symptoms tend to evolve with increasing both the areas and magnitude involved, so a typical GBS patient will eventually have weakness in all limbs, areflexia and paraesthesias. As previously stated, weakness in a typical

GBS variants	• Miller-Fisher Syndrome: · Ophthalmoplegia, areflexia, ataxia • Axonal loss variants • AMAN (acute motor axonal neuropathy) • AMSAN (acute motor sensory axonal neuropathy) • Pharyngeal-cervical-brachial
AIDP (acute inflammatory demyelinating polyradiculopathy)	
Tick paralysis	

Poisoning	• Marine toxin ingestion: severe paraesthesia with limited weakness:
	  · Ciguatoxin (salt water fish that consume certain types of algae)
	  · Tetrodotoxin (pufferfish consumption)
	  · Saxitoxin (shellfish consumption)
	• Heavy metals:
	  · Arsenic: distal extremity paraesthesia followed by glove and stocking, large and small fibre sensory loss
	  · Gold: complication of rheumatoid arthritis treatment, polyneuropathy with or without stomatitis and dermatitis
	  · Thallium: found in rodenticides and insecticides
	• Result of homicidal or suicidal action

Table 75.3. **Differential diagnosis of a patient who presents with GBS, a GBS variant or a clinically similar picture.**

GBS patient is an ascending process beginning in the lower extremities followed by the arms; however, a minority of patients (5-15%) will clinically present with cranial nerve deficits first, then a descending pattern of weakness. Facial and neck weakness will occur in half of patients with ptosis in 5-10%, ophthalmoplegia in 15%, and oropharyngeal weakness in 40%. Diaphragmatic dysfunction is seen in up to 50% of patients, with a combination of both weak shoulder shrug and neck flexion as surrogate markers heralding diaphragmatic weakness and respiratory failure. Sensory symptoms can precede weakness by 1 to 2 weeks, with an early nondescript complaint of generalized malaise and pain (>50%) in the spine. The typical paraesthesia described by patients begins in the fingers as "pins and needles" and is seen first before sensory changes are reported in the distal extremities. As the sensory symptoms evolve, they transition from paraesthesias to a lack of sensation and numbness. Unlike weakness, sensory disturbances in the face and trunk are rare. Autonomic dysfunction, including tachy-brady arrhythmias, orthostatic hypotension, ileus, bladder dysfunction, and abnormal sweating, is seen in up to 50% of patients. Most symptoms will plateau within 2 weeks; rarely, some will take 4 weeks.

The differential diagnosis of a patient who presents with GBS, a GBS variant or a clinically similar picture is very broad and beyond the scope of this chapter, but is listed in Table 75.3.

The diagnosis of GBS is based on typical clinical presentation, lumbar puncture and neurophysiology studies (nerve conduction studies). Lumbar puncture should demonstrate elevated protein and very mild pleocytosis. Elevated CSF protein (50-200 mg/dl), which should peak between the second and third week, results from breakdown of the blood-brain barrier; moreover, a patient suspected to have GBS without elevated CSF protein for 2 weeks should be considered rare. CFS pleocytosis should be <10 cells/mm^3 within the first 2 weeks of illness. Caution should be used when making decisions in immunocompromised patients because the sensitivity and specificity of CSF studies in patients with suspected GBS are limited. Specialty serology and CSF PCR to be considered include serum anti-ganglioside antibody panel, *Mycoplasma pneumoniae* serum titre, CMVs and EBV PCR. Patients with a good clinical history and exam, even after repeatedly normal CSF examinations, still should be diagnosed with GBS until proven otherwise. Finally, nerve conduction studies should be performed to confirm the clinical diagnosis. The results will vary based on at what time point in the illness the patient was examined and which nerves were examined. A patient clinically diagnosed with GBS should demonstrate progressive loss of compound muscle action potentials (CMAPs), slowed nerve conduction velocities and loss of F wave and/or H reflex. Initial examination may be normal and repeat studies may be warranted.

The most common cause of respiratory failure in GBS patients is diaphragmatic weakness. Anticipation of respiratory complications begins on admission with bedside spirometry. Twice daily evaluation will establish a baseline and monitor the need for ventilatory support. Predictors of the need for early intubation and mechanical ventilation include:

- Patients with increased respiratory rate and shortness of breath during speaking.
- Time between onset of disease and hospital admission <7 days.
- Inability to lift the head and severe bulbar dysfunction.
- Repeated cough, difficulty with secretions and aspiration after swallowing.
- Vital capacity (VC) <60% of predicted or <15 ml/kg to 20 ml/kg.

Anticipation of early respiratory failure and the need for elective intubation during the daytime is crucial to avoid "crashing" in the middle of the night. Light sedation will be required to maintain ease of ventilation in a patient with neuromuscular weakness and preserved mental status. Most patients with GBS who evolve to require intubation may

require mechanical ventilation for 2 to 3 weeks; therefore, early tracheotomy should be considered, especially in patients with predominantly bulbar symptoms.

When GBS is suspected, the following recommendations should be considered. The mainstay of medical treatment for a patient with GBS is either IVIg treatment or plasma exchange. Both have been studied in trials which evaluated them individually and in combination. Plasma exchange and IVIg have been shown to carry equal efficacy, but plasma exchange requires central venous access and therefore confers a greater risk for side effects. Combining the two is not recommended. Steroid therapy is not recommended because it has not been shown to be superior to either IVIg or plasma exchange and carries long-term sequelae in patients potentially bed-bound for an extended period. IVIg should be considered for patients with a symptom onset <2 weeks but who remain ambulatory. The recommended regimen is 2 g/kg (ideal body weight) divided into 5 doses given once daily as 0.4 g/kg (ideal body weight). Plasma exchange is recommended in patients who are non-ambulatory within the first 4 weeks of symptom onset and those who require urgent mechanical ventilation

In the authors' experience, the following pearls are useful tips to remember when treating patients with IVIg. First, when calculating the dosing, you may land on a dosage that is in between two vial sizes. We recommend simply rounding up to the next highest dose (calculated 32 g per day rounded to a 35 g vial). Second, familiarize yourself with the common side effects (flulike symptoms, headache, hypotension, aseptic meningitis) and potential adverse events (myocardial infarction, stroke, renal failure, anaphylaxis) secondary to IVIg administration and discuss these with your patient because this will increase both adherence to the protracted time needed to infuse each dose and patient tolerance of side effects. Subsequently, when ordering baseline serology, also include a serum IgA level to screen for patients with IgA deficiency who may be at risk for anaphylaxis. Many IVIg formulations are available. At our institution we attempt to minimize the risks by using only IgA depleted, sucrose-free IVIg. In addition, running the infusion overnight (6-8 h infusion time) minimizes patient discomfort and being bound to an IV pole. During treatment, we suggest continued IV hydration. Daily basic metabolic panel (BMP) and complete blood count (CBC) should be performed with attention to renal function, WBC count and platelet levels. Finally, 5 days of IVIg infusion and maintenance fluids may create volume overload for some patients and therefore concurrent use of diuretics may be warranted in those specific circumstances.

75.3.3 Myasthenia Gravis

Myasthenia Gravis (MG) is an autoimmune neuromuscular disease of the neuromuscular junction (NMJ) that leads to painless, fatigable muscle weakness. The autoimmune antibody produced most commonly is targeted at the postsynaptic skeletal muscle nicotinic acetylcholine receptor (AChR). The antibodies themselves are not directly pathologic, instead they trigger the processes: complement-mediated lysis of the postsynaptic muscle membrane, immune-mediated destruction of AChR, and blocking of the AChR. Approximately 80-85% of patients with MG are seropositive for postsynaptic AChR antibodies and 10-15% of seronegative myasthenia gravis patients are positive for antibodies to muscle-specific receptor tyrosine kinase (MuSK) antibodies. These antibodies act to ultimately decrease the total number of functional postsynaptic receptors. Population studies demonstrate a prevalence of 20 per 100,000, with a bimodal distribution of both early and late onset. Early-onset women outnumber men during the second and third decades of life, while late-onset men outnumber women during the sixth and seventh decades. Thymic hyperplasia is found in up to 50% of patients with MG and 10-15%

of patients may also have a thymic tumour. Thymectomy is recommended for patients with generalized weakness prior to the age of 50 years. Approximately 15 to 25% of patients with generalized weakness due to a myasthenic exacerbation will evolve into myasthenic crisis requiring ventilatory support, with a mortality rate of 4 to 13%. Respiratory weakness is the initial presenting symptom in 1% of patients.

The initial clinical presentation can occur in a variety of clinical settings, from the outpatient clinic to the ICU. The key feature to MG is fatigable weakness which may be reported as worse at the end of the day, with proximal muscles more affected than distal muscle groups. In addition, fatigue should improve with rest, which differentiates MG from generalized exhaustion. The most common presenting symptom in MG is ptosis and diplopia; within 2 years of diagnosis, 85% of these patients will go on to experience an episode of generalized weakness. Ptosis can vary between each eye, daily, and even throughout the day. Seeking a previous picture or accounts from family members of changes noticeable to others is important in establishing a baseline. Pupillary response is not affected in MG and ptosis can be worsened in the contralateral lid by manually retracting the more affected lid. Diplopia is due to cranial nerve III, IV or VI weakness in either eye or simultaneously with no discernible pattern. Patients can also present with a "pseudo-intranuclear ophthalmoplegia" (INO) due to ocular muscle weakness. When attempting to elicit ptosis, the examiner should fatigue the patient with sustained upgaze for 60-180 seconds, while having the patient sustain gaze in any field for 30 seconds should test cranial nerve weakness. Bulbar weakness can be noted with drooping at the corner of the mouth when smiling, recent history of dysphagia and dysarthria. Dysphagia is often due to soft palate and tongue weakness that may lead to difficulties with swallowing a food bolus. Furthermore, difficulty chewing food due to muscle fatigue is not uncommon and weakness with jaw opening but not with closure is common in MG patients. Patients may also note a change in their voice to a more hypophonic/nasal quality due to a combination of facial and tongue weakness. If the neck muscles are involved, flexors are usually weaker than extensors. Testing muscle weakness in limb muscles is often facilitated by having the patient repeat functional actions 10 to 20 times in between examinations to check for diminishing strength. Having the patient raise their leg and hold it at 30-40 degrees for 1-2 minutes, or rising from a chair or squatting 10-20 times are simple tests for revealing fatigable weakness. Finally, one of the most feared complication is respiratory weakness, which may be underappreciated in a patient with a chief complaint of generalized weakness. Often, these patients are tachypneic and have shallow breathing. Any combination of weakness with inspiration/expiration and a weak cough in the setting of tachypnea are signs of impending respiratory failure. Even in a patient with a known history of MG, differential diagnosis for localized or generalized weakness should also include these entities:

- GBS (Guillain-Barré Syndrome).
- GBS Mimics:
  - Miller-Fisher Syndrome.
  - Acute motor axonal neuropathy (AMAN).
  - Acute motor sensory axonal neuropathy (AMSAN).
  - Pharyngeal-cervical-brachial acute demyelinating polyneuropathy (AIDP).
  - Heavy metal neurotoxicity with arsenic, gold or thallium.
  - Organophosphate exposure.
  - Drugs: amiodarone, cytarabine, suramin.
  - Acute intermittent porphyria.
- West Nile Virus.
- Lambert-Eaton Syndrome.
- Botulism.

- Motor neuron disease.
- Recent cosmetic Botox application.
- Cholinesterase overdose.

In a patient with a previous diagnosis of MG, exacerbations can be due to many reasons. Recent illness (urinary tract infection, respiratory infection) or a decrease in baseline steroid or immunosuppression can trigger an exacerbation. Many medications are also known to trigger exacerbations such as calcium channel blockers (diltiazem, verapamil), aminoglycosides (gentamicin, clindamycin) and beta blockers. During pregnancy, the immediate post-partum period and during labour, medications such tocolytic agents (terbutaline), as well as magnesium sulphate, can worsen myasthenic symptoms.

The diagnosis of myasthenia gravis is based on history and physical findings, then confirmed by serum studies, neurophysiologic testing and/or pharmacologic testing. Classic pharmacologic testing has been based on edrophonium (tensilon) testing. This test is the classic method for evaluating a patient with observable or subjective weakness; however, it is no longer performed routinely in the United States due to risks to the patient and lack of the medication itself. If the test is being considered, it should be deferred in patients with respiratory insufficiency because it can increase pulmonary secretions. Most pharmacologic confirmation comes from a diagnostic and therapeutic trial of cholinesterase inhibitor and the most commonly prescribed drug is oral pyridostigmine bromide (Mestinon). Patients can sense an onset of the medication effect within 30-45 minutes, which allow for this diagnostic and therapeutic trial to easily occur in an emergency room setting. One indirect method that acts as a local cholinesterase inhibitor is the “ice pack” test. By placing a small bag of ice on the lid of a patient with ptosis, the breakdown of acetylcholine should be slowed temporarily and the ptosis should improve. Nerve conduction studies and electromyography (NCS/EMG) testing performed by a trained neurophysiologist is a very important tool in the diagnosis of MG. Such testing should be performed in all patients suspected with MG to narrow the differential diagnosis. Patients with MG should have normal nerve conduction studies and EMG should rule out myopathy plus demonstrate no spontaneous discharges. The next step in neurophysiologic testing is repetitive stimulation. Repetitive stimulation (2-5 Hz) should cause a decreasing response and lead to failure at the neuromuscular junction. Yet, repetitive nerve stimulation sensitivity is not equal for all forms of MG (50-100% for generalized MG vs. 10-20% for ocular MG). When in doubt, a single fibre EMG (SFEMG) is recommended, which is a specialized type of EMG performed by a neuromuscular specialist. Due to the complex nature of antibody testing, most often the previously mentioned methods for diagnosing the various forms of MG can be performed in a variety of clinical settings when a diagnosis is needed immediately. When sending serology to confirm the diagnosis of MG, the most common study is for anti-acetylcholine receptor antibodies. As previously mentioned, this can be found in a majority of patients with generalized MG (80-85%); however, its absence can be seen in patients with ocular MG (up to 50%) and therefore does not exclude the diagnosis of MG. When a patient is classified as “seronegative” MG, then further antibody tests can be ordered. Anti-muscle specific tyrosine kinase (anti-MuSK) antibodies are found in up to 40% of patients deemed “seronegative” with generalized MG. Finally, acetylcholine receptor-blocking antibodies and receptor-modulating antibodies can also be found in a small percentage of patients.

Management of MG in the outpatient setting is beyond the scope of this chapter. Here, we will discuss management of MG exacerbations in the emergency room, inpatient and ICU settings. Enough emphasis cannot be placed on the importance of both a thorough history and physical exam when an examiner first encounters a patient with neuromuscular weakness. Especially in patients with MG, understanding their previous med-

ication regimen, any recent changes to it, and working with their neurologist is key to a successful inpatient encounter. Management begins with deciding the level of acuity, which is aided by evaluating the patient's respiratory status; hand-held spirometry is key to making this decision. Often, temporary increases in a patient's Mestinon or prednisone dose and concurrent treatment of the underlying trigger can allow a patient to follow-up with their neurologist for minor exacerbations. Once a patient is felt to require inpatient admission, a few simultaneous events should occur. The goal of basic serology (BMP, CBC, CPK, calcium, magnesium, phosphate, coagulation profile, blood culture and urinalysis) is to discover the triggers for exacerbation, such as infection, and to establish a baseline prior to immune directed therapy. Next, a CXR is important to diagnose and treat aspiration pneumonia or atelectasis. Once the patient is stable, an infused CT scan of the chest is important to evaluate for thymoma. During initial clinical assessment, if the patient demonstrates "paradoxical breathing" (movement of chest outward and abdomen inward), shortness of breath (inability to count beyond 20 in one breath) and/or tachypnoea, the physician in charge should anticipate the probable evolution of a myasthenic exacerbation of a myasthenic crisis. Myasthenic crisis can be defined as a patient who develops respiratory insufficiency that may necessitate mechanical ventilation. To help quantify a patient's respiratory status, immediate bedside spirometry should be performed. Initial data from bedside spirometry should include maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), vital capacity (VC), and forced vital capacity (FVC). The following parameters are influential when interpreting the data:

- Normal vital capacity (VC) is approximately 50 ml/kg:
  - Cough is impaired with VC <30 ml/kg.
  - Increased likelihood of mechanical ventilation need with VC 15-20 ml/kg.
- Hypercapnia is common with MIP lower than -20 cmH_2O.
- Effective clearance of pharyngeal secretions is decreased when MEP <40 cmH_2O.
- Bedside spirometry may be difficult to perform in a patient with facial weakness.

In addition to bedside spirometry, further data to be collected are arterial blood gases, continuous pulse oximetry, cardiac telemetry and serial mental status assessment. Arterial blood gas (ABG) provides a baseline for future ventilatory management, current ventilation efficiency (hypercapnia) and screening for atalectasis-induced hypoxia due to ventilation-perfusion (V/Q) mismatch. If ABG is not obtainable, then a venous blood gas (VBG) can indirectly demonstrate arterial CO_2 (arterial CO_2 >50 and/or PaO_2 <70 mmHg are indexes which may warrant mechanical ventilation). Continuous pulse oximetry (SpO_2) is a useful tool; however, one should recall that a SpO_2 >90% is equivalent to an arterial pressure of O_2 > 60 mmHg; therefore, hypoxia can occur even if the machine isn't beeping. Cardiac telemetry is also important because arrhythmias are a common cause of death in myasthenic crisis. Serial mental status examination is a useful means to monitor the patient for respiratory compromise and decreasing airway protection.

Evaluation for early elective mechanical ventilation will avoid emergency intubations and decrease the risk of aspiration pneumonia. When in doubt, elective intubation is probably the safer choice. The two modalities for mechanical ventilation are non-invasive, positive pressure ventilation using continuous positive airway pressure/bi-level positive airway pressure (CPAP/BiPAP) and oral intubation. The first choice, non-invasive positive pressure ventilation, may be a viable option in patients without hypercapnia and it may afford enough time for medical therapy to take effect. Signs that positive pressure ventilation is no longer efficient include a worsening ABG, increasing patient anxiety due to "air hunger" or decreasing mental status. Especially with a change in mental status, the patient will no longer be able to protect their airway by removing the facemask. Invasive mechanical ventilation is the next step in providing ventilator support. Synchronized intermittent mandatory ventilation with tidal volumes around 7-10

ml/kg, pressure support of 5-15 cmH_20, positive end-expiratory pressure (PEEP) of 3-15 cm are parameters that may be needed to maintain PaO_2 >90, and PCO_2 <40 is a good starting point when ventilating patients with neuromuscular weakness. One final note regarding mechanical ventilation is to not overlook the importance of discussing with the patient and family members the future possibility of ventilatory support prior to its need. Especially in the elderly or those with advance directives, knowing that intubation during a myasthenic crisis often acts as a temporary bridge, helps patients and their families make fully informed decisions. This also allows the clinician to make an educated decision if respiratory failure occurs in the middle of the night and the patient no longer retains a decision making capacity.

Treatment strategies for both myasthenic exacerbation and myasthenic crisis involve a combination of pyridostigmine bromide (PO or IV), prednisone (PO and/or IV), intravenous immunoglobulin (IVIg) or plasma exchange. Please refer to the previous section (Guillain-Barré syndrome) regarding "pearls" when using IVIg or plasma exchange. The first decision to make is to use either IVIg or plasma exchange; this decision is a balance between the risks and benefits of each therapy applied to the patient at hand. In fact, both IVIg and plasma exchange can be considered inducers of immunosuppression, with corticosteroids as the vehicle to maintain this goal. Current thinking is that mild to moderate myasthenic exacerbations can be successfully treated with IVIg (0.4 g/kg for 5 days). Initial concomitant introduction of high-dose steroid therapy is not recommended due to the possibility of exacerbating myasthenic symptoms; however, if the patient begins to improve by day 3, one can consider its addition. Oral prednisone (40-60 mg) can be initiated based on the patient's treatment plan after induction of immunosuppression. Patients who evolve into a myasthenic crisis or present with one require plasma exchange therapy, which provides slightly more robust results in a shorter time period. In addition, it has been suggested the risk of IV steroids worsening symptoms is decreased with concomitant plasma exchange therapy due to their mechanism of action with plasma exchange. With any suspicion of pneumonia or other source of infection, treatment of that infection is equally important.

75.3.4 Critical Illness Sensorimotor Polyneuropathy and Myopathy (CIP/CIM)

This condition has been present for many years but only recently has it been further characterized as common complication of sepsis and multiorgan failure. The incidence of critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) approaches 70% in patients with sepsis, up to 100% in patients who also develop multiorgan failure, and is seen in 50-80% of patients who are in an ICU setting for more than 7 days. CIP/CIM is often first discovered as difficulty weaning a patient from mechanical ventilation or when recovering from prolonged encephalopathy. The incidence of CIM peaks during the sixth decade of life, while the pathogenesis of CIP/CIM is currently based on its association with risk factors identified, including hyperglycaemia, corticosteroid therapy, severity of illness, duration of ICU stay, vasopressor support, and many others. CIM is commonly seen in patients exposed to corticosteroids (methylprednisolone, hydrocortisone, prednisone, betamethasone, dexamethasone) and neuromuscular blockade agents such as pancuronium, vecuronium, atracurium) and prolonged exposure to propofol.

Clinical presentation of CIP varies slightly with CIM. Initially, it is helpful to establish the patient's baseline functional status by chart review and/or speaking with family members. CIP should be suspected in an ICU patient who demonstrates diffuse, distal muscle

weakness; on bedside examination, their weakness may be severe enough to resemble a patient with quadriplegia. CIP affects the sensory nerves greater than the motor nerves; therefore, patients on reflex exam will be hyporeflexive or areflexic. Yet, up to one third of patients may have retained reflexes and cranial nerves are often spared. Often patients who initially begin with CIP can develop CIM secondary to denervation, which is why these two disease processes can be difficult to clinically distinguish by examination alone. In a patient with previous spontaneous movements and intact sensation, failure to withdraw to painful stimuli applied to a distal extremity should suggest sensory loss. CIM should be suspected in a patient with equal distribution of weakness in both proximal and distal muscle groups. Often, reflexes are normal or slightly decreased and the sensory exam should remain intact. Whenever evaluating a critically ill patient, it is important to assure that the patient is awake, alert, and understands your commands. A complete neurologic examination, serology, electroencephalogram (EEG) and imaging should be performed to ensure no confounders are present. If on clinical exam focal deficits are elicited, then the diagnosis of CIP/CIM should fall lower on the differential.

Diagnosis of CIP/CIM is based on the diagnostic information obtained by electrodiagnostic studies, specifically, nerve conduction studies (NCS) and electromyography (EMG). It should be kept in mind that in patients with CIP or CIM, NCS/EMG results may be less robust due to surrounding electrical interference in the ICU setting. With pure CIP, nerve conduction studies should demonstrate normal nerve conduction velocities and distal latencies, with reduced to absent compound muscle and sensory nerve action potentials (CMAP and SNAP). The reason for a reduced or absent CMAP may be due to muscle inexcitability rather than axonal loss. EMG in CIP may show abnormal spontaneous activity in both proximal and distal muscle groups and reduced motor unit potentials due to denervation. NCS in CIM should demonstrate preserved conduction velocities and distal latency and low amplitude CMAPs. If weakness is mild, CMAP may be normal. In CIM, once myopathic changes have occurred, motor unit potentials are small and polyphasic, with early recruitment and fibrillation potentials. Direct muscle stimulation may be a helpful technique in distinguishing CIP from CIM because with CIM, the muscle is electrically unexcitable. Diagnosis can also be further aided in CIM by ruling out mimics including hypokalaemia, hypophosphataemia and hypermagnesaemia. With respect to creatine kinase (CK) in CIM, it may be elevated up 100 times above normal but 15% of patients can have a normal CK level as well. Finally, when CIP or CIM is suspected, nerve and muscle biopsy is the gold standard for diagnosis. Selecting where to biopsy should be based on an area that has not undergone extensive disease because results may be non-diagnostic. In CIP, nerve biopsy may demonstrate axonal degeneration of motor and sensory nerves without evidence of inflammation or primary demyelination. CIM muscle biopsy features range from atrophy of type I or type II fibres, with necrosis as a variable but often minimal finding. In CIM, electron microscope ultrastructure evaluation demonstrates a selective loss of myosin thick filaments, which is the key finding.

Unfortunately, no specific treatment regiment has been defined for CIP or CIM. Early and definitive treatment of the underlying aetiology for sepsis and SIRS in concert with intensive serum glucose control is the best prevention. In addition, aggressive physical rehabilitation provides the best chance to regain function.

75.3.5 Poisoning of the Neuromuscular Junction

The neuromuscular junction is a dynamic arena where multiple processes occur at all times to ensure proper muscle contraction. In the previous sections we examined acquired injury to the peripheral nervous system (PNS); in this section we will examine poi-

soning specific to the neuromuscular junction. Poisoning of the neuromuscular junction can be broadly categorized into pharmacologic, biologic and environmental.

Pharmacologic: Persistent Neuromuscular Blockade

Residual neuromuscular blockade has recently increased in incidence as the utilization of neuromuscular blockade has moved beyond intubation and the operating room. Agents for neuromuscular blockade are grouped into two categories: depolarizing (succinylcholine) and non-depolarizing. Depolarizing agents act by binding to the postsynaptic nicotinic acetylcholine receptor, leading to persistent depolarization. The mechanism of action for this group limits its current use beyond rapid sequence intubation. Non-depolarizing agents bind with postsynaptic nicotinic acetylcholine receptors and prevent acetylcholine from reaching its target, thereby preventing depolarization. This mechanism of action leads to fewer side effects; and, therefore, especially in the ICU setting, non-depolarizing agents are utilized. Commonly used non-depolarizing agents used and clinical settings where they are applied are summarized in Table 75.4.

Since these medications are used frequently without side effects, concurrent factors have been identified which can increase the risk for neuromuscular weakness due to residual neuromuscular blockade. Advanced age, renal insufficiency (pancuronium, vecuronium and rocuronium), hypermagnesaemia, metabolic acidosis and edematous states which require higher doses for clinical effect are all clinical situations which can prolong neuromuscular blockade. Also, some medications including beta-blockers, calcium channel blockers, aminoglycosides, clindamycin and cyclosporine have been implicated. Furthermore, some data suggest that concurrent corticosteroid and pancuronium or vecuronium use can have myotoxic side effects. If residual neuromuscular blockade is suspected, clinical features on examination are: persistent, flaccid, areflexic quadriplegia, ptosis and ophthalmoplegia (rarely seen in CIP and CIM), and no spontaneous respiration.

Diagnosis of residual neuromuscular blockade is often made at the bedside using a technique called train of four (TOF). TOF uses common, easily accessible nerve and muscle units to test for contraction when supramaximal stimulation is applied. When using TOF, always clean the patient's skin with alcohol, place the electrodes <6 cm apart with the negative electrode distally, and skin temperature should be >32^0 C. The most common nerve and muscle unit used is the ulnar and adductor pollicis. If this is not accessible, then the tibialis posterior and the flexor hallucis brevis muscle are also acceptable. Elec-

Common agents	• Benzylisoquinolinium compounds:
	  ▪ Cisatracurium
	  ▪ Atracurium
	• Aminosteroid compounds:
	  ▪ Pancuronium
	  ▪ Vecuronium
	  ▪ Rocuronium

Common clinical settings	• Facilitating mechanical ventilation
	• Shivering protocols in cooled patients
	• Treating malignant elevated intracranial pressure
	• Reduce muscle contraction and oxygen consumption associated with:
	  ▪ Tetanus
	  ▪ Drug overdose
	  ▪ Status epilepticus
	• Eliminate movements that interfere with beside diagnostic or therapeutic procedures

Table 75.4. **Commonly used non-depolarizing agents used and clinical settings where they are applied.**

trical stimulation occurs with four shocks at 2 Hz and allowing at least 10 seconds between rounds. If no neuromuscular blockade is present, all four shocks should result in muscular contraction of the same amplitude (height). Loss of the contraction from the fourth shock equates to a 70% neuromuscular blockade, with subsequent shocks three and two lost equalling up to 100% neuromuscular blockade. Another measure of body neuromuscular blockade is the TOF ratio, which is obtained by dividing the amplitude of the fourth shock by the first shock, but this requires EMG assistance. EMG assistance does help to distinguish neuromuscular blockade from CIP by demonstrating and absent CMAP but SNAP should be normal.

Treatment is based on reversal of the non-depolarizing agent and time. Paralysis can be transiently reversed with neostigmine or edprophonium but they should not be used routinely and only as needed. Reported side effects of neostigmine include arrhythmias, bronchospasm and the potential for acetylcholinesterase inhibitor to cause neuromuscular junction desensitization itself. Ultimately, weakness should resolve within a few days after discontinuation of a neuromuscular blockade agent.

Biologic: Organophosphate Poisoning

This entity is important to recognize because of the widespread use of organophosphate (OP) compounds, including insecticides, livestock and agriculture. They are also used in chemical warfare and suicide. Ultimately, these compounds act as irreversible cholinesterase inhibitors, specifically for both plasma and acetylcholinesterase inhibitors. OP enters the human body via ingestion, inhalation, injection and absorption across the skin.

Clinical examination of a patient with OP poisoning demonstrates the classic symptoms of excessive cholinergic stimulation seen in many areas of the body. Classic examples relate to muscurinic overstimulation that results in bradycardia, bronchospasm, diarrhoea, lacrimation, salivation, miosis, vomiting and urination. Nicotinic overstimulation of the CNS leads to agitation, confusion, coma and respiratory failure. Finally, overstimulation of the neuromuscular junction leads to fasciculation, muscle weakness and paralysis. Current diagnosis relies on recognition of the clinical signs, suspicion based on recent history, and confirmation using serum assays of plasma acetylcholinesterase activity.

Treatment always begins with basic life support ABCs (Airway, Breathing and Circulation). Crisis situations involve airway management with attention to the removal of excess secretions and atropine sulphate to treat CNS overstimulation. Additional help with managing secretion production can be aided by using Robinul (glycopyrrolate). If seizures occur, the drug of choice is a benzodiazepine. It should also be remembered that for rapid sequence intubation of this patient population, succinylcholine should be avoided because it is dependent on the acetylcholinesterase enzyme for degradation. Next, decontamination of the patient by washing with soap and water should hydrolyze the OP compound and prevent its further absorption. Also, healthcare providers should protect themselves and other patients from exposure by using gloves and a protective gown. Overall, atropine is the drug of choice due to its ability to enter the CNS; however, some controversy exists over the selective addition of pralidoxime (2-PAM), which acts as an antidote by binding to the OP molecule.

Environmental: Botulinum Poisoning

Botulinum toxin poisoning can be seen in both adults and infants, from unintended exposure and as a consequence of its expanded medical application. Currently, the U.S. Food and Drug Administration approves botulinum toxin for the treatment of strabismus, cervical torticollis and blepharospasm; however, there are many more off-label and cosmetic uses today as well. Botulinum toxin is produced by *Clostridium botulinum*,

a spore-forming anaerobic, Gram-positive bacillus. Historically, because botulinum toxin is ubiquitous in soil and water, toxicity commonly appeared secondary to ingestion. Clinical botulinum toxicity has been documented to occur in persons exposed to preformed toxin (adult and infantile ingestion, inhalation, injection) and colonization by *Clostridium botulinum* with subsequent toxin production (wound and gastrointestinal tract). Although seven types of botulinum toxin are known, types A, B, E and F are most frequently the cause of botulism in humans. Botulism is considered a public health issue; therefore, confirmed cases should be reported to state health officials so that a possible outbreak can be caught early. As previously mentioned, the clinical circumstances where botulism occurs are through ingestion, infection, inhalation and injection. The least prevalent is via inhalation, but the implications of aerosolization of botulinum toxin are far-reaching and its use may be seen as a biological weapon. Injection of preformed botulinum toxin is seen with injection drugs (black tar heroin and cocaine) and medical application. Drastically smaller doses of the toxin are used in medical and cosmetic applications; as a result, the only adverse events are seen when therapeutic doses extend beyond their target muscles. Infection of a wound with *Clostridium botulinum* is seen with IV drug use when dirty needles are shared; therefore, an injection drug user with respiratory weakness should not be missed. The last clinical scenario to consider is ingestion of the bacteria or preformed toxin. This has become exceedingly rare as preventative measures with food preparation have advanced.

Overall, botulism presents with multiple cranial nerve palsies, followed by symmetric, descending flaccid paralysis. Prominent ptosis, dilated pupils, blurred vision, diplopia, dysarthria, dysphonia and general facial weakness are the clinical manifestations of multiple cranial nerve palsies from botulism. As the paralysis descends, constipation will eventually occur in all patients. Diagnosis of botulism is very difficult due to both the general lack of cases seen in practice and the broad differential diagnosis of painless, descending weakness (stroke syndromes, Guillain-Barré Syndrome and its variants, myasthenia gravis, Lambert-Eaton Syndrome, tick paralysis). Initial history, recent travel, food ingested in the last week, and any history of IV drug use should place botulinum on the differential. Common serology, radiology and CSF studies will be normal in a patient infected with botulinum toxin. The key to diagnosis is isolation of the toxin from the wound or food samples, secretions, stool, serum or gastric secretions.

Treatment is based on a two-armed approach. First, patients suspected of botulism should be immediately admitted to the ICU and monitored frequently for signs of respiratory insufficiency. Since botulinum toxin causes paralysis of skeletal muscle, patients with air hunger and hypoventilation may not present with agitation. Furthermore, if paralysis compromises respiratory function, recovery can take weeks to months. This is why intensive care is so important to help bridge patients to recovery. Second, the only specific targeted treatment for botulism is botulinum antitoxin. Antitoxin can prevent further weakness and paralysis by binding to free toxin; however, if given once the toxin has bound to nerve endings, its utility is greatly diminished. Again, working with your state and local agencies is key to treatment by isolating those infected and preventing further spread of the disease.

75.4 Myopathy

Among the many aetiologies for acute neuromuscular weakness, encountered in both the inpatient and ICU setting, one source of weakness that can go unrecognized is systemic muscle decompensation. Myopathies are commonly chronic disease processes

Inflammatory myositis	• Polymyositis dermatomyositis
Viral myopathy	• Influenza A and B (most common reported) • Enteroviruses (coxsackie B and ECHO virus) • HIV • HTLV-1
Endocrine myopathies	
Hypokalaemic periodic paralysis	

Table 75.5. **Myopathies that should be recognized and treated when a patient is suspected of having systemic muscle weakness.**

due to a variety of conditions such as autoimmune connective tissue diseases, secondary to infection (bacterial, viral, fungal and parasite) or sequelae of treatment regimens. Critical illness myopathy is the most prevalent myopathy that will be seen in the intensive care setting; however, in Table 75.5 there is a selection of myopathies that should be recognized and treated when a patient is suspected of having systemic muscle weakness.

For patients with suspected inflammatory myositis, a disciplined approach to the history and exam is very important because patients with polymyositis often lack the cutaneous features of patients with dermatomyositis. One clue to inflammatory myopathies is an association with autoimmune connective tissue diseases. Dermatomyositis on clinical examination should reveal nearly pathognomonic cutaneous signs of both a heliotrope rash and Gottron's papules. The heliotrope rash is a dusky erythematous rash with a symmetrical periorbital distribution. Gottron's papules are slightly violaceous papules localized to the dorsal and extensor surface of multiple bony joints. The most common joints involved are the metacarpal and interphalangeal joints, while less common areas are the wrists, elbows and knees. Since inflammatory myopathies are mostly chronic, initial complaints are myalgia, fatigue and proximal, symmetric muscle weakness. Patients will report difficulty with repetitive movements such as climbing stairs or raising their arms. Rarely, patients will experience an acutely malignant acceleration of weakness involving the pharyngeal muscles, increasing the risk for aspiration; and, ultimately, if the diaphragm is involved, respiratory compromise will occur.

The most commonly seen viral myopathy is due to influenza A or B inflection. In addition to typical upper respiratory complaints, myalgias are often only initially present. With time, a focal, intense myositis affecting the calf muscles appears, which is a hallmark of influenza infection. Also, another less common consequence of influenza (HIV and enterovirus as well) infection is rhabdomyolysis. Whereas influenza causes a focal myositis, HIV infection can cause a wide variety of muscle diseases including myopathy, polymyositis and rhabdomyolysis. HIV myopathy can occur during both the acute infection as well as late disease; it should be considered a diagnosis of exclusion after medication-induced (HAART) or opportunistic infections, and wasting have been ruled out.

Endocrine myopathies can be caused by pituitary, thyroid, parathyroid or adrenal dysfunction. In reality, these endocrine organs are interconnected physiologically and therefore a lack of function in one area may lead to a loss of function downstream. For example, loss of proper hypothalamic function often leads to secondary pituitary and adrenal dysfunction. If endocrine dysfunction is suspected, the clinical examination should reflect the underlying endocrine loss or gain of normal activity.

Periodic paralysis is an episodic weakness due to channelopathies at the muscle membrane. These abnormal ion channels lead to hypoexcitability or hyperexcitability. Hyperexcitable muscle clinically presents as either myotonia (delayed relaxation after voluntary muscle contraction) or paramyotonia (myotonia that worsens with exercise), whereas hypoexcitation of the muscle membrane leads to periodic paralysis. The most common channels found to cause myopathies include sodium, calcium and potassium. Here, our focus will be on the sodium channelopathy on that leads to hypokalaemic pe-

riodic paralysis. These episodes of periodic paralysis can be precipitated by large carbohydrate meals, electrolyte disturbances and thyrotoxic states.
Diagnosis of myopathic disease should include serologic markers of muscle disease. These markers include creatinine kinase (CK), aldolase, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH). These initial studies help with diagnosis and also serve as a baseline to follow once treatment is started. Electrodiagnostic studies in acute weakness, both electromyography and nerve conduction studies, are crucial to categorizing neuropathic versus myopathic weakness as well.

75.5 Conclusion

Pathognomonic signs are very rare and the underlying aetiology almost never reveals itself when a patient presents for the first time with neuromuscular weakness. Every encounter should begin with a history of present illness that inquires about recent illness, transient neurologic symptoms, and focuses the symptoms tempo, localization and progression. Neuromuscular disease can be localized to the central nervous system or the peripheral nervous system; therefore, a complete neurologic examination is crucial to guide what the next step should be. Patients who present with acute onset of bilateral lower extremity weakness and myelopathic features should receive an MRI with contrast as soon as possible. On the other hand, patients presenting with a progressive weakness should be monitored for respiratory compromise because their symptoms may yet plateau. Electrodiagnostic studies, serology and CSF studies will always help narrow the differential diagnosis, but ultimately each clinician should use their clinical exam to define the diagnosis and therapy to use. Corticosteroid therapy has been used in many clinical settings, but recent advancements in immune therapy provide us with a more effective means to treat patients with a wide variety of neuromuscular disease. Weakness leading to respiratory compromise is one of the most important complications to avoid, which is why early aggressive intervention can often prevent this from occurring. Finally, prognosis is often determined by the patient's condition prior to insult, location and severity of the injury, and the potential for rehabilitation.

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76 Acute Paraplegias and Quadriplegias of Non-traumatic Cause

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76.1 Introduction

The part of this chapter gives a brief overview of the problem, listing the steps to be followed so as to obtain a first diagnosis and save time using systematic reasoning and approach.
The second section provides the reader with basic information about the distinct etiologies.
How to approach a recent motor deficit without indicators of brain compromise.
Here, we present a step-by-step approach to initial diagnostic and treatment:

- The first question to be answered when facing a recent non-brain motor deficit (quadriplegia/paresis or paraplegia/paresis) is: Is the motor deficit medullar or non-medullar? According to semiology, there are flaccid paraplegias of medullary origin, flaccid paraplegias of non-medullary origin, and spastic paraplegias. We will use here the term “paraplegia” which embraces possible cases of quadriplegia.
- The second issue to be resolved is whether we are dealing with a hyperacute, acute or subacute case. This will give us a guideline to the etiological definition.
- The third issue is an approximate definition of the topography. This is a key element for the correct choice of complementary studies.
- Once steps 1-3 have been accomplished, we should define what type of studies should be carried out.

76.2 Overview

76.2.1 First Step: Is the Deficit Medullary or Non-medullary in Origin?

The data from the patient’s clinical history that become relevant are:

- Discomforts that preceded the deficit. The presence of fever, paraesthesias, radicular pain prior to the deficit can be indicators of the Guillain-Barré syndrome. Intense pain in a well-defined segment of the vertebral column can be an indicator of a medullary compression syndrome.
- Pre-existing pathological data, such as metabolic disease or exposure to toxic agents can be signals of a peripheral injury (diabetic polyneuritis, toxic causes such as alcoholism, plumbic neuritis, etc.). The presence of a severe oncologic or rheumatologic disease can be an indicator of extrinsic medullary compression.

- Test findings provide clues to identify the problem as a medullar injury or a non-medullar injury (roots, plexuses, nerves, neuromuscular junction).

Flaccid paraplegia of medullary origin results from injuries to the motor neurons of the anterior horns of the spinal cord as well as their intramedullar axis-cylinder prolongations. In such cases there are signs of paralysis, flaccidity or accented hypotonia, sphincter dysfunction, deep areflexia, Babinski's sign, and others which can be present from the very beginning or emerge suddenly, reflexes of medullary automatism, anaesthesia with a well-defined topography and rapid trophic phenomena, as well as vasomotor paralysis. Initially, there can be bladder retention (balloon) and intestinal paralysis (abdominal strain) prior to incontinence.

Spastic paraplegias ensue from bilateral injuries of the pyramidal tract; they are characterized by paralysis with spasticity and evident hypertonicity. Spasticity usually predominates over paralysis. Initially, they can go through a more or less brief phase of flaccid paralysis or gradual simultaneous paralysis and spasticity. The lower limbs are usually extended with tight thighs and knees as well as cauda equina. There will be spastic muscles. The pyramidal syndrome is evident: osteotendinous hyperreflexia, clonus and Babinski's sign. According to the level of damage, the cutaneous abdominal reflexes can be missing or can also be missing earlier in multiple sclerosis. The reflexes of medullary automatism are usually exaggerated, sphincter function is also compromised and walking becomes difficult or impossible. Less frequently, spastic paraplegias are of the flexion type instead of the extension type. In general, they are the result of medullary compression processes, though some other causes such as multiple sclerosis, syringomyelia or other inflammatory processes (syphilis, tuberculosis, etc.).

Flaccid paraplegias of non-medullary origin can have radicular and neuritic causes. If the pain is radicular (polyradiculoneuritis, Guillain-Barré syndrome), a hypotonic quadriplegia with distal hyporeflexia or areflexia will be present. In this case, neither the Babinski sign nor sphincter function is affected and sensitive function is also preserved. Quadriplegias caused by severe polyneuritis are predominantly distal in the motor deficit and

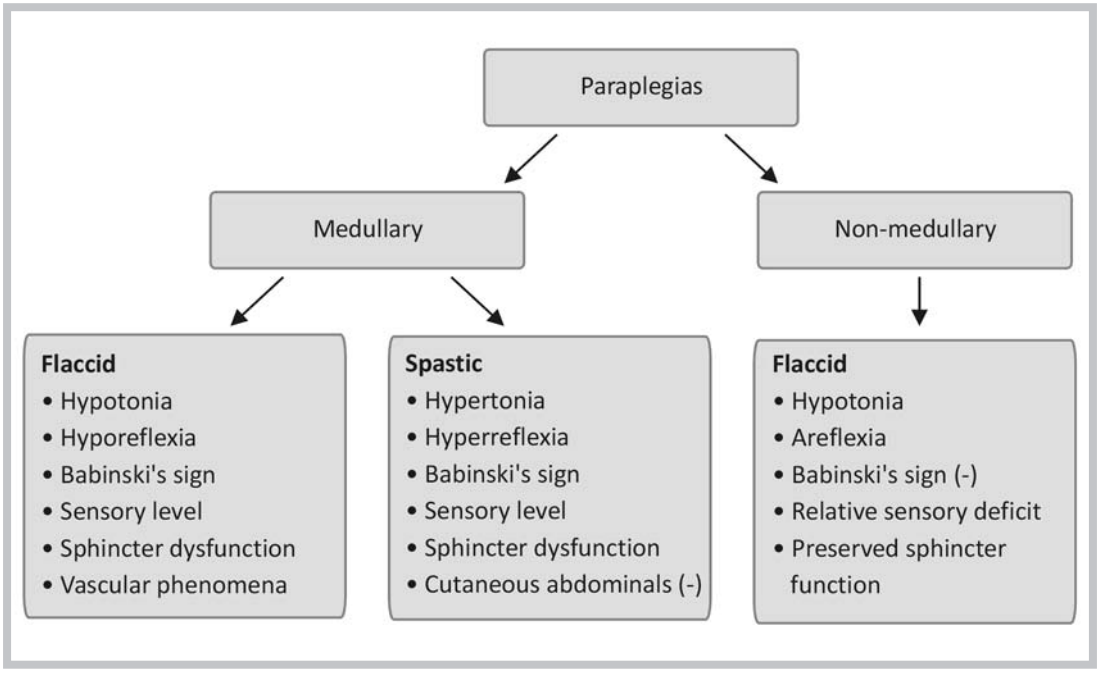

Figure 76.1. Flow chart for the management of paraplegias.

the sensory deficit is usually in the area of the hands and feet, in many cases with a clear tendency towards hyperaesthesia. Figure 76.1 shows the flow chart for the management of paraplegias.

76.2.2 Second Step: Are We Dealing With a Hyperacute, Acute or Subacute Injury?

Hyperacute injuries manifest suddenly and evolve within a couple of minutes or hours. They generally present as a syndrome of complete or almost complete medullary section, i.e., they start as a spinal cord shock with the interruption of motor, sensory and vegetative functions below the level of the injury. This kind of evolution could indicate the possibility of an epidural hematoma or a hematomyelia. Medullary infarction also leads to a sudden deficit, however, as the anterior spinal artery is compromised, it affects the anterior two thirds of the medulla; as a consequence, deep sensibility of the posterior third remains unaffected.

Kind of injury	Examples
Hyperacute (within minutes or a few hours)	• Epidural hematoma • Hematomyelia • Medullar infarct
Acute or subacute (within several hours or days)	• Extrinsic compression (spinal metastasis, epidural abscesses, intradural extramedullary tumours, etc.) • Intrinsic compression (intramedullary tumours) • Inflammatory-degenerative lesions (multiple sclerosis, Devic's disease, etc.)

Table 76.1. Hyperacute, acute or subacute injuries.

Acute and subacute damage develops over several hours or days. It could result from myelopathies, with the presence of more or less complete medullary syndromes or radicular injuries (classical Guillain-Barré syndrome or its variants) or other acute neuropathies (toxic, acute porphyria, multiorgan failure, etc.). Numbering among acute or subacute medullary injuries are extrinsic compressive injuries (secondary tumour metastases to the spine, epidural or subdural abscesses, etc.); extramedullary or intradural tumours (meningioma, schwannoma) and intramedullary tumours (ependymoma, glioma, etc.) (Table 76.1). Inflammatory-degenerative diseases such as transverse myelitis or Devic's disease must also be considered.

76.2.3 Third Step: What Topography Does the Injury Have?

Assuming that the patient's medical history and the neurological test have already told us whether the lesion is medullary or non-medullary, we will now consider some simple elements that can help us to identify the topography.

Segmental sensory responses:

- C3 innervates the front aspect of the neck.
- D4 borders on D5 at the level of the nipples or the equivalent area in males.
- D6 and D7 border on the xiphoid appendix.
- D10 and D11 are located at the level of the navel.
- D12 and L1 are located in the inguinal region.

Resolution of some osteotendinous reflexes (deep reflexes):

- The bicipital reflex has its centre in cervical segments IV, V and VI.
- The patellar reflex corresponds to lumbar segments II, III and IV.
- The Achilles reflex corresponds to lumbar segment V and to sacrum segments I and II.

76.2.4 Fourth Step: What Studies Should Be Carried Out?

If a primary medullary injury is suspected (intramedullary tumour, syringomyelia, demyelination disease, etc.) or secondary medullary injury (compression caused by tumour, epidural hematoma, pyogenic collections, etc.), magnetic resonance imaging (MRI) will be the most preferable study. If there is a suspicion of multiple injuries, MRI is mandatory. It should be borne in mind that computed tomography (CT) with contrast fluid administration can provide rapid screening, with good definition when there is suspicion of multiple tumour metastases to the bone. There is no doubt that due to the notable

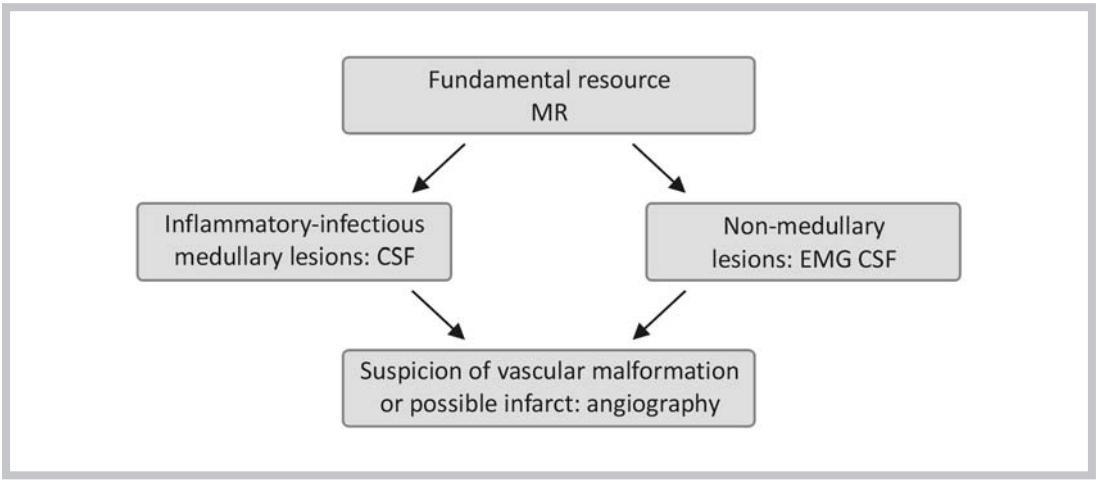

Figure 76.2. Tests that should be performed.

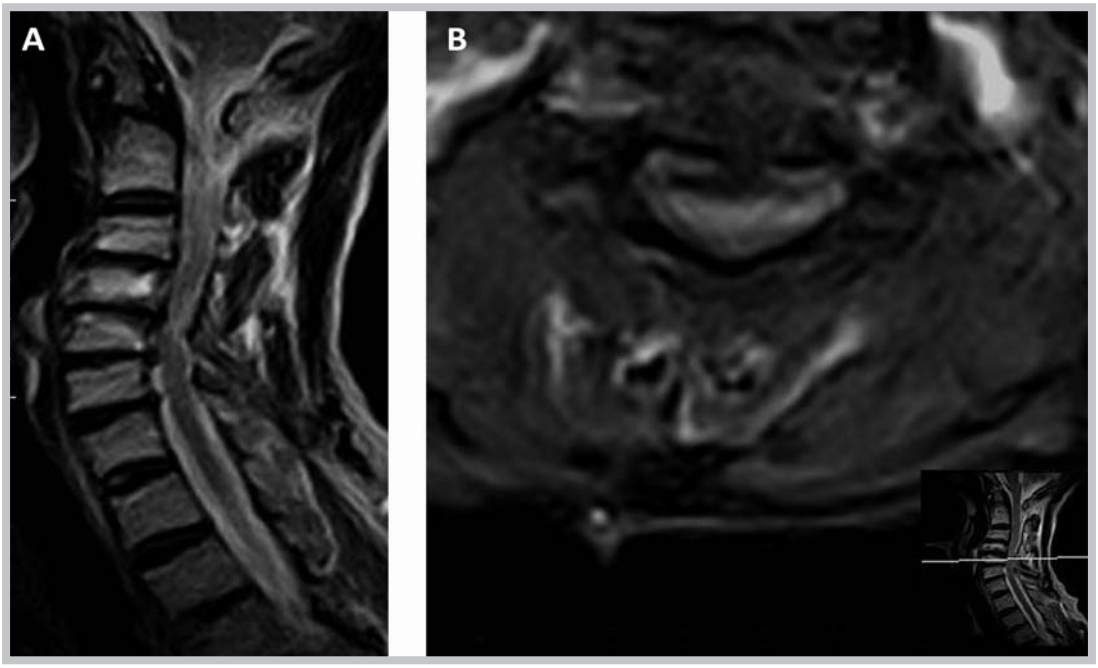

Figure 76.3. A 68-year-old woman with progressive quadriparesis and pyramidal signs. The MR images show the spondyloarthrotic changes and a narrow canal and the secondary myelopathy, with signal changes in medullary area [Images courtesy of the Neuroradiology Department, Sanatorio Pasteur, Catamarca].

development of neuroimaging techniques, the diagnosis is based fundamentally on MR in most cases.
If there is suspicion of a flaccid paraplegia of non-medullary origin, electromyography (EMG) and laboratory tests must be used. The typical cerebrospinal fluid (CSF) albuminocytologic dissociation (hyperalbumin with normal cellulose) is found in the Guillain-Barré syndrome. This finding can be present after the first week and only rarely will the CSF remain normal until the tenth week. Figure 76.2 summarizes essential tests, while Figure 76.3 shows some explicative images.

76.3 Etiology

Here we present a brief overview of the clinical picture, together with recommended management of the most frequent paraplegias of non-traumatic cause.

76.3.1 Extrinsic Medullary Compression

The most frequent medullary compression is caused by oncological disease. It can be a pre-existing cancer or one whose onset becomes evident from the metastasis that causes the compression.
It must be taken into account that cancer is not the only cause of medullary compression. There are other less frequent causes such as epidural abscesses, epidural hematoma, lipomatosis, etc.

76.3.2 Epidural Metastasis

Due to its frequency and impact, epidural metastasis stands out among other etiologies. It is estimated that at some point between 5% and 10% of all cancers develop metastases in the spine. The most frequent ones are lung cancer, breast cancer, melanoma, lymphoma, prostate and colon cancer. In almost one third of cases, multiple spinal metastases are found and in 70% of cases they are located in the dorsal spine. Lymphomas can be located in the epidural space without bone involvement.
Mechanical compression is not the only factor responsible for signs and symptoms. There is also secondary damage caused by venous obstruction or arterial ischemia. The spinal cord edema can generally be improved with the use of corticoids at a first stage.
Pain is usually the earliest symptom. It can be local, increasing while in bed, or it can also be radicular. When percussion of the spinous process causes precisely located pain, this can lead us to suspect mechanical spinal cord compression.
The onset of paraparesis at a later stage worsens the prognosis. In general it will be a case of acute or subacute paraparesis that will develop pyramidal signs. Motor difficulty can result from impairment of the spinocerebellar tracts, and the symptoms will be clumsiness and ataxia.
Sphincter function is usually affected at a later stage and can be interpreted as sign of poor functional prognosis.
Hypoesthesia and anaesthesia affecting well-defined segments of the body are detected in almost half of patients at diagnosis. Sensory examination must not be omitted, although it is usually an element that has been found to be subjective. It should be taken into consideration that it is a very helpful sign in topographical orientation, without forgetting that the level can be found several levels below that of the injury.

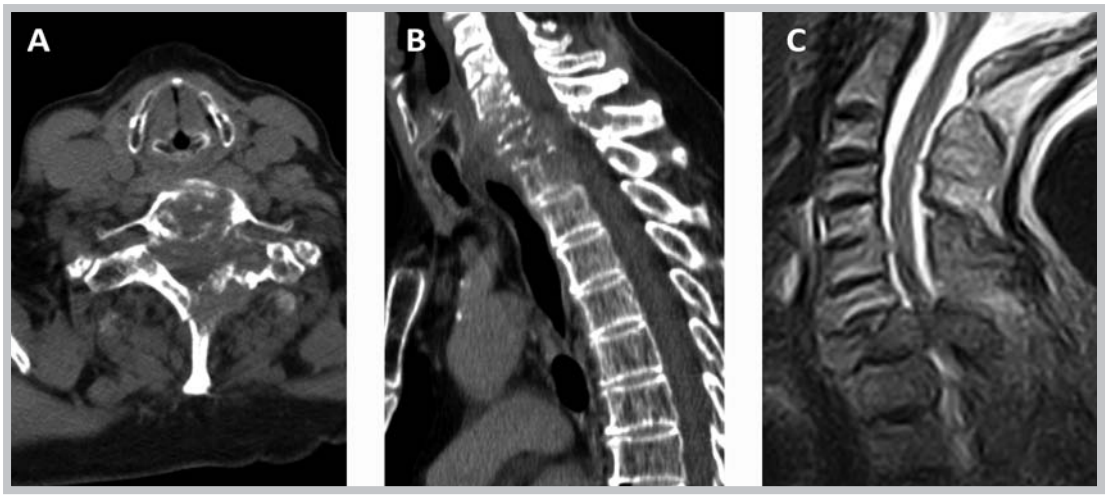

Figure 76.4. An 86-year-old woman with paraplegia caused by metastasis to D1 from lung cancer. Radiotherapy was prescribed. (A) CT scan; (B, C) MRI images. Note the better bone definition with CT and the better definition of medullary changes with MRI [Images courtesy of the Neuroradiology Department, Sanatorio Pasteur, Catamarca].

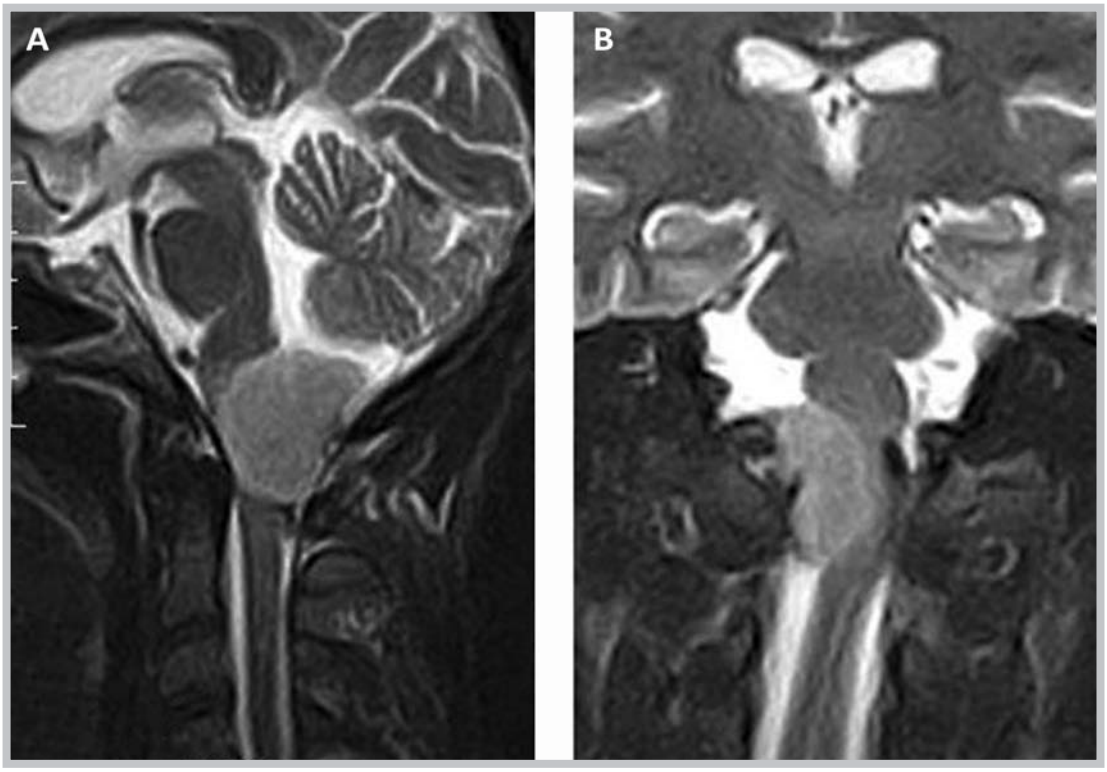

Figure 76.5. A 52-year-old woman with minor quadriparesis and some pyramidal signs. MR images showing a meningioma of the magnum foramen. Extramedullary intradural compression [Images courtesy of the Neuroradiology Department, Sanatorio Pasteur, Catamarca].

Certainly functional MRI will provide the most reliable information (see Figures 76.4 and 76.5 for examples). Differential diagnosis will include other causes of extradural compression (bar discs, spondylolisthesis, epidural hematoma, etc.), extramedullary or in-

tradural neoplastic processes (meningioma, schwannoma), intramedullar processes (ependymoma, astrocytoma, transverse myelitis, etc.).

76.3.3 Metastasis Treatment

The functional impact at diagnosis is essential for establishing the prognosis. In general terms it can be said that if the patient has had paraplegia for longer than 24 hours, the prognosis is poor. Histology and tumour staging will complete the prognosis. There is some evidence of types II and III but a few of type I to define the therapeutic behaviour. It is generally recommended that patients experiencing pain without a neurological deficit should be examined as soon as possible. If neurological signs are found, we are dealing with an emergency and such patients must be hospitalized. High-dose endovenous corticoids must be administered, for example in an initial bolus of 96 mg dexamethasone plus another 96 mg/day.
Generally speaking, radiotherapy is the first option in spinal metastasis. It seems that similar results are obtained with decompression laminectomy, though with higher associated morbidity. In such cases, the tumour site must be considered, as well as the existence or not of a defined histology since this is the opportunity for the etiological definition. Figure 76.6 shows an example of clinical findings in these kind of patients.

76.3.4 Spontaneous Epidural Hematoma

This is a rare and hyperacute cause of paraplegia. The diagnosis can be established on the basis of MR findings. The image will show a bright signal in T_1, and occasionally an

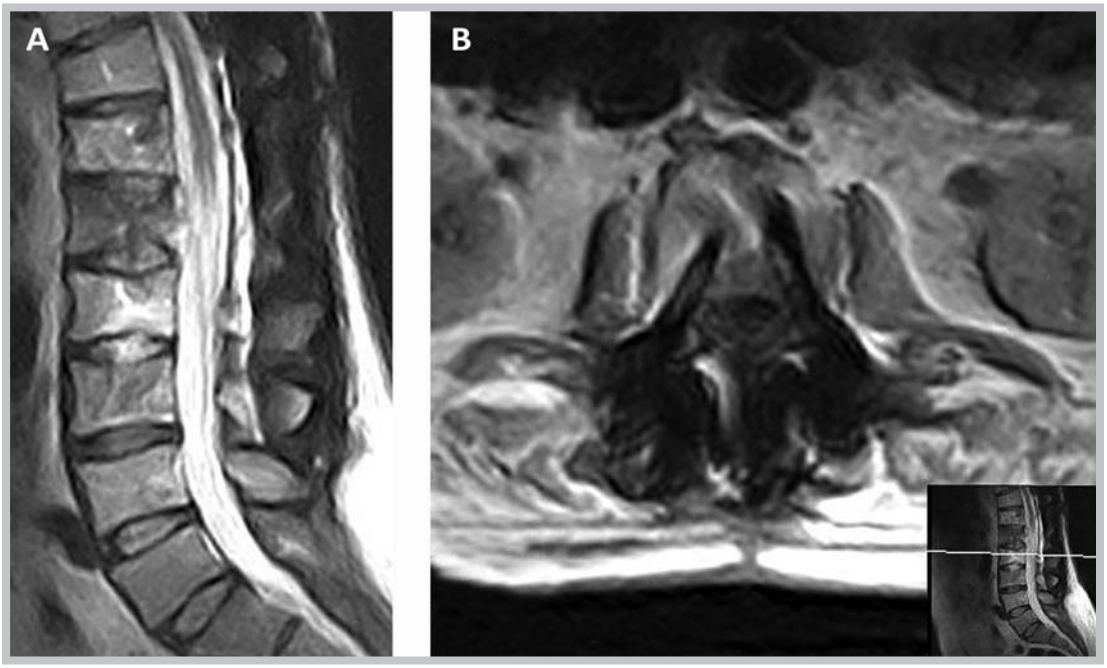

Figure 76.6. **A 60-year-old man with lumbar metastasis from prostate cancer. When he consulted, paraplegia had already begun. He was prescribed surgical decompression and stabilization with a titanium prosthesis. The motor deficit was reduced and the patient could walk again. He was later irradiated [Images courtesy of the Neuroradiology Department, Sanatorio Pasteur, Catamarca].**

empty signal in arteriovenous malformation (AVM). Anticoagulant treatment and possible hemorrhagic diatheses must be investigated. If we are uncertain about the cause, an arteriographic study should be obtained. If the patient's general condition does not improve at diagnosis, urgent surgical decompression is indicated. It is worth remembering that a major epidural circulation is the cause of the more frequent presence of hematomas in this space rather than medullary subdural hematomas.

76.3.5 Epidural Abscess

The hematogenic route can be the result of cutaneous, pulmonary or pelvic infection. It could be an infection caused by continuity from one vertebra to another or the result of an invasive procedure (lumbar or anaesthesia puncture). The most frequent pathogen is *Staphylococcus aureus*.
The symptoms are a combination of pain, deficit signs and fever. The condition can worsen rapidly and can be injurious, which is why it is advisable to adopt an aggressive approach and operate the patient immediately.

76.4 Intramedullary Injuries

76.4.1 Hematomyelia

Hematomyelia is less frequent than epidural hematoma and its causes can be the same. Intramedullary AVMs are found more often in the cervical area. Intratumoural bleeding must always be considered.

76.4.2 Medullary Infarction

Injuries in the aorta (dissecting aneurysm, traumatic or surgical injuries) can affect the anterior spinal artery. A hemodynamic shock or an embolic accident can also be the cause of an ischemic event. It usually appears as a medullary section, without pain (except for the pain that an aorta dissecting aneurysm may cause) and with the preservation of deep sensibility. MR may show spinal cord enlargement in T_2 with a bright signal in the anterior medullary area. These findings are not consistent; however, this study will serve to exclude other causes of spinal cord injury. In general, this is a case of hyperacute paraplegia. It must be taken into account that transient ischemic medullary attacks can be present as a result of vascular malformations, embolus, temporary increases in venous pressure, etc. In such cases, differential diagnosis will include other causes of transient medullary dysfunction such as narrow canal, demyelination disease, tumours, etc.

76.4.3 Acute Transverse Myelitis

Practice shows that acute transverse myelitis is most often idiopathic, and only in one third of cases can an etiological definition be reached. Those caused by infections can be viral (adenovirus, HIV, herpes virus, etc.) or non-viral (luetic vasculitis, tuberculosis, mycoplasma, etc.). Their etiology can be related to post-immunization reactions or collagen diseases or paraneoplastic (bronchogenic carcinoma) processes.

A particular group (<10%) evolves in time towards multiple sclerosis; its frequency is higher among children and young adults and most often arises in the dorsal area. MR can be normal in at least 50% of cases in the acute stage. When it is positive, local edema is perceived with a poorly defined bright signal in T_2 and possible highlighting with contrast. Since the onset of multiple sclerosis remains possible, the brain must be examined for other injuries. The CSF can show cellularity and high protein levels. A hyperacute presentation usually carries a poor prognosis. Complete recovery is achieved in one third of cases, partial in another third, and loss of walking ability and sphincter control in the remaining third. Young age, incomplete set of symptoms, maintenance of deep sensibility and a MR with few findings are indicators of a better prognosis.

76.4.4 Devic's Disease (Optic Neuromyelitis)

Devic's disease differs from multiple sclerosis and can be monophasic or recurrent. Medullary damage is usually acute while optic damage can be acute or subacute and symptoms can appear simultaneously or sequentially. In the recurrent types, medullary onset is usually separated in time from optic symptoms (>3 months). Most relapses occur within a period of 6 months, affecting mainly older adults with an associated autoimmune disease. MR usually shows lesions of more than three spinal cord segments. Hyperintense signals in T_2 in the optic nerves, chiasm and spinal cord must be searched for (Figure 76.7). Over the following weeks, treatment with steroid pulses and oral steroids is used.

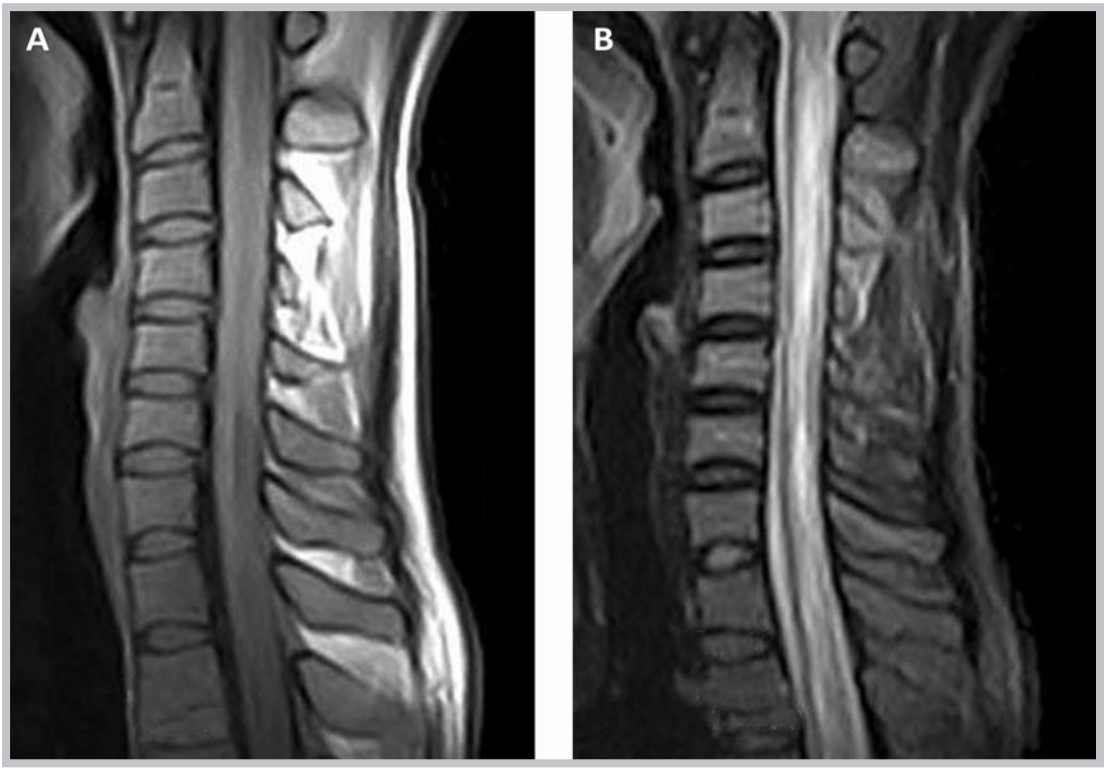

Figure 76.7. **T_1 and T_2-weighted images of the cervical spinal cord in Devic's disease (young woman). Small hypointense signal is seen in T_1. T_2 shows hyperintense signal covering several medullar segments [Images courtesy of the Neuroradiology Department, Sanatorio Pasteur, Catamarca].**

76.4.5 Intramedullary Tumours

The most frequent intramedullary tumours are astrocytoma (30%) and ependymoma. Glioblastoma, dermoid tumours and oligodendroglioma are much less frequent.
Onset is normally marked by pain followed by motor disorders that usually appear after sensory symptoms. These can be a spinal cord hemisection syndrome (Brown-Séquard) or a syringomyelia syndrome (segment paraesthesia or a level deficit in the upper limbs and dissociated anaesthesia).
MR is the imaging study of choice, though it can lead to wrong conclusions when it shows edema or cystic injuries that can be misinterpreted as necrosis.
The evolution of the patient's general condition is gradual, subacute, though it can have an acute or hyperacute onset in children.
Ependymomas in general have a better surgical prognosis than astrocytomas, with total resection achieved in more cases. Astrocytomas in general cannot be excised completely because of a lack of well-defined planes. In more serious astrocytomas, surgery and radiotherapy are combined.

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77 Status Epilepticus

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Two to three million people in the United States suffer from epilepsy. Approximately 15 percent of these patients will experience status epilepticus (SE) in their lifetime, leading to an estimated 100,000 to 200,000 cases per year [1]. The definition of SE is based on the clinical manifestation as well as the duration of seizure or seizures [2]. Nonconvulsive status, a common presentation of SE, is a frequently missed or delayed diagnosis in critically ill patients [3,4].
The mechanism by which SE develops is thought to be via an imbalance between inhibitory and excitatory factors in the central nervous system, and can arise from several different etiologies [5]. The consequences of SE have been studied in animals [5]. The longer the seizure, the higher the morbidity and mortality in patients [5]. Recognizing and treating SE in the acute and intensive care setting is essential for all health care providers, including internists, emergency care physicians, intensivists, nurses and paramedics.

77.1 Definition

Longer seizures are more difficult to break and cause significant brain damage. The Working Group on SE of the Epilepsy foundation of America defines SE as continuous seizure activity greater than 30 minutes, or two or more sequential seizures without full recovery of consciousness [6]. Animal studies from the 1970s have shown that seizures lasting longer than 30 minutes cause considerable brain damage, affecting even subcortical structures [7]. However, because seizures lasting longer than 5 minutes are unlikely to remit spontaneously, and due to the brain damage observed with long seizure activity, a revised definition of SE has been proposed: a continuous, generalized convulsive seizure lasting greater than five minutes, or two or more seizures without recovery of consciousness [8].
The definition of nonconvulsive SE (NCSE), variously termed intensive care unit (ICU) status, subtle status, and epileptic encephalopathy, generates more controversy. NCSE is characterized by many clinical states, depending on the regions of the brain involved. Signs and symptoms of NCSE can range from diminished responsiveness, aphasia, occasional automatisms, and is therefore under-diagnosed [9,10]. Recent data suggests that in an ICU population, 5% to 10% of comatose patients examined by EEG (electroencephalogram) were in NCSE [11,12]. This proportion rises sharply, to more than one third of patients, in the neurologic ICU [13]. Studies in adults, as well as in the pediatric population, show that a significant proportion of patients in convulsive status or after an isolated seizure go on to nonconvulsive status [12,14]. Without EEG monitoring following the convulsive state, NCSE would be missed.

77.2 Pathophysiology

More than a prolonged seizure, SE represents a state in which the normal balance between inhibitory and excitatory factors in the brain breaks down. GABA-mediated inhibition of an ictal focus will normally prevent secondary generalization of a seizure [15]. Recurrent or prolonged seizures enable a neurochemical feedback loop that lacks a normal inhibitory network, perpetuating more ictal activity [15].
The initial systemic effects of convulsive SE reflect the body attempt to maintain homeostasis, involving elevations of blood pressure, blood glucose, and heart rate [16]. This is accompanied by a transient increase in lactate and decrease in pH. After about 30 minutes, efforts to maintain homeostasis exhaust, and significant compromise to systemic stability follows, resulting in electrolyte imbalances, hyperthermia, and respiratory failure [16]. Initially cerebral blood flow is maintained to meet the elevated demands, but neuronal damage ensues when blood supply no longer matches the increased oxygen and glucose consumption [17]. The mismatch between blood supply and demand is not the only mechanism by which tissue damage occurs, as studies that have controlled for these factors still show damage in animal models [7]. Complex neurotoxic cascades against which therapy might be aimed (such as GABA agonists or NMDA receptor antagonists) are thought to be an important cause of neuronal damage [16]. The systemic and cerebral effects of NCSE are thought to be much less severe or lasting, confer a better prognosis than convulsive status. As such, aggressive treatment is controversial [18,19].

77.3 Classification and Clinical Manifestations of SE

In the ICU, generalized convulsive SE (GCSE) and NCSE are the two most common types. GCSE is generally diagnosed on a clinical basis, as convulsions are obvious. NCSE has two main subtypes described below, generalized and focal, which have in common only a persistent dysfunction of the neurologic examination, and usually require EEG for diagnosis.
GCSE is usually overt and relatively easy to diagnose clinically, although subtle motor manifestations may not be as apparent and also require EEG for diagnosis [20, 21]. Generalized bisynchronous convulsions, either clonic, tonic, or both, with loss of consciousness, are the typical clinical manifestation. In the ICU, GCSE is an important cause of death, with mortality approaching 20-25% [21].
NCSE describes a variety of continuous nonmotor seizures that can present clinically in many ways, including confusion, psychiatric symptoms, aphasia, and coma [10]. Generalized SE without convulsions (absence) and focal SE with alteration of consciousness (complex partial) are two seizure types classified by their EEG pattern since the clinical manifestations may be similar. A prospective study of 236 comatose patients at the Medical College of Virginia Hospitals found that EEG demonstrated 8% of patients to be in NCSE. In the ICU, NCSE occurs in up to 10% of patients with altered mental status [15].
Focal SE (epilepsia partialis continua, or simple partial SE) without impairment of consciousness, is much rarer in the ICU, and can be exceedingly difficult to control [21]. This type of seizure may present as continuous, repeated focal motor (twitching of one limb), focal sensory, or focal cognitive impairment (aphasia). By definition, this seizure type is not generalized, therefore it is not considered GCSE. Due to its common motor involvement, simple partial seizures do not fit neatly under the category of NCSE. A separate scheme, based on area of cortical involvement, is proposed in some literature [21].

77.4 Etiologies

It is important to identify the causes or predisposing factors leading to SE to optimize management. Nearly all acute or chronic brain lesions, in addition to numerous metabolic or toxic derangements, can cause SE [22,23]. These include anticonvulsant noncompliance or discontinuation, withdrawal or overdose of medications, alcohol withdrawal, acute structural injury (stroke, trauma, encephalitis), hypo- or hyper-glycemia, uremia, hepatic encephalopathy, and electrolyte abnormalities. In a population-based prospective epidemiologic study in Richmond, Virginia, the most common cause of SE in an urban setting was anticonvulsant withdrawal (26% of cases); the second most common cause was related to alcohol (24% of cases). Drug toxicity and CNS infection were among the most common causes as well, at about the same rate, 10% and 8% of cases [1,2]. In the pediatric population from Richmond, antiepileptic medication withdrawal was an important cause, but infection, either of the CNS or causing febrile seizures, was by far the most common cause of SE, occurring in 35.7% of cases [24,25]. Some studies report up to 51% of SE cases in children to be secondary to infection [26]. Other authors have reported a higher frequency of stroke, anoxia and hypoxia in the community compared to that seen in an urban hospital setting [1,2].

77.5 Management and Treatment of SE

Because the systemic effects of SE compromise cardiovascular and respiratory function, airway, breathing and circulation must be assessed and secured promptly. In the field, a blood glucose level can easily be obtained. Once IV access has been obtained, a dextrose bolus (along with thiamine) can be administered if hypoglycemia is diagnosed. Basic laboratory studies should be obtained, including basic metabolic panel, anticonvulsant levels, complete blood count, urinalysis, and urine toxicology screen [2]. If the preliminary studies discussed or the history are not forthcoming as to the etiology of the seizure, further workup should include neuroimaging, and lumbar puncture. A CT scan without intravenous contrast is usually available in emergency departments, and should identify conditions that need to be immediately addressed, such as an intracranial hemorrhage, hydrocephalus, or mass effect from a space occupying lesion (including abscess, tumor, or subacute infarction). A lumbar puncture should be considered in a febrile patient, especially where another source of fever cannot be found. An MRI of the brain will be more sensitive for acute ischemia, and may provide more clues as to the nature of space occupying lesions, but is rarely the first investigation to perform in the SE patient. Animal models demonstrate that despite adequate oxygenation, control of blood pressure, and temperature, significant brain damage occurs after 30 minutes of seizure activity [7,17]. Treatment should therefore be aimed at controlling SE as soon as possible. Benzodiazepines remain the first line of therapy in SE because of their potential to rapidly control seizures [27]. The three most commonly used benzodiazepines are diazepam, lorapezam and midazolam.

Diazepam is more lipid solubile than lorazepam; this allows it to rapidly cross the blood-brain barrier and therefore can control seizures in as little as 10-20 seconds. Also because of its high lipid solubility, its effects in the CSF wear quickly when it redistributes in adipose tissue, and there is a high chance of recurrent seizure if no other medication is added [28].

Lorazepam has a slightly slower slower onset of action due to its lower lipid solubility. However, a head to head comparison of lorazepam (up to 2 doses of 4 mg) to diazepam

(10 mg) intravenously, showed no significant difference in the times for onset of action. It also found that there was no significant difference between the two medications in the rate of seizure control [29]. The clinical advantage of lorazepam is its longer duration of action [30]. The Veterans Affairs SE Cooperative Group conducted a study of 570 patients with either overt GCSE or subtle SE to four different treatment groups: lorazepam, phenytoin, diazepam plus phenytoin, or phenobarbital. In the group with overt GCSE (384 patients), lorazepam was found to be most effective in controlling seizures within 20 minutes, and preventing recurrence within 60 minutes. This advantage was attributed to lorazepam ease of use and, at least when compared to phenytoin, faster infusion rate [31].

Midazolam is thought to be as effective in controlling seizures as lorazepam and diazepam. Additionally, it may be advantageous to use in a seizing patient where intravenous access may be too difficult to obtain, as it is available in an intramuscular formulation due to its high water solubility [30]. Diazepam in a rectal gel formulation is another option when IV access is an issue [32], and is a favored method of seizure termination in children, although buccal midazolam may be more effective [33]. Midazolam is also considered very effective treatment in refractory SE.

Based on the VA Cooperative Study cited above, lorazepam is the drug of first choice, and should be given as a 0.1 mg/kg infusion over about four minutes. Another agent should be used if his dose is reached without seizure termination [2].

Fosphenytoin is highly water soluble, in contrast to phenytoin, which requires sodium hydroxide at a pH of about 12 and propylene glycol for solubility. Fosphenytoin, therefore, can be delivered several times faster than phenytoin, at 150 phenytoin-equivalents mg/min vs. 50 mg/min of phenytoin, without the risks of irritation at the infusion site of phenytoin, or the severe tissue damage which often follows extravasation [2]. However, fosphenytoin is no less likely to produce hypotension or cardiac arrhythmias than phenytoin. Fosphenytoin was found to be effective in controlling 93.8% of seizures in a small group of 81 patients. Additionally, it is better tolerated, and plasma concentrations can actually be achieved more rapidly with fosphenytoin than phenytoin infusion [34]. The traditional dose of phenytoin is 15-20 mg/kg load in acute SE; fosphenytoin is administered at the same dose, as it is manufactured in phenytoin equivalents. Fosphenytoin, the prodrug of phenytoin, is bioequivalent to phenytoin when given intravenously [35]. Fosphenytoin may be given intramuscularly, but this is of little relevance in the treatment of SE as the patient will not achieve a useful serum concentration of phenytoin for several hours. Phenytoin should not be given intramuscularly because it forms sterile abscesses from which the drug is released over days. In the VA Cooperative Trial, phenytoin alone was the least useful of the four anticonvulsant regimens tested for the termination of SE [31].

Barbiturates and benzodiazepines act on the same $GABA_A$ receptor subtype, but have different mechanisms of action by acting on a different part of this chloride channel; barbiturates appear to stabilize the open configuration, leading to hyperpolarization and amplification of GABA inhibition [36]. The benzodiazepines, in contrast, increase the affinity of the receptor for GABA without affecting the open time of the channel. Phenobarbital and pentobarbital are the two most commonly used barbiturates in the treatment of SE.

Phenobarbital was found to be slightly less effective than lorazepam, and slightly more effective than diazepam plus phenytoin in the VA cooperative study [31]. Each of these three arms was statistically superior to phenytoin alone. While it is still the agent of choice in neonates [37], it is generally not used as a first-line agent in adults because of its slow administration and side effect profile, although a small randomized control study did not demonstrate significant difference of intubation, hypotension or cardiac arrhythmia [38].

The VA cooperative study demonstrated that if SE does not respond to one agent, adding a second rarely results in termination of SE [31]. Non-sedating agents such as levetiracetam and valproate are important in these situations, as the only alternative is induction of coma with anesthetic antiepileptics and burst suppression. Although these agents require further study to define their role in status epilepticus, they show promise.

Levetiracetam. The efficacy of levetiracetam in the setting of SE has not been studied in direct head to head trials. Although it is not approved by the United States Food and Drug Administration, it shows promise in a few recent case series of SE and refractory SE as adjunctive therapy to benzodiazepines, or other first line pharmacologic agents [48-50]. These studies do not classify patients according to etiology of SE, which is an important factor in the prognosis of SE.

The Spanish Group for the study of IV levetiracetam in SE conducted a multi-center retrospective observational study of patients in SE who were treated with a benzodiazepine plus a second standard agent, with IV levetiracetam administered as a third agent in refractory cases, or earlier in treatment in patients with contraindications to first line treatments (such as phenytoin). Forty patients were analyzed. Leveteracitem was found to be effective in terminating SE in more than half the patients, and higher efficacy was seen with earlier use of the drug. Unlike in prior studies, the Spanish group classified patients in terms of etiology, and found lower efficacy in patients with tumors, and those with acute CNS injury (such as stroke and trauma). In comparison, those with chronic injury, toxic metabolic injury, medication non-compliance, treatment was more effective. Levetiracetam is well tolerated, with few side effects (predominantly neuropsychiatric symptoms such as pyschosis, agitation, or sedation), and few drug interactions. Leveteracitam can be considered as adjunctive therapy in the current management of SE.

Valproate. There is limited available data for the efficacy of valproate in the treatment of SE. Some limitations to the use of valproate in SE is that the FDA approved of infusion rate may not be high enough to effectively terminate seizures, since rapid infusion may cause hemodynamic compromise. Maximum rates of 6 mg/kg/min after a loading dose of 20 mg/kg has been found to be safe [53].

Rapid infusion may also cause hyperammonemic encephalopathy, characterized by decreased level of consciousness, nausea and vomiting, cognitive impairment, or focal neurologic deficits. Carnitine supplementation during Valproate therapy is recommended for the prevention of valproate induced hyperammonemic encephalopathy in high risk patients [52]. Since risks factors for carnitine depletion include the presence of concomitant neurologic or metabolic disorders, and receipt of multiple antiepileptic drugs, most patients in status epilepticus can be considered high risk.

Experience with valproate is limited [51-54]. In one retrospective study, valproate was found to control seizures at a higher rate than Levetiracetam [51]. In a small case series, it was found to be as effective in terminating seizures as phenytoin [54]. Valproate can be considered as adjunctive therapy following administration of benzodiazepines if seizures continue.

Topiramate. A recent retrospective case study of a few patients in refractory SE found topiramate to be effective in terminating seizures, in a variety of seizure types and after failing first and second line agents [56]. The efficacy of topiramate may be attributed to the drug's broad mechanism of action and potentiating effects at various sites. Case reports suggest that topiramate may be used safely and considered as a second line agent in cases of refractory SE [57-58]. Given limited experience with this agent, it is not broadly recommended in the literature, and prospective studies must be conducted to determine its efficacy in SE.

77.6 Treatment of Refractory SE

Although the majority of patients in SE will respond to initial treatment, the addition of a second conventional agent is unlikely to be effective [31,39]. For this reason, authors argue that refractory SE should be defined as failure to one first-line agent [40] and a more definitive strategy is recommended [2]. By the time a patient is considered to be in refractory SE, endotracheal intubation prior to initiation of definitive therapy is necessary if this has not already been accomplished. Blood pressure support will likely be necessary with intravenous fluids and vasopressors. Additionally, EEG monitoring should be available emergently, as it will be necessary to recognize seizure termination in a sedated patient with compromised neurologic exam, and is the only guide of therapy.

Therapy for refractory SE should proceed on three fronts: termination of SE, prevention of its recurrence, and treatment of its complications.

Pentobarbital is initially loaded at a dose of 5-12 mg/kg, followed by continuous infusion, titrated to achieve seizure termination. Burst suppression is defined as episodes of flat or near-flat electroencephalographic activity, 5-10 seconds long, with shorter intrusions of epileptic activity (Figure 77.1).

Burst suppression pattern is used as a clinical tool to avoid over-medicating when the neurologic exam is obliterated by anesthetic medications. This EEG pattern has often been suggested as a goal for therapy in refractory SE, but achieving burst-suppression is neither necessary nor sufficient for the control of SE. Therefore, the goal should be seizure suppression; this is usually maintained for 12 to 24 hours, and then decreased by some arbitrary degree, such as 50%, for several hours while observing for seizure recurrence. Simultaneously, an anticonvulsant or an appropriate combination is added, with the goal of maintaining a seizure free state once barbiturate is cleared. Continuous EEG

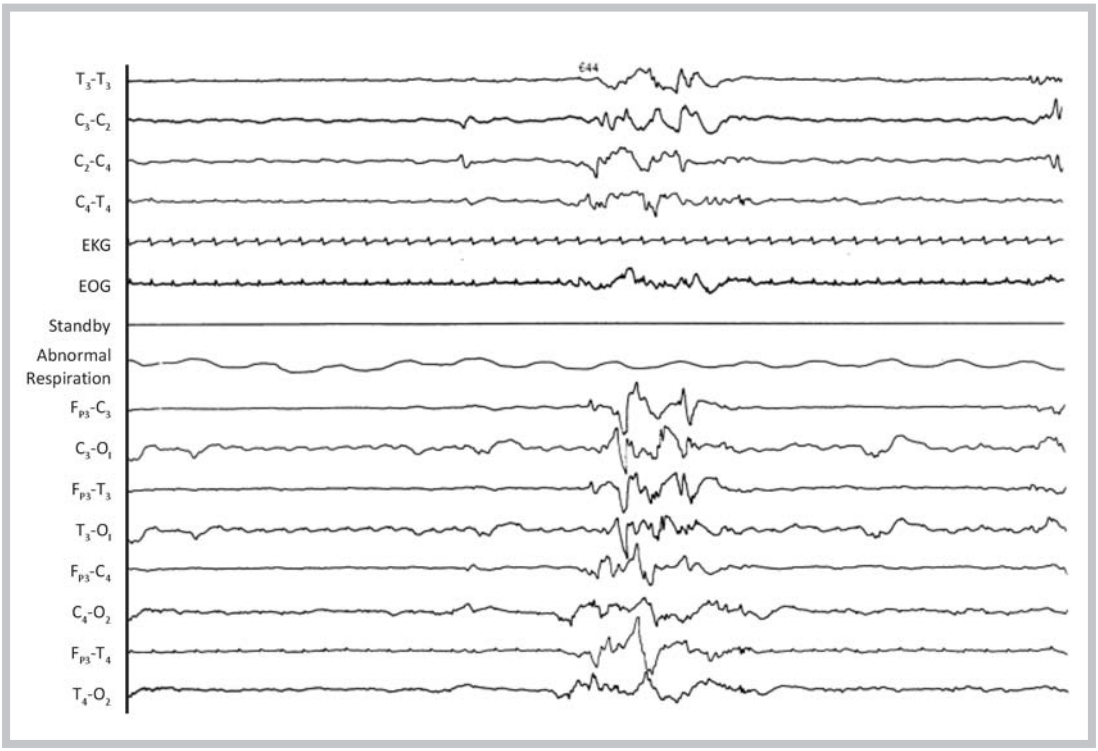

Figure 77.1. EEG burst suppression pattern (HF 70 Hz, LF 1 Hz SEN 5 μV/mm) [54].

monitoring is required during this weaning process, as recurrence of seizure activity prompts a return to the previous dose with adjustments in doses or types of the other anticonvulsants [21].

Midazolam infusion in the setting of refractory SE offers a favorable pharmacokinetic profile [40]. One small study showed rapid control of seizure that had failed multiple medications, including diazepam, lorazepam, phenytoin, with or without phenobarbital, with minimal hypotension [41]. In critically ill patients, midazolam can accumulate, es-

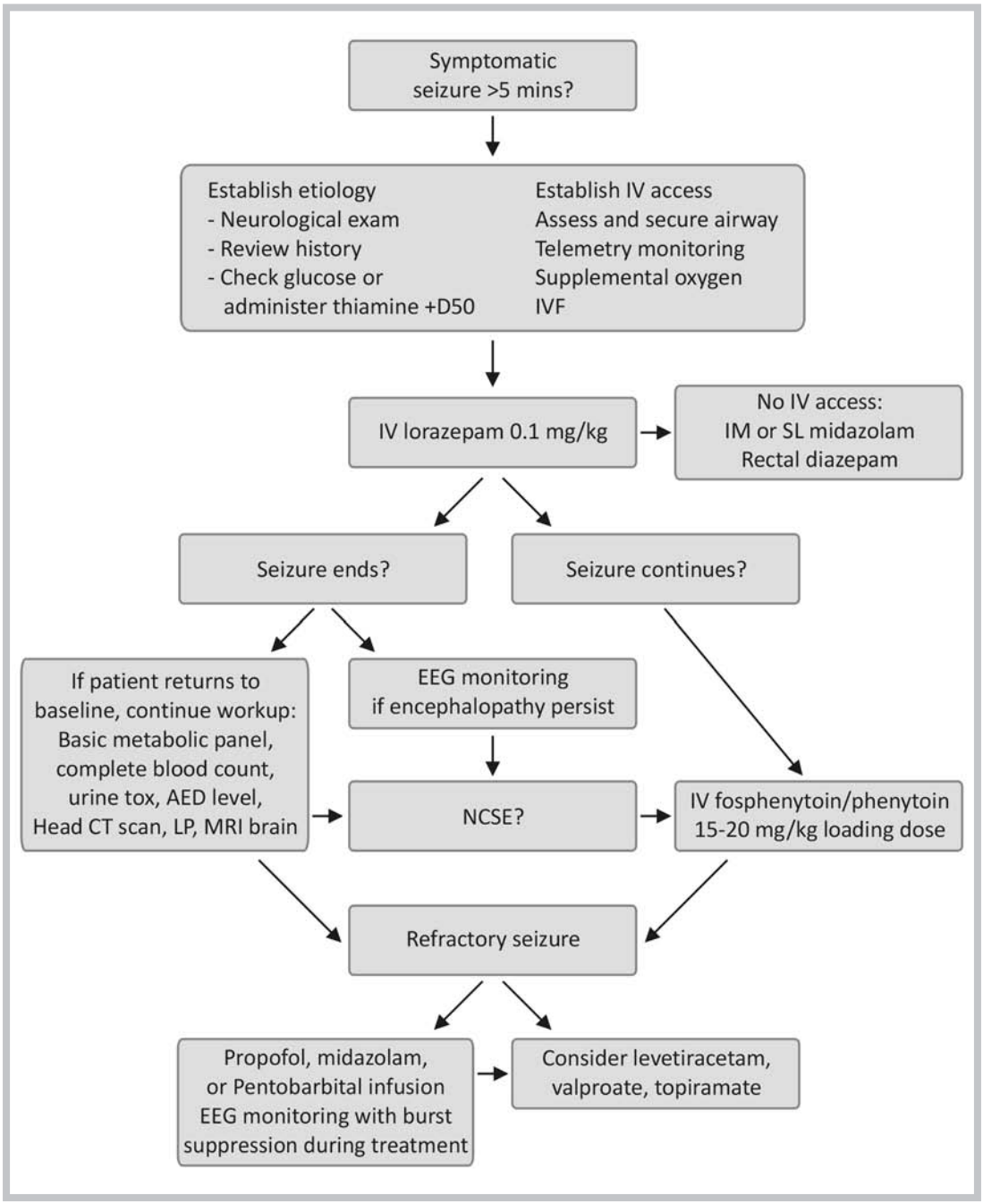

Figure 77.2. **Management of status epilepticus.**

pecially as increasingly higher doses of midazolam are usually required to maintain burst suppression. Some studies have shown that there may be lower mortality in a select group of patients treated with a midazolam infusion compared to those treated with a propofol infusion [42].

Propofol has a very short half life in comparison to the alternatives discussed for refractory SE treatment. Additionally it is highly lipid soluble and therefore fast acting in CNS. Several studies and reviews have demonstrated its effectiveness in treating refractory GCSE and NCSE [43-46]. Some recent studies have suggested an increased mortality associated with propofol infusion [41], but others have not supported this trend when compared to pentobarbital or midalozam at anesthetic doses for the treatment of SE [46]. Care must be taken to not discontinue propofol abruptly, as this may be associated with recurrent seizures. Hypotension is more common with propofol than with midazolam. Triglyceride levels must be monitored during prolonged infusion as development of hypertriglyceridemia may prompt discontinuation of propofol infusion. The clinician should observe carefully for development of the the propofol infusion syndrome, which may manifest as either a metabolic acidosis or rhabdomyolysis. If either of these occur, propofol should be discontinued and another agent substituted.

77.7 Conclusions

In the ICU, mortality associated with SE is high, and irreversible brain damage ensues quickly. The detection and diagnosis of SE, along with identification of its etiology, is crucial for clinicians at all stages of this condition, as the goal must be termination of seizure as soon as possible. A systematic yet aggressive approach to the treatment of SE is recommended. The clinician must be prepared to escalate rapidly to more potent anesthetic medications while providing basic life support measures, until either clinical or electrographic end of seizure is apparent.

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78 Metabolic Encephalopathies

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78.1 Definition and General Clinical Manifestations

Metabolic encephalopathies are characterized by a general impairment of cerebral activity in the absence of overt structural abnormalities or visible inflammatory reaction. There is a spectrum of degrees of impairment of consciousness ranging from delirium to coma. Milder degrees of encephalopathy often show marked fluctuation in degrees of alertness and awareness within a day, in contrast to the dysfunction found in neurodegenerative disease and structural brain lesions. Also, in contrast to dementing illnesses, patients with metabolic encephalopathies are as likely to be disoriented in place as well as in time, while demented patients typically develop disorientation in time before they lose spatial orientation. Brainstem reflexes are typically spared, with the exception of Wernicke's encephalopathy, in which ophthalmoplegia is a common and helpful diagnostic feature. Motor signs that suggest a metabolic encephalopathy include tremor, asterixis and multifocal myoclonus. Metabolic tremor is typically of the postural-action type rather than alternating/rest or intention tremor. Asterixis is a loss of postural tone, often revealed by having the patient hold the arms outstretched with the wrists dorsiflexed and the fingers extended. The lapse of tone causes a "flapping tremor" that may be synchronous or asynchronous; this has its origin in the brainstem reticular formation (It should be noted that unilateral asterixis is sometimes/rarely found with parietal lobe lesions or with structural midbrain damage.) Multifocal myoclonus, a sign specific for metabolic/toxic encephalopathies, is the asynchronous jerking of various muscles in various limbs in a seemingly random fashion. Again, the origin of multifocal myoclonus is in the nucleus reticularis gigantocellularis in the medulla.

78.2 Differential Diagnosis of Metabolic Encephalopathy

The history can provide useful clues as the cause of the encephalopathy, e.g., a past history of illnesses and associated medications, e.g., diabetes mellitus, cancer, alcoholism, thyroid disease, pulmonary disease, or tuberculosis. Recent illnesses, especially associated with fever or infection or sudden collapse due to seizures, can help point to a metabolic encephalopathy, although a central nervous system infection sometimes must be considered. Conversely, a history of brain tumor or systemic cancer, previous stroke or trauma suggest a structural brain lesion. Interviewing relatives or cohabitants, reviewing medical records, looking for health information on the patient, e.g., information bracelets, and drug lists can be helpful.

Next one should examine the patient to help determine the site of the brain dysfunction. Intact brainstem reflexes points to a cause above the brainstem. In that event, lateralizing signs, e.g., hemiplegia or focal seizures suggest a supratentorial structural lesion, although some metabolic disorders, e.g., acute hepatic encephalopathy or hypoglycemia, can occasionally produce "focal signs". Delirium, acute confusional state, is in itself usually due to a metabolic or drug-related encephalopathy, although CNS in-

flammation may also produce this picture. Subhyaloid hemorrhages in the fundi almost always relate to a ruptured intracranial aneurysm; Roth spots (white-centered retinal hemorrhages) suggest endocarditis or leukemia. Meningismus, suggestive of meningeal irritation from blood or infection, disappears in deep coma.

The general examination should be performed systematically. Vital signs can be helpful, e.g., fever (usually an inflammatory process that is systemic or in the central nervous system) or severe hypertension (raising the possibility of a hypertensive encephalopathy or pointing to underlying renal disease or drugs). Marked hypothermia in itself can produce coma, but can also be found in some septic patients and in myxedema coma, some with Wernicke's encephalopathy and intoxications. Severe hypotension may relate to septic shock or adrenal failure/crisis. Examining the respiratory pattern, coupled with blood gas determination, can help narrow the diagnostic possibilities. For example, hy-

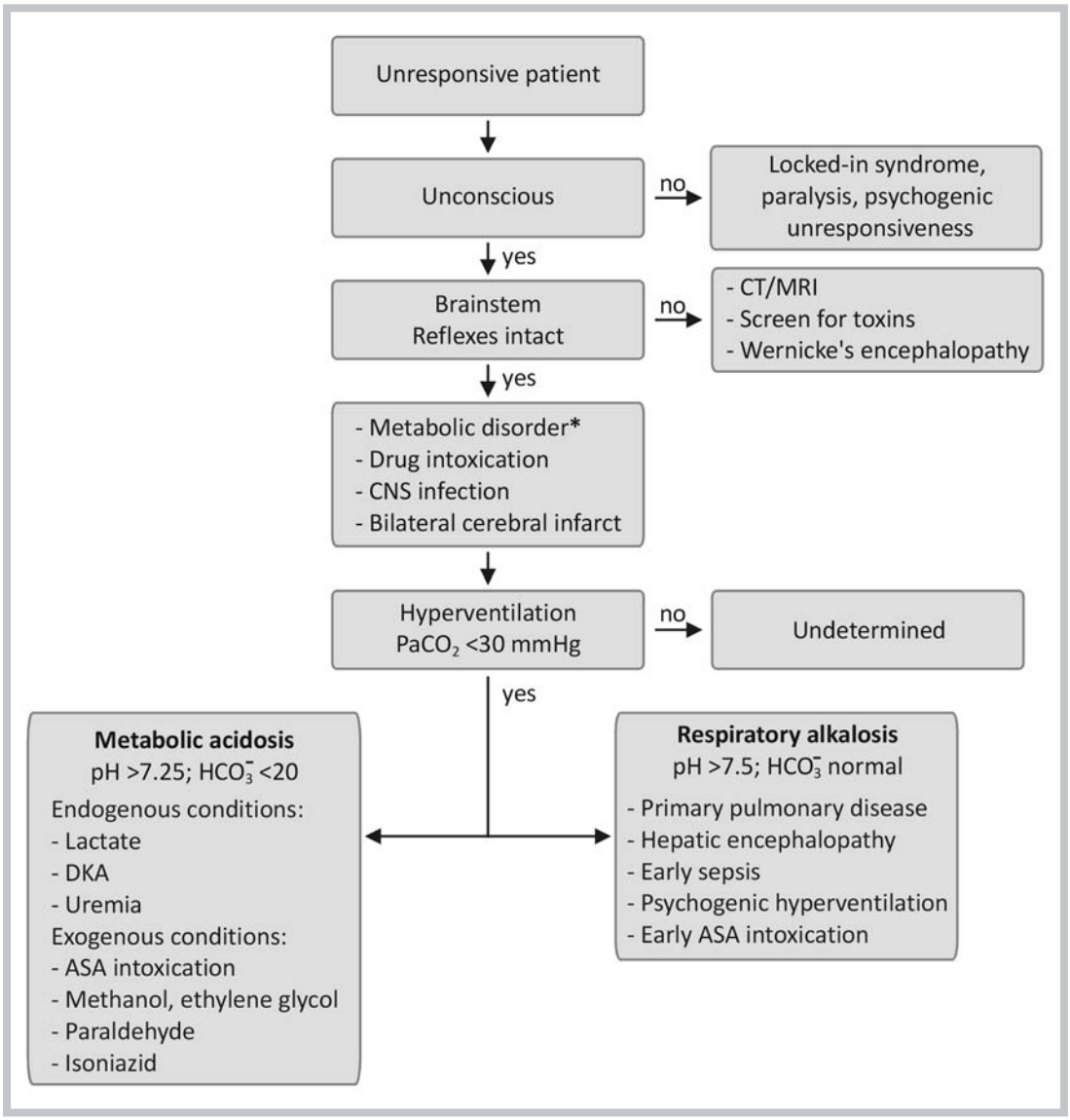

Figure 78.1. **Algorithm for the unresponsive patient.**
* Tests for metabolic disorder: EEG, laboratory, cultures

Encephalopathy	Distinguishing clinical features	Laboratory features
Hepatic encephalopathy	Hyperventilation, jaundice, ascites	Abnormal liver function tests, increased INR (with acute liver failure), respiratory alkalosis, triphasic waves on EEG
Hypoglycemia	Seizures, myoclonus, sweating, agitation progressing to stupor or coma	Serum glucose <2.5 mmol/l, MRI may show DWI changes in cerebral cortex, hypocampus, but sparing of thalamus and cerebellum
Hyperglycemia	Often seizures and fluctuating signs in nonketotic hyperglycemia, hyperventilation in DKA	Serum glucose usually >20 mmol/l for coma
Hyponatremia	Vomiting, seizures, focal signs (occasionally)	Cerebral edema, serum sodium often <120 mmol/l for severe encephalopathy; CPM if overly rapid correction
Hypernatremia	Preceding dehydration (e.g., gastroenteritis), seizures	Serum Na usually >160 mmol/l for severe encephalopathy; brain shrinkage; subdural hematomas
Hypermagnesemia	Profound weakness, parasympathetic paralysis	Serum Mg usually >2.5 mmol/l for severe encephalopathy
Hypomagnesemia	Preceding muscle cramps, hyper-reflexia, seizures	Serum Mg usually <0.5 mmol/l for coma
Hypophosphatemia	Seizures, myoclonus, profound weakness, coma often after refeeding nutritionally deprived individuals	Encephalopathy usually with serum PO_4 <0.5 mmol/l
Hypercarbia	May have papilledema with raised ICP, tremor, asterixis and myoclonus	$PaCO_2$ usually >60 mmHg; pH <7.2 with acute respiratory failure with coma.
Hypercalcemia	Preceding renal stones, bone pains	Serum Ca usually >3 mmol/l; findings associated with underlying cause, e.g., malignancies, hyperparathyroidism
Hypocalcemia	Hyperexcitability, tremor, chorea, seizures	Symptomatic when serum Ca <0.5mmol/l
Hyperthyroidism	Tachycardia, sweating; warm skin; tremor; goiter; ophthalmoparesis (e.g., inferior rectus deposits lead to impaired upgaze)	Elevated free T4 and T3, reduced TSH in serum
Hypothyroidism	Hypothermia and bradycardia, thick tongue; pale, puffy skin, slow relaxation of DTRs	With primary thyroid failure: elevated TSH, low T4 and T3, elevated $PaCO_2$, EEG is suppressed in voltage and slow in frequency
Adrenal insufficiency	Hypotension, hyperpigmentation of gingivae and palmar creases	Hyperkalemia, hypoglycemia, low serum cortisol
Septic encephalopathy	Paratonic rigidity, features of systemic inflammatory response syndrome, e.g. fever or hypothermia, tachycardia.	Increased WBC, evidence of infection or systemic inflammation; slowing or triphasic waves on EEG
Uremic encephalopathy	With acute uremia, hyperexcitability, multifocal myoclonus, seizures	Elevated serum urea and creatinine

Table 78.1. **Principal metabolic encephalopathies.**

perventilation due to a metabolic acidosis limits the possibilities to renal failure, diabetic ketoacidosis, lactic acidosis, exogenous agents (e.g., methanol, ethylene glycol, and salicylates). Hyperventilation with respiratory alkalosis can occur with early sepsis or the initial phase of salicylate intoxication, acute pulmonary disease or hepatic failure. The general examination may also reveal the stigmata of chronic liver disease; needle tracks suggest drug intoxication or infection. Cherry-red lips imply carbon monoxide intoxication; fever and a cardiac murmur suggest bacterial endocarditis. A tongue bitten on its lateral aspect suggests a convulsive seizure. Purpuric lesions may be found in meningococcemia or thrombotic thrombocytopenic purpura.

Psychogenic unresponsiveness or pseudoseizures may also mimic acute encephalopathies. One looks for inconsistencies and normal findings on exam to help. A history of psychiatric illness also raises, but does not in itself establish, the possibility of non-organic brain disease.

Laboratory tests are helpful, but should be guided by the history and examination findings. As mentioned, blood gas determination is invaluable in cases of hyperventilation. For apparent diffuse encephalopathies the following are indicated: hemoglobin, white blood count and platelet count in the peripheral blood, serum electrolytes, calcium, magnesium, glucose, urea, creatinine and a screen for drugs (often guided by toxidromes). When indicated, liver function tests, blood cultures, thyroid and adrenal function, carboxyhemoglobin, and special hematological tests (screening for disseminated intravascular coagulation or TTP) should be conducted. Electroencephalography can be of great help in diagnosing nonconvulsive status epilepticus, which could mimic metabolic coma, as well as in helping to confirm the latter (e.g., trochaic waves are most commonly seen in hepatic of renal failure or with sepsis-associated encephalopathy). Periodic epileptiform discharges from the temporal lobes in the context of an acute febrile encephalopathy favors herpes simplex encephalitis. Lumbar puncture is indicated for meningitis and encephalitis and to confirm subarachnoid hemorrhage if the diagnosis is in doubt after neuroimaging. Neuroimaging with CT or MRI is helpful in ruling in or out structural brain lesions. TA classification of metabolic encephalopathies is provided in Table 78.1, which lists principal metabolic encephalopathies, along with some distinguishing clinical and laboratory features.

78.3 Hepatic Encephalopathy

Hepatic encephalopathy can be divided into acute and chronic, two quite different disorders in terms of their underlying liver disease, clinical presentations and treatment. They will be discussed separately.

78.3.1 Acute Hepatic Encephalopathy

Acute liver failure is due to impaired hepatocellular function and develops within 6 months from onset; a subset, acute fulminant liver failure, develops over 8 weeks.

Acute liver failure is commonly due to acetaminophen poisoning, viral and auto-immune hepatitis, ecstasy and other toxins, liver infarction, Wilson's disease, Bud-Chiari syndrome, acute fatty liver of pregnancy, lymphomatous infiltration, heat stroke and malignant hyperthermia are other causes.

Ammonia is still thought to play a key role in the pathogenesis of both acute and chronic hepatic encephalopathy, even though serum ammonia concentrations show at best only a crude correlation with the severity of brain dysfunction [1]. Glial swelling, related to in-

creased glutamine production and mitochondrial toxicity, account for most of the cerebral edema. As a corollary, one should not be overly pessimistic when diffusion-weighted MRI scans show marked signal change in the cerebral cortex (Figure 78.2).
Acute hepatic failure most often presents in a dramatic fashion with rapid development of delirium or organic psychosis (Grade 1 hepatic encephalopathy is associated with an agitated delirium; Grade 2 is associated with blunting of consciousness) that can quickly progress to stupor (Grade 3 encephalopathy) and coma (Grade 4). Seizures can accompany severe or rapidly progressive disease. These features may occur so abruptly that they may precede the usual signs associated with liver failure, e.g., jaundice.
Cerebral edema is common with acute hepatic failure (most commonly the acute fulminant type). This can be life-threatening and needs to be detected and managed aggressively. We have found serial CT head scans to be an effective means of monitoring cerebral edema, especially if "baseline" CT head scans are done when the patient presents (before established encephalopathy) [2]. This is probably more practical and safer than intracranial pressure (ICP) monitoring, which shows rises only when compensatory mechanisms are exhausted. The main advantage of ICP monitoring is that allows for adjustment of blood pressure to allow a mean cerebral perfusion pressure of at least 60 mmHg. Intermittent hypertonic saline (rather than mannitol) with hypothermia are sometimes helpful, but hepatic transplantation should be considered in severe, rapidly progressive cases.

78.3.2 Chronic Hepatic Encephalopathy

Chronic hepatic failure, which takes over 8 months to become manifest, almost always relates to shunting of blood from the portal to the systemic circulation, bypassing the detoxifying effect of the liver on blood from the gut. Urea cycle abnormalities constitute a rare cause of chronic ammonia intoxication.
Chronic hepatic encephalopathy most often relates to varices (allowing portal-systemic shunting) associated with alcoholic and viral hepatitis, Wilson's disease and transjugular intraheptic shunts (TIPS). Rarely urea cycle abnormalities produce hyperammonemia, which can produce a syndrome indistinguishable from encephalopathy due to liver dysfunction.
Cerebral edema is not as common with chronic hepatic encephalopathy as with the acute form, as the brain can compensate in the former. Severe exacerbations may be accompanied by seizures, coma and brain swelling, however.
Management consists of reducing ammonia production in the gut by limiting protein in the diet and the use of lactulose, detecting and treating precipitants (including gastrointestinal bleeding, intercurrent infections and electrolyte disturbances), using nonabsorbable antibiotics to kill bacteria in the gut and, in severe cases, hepatic transplantation. Sedative drugs should be avoided. Seizures are managed symptomatically; we have used various agents, but those without clearance by the liver, e.g., levetiracetam or gabapentin, have some advantages.

78.4 Uremic Encephalopathy

Central nervous system complications of uremia can be divided into direct effects of acute and chronic renal failure as well as side effects/complications of therapy (Table 78.2).

Treatment	Neurological complications
Dialysis	• Dialysis dysequilibrium (related to osmotic shifts and cerebral edema) • Wernicke's encephalopathy (related to loss of thiamine during dialysis) • Dialysis dementia (related to aluminum poisoning from dialysate or phosphate binders – now rare) • Posterior reversible leucoencephalopathy syndrome (PRES), related to accelerated hypertension
Renal transplantation	• PRES related to calcineurin inhibitors (cyclosporine, tacrolimus) • Opportunistic infections (e.g., *Crypococcosus* or aspergillosis) due to immunosuppression • CNS lymphoma/post-transplant lymphoproliferative disorder (after immunosuppression) • Ischemic stroke: often related to comorbidities, e.g., hypertension, dyslipidemia

Table 78.2. Complications of therapy of renal failure.

Both acute and chronic uremic encephalopathy relate to accumulation of uremic toxins and the loss of homeostasis normally provided by the kidneys. There is probably no single "uremic toxin", but many compounds that play a synergistic role: guanidino compounds, parathormone, urea, middle molecules, phenols, amines, myoinositol, aluminum and other chemicals [3]. Poor clearance of drugs can contribute to encephalopathy and we have seen encephalopathy due to the use of standard antiepileptic drugs that rely on renal clearance, e.g. gabapentin and levetiracetam. One should not ignore encephalopathies due to the disorders that caused renal failure, e.g., systemic lupus erythematosis and other autoimmune disorders, diabetes mellitus and severe hypertension.

78.4.1 Acute Uremic Encephalopathy

As with acute liver failure, the neurological presentation is dramatic. Impairment of alertness and awareness can vary from a mild confusional state, through delirium to stupor and coma. Acute uremia is often accompanied by signs of increased excitability, including myoclonus (usually multifocal), seizures and tremor. Asterixis can be prominent. Hyperventilation may reflect agitation or a metabolic acidosis.
Investigations reveal the biochemistry of acute renal failure, with elevated serum urea (usually >27 mmol/l) and creatinine (usually >300 µmols/l), electrolyte disturbances and a metabolic acidosis.

78.4.2 Chronic Uremic Encephalopathy

Chronic uremic encephalopathy is much more insidious than the acute form. Patients often fluctuate in impairment of mental status; they show sleep disturbances. In severe cases the same motor findings as in acute uremia may be present. With dialysis therapy, these more dramatic manifestations are uncommon. It should be noted that the PRES (Table 78.1), which typically presents with cortical blindness, seizures and varied degrees of impaired consciousness, is more a feature of chronic than acute uremic encephalopathy; it can also be seen as a complication of calcineurin inhibitors.
Management of uremic encephalopathy is largely symptomatic. Seizures may require maintenance antiepileptic medications, e.g., phenytoin or valproate. Myoclonus in uremia often responds to clonazepam. Hypertension should be treated appropriately, both in the acute and chronic situations. The neurological complications are minimized by ad-

equate dialysis therapy and eliminated by renal transplantation (although the latter may have complications of its own. See Table 78.2).

78.5 Sepsis-associated Encephalopathy (SAE)

Sepsis, the systemic response to micro-organisms or their toxins, is produced by inflammatory mediators or cytokines in the presence of infection. Brain dysfunction or encephalopathy is a common accompaniment to sepsis. Septic encephalopathy, or better, sepsis-associated encephalopathy (SAE) is a common problem with potentially serious consequences. In our studies of hospital patients with bacteremia, 87% had abnormal electroencephalograms (EEG) and 70% were diagnosed with neurologic symptoms ranging from lethargy to coma. Forty-six percent of these patients with brain dysfunction were in the intensive care unit, with the rest on the wards. Survivors of severe sepsis were sometimes left with debilitating cognitive and behavioral problems that persisted for years or were irreversible [4].

The diagnosis of SAE is one of exclusion. One should exclude direct central nervous system infection, e.g., meningitis, drug-induced encephalopathy and other conditions, e.g., bilateral subdural hematomas, that are capable of causing fluctuating mental status and symmetrical motor signs without lateralizing features.

As with uremia, there is unlikely to be a solitary mechanism for SAE. Cytokines undoubtedly play a role. Indeed, interleukins 1 and 6 and tumor necrosis factor alpha may act on the brain to alter hypothalamic nuclear function [5] and tryptophan metabolism [6]. Some of our SE patients with post-mortem examinations had multiple microscopic infarctions [7]. Indeed, reduced cerebral blood flow and increased cerebrovascular resistance are found in human cases of SE. Microthromboses and microinfarctions may also occur, as well as damage from oxidative stress. At least some of these phenomena likely relate to the production of cytokines [e.g., tumor necrosis factor-α (TNF-α), interferon-γ (IFNγ) and interleukins] and their effects on the production of nitric oxide (NO) by endothelial nitric oxide synthase (eNOS) [8]. Inhibition of eNOS leads to impairment of the microcirculation of the brain and other organs by causing vasoconstriction. In addition, sepsis is a procoagulant state that rests with endothelial dysfunction: endothelial cells convert protein C to activated protein C that has anti-inflammatory and profibrinolytic properties. The brain may be similar to other organs in this respect. Apoptotic mechanisms may also be operative [4]. Some effects may be purely metabolic, e.g., altered amino acid mix (higher aromatic vs. branched chain amino acids), which could alter the neurotransmitter balance; the metabolic effects of other organs can affect the brain [4].

Clinically the neurological manifestations begin with altered mental status, often a fluctuating confusional state or delirium, which may be accompanied by hyperventilation. The level of consciousness deepens with worsening of the systemic illness; indeed brain function acts as an index of the severity of the systemic inflammatory response syndrome and failure of other organs. The principal motor finding is paratonic rigidity or *gegenhalten*, a velocity-dependent increase in the resistance to passive movement of the limbs or neck. If the movements are rapid the increase in tone is felt by the examiner; if the movements are made very slowly, there is no increase in tone. Tremor, multifocal myoclonus and seizures are not common in SAE [4].

The EEG reflects in an objective manner the severity of the encephalopathy and systemic illness [9]. Mild cases show mild slowing. As the encephalopathy worsens delta (waves of 4 Hz or less) appear, followed by triphasic waves and then a burst-suppression pattern

as the encephalopathy worsens. The EEG changes are usually reversible and some patients even with burst-suppression can survive without serious brain dysfunction.
Management of SAE is chiefly treatment of the underlying systemic infection [4]. Prompt antimicrobial therapy, drainage of abscesses, activated protein C, which antagonizes the procoagulant effects of sepsis, can help the systemic illness and may also benefit the brain [4]. Other complications, e.g., seizures, must be managed symptomatically, e.g., with phenytoin.

78.6 Key Concepts

- Metabolic encephalopathies are common and varied. A common feature is that, at least in mild-moderate cases, they are not associated with structural changes in the brain.
- Changes in mental status vary from delirium to deep coma. In the early phase of most metabolic encephalopathies, there is often marked fluctuation in mental status.
- Cranial nerve functions are spared (except for ophthamoplegia in Wernicke's encephalopathy).
- Motor findings typical of metabolic encephalopathies include postural-action tremor, asterixis and multifocal myoclonus. Seizures, usually generalized in type, may occur in some encephalopathies.
- Specific laboratory tests are ordered to confirm the specific diagnosis, depending on the history and physical examination. The EEG can be helpful in grading the encephalopathy and in establishing that the condition is a metabolic encephalopathy and in differentiating it from structural lesions, encephalitis and seizures.

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79 Hypoxic Ischemic Encephalopathy Post Cardiorespiratory Arrest

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79.1 Introduction

Sudden cardiac death is an unexpected event, without traumatic cause, which affects approximately 300,000 people in the United States of America and more than 600,000 people in Europe each year. It is characterized by the cessation of effective cardiac functioning, with or without symptoms, for a period of less than 1 hour. The cessation of cerebral blood flow derived from it causes neurological injury with varying evolution and prognosis.

Cardiopulmonary resuscitation (CPR) is a manoeuvre that attempts to restart spontaneous circulation and maintain perfusion of different organs. Between 1% and 2% of patients with sudden death receive CPR, where chest compression is the main measure for attempting to restore flow. Under the best circumstances chest compressions generate from 25% to 30% of normal cardiac output, bringing about systolic pressure that reaches between 60 and 80 mmHg, while diastolic pressure rarely exceeds 20 mmHg. This creates a severe compromise in cerebral perfusion, which is barely able to retain between 10% and 15% of the normal flow. As a result, recovery without residual neurological damage is rare, and many of the survivors evolve with neurological damage of varying degrees of severity or progress to a persistent vegetative state. Moreover, there are no effective indicators of the neurological functioning status after the event, a situation that creates uncertainty in the medical team, family grief and a high economic cost.

79.2 Development

The brain is highly dependent on oxidative metabolism, and in spite of accounting for only 2% of body weight, it is responsible for 20% of total oxygen consumption and 60% of glucose consumption. It does not have an energy reserve, and in low input conditions, its ability to compensate by increasing oxygen extraction is much lower than in other tissues. This makes it highly susceptible to states of hypoxia and ischemia, where rapid changes in mitochondrial function occur, affecting cell survival. The cells in the cerebral cortex are especially affected, since they consume 75% of the cerebral metabolic requirements [1]. Under conditions of adequate oxygen supply, ATP used as an energy source is produced by glycolysis and oxidative phosphorylation. In the cytosol, glucose is converted to two pyruvate molecules that are oxidized and produce acetyl coenzyme A, which enters the mitochondria to form part of tricarboxylic acid, and by means of oxidative phosphorylation, generates 36 ATP molecules for each glucose molecule.

Under anaerobic conditions, decoupling occurs between oxygen transport and consumption. Pyruvate, instead of oxidizing to produce acetyl coenzyme A, is acted upon by lactate dehydrogenase (LDH), becoming a lactate with potentially harmful effects at the neuronal level.
The energy produced in these processes generates an electrochemical gradient that preserves the transport of hydrogen ions by means of the inner mitochondrial membrane.
More than 95% of the carbohydrates that enter the brain are used by the mitochondria, while more than 95% of ATP is generated by mitochondrial oxidative phosphorylation. Hence, ensuring blood flow and constant oxygen supply is necessary to maintain neuronal functioning.

79.3 Damage Mechanisms

After circulation stops, three stages have been described in cerebral blood flow (CBF); the first, immediately after the event, is characterized by moderate non-uniform hyperaemia where there is a release of neuronal nitric oxide, endothelial damage by reperfusion and exposure of membrane phospholipids, which, together with free radical generation, increase endothelial and diffuse cellular damage.
A second delayed hypoperfusion stage, where there is vasospasm, cytotoxic edema and no reperfusion phenomenon, which causes a decrease of up to 50% in cerebral blood flow, occurs between 2 and 12 hours after circulatory arrest.
Finally, there is the third, less defined stage, where the CBF can return to normal or be reduced to a minimum.
As there is a decrease in CBF, interference is generated in the mitochondrial oxidation processes, as is the production of free radicals and the accumulation of amino acids, with harmful potential at the neuronal level. All of this is a continuous process where injuries have been found to occur twice and several agents have been identified.
At first, when the decrease in CBF generates a loss of consciousness in a matter of seconds, global hypoxia causes an increase in compensatory CBF, with a sharp reduction in ATP production. This starts to be processed by glycolysis, depleting reserves of glycogen and high-energy phosphates (energy failure) within minutes, producing membrane alterations (depolarization failure), and generating lactic acid and the release of glutamate with cytotoxic effects (anaerobiosis-acidosis).
Under these conditions, during the first minutes after oxidative phosphorylation is stopped, the brain has two rescue paths to maintain intracellular ATP production. The first is a reaction catalyzed by creatine kinase, which produces a reversible transference of phosphate from phosphocreatine (PCr), converting ADP to ATP, and the second a reaction catalyzed by adenylate kinase, in which two ADP molecules are transformed into one ATP molecule and one AMP molecule.
Next, the glycolytic production of ATP starts to be regulated mainly by the inhibition or activation of phosphofructokinase (PFK), which catalyzes the conversion of fructose 6-phosphate to fructose 1,6-diophosphate. PFK is inhibited at a low pH, but in hypoxia/ischemia situations, it stops responding to this stimulant, significantly increasing its activity.
Most of the ATP formed is used to maintain ionic transmembrane gradients. It is worth noting that intracellular potassium levels are approximately 30 times higher than extracellular levels, sodium and chloride levels around 7 times less, and calcium levels around 10,000 times less. Because of this, the decrease in energy production significantly compromises homeostasis.

As indicated above, the energy obtained by glycolysis generates lactate and hydrogen ions; this causes the intra- and extracellular pH to immediately begin to descend. The speed of this decline is directly proportional to pre-ischemic glucose levels. The interval between the onset of ischemia and complete cellular depolarization is called anoxic depolarization (AD) and can be prolonged or decreased depending on the amount of energy substrate produced, so that in pre-ischemic hyperglycaemic states the AD time will be longer and the pH will have a greater decline than in normoglycaemia.

In turn, acidosis inhibits ion flow through the plasma membrane, reducing the energy requirements for maintaining ionic gradients. Therefore, pre-ischemic hypercapnic states also prolong AD time.

Calcium, in a wide variety of cells, acts as a messenger ion, transmitting messages received at the cell surface to the intracellular machinery. This requires only a low ionic flow through the cell membrane, at very low and closely controlled concentrations. When the concentrations increase, they are detrimental to normal cell functioning, and prolonged increase can result in cell death.

At rest, calcium concentration in the medium surrounding the cells is usually from 1 to 2 mM, whereas the intracellular concentration is nearly 0.1 µM (100 nM). During the AD period, the cells obtain more than 90% of the calcium from the extracellular fluids, and when they are activated, the level of pre-ischemic calcium is reduced to approximately 0.1 mN, while in the cytosol it increases up to 500 to 1000 nM.

Calcium cell traffic is mainly by channels with NMDA receptors, using a sodium-calcium exchanger, where for every three sodium molecules mobilized inside, one calcium molecule is transported to the outside. The energy source is the sodium electrochemical gradient. So, in AD states, the sodium gradient collapses and the electrochemical gradient of calcium ions reverts the pump, causing a massive calcium transit into the cell, which leads to its accumulation in the mitochondrial matrix of values up to nearly 0.5 µM, while in the endoplasmic reticulum, the concentration can reach up to 100 µM [2].

Just as the pre-ischemic glycaemic levels influence the AD time, they also influence calcium flow during ischemia. In this sense, high glucose levels reduce cellular calcium flow. Because acidosis significantly reduces uptake, the majority of the calcium in these conditions enters the cell thanks to the reverse sodium/calcium exchange, significantly increasing the amount of the latter in the glial cells, which adversely affects their survival.

In this first stage, we could say that, after periods of transient ischemia, mitochondrial metabolism after 1 or 2 minutes is capable of complete and immediate recovery, but if ischemia is prolonged, there are significant alterations in the concentrations of the metabolites involved in the energy generation processes. After 15 minutes of ischemia, glucose and glycogen levels are depleted, lactate increases significantly and high-energy phosphate levels decline markedly. The metabolites involved in the citric acid cycle also undergo significant changes; succinate increases by approximately 270 times, malate, citrate and fumarate decrease, and levels of substances such as GABA, alanine and ammonia increase.

Without a rapid supply of blood and oxygen, these processes inevitably cause cell death in a matter of minutes. However, after successful resuscitation, there are more detrimental effects on the mitochondrial level, due to the reperfusion of ischemic cells, with two major agents: calcium and oxygen.

At approximately 5 minutes of reperfusion, the high-energy phosphate levels recover; much of the ammonia is detoxified by amidation of glutamate in the astrocytes in an ATP-dependent process and through the action of glutamine synthetase, with the consequent formation of glutamine.

It has been shown that immediately after reperfusion, lactate levels remain high, on some occasions three times higher than normal, which suggests that in this period there is an alteration in the use of pyruvate by the mitochondria, probably due to a temporary inhibition of pyruvate dehydrogenase. It is further believed that in this period the substrate for high-energy phosphate formation is the succinate of the mitochondrial respiratory complex type II, in a reaction that generates electron loss, which, in turn, leads to the release of free oxygen radicals. These act at the level of membrane lipids, causing peroxidation with primary necrosis, or trigger apoptosis.

Together with the release of free radicals, the presence of other mediators during the reperfusion stage (6 to 24 hours after) creates chemical cascades that result in excitotoxicity in vulnerable neurons.

As stated above, calcium concentrations are higher at the blood level than the intracellular level, allowing a transmembrane gradient to be maintained, which uses the ATP as an energy source. During reperfusion, re-oxygenation causes constant overloads of intramitochondrial calcium, causing iron release and increasing free radical production. In addition to all of this, there is an increase in platelet aggregation, vasoconstriction and pre-capillary edema [3].

Intracellular calcium influx caused by mitochondrial bioenergetic dysfunction repletes the endoplasmic reticulum and mitochondria, and causes damage in two ways. The first is by acting as a protease and phospholipase enzyme co-factor, causing delayed death of neurons, oligodendrocytes and astrocytes. Second, it acts together with oxygen in the generation of free radicals. It is worth considering that free radicals in physiological conditions are present in the mitochondrial transport chain, where they maintain stability thanks to chemical and physical coupling, and where their harmful effect is inhibited by defence mechanisms. Numbering among these mechanisms are the maintenance of low partial pressure of oxygen at the cellular level, an adequate enzymatic breakdown by enzymes and removers such as superoxide dismutase and catalase, and the presence of antioxidants such as alpha tocopherol (vitamin E) and ascorbic acid (vitamin C).

Superoxide dismutase inactivates the superoxide ions, while catalase counteracts the effects of hydrogen peroxide. This is important in therapy, as we will see later.

Under anaerobic conditions, ATP is degraded in supranormal quantities via ADP-AMP, producing inosine and hypoxanthine, and finally urate acid through xanthine dehydrogenase. In the next process the increasing calcium in the cytosol activates proteases, converting xanthine dehydrogenase to xanthine oxidase, and stimulating the production of superoxide anion.

Once formed, these radicals combine with iron salts in the Haber-Weiss reaction to form perhydroxyl radicals, a chemical process that occurs only in the presence of free iron, such as in hemorrhage or in cells with a high iron reserve such as myoglobin. Free iron is not normally found in peripheral circulation, but under certain conditions, such as severe hypoxia, it is released from ferritin, just as superoxide anions are also capable of dissociating the ferritin iron complex. Under hemorrhage conditions, levels are optimal for these deleterious reactions. Polyunsaturated fatty acids in the middle layer of the membranes are the target of perhydroxyl radicals.

Under hypoxic ischemic conditions, proteases and phospholipases activated by calcium attack the membrane and convert it to a new source of oxygen radical production, perpetuating the damage.

The superoxide anion, in turn, steals a proton from the polyunsaturated fatty acid, creating a lipid with an unpaired electron. This new lipid radical reacts with oxygen during reperfusion and forms a new peroxyl lipid radical, which, in turn, removes a proton from another polyunsaturated acid, creating a new radical and giving rise to a chain reaction.

In the formation of free radicals, arachidonic acid also plays a key role. It is degraded by three enzymatic pathways: that of cyclooxygenase, which forms prostaglandins and thromboxanes that have effects on microcirculation, the lipoxygenases that release leukotrienes and cause edema and necrosis in microcirculation, and cytochrome P450 that acts directly upon the formation of free radicals. These three pathways interact at different levels of the cascade, inhibiting or stimulating the other components.
There are other mechanisms in the formation of free radicals, mediated by membrane-binding enzymes on the surface of neutrophils and phagocytes, and are activated by bacterial or cytokine endotoxins in the so-called respiratory burst.
A second mechanism associated with calcium involves mitochondrial activation of permeability, by means of opening non-selective pores in the inner membrane, causing a decoupling of oxidative phosphorylation and the physical rupture of the mitochondrial outer membrane [4].

79.4 Nitric Oxide

Nitric oxide, a simple molecule synthesized from L-arginine by the nitric oxide synthase in endothelial cells, is a reactive free radical that inhibits mitochondrial respiration, and which has been linked as a messenger mediator in the central nervous system (CNS). There is evidence that it contributes to excitotoxicity.
There are several isoforms, and among these, some are neuronal, activated by high concentrations of cytosolic calcium. Once formed, it spreads to neighbouring cells and reacts with guanylate cyclase, inducing the formation of cyclic guanosine monophosphate from guanosine triphosphate. This compound relaxes muscle cells, including blood vessels. Nitric oxide in the presence of superoxide anions gives rise to the formation of highly reactive nitrite peroxide, which is damaging to cells.
The resulting fall in cyclic GMP leads to vasoconstriction. Moreover, nitric oxide can be altered to a chemical state with opposite effects, for example, a protective effect in the presence of electron donors such as cysteine or ascorbate, forming a nitrosonium ion. This is because of the union to a regulatory site in the most prominent part of the excitatory amino acid receptor, resulting in decreased activity in this receptor.
The deleterious effects of the free radicals occur during reperfusion, after ischemia, and the ability to neutralize this effect is called antioxidant capacity.
Based on these findings, research on these compounds has attempted to attenuate hypoxic ischemic damage, such as N acetyl cysteine, dimethyl sulfoxide, allopurinol, 21-aminosteroid, and calcium channel blockers; we will go into detail on these later. However, none of these compounds have been successful in a clinical setting, perhaps due to the treatment starting after the damage has been done.

79.5 Role of Excitatory Amino Acids

Excitotoxicity is a process by which the excessive release of synaptic glutamate activates postsynaptic receptors and leads to large neuronal loads of calcium and sodium, which ultimately cause cell death. In this process, there are other alterations in mitochondrial function, such as the loss of membrane potential, release of the cytochrome c in the cytosol, and increase in the production of oxygen free radicals, events that seem to occur in varying degrees and constantly producing neuronal injury. It has been suggested that

the release of cytochrome c induced by calcium may be the cause of increased production of free radicals in excitotoxicity.
Deterioration in the electron transport chain caused by loss of cytochrome c causes metabolic failure and loss in ionic homeostasis, leading to neuronal death, probably due to oxidative stress. While the accumulation of mitochondrial calcium with the generation of free radicals can contribute to a prolonged alteration in calcium regulation, it is not sufficient to trigger acute neuronal degeneration. For this reason, it is suggested that glutamate action on receptors in the synaptic gap is necessary to produce damage.
Normally, glutamate is released in the synaptic gap, where it makes contact with its receptors. At the distal end of the synapse, glutamate breaks down to glutamine, and then goes one of two ways: uptake and entry into the pre-synaptic gap, or reuptake by a glutamate transporter and release in a nearby astrocyte for later transformation in an energy-dependent process.
In energy deficit situations like ischemia, glutamate is accumulated in the extracellular space due in part to the decline in the transmembrane sodium and potassium gradients, which is coupled with an alteration of the glutamate transporter in the astrocyte, or otherwise because its function can even be reversed, producing more extracellular glutamate.
Moreover, cell damage causes glutamate to leave the injured cells and enter the extracellular space, and due to the high content in each cell, this can cause considerable damage in neighbouring cells.
With the abnormal accumulation of excitatory amino acids, such as glutamate and aspartate, neuronal over-stimulation is produced, which ultimately leads to cellular dysfunction and neuron death. The inhibitory effect is from the gamma-amino butyric acid that modulates the action of the excitatory amino acids.
In the synaptic gap, there have been identified at least three types of glutamate receptors, with different anatomical locations and functions. They are classified according to their typical agonists, such as N methyl aspartate (NMDA), quisqualate (QA), kainate (KA), and 2 amino 4 phosphonobutyrate (AP4). These receptors modulate the activity of sodium, calcium, chloride, magnesium and other ions, along with water flow into the cell. In summary, the action of these receptors is central to the concept of excitotoxicity. Glutamate accumulation in extracellular space causes neuronal over-stimulation with excess anionic and cationic fluxes, in addition to intracellular edema and osmotic lysis, causing instant cell death.
This effect, plus the damage from increased cytoplasmic calcium, causes neuronal damage. There have been attempts to reverse this damage by intervening independently or jointly in both pathways.

79.6 Pathology

For these reasons, cell damage in hypoxic ischemic encephalopathy (HIE) is heterogeneous and multifactorial. Its intensity depends on several factors, such as variability in neuronal susceptibility, the white matter being more vulnerable than the gray matter, age and prior vascular conditions of the patient, degree of hypoxia and hypoperfusion, glycaemic level prior to the event, blood pH and duration of the injury. During periods of ischemia <5 minutes, only the susceptible neurons in the hippocampus (zones CA1 and CA 4-6) and Purkinje cells in the cerebellum die [5,6].
At least two factors are involved in this process 1) amino acid receptor distribution and the zonal differences in their concentrations, which causes damage in zones with

higher receptor density, and 2) the damage from reperfusion through the action of free radicals, above all in zones with a high iron concentration, such as the thalamus, globus pallidus, substantia nigra, and several cortical layers. If the injury is prolonged, necrosis can occur in the middle layer of the cerebral cortex (layers 3, 5 and 6), amygdaloid nucleus and basal ganglia [1,4]. The presence of diffuse cerebral edema is frequent.

Histopathologically, microvacuolization and neuronal cytoplasmic eosinophilia have been described after 1 hour. If the patients survive long enough, gliosis is produced in the dead neurons. Autopsies of patients who, after surviving cardiac arrest, remained in a persistent vegetative state, revealed extensive cortical laminar necrosis and multiple microinfarctions.

79.7 Evaluation and Prognosis

Evaluation of patients with HIE is based on a detailed clinical examination, considering the variables that may affect the neurological examination such as drugs, metabolic encephalopathy and seizures.

However, data published suggest that a clinical examination alone predicts the prognosis in only 58% of cases, improving up to 82% when combined with evoked potentials and electroencephalography (EEG), which alone could predict the prognosis at 59% and 41%, respectively.

79.8 Clinical Evaluation

Several clinical signs have been described which point to ominous prognoses; however, their sensitivity and specificity are motives for controversy. It is known that among patients who wake up, 90% do so within the first 3 days, and waking up after this time is associated with a persistent vegetative state. The possibility of waking up decreases 50% the first day, 20% the third day, and 10% the seventh day.

It has been agreed that clinical, laboratory and imaging data must be used to improve prognostic accuracy.

In the clinical examination, brain stem reflexes must be examined: corneal, oculocephalic, oculovestibular and pupillary. This last reflex has been used to predict prognosis, since immediately after recovery from sudden cardiac arrest, the absence of the pupillary reflex is not a sign of a poor prognosis; rather, its presence constitutes a factor of a good prognosis. If the absence of pupillary reflex persists for 12 hours after sudden cardiac arrest, it becomes a sign of a poor prognosis. The persistence of fixed pupils on the third day is a sign of a poor prognosis.

Motor responses. These are differentiated as localization, withdrawal, decerebration or decortication rigidity, or the absence of response, and the less sustained the response in a given time, the worse the prognosis. The withdrawal reflex is an indicator of a good prognosis; however, its absence is not necessarily synonymous with a poor prognosis.

Involuntary movements. The presence of brain stem automatisms (blinking, swallowing, cough, etc.), myoclonus and nystagmus suggests indemnity of the brain stem. It must be considered that blinking, myoclonus and nystagmus can also be observed in patients in non-convulsive epileptic states. An involuntary conjugate eye movement has been described, characteristic of HIE, called ocular dipping, and it consists of extreme vertical

deviation of the downward gaze that is maintained for several seconds to then quickly return to neutral.

Myoclonus. Initially, this was reported as a sign of dying because all those who experienced it later died; however, this finding was later contradicted by several reports of cases that showed great variation in the values of sensitivity and specificity for this sign in relation to neurological prognosis (sensibility, 25-92%, and specificity, 16-85%). Moreover, there were also reported cases of survival after the appearance of myoclonus, and convulsive activity of some sort is reported in 30% of patients (17% myoclonus, 33% partial seizures and 50% generalized). Overall survival for the group that experienced convulsions was 32%, and 43% for the group that did not experience convulsive activity according to this study. Later studies reported no relationship between the presence of convulsive activity and the neurological prognosis either, except in cases with convulsive states, in which it was determined that there is a higher risk of persistent coma and brain death. The presence of myoclonic status and conjugate vertical upward gaze deviation on the first day are signs of a poor prognosis.

The absence of pupillary reflexes, together with the absence of motor response to pain and potential altered evoked potentials, on the third day after the event, is associated with a poor neurological prognosis with a specificity of 100% [7].

79.9 Glasgow Coma Score Assessment

The Glasgow neurological scale (GCS) has been used as a neurological predictor in different pathologies. With respect to HIE, several systematic reviews show that a GCS score <5 in the first hours is not useful as a predictor of poor prognosis, but a score ≥10 is a predictor of a good prognosis. Basetti et al. used the GCS together with somatosensory evoked potentials, and found that a GCS ≤8 in addition to alteration of evoked potentials had a specificity for brain death of 97%. In a review done in 2004, it was found that the absence of motor response a poor prognosis likelihood ratio of 9.2. In these circumstances the isolated use of the Glasgow scale as a prognostic predictor is not considered viable.

79.10 Evoked Potentials

voked potentials have been studied as prognostic predictors for coma for more than 20 years. Their advantage is that they can be carried out at the bedside, are non-invasive and easily reproduced, and are not affected by sedation or metabolic encephalopathy.

Evoked potentials can provide information about the location and severity of dysfunction in sensory pathways of the CNS. Alteration of evoked potentials has been associated with a poor prognosis; however, their normality does not predict recovery. There is consensus that late latency responses (N70), which represent the activity of cortico-cortical interactions, have a greater prognostic value than measurement of short latency responses (N13, N19). Most projects use somatic-sensory evoked potentials (SSEP) of the median nerve, which come from the somatosensory cortex. If the cortical bilateral somatosensory response is absent within the first 8 hours after the event, the mortality rate is 98%. Auditory evoked potentials have a poor correlation with prognosis (Figure 79.1 and 79.2).

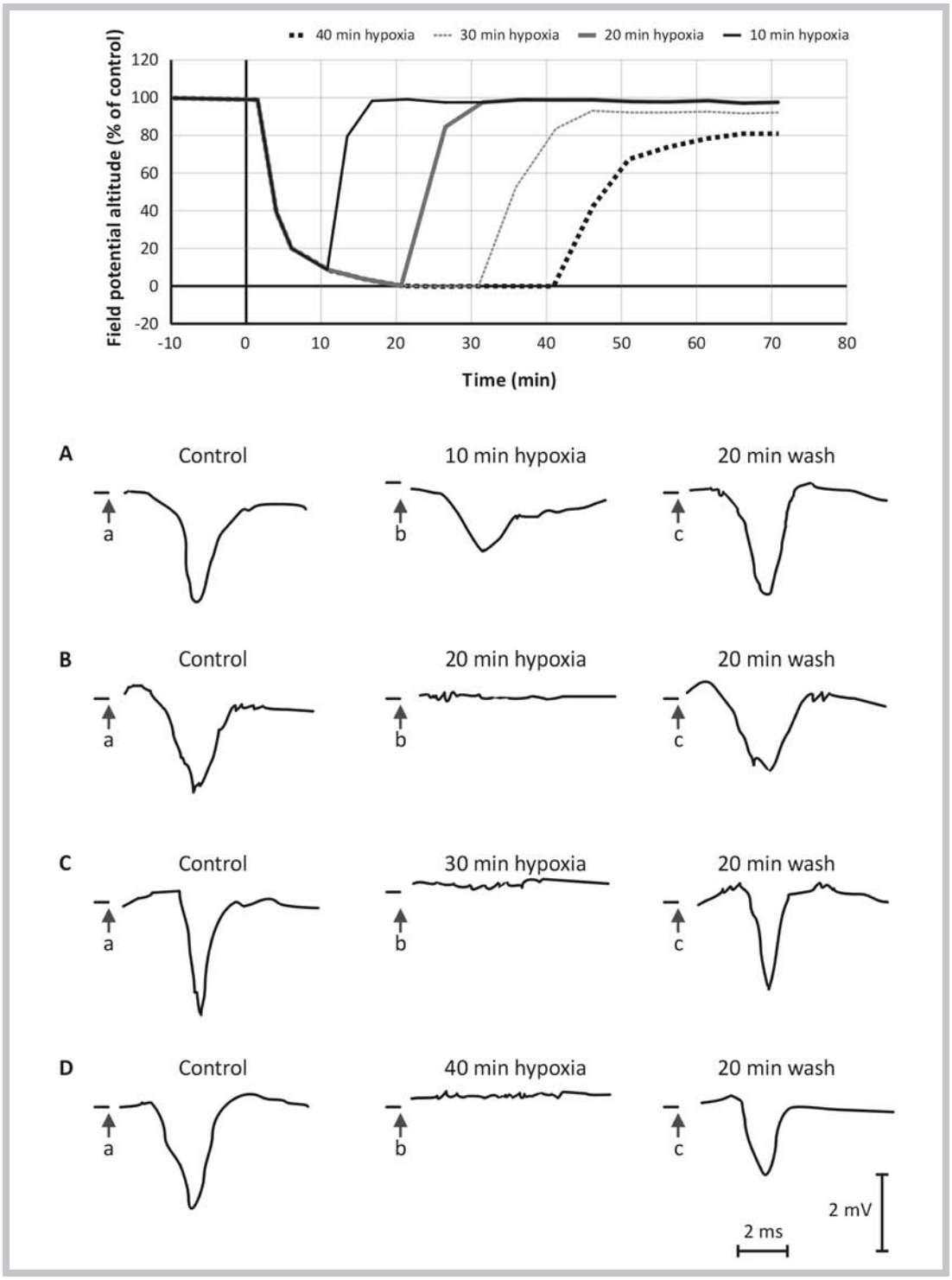

Figure 79.1. **The effects of oxygen deprivation on corticostriatal field potential in Wistar rats. The upper part shows the effects of different periods of hypoxia on the field potential amplitude. In all of the experiments, hypoxia was initiated at time 0 and lasted 10, 20, 30 or 40 minutes. At the bottom, A, B, C and D represent the field experiments showing the potential amplitude before (a), in (b) and after (c), in different periods of hypoxia. Calibrations in D also apply to A, B and C.**

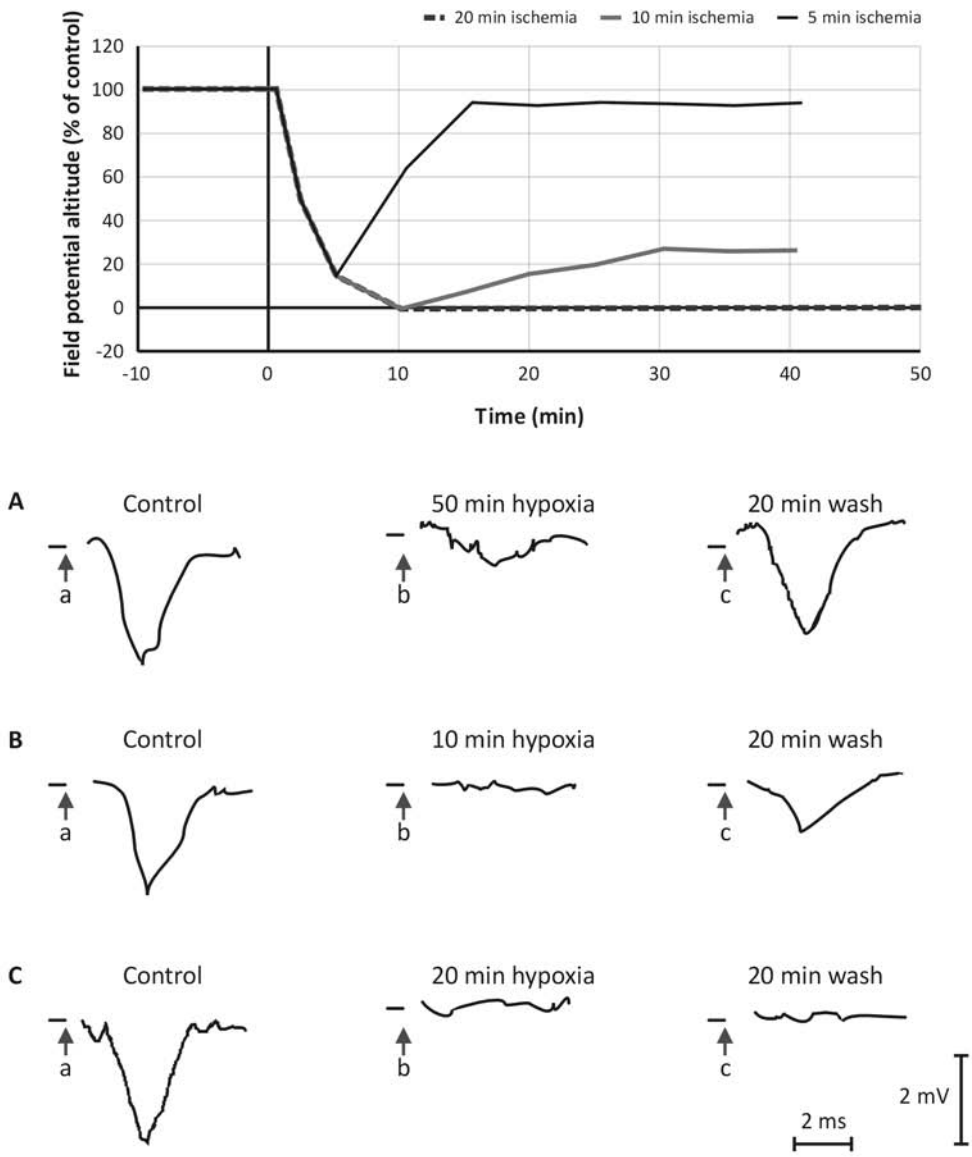

Figure 79.2. **The effects of ischemia on corticostriatal field potentials of the brains of Wistar rats. The upper part shows the effects of different ischemia periods on the field potential amplitude. In all of the experiments, ischemia started at time 0 and lasted 5, 10 or 20 minutes. At the bottom, A, B and C represent experiments showing the potential amplitude before (a), in (b) and after (c), from different ischemia periods. Calibrations in C also apply to A and B [15].**

79.11 The Electroencephalogram

This simple method is available in most centres and has high sensitivity. It has even been used as a form of continuous monitoring in patients with HIE. It must be taken into ac-

count that its interpretation can be affected by pharmacological action, particularly benzodiazepines and barbiturates.
There is some consensus that some patterns show poor prognosis: suppression paroxysm, presence of periodic discharges and electrical silence. In 1990, an electroencephalographic (EEG) grading scale was created which was applied 24 hours after successful cardiopulmonary resuscitation, yielding prognostic values with 98.4% veracity; since then, several studies have attempted to verify these findings. The scale assigns 5 grades, where grades 1 and 2 are predictors of full recovery, and grades 4 and 5 denote a poor neurological prognosis (Table 79.1).

Grade I	Dominant alpha rhythm with some theta-delta activity, reactive
Grade II	Theta-delta activity with some normal alpha activity, reactive
Grade III	Predominantly theta-delta activity without normal alpha activity
Grade IV	Low voltage delta activity, not reactive Alpha coma (generalized non-reactive alpha activity) Paroxysm-suppression pattern
Grade V	Isoelectric

Table 79.1. **EEG grades in patients with HIE.**

79.12 Neurobiochemical Markers

The difficulty in establishing a clinical prognosis has led to research into finding biochemical markers that have a close correlation with neurological prognosis.

79.12.1 Creatine Kinase Isoenzyme BB in Cerebrospinal Fluid

The brain is rich in creatine kinases and its BB enzyme, and it does not have types MM and MB. For this reason, CKBB activity is not affected by extracerebral factors. At experimental levels a good correlation has been shown between the elevation of this enzyme and the degree of neurological damage. The peak elevation occurs within the first 48 to 72 hours after cardiac arrest, has a sensitivity of 82% and a specificity of 85%, and a positive predictive value for persistent vegetative state of 0.96 when levels reach or exceed 50 UI/l, reaching a specificity of 100% with cut-off values of 205 IU/l.

79.12.2 Serum Neuron-specific Enolase

Levels reflect structural brain damage; values of 33 ng/ml predict persistent coma or brain death with a specificity of 100% and a sensitivity of 80%. However, one limitation is that there is no temporal correlation known to confirm a prediction.

79.12.3 Serum Astroglial S100 Protein

Just like neuronal enolase, S100 protein reflects structural brain damage. Values ≥0.2 ng/ml from the second day on have a positive predictive value of 100% for mortality, while values <0.2 ng/ml within the first 14 days show a survival prognosis of 89%. When the evaluation is conducted immediately after the event, S100 protein values are significantly higher in patients with persistent brain damage than in those who recover without neurological sequelae.

A systematic review of the usefulness of biochemical markers as predictors was published in 2001, which concluded that although the CKBB results were interesting, there were methodological flaws and an inadequate number of patients; therefore, they are insufficient as isolated prognosis guides.

79.13 Images

During the first 24 hours, the brain computed tomography (CT) scan lacks sensitivity, so a slight or moderate alteration can pass unnoticed, while if there is evidence of injury, the damage is significant. The most common early finding is the disappearance of grooves caused by cerebral edema. After 48 hours, hypodense lesions in the cerebral cortex, cerebellum and basal ganglia appear evident on the image. Bordering infarcts and brain atrophy are evident in the following days.

Magnetic resonance imaging (MRI) is more sensitive for detecting infarctions and cerebral edema, above all with the diffusion technique, which can appreciate gray matter alterations during the acute period, alterations in the white matter during the subacute period, and return to normal during the chronic phase. From the second week on, in T_1, T_2 and fluid-attenuated inversion recovery (FLAIR) sequences there appear hyperintense cortical lesions, which represent cortical laminar necrosis.

As for other techniques, such as MR spectroscopy and single-photon emission computed tomography (SPECT), some interesting data have been presented, but their diagnostic and prognostic values are still under study.

79.14 Therapeutics

Successful resuscitation of a patient from a sudden death event is only the beginning of a therapeutic process which under the best circumstances will return the patient to daily activity with total self-sufficiency. However, the figures derived from several studies are not as encouraging in these results; they indicate that barely 20% of patients return to absolute self-sufficiency without residual or minimal deficit.

Some 80% of survivors end up with a result that can vary from partial to total dependence, with the consequent family and social costs.

Managing a patient after a sudden death episode is therefore extremely complex, and all information that can be obtained is critical, both for immediate management as well as subsequent therapeutic decisions. In this sense, it is very important to know the levels of self-sufficiency prior to the event, the associated co-morbidity that can have a triggering or aggravating effect, and the perspective from the social and family environment.

A few years ago, treatment of patients suffering from cardiorespiratory arrest was based on cardiovascular resuscitation and general medical treatment. The absence of specific therapies marked an uncertain, and usually poor neurological prognosis, the majority evolving to total dependency, persistent vegetative state or death [8].

In recent years, different measures have been questioned in the treatment of HIE, most of which supported by pathophysiological reasoning, as several studies have failed to demonstrate significant differences in their use in clinical practice. However, the use of induced hypothermia has shown promising results.

Currently, we have measures directed at counteracting different points in the chain of injury. Among general neurological protection measures are ensuring CBF by maintaining normal or moderately high blood pressure, providing adequate oxygen supply to reach a PO_2 of 100 mmHg, and trying mild hyperventilation, 30 to 35 mmHg.
In an injured brain, it is necessary to prevent further damage that could worsen its condition; as we have seen, hypoxia and ischemia bring about greater fragility and predisposition to injury from other causes. Under these conditions, considering that 30% of patients have seizures, the prophylactic use of anticonvulsants is recommended. Achieving metabolic stability, with internal environmental balance and no imbalances in either glucose or intra- and extracellular components, is one of the primary objectives. Within these, there is a special attention to calcium, since as we have seen it plays a significant role in many neuronal injury processes.

79.14.1 Calcium Antagonists

Numerous studies have failed to demonstrate the usefulness of calcium in ischemic encephalopathy, despite having a pathophysiological basis that supposes a beneficial effect. More than 30 studies that included oral and intravenous calcium antagonists were analyzed, many of which were excluded due to methodological flaws, and none showed a clear benefit. It is worth noting that a statistically significant difference was found in one study, where a subgroup that received nimodipine within the first 12 hours of the event was analyzed. This suggests that failure to prove utility is probably due to administration subsequent to establishment of the injury [9].

79.14.2 Hypothermia

Around 40% of patients survive cardiorespiratory arrest in the extra-hospital environment, but it is estimated that near 20% of these will have limiting neurological damage. Hypothermia has been used as a therapeutic method with good results; however, the exact mechanism by which it acts on HIE is not known. Many mechanisms have been proposed, including reduction of released mediators during hypoxia, delayed production of enzyme products and free radicals, protection of lipid membranes, decreased metabolism and cerebral oxygen demand, reduced intracellular acidosis, reduced intracranial pressure, and protection of ongoing ischemia. Early work on the use of hypothermia began in 1950 when it was used in cardiac surgery. In the 1990s its use was intensified in experimental animal models, and most recently it has been used in human studies in an attempt to find its application in different, mostly neurological, pathologies.
Canine models showed a lower incidence of neurological deterioration after the application of hypothermia, and interestingly, an increase in tolerance to global ischemia, which increases as temperature decreases. For example, if the temperature is reduced from 37°C to 25°C, the time without damage lasts 5 times longer [10].
In humans, two prospective, multicenter, randomized controlled studies have been performed to date; the first was done by a European group and included 273 patients who suffered extra-hospital cardiac arrest, 136 of which were treated with hypothermia between 32° and 34°C for 24 hours, while in 137 normothermia was maintained. After 6 months, the neurological outcome in 55% of patients in the hypothermia group was good, with independence and re-insertion to work, at least part time, as compared with 39% of patients in the control group. (RR 1.4, 1.08-1.81); the number needed to treat (NNT) was 6 (95% CI 4-25]. The mortality at 6 months was 41% in the treated group and

55% in the control group (RR 0.74, 0.58-0.95); the NNT was 7 (95% CI, 4-33). There was no difference in medical complications between the groups [11].

The second study was done in Australia and included 77 patients resuscitated from an extra-hospital cardiac arrest; 43 were treated with hypothermia at 33°C for 12 hours and in 34 normothermia was maintained. At discharge, 49% of the patients treated with hypothermia had a good neurological state, being discharged to their homes or a rehabilitation centre, while in the normothermia group, only 26% achieved this goal (p=0.046). There was no statistical difference in terms of mortality (51% in hypothermia and 68% in normothermia). There were also no significant medical complications reported in the group treated with hypothermia [12].

It must be noted that in both studies, there is a duality in the result of hypothermia application, since almost all treated patients either die (41% and 51%, respectively) or end up without severe neurological damage (55% and 49%, respectively).

In a meta-analysis by Holzer et al., it was found that hypothermia at 33°C applied to resuscitated patients with extra-hospital cardiac arrest statistically increased the possibility of patients with a favourable neurological recovery at discharge (OR 1.68, 1.29-2.07), with an NNT between 4 and 13 [13].

Since 2003, with these data, the International Liaison Committee on Resuscitation (ILCOR) has incorporated moderate hypothermia at 32-34°C for 12 to 24 hours as a recommendation for patients who have been resuscitated from extra-hospital cardiac arrest [14].

Figure 79.3 shows a patient with HIE secondary to a sudden cardiac death episode under moderate intravascular hypothermia, while Figure 79.4 summarizes the flowchart for resuscitated sudden death event.

Figure 79.3. **Patient with HIE secondary to a sudden cardiac death episode under moderate intravascular hypothermia. The monitor to the right displays a temperature of 33.1°C.**

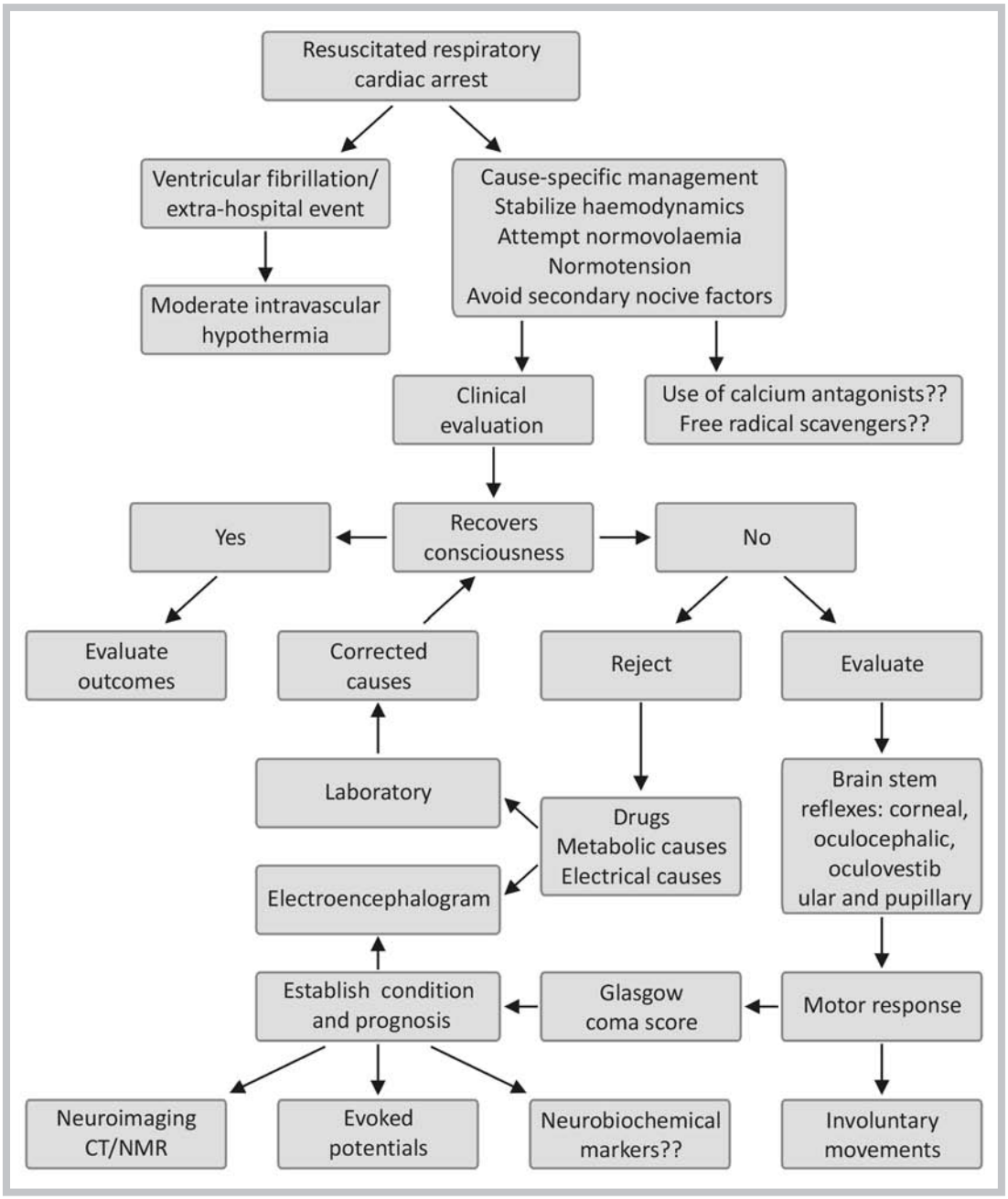

Figure 79.4. **Flowchart for resuscitated sudden death event, with an emphasis on addressing hypoxic ischemic encephalopathy.**

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80 Perioperative Management of Patients With Brain Tumours

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80.1 Introduction

In recent years advances in cancer treatment have been generally encouraging except in the treatment of gliomas: its natural history remains unchanged and its prognosis is grave. Unlike other tumours, malignant gliomas have not benefitted from adjuvant therapies or new imaging or neurosurgical techniques.
The therapeutic approach to tumours arising in the central nervous system (CNS) differs consistently in both practice and theory from that to other kinds of tumours. For example, the concepts of benign and malignant, which are absolute for tumours with other localizations, are only relative when applied to the CNS: a brain tumour composed of benign cells but located in a vital area can be considered life-threatening although the tumour and its cells would not be classified as malignant.
The prognosis of such tumours depends on: tumour histopathology and anatomic localization, and patient age and neurological state.

80.2 Epidemiology

Primary brain tumours consistently contribute to morbidity and mortality in all age groups. In paediatric patients, brain tumours are the second most common type of cancer after leukaemia. In adults, primary brain tumours are the 13th most frequent of all cancers. Depending on the age of the population studied, the incidence of these cancers has been estimated to be between 4.8 and 10.6 years of age per 100,000 inhabitants/year. In the United States, the incidence can vary for different geographical regions. The sex distribution also differs, with benign tumours more prevalent in females, while malignant tumours and the overall number are more prevalent in males. Statistical data show a mortality rate of 6.5 per 100,000 inhabitants/year for males and 4.5 for females. The incidence of brain tumours increases dramatically with patient age, peaking between age 75 and 85 years in both females and males; the most frequent brain tumours in the elderly are multiform glioblastoma and astrocytoma. Although only 1.5% of all cancers are observed in children, the incidence of CNS tumours in children is high, accounting for the second leading cause of cancer in this population. Medulloblastoma is the most frequent in children and, together with cerebral astrocytoma, is considered a typical paediatric tumour.

80.3 Classification

Brain tumours are found in around 1-2% of autopsies. The histological classification of CNS tumours has evolved since the first scheme devised by Bayley and Cushing in 1926.

Tumours of glial tissue	Tumours of the meninges	Germ Cell Tumours	Tumours of the sellar region	Others
• Astrocytic tumours: astrocytoma, glioblastoma multiforme • Oligodendroglial tumours: oligodendroglioma • Ependymal tumours: ependymoma • Choroid plexus tumours: papilloma, carcinoma • Embryonal tumours: medulloblastoma • Pineal parenchymal tumours	• Meningioma • Hemangiopericytoma • Melanocytic tumour • Hemangioblastoma	• Germinoma • Embryonal carcinoma • Teratoma • Endodermal sinus tumour	• Pituitary adenoma • Pituitary carcinoma • Craniopharyngioma	• Metastatic tumours • Nerve sheath tumours • Schwannoma • Neurofibroma • Primary CNS lymphoma

Table 80.1. **Histological classification of central nervous system tumours.**

Slow-growing tumours (low grade)	• Grade I tumours: benign, slow growing and circumscribed • Grade II tumours: grow slowly, but with imprecise boundaries, or extension
Rapidly progressive tumours (high grade)	• Grade III tumours: anaplastic tumours, their evolution is faster • Grade IV tumours: malignant tumours show histologic evidence of very rapid growth in all regions examined

Table 80.2. **Tumors classificaion according to their rate of malignancy.**

In 1979 the World Health Organization (WHO) established a useful classification which has been revised many times over the years (Table 80.1) [1]. As shown in Table 80.2, tumours can be classified according to their rate of malignancy (in particular, astrocytoma).

80.3.1 Description by Tumour Type

Astrocytoma

Astrocytoma accounts for 25-30% of all gliomas. They arise in the brain hemispheres in adults and in the cerebellum in children. They are characterized by slow growth and infiltration.

Oligodendroglioma

Oligodendroglioma accounts for 6% of gliomas and is the most common between the fourth and fifth decades of life. It is most frequently found in the temporal and frontal lobes.

Malignant Gliomas

Malignant gliomas are the most frequent and varied primary brain tumours. They are responsible for 2% of all tumour-related deaths. The most common histopathological types are glioblastoma multiforme, anaplastic astrocytoma, and anaplastic oligodendro-

glioma. They are characterized by a high rate of local recurrence after surgical treatment, with local progression and ultimately death. They are mainly disseminated in the white matter or cerebrospinal fluid (CSF). Unlike other advanced malignant tumours, they don't cause distance metastases.

Glioblastoma Multiforme

Glioblastoma multiforme is the most severe and aggressive type of astrocytoma (grade IV WHO). The average 2-year survival is 10%.

Meningiomas

Meningiomas account for 15-20% of primary intracranial tumours. They are more frequent in persons between 20 and 60 years of age. They originate from the arachnoidal cells in the meninges. Usually benign in nature, they are typically well encapsulated and can be found anywhere in the brain (supra- and intratentorial).

Secondary Tumours (Metastases)

Cancer cells can break away from the primary tumour site and travel through blood, cerebrospinal fluid and lymphatic vessels. The brain is a preferred site for melanoma and small-cell lung cancer metastases. In males, metastases usually originate from the lung, colon and kidney. In females, they most often spread from breast cancer, lung, colon and melanoma. Spinal metastases occur in 5% of cancer patients, frequently in those with breast or prostate cancer or multiple myeloma.

80.4 Clinical Features

Many different signs and symptoms can be present. The tumour can be asymptomatic, totally aspecific or inclusive, depending on its characteristics and type.
For example, glioblastoma multiforme, characterized by rapid growth, differs from meningioma, which can evolve for years. Also localization, speed of growth, presence of edema and size can all influence clinical features. This aspect should be taken into consideration in diagnosis because it can influence the prognosis.
Another fundamental aspect is that tumours can produce symptoms similar to those of other CNS diseases, but unlike CNS diseases, tumours typically have a slow and progressive onset (for example, motor deficit due to cerebrovascular injury has a rapid onset, while the onset is slow and worsens over time if the cause is neoplastic).
The most frequent onset signs are progressive neurological deficit (68%) and, less frequently, motor debilitation (45%) [2].
Endocranial tumour presentation can distinguished on the basis of three clinical symptoms:

- Altered higher mental functions.
- Intracranial hypertension syndrome.
- Syndromes specific to certain kind of tumours.

80.4.1 Altered Higher Mental Functions

Cognitive Impairment

The most common signs are emotional liability, altered behaviour, asthenia, depression (it is always important to rule out organic causes in depressive patients). Patients lose in-

terest in their routine activities and display lack of initiative, apathy and indifference to everyday social activities. They frequently forget things and find it difficult to remember recent facts; sometimes signs of dementia are present.

Cephalea

Headache is a temporal sign in almost the one third of patients and is an onset symptom in 55% of cases. Varied in nature, headache lacks any typical feature; it may occur more often at night or it may be more intense in the morning (the more frequent presentation). Usually, it worsens with cough; in 40% of cases it is associated with nausea and vomiting, which can sometimes alleviate the pain.
It is difficult to distinguish tumour-associated headache from other kinds of headache (e.g., tension, migraine, etc.). In 77% of cases, tumour-associated headaches are resemble tension headaches and in 9% present migraine features [3]. But in only 8% of cases do patients present with such features.

Seizures

Seizures occur in 20-50% of patients and can constitute the onset symptom in 25% of cases. They can be generalized or partial and can occur before or after (weeks, months) the onset of other symptoms. «A first seizure during adult life is always suggestive of a tumour».

80.4.2 Intracranial Hypertensive Syndrome

The syndrome is characterized by the classical triad of headache, vomiting and papilledema, although the last sign is noted more often in frontal tumours. With the advent of more sophisticated imaging methods, it may become a diagnostic feature before disease onset.

80.4.3 Specific Symptoms of Specific Tumours

In some patients with intracranial tumours signs and symptoms allow clinical localization of the lesion; for such tumours the onset signs are specific. For example, acusticus neurinoma, hypophysis adenoma, craneopharyngioma, brainstem glioma, cavernous sinus meningioma, and olfactory groove meningioma among others. In this group of tumours, signs and symptoms of brain alteration or intracranial hypertension syndrome do not occur or have a late onset.

80.5 Diagnosis

Careful history taking and neurological examination are the first steps to reach a diagnosis. Some specific symptoms, together with disease progression, are important in differential diagnosis. For example, typical headache (predominantly during the night, no improvement with pharmacologic treatment, accompanied by vomiting) or the first seizure episode.
Computed axial tomography (CT) and magnetic resonance imaging (MRI) are the gold standard diagnostic techniques. Some other techniques, described later in this chapter, may also be of help.

80.5.1 Computed Tomography

Different images are obtained depending on the tumour, and can vary from hypodense images that enhance heterogeneously and serpiginously following contrast infusion (e.g., in high-grade astrocytoma) or well-circumscribed images with intense homogeneous enhancement as seen in meningiomas. CT images can help the clinician by visualizing calcium (which is more visible on CT than on MRI scans) or small bleedings.
Performing CT is important because it can aid in the etiologic diagnosis and highlight features such as metastases that are not otherwise visible with other techniques. For example, metastases commonly release the contrast agent in a ring-shaped hypodense area (edema), causing displacement of adjacent structures.

80.5.2 Magnetic Resonance Imaging

MRI is the gold standard for diagnosis and planning surgical treatment. It is much more precise than CT in differentiating between different kinds of tumours and grade of malignancy, and it is able to show small tumours localized to such areas as the posterior fossa which are not visible by CT. With MRI we can see image features suggestive of some kinds of tumours.
Glioblastoma multiforme crosses the corpus callosum to the opposite side, yielding a butterfly wing-like appearance on MRI.
Meningioma appears as a homogeneous, clearly circumscribed area, with broad implantation on the underlying dura mater.
MRI allows us to know whether a tumour is limited or metastasis should be suspected; furthermore, it allows the identification of typical tumours, such as acoustic neurinoma or the adenoma of the hypophysis.
It also plays an important role in the postsurgical follow-up and in the control of recurrent diseases.

80.5.3 Spectroscopy

Spectroscopy is used to study brain metabolites, allowing the differential diagnosis with other diseases (e.g., ischemia, infectious lesions).

80.5.4 Cerebral SPECT

Single-photon emission computed tomography (SPECT) helps in identifying recurrent tumoural lesions and differential diagnosis with radionecrosis.

80.5.5 Magnetic Resonance Angiography

Angiography studies the vascular supply to the tumour, identifying the lesions at high risk of bleeding and the anatomic relationships between the tumour and the vessels around it.

80.5.6 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) delimits the relationships between the tumour and the brain's vital areas, such as the motor area, speech or vision area. Its ba-

sic principle is identification of the cerebral areas with maximum oxygen consumption. To study the motor area of the upper limbs, fMRI is performed while the patient does repeated movements of the fingers of the hand that we wish to study.

80.6 Treatment

Treatment of brain tumours will take into consideration different the patient's age, general health condition, neurological status, and tumour characteristics (localization, type, size).

80.6.1 Control and Observation

In small benign tumours or those localized to the deep areas of the brain, periodical controls with MRI are carried out every 6 months or once a year. This management is usually reserved to small meningiomas or low-grade astrocytomas, given that in these last cases follow-up control should take into consideration the possibility that the tumour can change its biologic behaviour.

80.6.2 Biopsy

Although information on tumour type can be gleaned from imaging studies in some cases, today it would be unthinkable to initiate treatment without the certainty of diagnosis**.** Stereotactic biopsy plays an important role in establishing the histological diagnosis of tumour in non-surgical cases in which accurate diagnosis may minimize the risk of complications (0.5% chance of bleeding). This procedure is useful in order to maintain the patient's quality of life because it can be done on an outpatient basis, under anaesthesia, with a small incision, and can be performed in 24 hours.
It is indicated in deep tumours, tumours located in eloquent areas, surgically inaccessible tumours, and large tumours invading the other hemisphere through the corpus callosum, multiple images as in MRI.

80.6.3 Surgery

Surgical removal is the most important method in the treatment of all primary brain tumours. It has three essential and immediate aims:

- Establish the histological diagnosis.
- Alleviate intracranial pressure and mass effect, thus improving neurological function.
- Allow oncologic cytoreduction to improve survival, and improve the safety and efficacy of co-adjuvant treatments such as radiotherapy.

With technical and theoretical advancements in neurosurgery, ever safer and more effective treatments have been developed. Tumours that were once considered inaccessible, such as those localized to deep regions, can now be safely managed with the help of surgical microscopy, microsurgery and microinstruments. Very few intracerebral tumours cannot be reached via direct surgical access with current technologies, ultrasound aspiration, intraoperative echography, intraoperative resonance, stereotaxic surgery and neuronavigation. Together, these innovations expanded surgical strategies for patients with brain tumours.

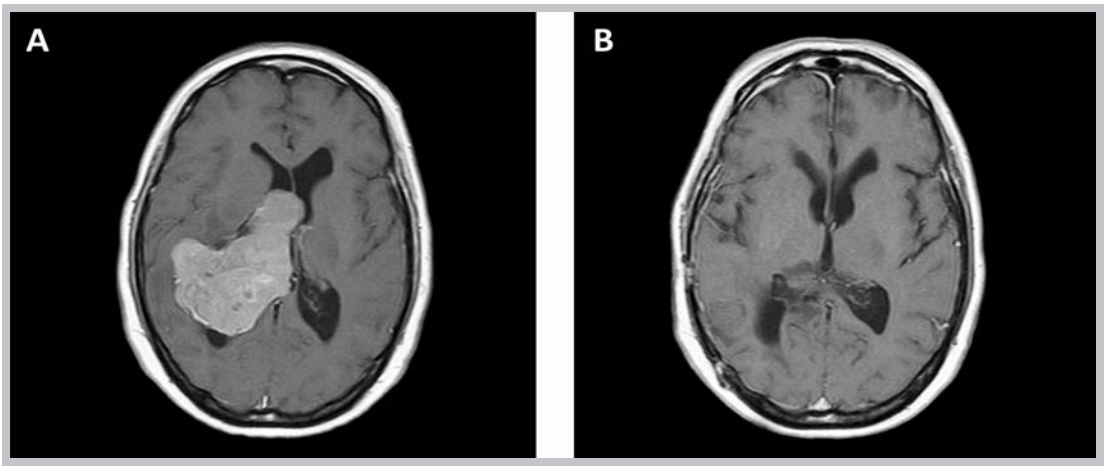

Figure 80.1. **Before surgery (A) and after surgery (B).**

In the majority of extra-axial benign lesions (meningiomas and acoustic neurinomas), the aim of surgery is complete removal. In such cases, it is important to eliminate as much of the tumour as possible, while minimizing the risk of possible trauma to adjacent neurological structures. These goals can be obtained with the use of intrasurgical electrostimulation techniques that can alert the surgeon to the presence of vulnerable neurological structures.

The same concept of complete removal is applied to benign tumours, usually meningiomas or even large tumours in deep brain areas, which can be managed with these new techniques without the risk of neurologic impairment (Figure 80.1).

In intra-axial infiltrating tumours, mostly originating from the glia, surgery allows histological diagnosis and provides a means of temporal control; surgery can reduce mass effect and intracranial hypertension. Because of their locally aggressive nature, malignant brain tumours are not currently curable and their control requires multimodal strategies. Despite discussion on the role of aggressive surgery in the treatment of these lesions, most neuro-oncologists agree that "cytoreduction" and elimination of the tumoural mass are the goals of surgical resection, when they are obtained without causing neurological impairment [4,5].

Morbidity and mortality after brain surgery has decreased consistently in the last decades. The 30-year mortality rate after brain tumour removal is generally <3%. The number of surgical complications depends on the nature of the tumour and its location. Severe complications (perioperative hemorrhage, infection and permanent neurological lesions) occur in <10% of patients [6].

80.6.4 Radiotherapy

The efficacy of radiotherapy has been demonstrated in the treatment most malignant brain tumours. Once the anatomopatologic diagnosis has been established and surgical resection completed, radiotherapy is usually indicated. Although different histological tumour types have different sensitivity to radiation, the improvement in 1-5-year survival obtained with this technique makes its use incontestable in most CNS tumours. The main limiting factor of its long-term effects is the level of the dose or radiation exposure, which can be higher than the CNS can tolerate. Even with exposure to radiation doses within the established limits (40-60 Gy), the brain is vulnerable to many toxic ef-

fects. Acute reactions immediately after radiation ensure from acute brain tumefaction and manifest as an increase in neurological deficit. Fortunately, such reactions respond well to steroids and are generally reversible. Within 1-3 months after irradiation, a similar but late syndrome, also reversible with steroids, may appear. A less common brain reaction is radiation necrosis, which can appear months or years after radiotherapy. It is a progressive brain reaction that is probably caused by direct toxicity in the brain and its microvascularization. Patients will present with insidious and progressive deterioration, focal neurologic signs and dementia. Radiation necrosis can be difficult to distinguish from tumour recurrence, because they share similar clinical and image features. In such cases, they can be differentiated by stereotactic biopsy or brain SPECT. Therapy can include steroids or decompressive treatment. Many patients have already arrived at a terminal stage, so that the most adequate treatment is conservative and palliative in most cases.

When survival is prolonged, different additional complications of long-term radiation appear that are increasingly worrying: hypopituitarism, occlusive arterial disease and radiation-induced oncogenesis. Tumours associated with radiation (meningiomas, sarcomas and gliomas) are a rare and late complication that can appear decades after irradiation to the brain. More worrying are the risk of radiation in small children, leading to learning difficulties, hypophyseal insufficiency, myelopathies and spinal cord deformities, accompanied by the adverse events due to medications. Since myelinisation of the CNS is completed between 2-3 years of age, radiotherapy before this age is particularly hazardous and should be avoided.

80.6.5 Chemotherapy

Following brief episodes of optimism, chemotherapy has brought about no important improvement in the treatment of malignant brain tumours. Practically all the available anti-cancer agents for the treatment of hematologic or systemic malignant neoplasms have also been studied in brain tumours. Apart from recent discoveries in paediatric tumours such as germinoma and medulloblastoma, chemotherapy has shown no efficacy in improvement. In oncologic terms, brain tumours, with their highly defined localization, relatively small tumoural mass and non-metastatic nature, could well be responsive to chemotherapy. Nonetheless, these factors are contrasted by the peculiar complexity of the CNS, where the blood-brain barrier limits the access of most anti-cancer agents. Even if the blood-brain barrier's integrity can be altered by different brain tumours, penetration by most chemotherapeutic agents is still limited. Nonetheless, a few liposoluble, low-molecular-weight and apolar agents exist that can pass across an intact blood-brain barrier. Among these, nitrosoureas, hydroxyurease and diazoquinon (AZQ).

The access of other less permeable agents (methotrexate, vincristine, cisplatin) can be improved by the rupture of the osmotic blood-brain barrier or with intrathecal or intracerebral administration. Among these agents, nitrosoureas and hydroxyurea are the most extensively studied. A recent analysis of prospective studies performed during the last 10 years demonstrated that chemotherapy administered after surgery and radiation therapy for malignant gliomas obtained a small improvement in survival. The 24-month median survival rate was 23.4% in the patients treated with chemotherapy and 15.9% in those treated with radiotherapy and surgery. This improvement, small but statistically significant, can be masked by other variables, such as age and functional status at tumour onset.

80.7 Complications and Postsurgical Management

As mentioned, variability in brain tumour is common, so that it is difficult to establish general rules for their management, depending as it does on tumour type, localization, and procedure among others. So we have patients who only undergo stereotactic biopsy and those who require therapy in order to go on breathing sensors for measuring intracranial pressure (ICP.)

Analogously, the same control should be maintained in a patient operated for a tumour of the posterior fossa, where edema can rapidly decompensate the patient, to a patient treated for a small convex meningioma with a Glasgow Coma Scale (GCS) score of 15.

Some general criteria and complications that can present in all operated tumours exist, as well as criteria that can be applied to all neurocritically ill patients.

On the basis of our experience, we recommend that the patient should stay for a minimum of 72 h in the intensive care unit (ICU); everybody knows the need for beds in our health system, but it is not uncommon that a patient who has performed well the first 24 hours will be transferred to a general ward, and then worsen again, and re-enter the ICU. In general, the cause is tumoural edema, which, as we will see, differs from traumatic edema which is sometimes present.

For example, we can operate metastasis in the posterior fossa, obtain a very immediate good postsurgical outcome, only to see edema develop days later when the patient is in the operating room. This edema can compress the brainstem and decompensate it rapidly, with the risk of late arrival because of not being in a place where it can be continuously monitored.

If the patient had a good neurological status before surgery and if the surgical procedure was not very invasive, administering therapy is recommended. On the contrary, if the operation lasted for many hours or in the case of large tumours, even if benign (basal meningiomas or others similar), it is sometimes recommended that the patient remain on assisted mechanical ventilation (AMV) and then be weaned gradually.

In such cases, or whenever the patient must remain on AMV, or when GCS cannot be assessed, a sensor to measure ICP should be placed. This highlights the need for close respiratory and hemodynamic monitoring in the first hours postoperatively, as well as monitoring the level of consciousness, electrolytes, coagulation and arterial blood gases, 24 hour-antibiotic prophylaxis, and control of arousal and pain.

Although neurological and extraneurological complications may arise, this chapter will cover only the first and most important, ones.

80.7.1 Convulsive Seizures

Almost 60% of patients with brain tumours can experience convulsive seizures or their first seizure episode after diagnosis or neurosurgery. Seizure is considered a consequence of craniotomy and occurs during the first week after surgery. The incidence of sudden seizures is between 4 and 19% in recent studies; the incidence of late attacks is 17-70%.

Seizures are complications exclusive of supratentorial lesions, particularly in the temporal, frontal, parasellar and parietal regions; even if some cases they have been reported after posterior fossa surgery, seizures most commonly occur in cortical tumours.

This complication can also be caused by indirect causes such as electrolyte abnormalities, hypoxia, or hypoglycaemia. The most common seizures in these cases are generalized, focal or simple and rare.

The consequences of seizure are severe neural lesions, increased intracranial pressure, and secondary increase in cerebral perfusion pressure; the systemic effect is hypoxia, metabolic acidosis and hyperthermia.
Prophylactic treatment is controversial. It is always necessary to take into consideration that medications can have adverse events and can interfere with steroids and chemotherapy [7].
A recent meta-analysis concluded that there is evidence both in favour and against prophylactic therapy; therefore, the decision to start anticonvulsive treatment for prophylaxis should be taken on the basis of individual risk factors, cortical localization and discussion with the patient.
The drug of first choice in adults is diphenylhydantoin, starting at a dose according to the patient's body weight. The aim is to maintain blood levels to presurgical standard values, followed by postsurgical maintenance doses.
Also controversial is how long the patient should receive anticonvulsants after surgery. This choice depends on many factors: presence of seizures before surgery, type of pathology, type of resection (total, partial), surgery area, encephalographic and tomographic findings. On this one can decide when to start treatment, which in some cases can continue for years and in others for months.

80.7.2 Postsurgical Intracranial Hemorrhage

Postsurgical hemorrhage is quite a frequent complication and a potentially very severe one after this kind of surgery. In order to avoid it, careful surgical technique and careful pre-surgical and post-surgical control of coagulation and platelet function should be performed.
Postsurgical intracranial hemorrhage is estimated to occur in 2-10% of cases, extradural hemorrhage in 0.9-7.1%, and intracerebral in 3.9%.
The main causes of postsurgical intracerebral hemorrhage are: inadequate haemostasis, high arterial pressure both peri- and/or postsurgery, sudden ventricle decompression, difficulties in tumour dissection, direct arterial lesion, alteration in blood circulation, thrombocytopenia. A higher incidence of hemorrhage is observed in primary gliomas.
There are two peaks of presentation: the first and most important one occurs within the first 6 hours after surgery and the second starting after the first 24 hours; the second one is closely related to the occurrence of perilesional edema. Morbidity and mortality are high (almost 30%), with major complications in 60% of cases.
The prognosis is worse in the following cases: hematoma >3 cm, suprasellar hemorrhage, and cerebral hemorrhage associated with intraventricular extension. Almost 40% of these patients die during the following 48 hours.
Early diagnosis is essential to avoid complications. The key to early diagnosis is immediate postsurgical neurological control in the ICU with neuromonitoring when needed, and intracranial pressure monitoring.
Progressive deterioration in the level of consciousness and neurologic focality (pupils, motor, seizures, etc.) or a sudden increase in intracranial pressure should prompt immediate treatment.
Maintaining normal arterial pressure is important because it is one of the main risk factors for hemorrhage (tumours have neoformation of vessels with weaker walls). Besides the misconception of not lowering blood pressure to prevent secondary injury, it is essential not to apply criteria of other diseases to tumours since they can show a very specific behaviour. This concept is even more important in cerebral ischemia where the risk of hemorrhage is high.

80.7.3 Cerebral Edema

Cerebral edema can be defined as the increase of water in cerebral tissue sufficient to produce clinical symptoms. The brain has three anatomic compartments that can accumulate excessive amounts of liquids:

- The vascular compartment composed of arteries, capillaries and veins.
- The cellular compartment composed of cells and their subcellular extensions.
- The extracellular compartment composed of interstitial spaces and the cerebrospinal fluid spaces.

Expansion of the volume of any one of these compartments can cause cerebral edema. Usually, two main types of cerebral edema are distinguished:

- Vasogenic edema ensuing from an increase in blood-brain barrier permeability.
- Cytotoxic edema characterized by abnormal water uptake by the cellular elements of the brain.

Vasogenic edema is seen in the vicinity of tumour masses because tumour cells release transudative microvascular factors such as proteases which weaken the microvascular blood-brain barrier and allow the passage of blood proteins. The small protein fragments generated by this protease activity will exert effects via vasogenic spread into the white matter of the brain.

The composition of the fluid of edema is similar to plasma (143 mEq/l Na^+, osmotic pressure 14 mmHg). This reflects the direct contribution of plasma extravasation. The high K^+ content of edema fluid (4.75 mEq/l), compared to the plasma concentration (3.94 mEq/l) or in the CSF (3.4 mEq/l), causes the extravasation of ions from the damaged tissue [8].

The main cause of vasogenic edema is the average arterial pressure that causes the filtration of plasma into the extracellular compartment and controls its subsequent formation. The relationship is direct and immediate. We can state than an increase in blood pressure is followed by a proportional increase in edema volume and speed of its formation. A decrease in blood pressure causes a decrease in both parameters (increase and formation of edema). From this we can appreciate the importance of maintaining normal blood pressure values.

The dimensions of edema depend on the degree of the alteration of the blood-brain barrier, the kind of lesion, and the length of time the blood-brain barrier remains open.

From a clinical point of view, the most important consequence of edema dissemination is related to local mass effect. With the expansion of edematous tissues, there is an increase in intracranial pressure and a deviation of cerebral compartments that can cause brainstem compression and produce rostro-caudal deterioration, characterized by bradycardia, hypertension and cardiorespiratory collapse. Edema- induced cerebral herniation is one of the most fearful postsurgical consequences of brain tumour.

Edema can occur in every kind of tumour, but it is more frequent in primary gliomas and metastatic tumours. It shouldn't be forgotten that, more than the type of the tumour, surgery characteristics and tumour localization are predisposing factors.

As mentioned, edema is often responsible for the patient's deterioration in the 48 hours following surgery.

Cerebral edema responds to glucocorticoids (another important difference from other pathologies is that traumatic or ischemic edema cannot be treated with corticoids), in particular dexamethasone 4 mg every 6 hours.

If the patient does not respond to corticoids, edema should be treated in the same way as in other neurocritically ill patients, sometimes with cranial decompression.

80.7.4 Hyponatremia

Hyponatremia is defined as a sodium concentration <130 mEq/l. In this hydroelectrolytic disorder, early diagnosis and treatment are essential to prevent severe neurological manifestations, including the patient's death. Hyponatremia is a common problem in the critically ill neurosurgical patient.
An alteration associated with this complication is cerebral salt wasting.
Hyponatremia is more frequent in tumours of cranial base and especially in the hypothalamic area and in hypophyseal adenomas.
While in the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), treatment is with fluid restriction, in the cerebral salt wasting syndrome it is necessary to add sodium and volume.
Its evolution should be closely controlled with a complete endocrinologic assessment to determine hypophyseal imbalance, especially hypothyroidism and suprarenal failure.

80.7.5 The Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

SIADH is characterized by excessive levels of ADH as a result of increased secretion of ADH from the neurohypophyseal cells or by ectopic production. It is associated with malignant tumours, pulmonary diseases, substance abuse or different kinds of CNS illnesses that include traumatic brain injury, intracerebral hemorrhage, and infectious diseases.
The primary pathogenic mechanism underlying SIADH is excessive antidiuretic hormone (ADH) release causing renal water reabsorption and resulting in expansion of the CSF volume; it is also associated with continuous secretion of sodium by the kidney. The standard diagnostic criteria are:

- Low levels of plasma sodium (<135 mEq/l).
- Low serum osmolarity (<280 mOsmol/l).
- High levels of urinary sodium (>18 mEq/l).
- Urinary osmolarity higher than serum osmolarity.
- Normal renal, thyroid and adrenal function.
- Absence of peripheral edema or dehydration.

The diagnosis should not be performed when severe pain, nausea, stress or hypotension are present, because they can stimulate the secretion ADH.

Treatment

Fluid restriction is the treatment of choice in patients with SIADH, usually with 500-1000 ml/24 h of an iso-osmolar solution, until sodium levels normalize. If hyponatremia is severe (<110-115 mEq/l) 3% or 5% hypertonic saline solution and furosemide should be administered. It is recommended to restore the normal sodium level approximately to 2 mEq/h in order to avoid pontine myelinolysis.

80.7.6 Cerebral Salt Wasting

Hyponatremia in patients with CNS disease can also be caused by cerebral salt wasting (CSW), especially hyponatremia that develops 2 weeks after a cerebral lesion. CSW refers to the loss of renal sodium during intracranial disease leading to hyponatremia and decreased extracellular fluid volume. It is frequently present in patients with subarach-

noid hemorrhage. Evidence from published trials shows that it is more common than SIADH in neurosurgical patients. Important for the diagnosis is to consider volaemia, a negative salt balance before or during hyponatremia, and enhanced response to replacement of volume and salt than to fluid restriction. These are the characteristics of CSW that differentiate it from SIADH. Failure to distinguish properly between the two disorders will result in treatment indicated for one disorder being inappropriately administered for the other, with potentially serious adverse outcomes.
The normal sodium concentration in urine is >50 mEq. The mechanism by which cerebral disease leads to renal salt wasting is poorly understood; neural or hormonal mechanisms can be involved. One of the possible processes is the central elaboration of a circulating natriuretic factor.

Treatment

Unlike SIADH patients, patients with CSW benefit from volume expansion with fluid therapy, even if some controversy exists about adequate treatment.
While the administration of solutions containing sodium can be effective, hypertonic solutions have recently been shown to be potentially effective (with close analytical and intracranial pressure monitoring) Sodium administration corrects both the depletion of volume and the hyponatremia. Some authors say that increasing the volume of sodium during CSW can only lead to increased renal sodium secretion, and instead recommend as more appropriate preventing the depletion of the volume reduction of renal sodium secretion; fluorocortisone acetate, a mineralocorticoid enhances sodium resorption by acting directly on renal tubules.
CSW can be associated with headache, anorexia, nausea/vomiting, and weakness. Unless treated, it can lead to comitial seizure, cerebral edema, apnoea, coma and death.
The differential diagnosis is very important because fluid restriction can improve the outcome in patients with SIADH but worsen it in patients with CSW.
Vasopressin, an arginine receptor antagonist, is one of the agents for the treatment of hyponatremia. Its therapeutic effects have been studied since 1992 and its use in neurological patients is in the experimental phase. It acts on arginine vasopressin (AVP) receptors: V1a receptors are present in many tissues, including blood vessels and hepatocytes, V1b receptors are found on the hypophysis and V2 on the renal medulla. They may reduce permeability and may have a corrective effect on hypo-osmolar hyponatremia, as in the case of SIADH [9].

80.7.7 Hydrocephalus

Hydrocephalus can present as a complication of the tumour; however, initial symptoms can be a consequence of hydrocephalus and not of the tumour. It may also be a squela of surgical tumour removal.
In some cases, surgical removal of the mass will relieve the pressure on the CSF spaces within the brain and reverse the hydrocephalus. In others it is necessary to divert the CSF flow either with a shunt procedure or endoscopic third ventriculostomy. It is important to remember that brain tumours usually don’t have metastases outside the CNS, so the possibility of a peritoneal tumour is extremely rare.
If there is a high risk of postoperative hydrocephalus, ventricular drainage is recommended even if there is no increase of the ventricle. A small edema in the posterior fossa can rapidly cause compression on the fourth ventricle and stop the drainage of CSF.
External ventricular drainage should usually be performed. A drain is left, most often in the occipital horn, and after a few days, if ventriculomegaly is not present, the system is closed, and it is removed if no clinical or topographic alterations are present.

As in any other diseases, if a drain must remain for more than 7 days, it should be changed to prevent infection [10].

80.7.8 Intracerebral Hypertension

In patients undergoing surgery for a brain tumour in whom postoperative GCS assessment is not likely to be possible, an intracranial pressure censor should be placed. It can be removed only when the patient can be clinically evaluated.
Monitoring should continue even if the blood pressure is normal for many days, until the situation is resolved.
A common error is to remove the sensor when blood pressure values normalize for 24 or 48 h; this can lead to possible both neurological (edema or infection) and extraneurological complications.
When intracerebral hypertension is develops, and systemic causes have been excluded, CT should be performed to investigate for bleeding, edema or hydrocephalia (the first two are the most common causes).

80.8 Conclusion

We are only at the beginning of the treatment of brain tumours. Even with the significant improvements in recent years we have been unable to significantly improve the life expectancy of patients with a brain glioblastoma.
Without doubt, the advancements in all fields are very important.
Nowadays, histological diagnosis of a brain tumour should be completed with immunohistochemical analysis and, possibly, with the evaluation of chromosomic alterations and other genetic analyses that allow the identification of different subtypes of glia tumours and the prediction of clinical results and response to treatment. The loss of PTEN and amplification of the epidemic growing factor receptor (EGF) define glioblastoma, while alteration of p53 and of the alpha-receptor of platelet-derived growth factor (PDGF) and p16 are associated with secondary glioblastomas deriving from low-grade astrocytomas. In oligodendrogliomas, on the contrary, the allelic loss of chromosomes 1p and 19q is, at the moment, considered predictive of prolonged response to chemotherapy and overall survival. Diagnostic techniques are sometimes precise and show the exact shape of the tumours, allowing higher precision in the surgical approach, spectroscopy, angioresonance, functional resonance, with sometimes better and more useful information.
Thanks to advanced techniques such as microsurgery, perisurgical morbidity and mortality rates are currently, even if not totally, absent.
The hope is that in the future, with advances in intrasurgical imaging (echography or intrasurgical magnetic resonance), surgical navigation systems assisted with orders and functional maps will allow the neurosurgeon to recognize the extension of infiltrative tissue and can resect more extensively with lower risk.
Hyperfractionated regimens in accelerated radiotherapy schemes and radiosurgery (especially indicated for metastatic tumours, VIII for neurinoma or meningioma <3 cm) have been used.
TMZ, an imidazolid derivative that alkylates DNA, is a promising new drug discovered in recent years, with an optimum safety profile, even in elderly patients. The response rates are 5.4-23.8% in patients with glioblastoma [10], with a 6-month progression-free survival of 26% and 31.8%, respectively [11].

Most of these advancements (stereotactic surgery or low-invasive, radiosurgery) have been developed to improve the quality of life of these patients, avoiding major procedures, adverse events or prolonged hospitalization, while rapidly obtaining the same results. This should always be taken into consideration in this pathology.

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81 Postoperative Complications After Neurosurgery

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81.1 Introduction

Surgery of the central nervous system (CNS) is complex and the potential for complications is high. Postoperative intensive therapy in the intensive care unit (ICU) relies on rigorous neurological examination, monitoring of heart rate, arterial pressure, and respiratory rate, and control of glycaemia, sodium, and other variables.

Monitoring allows the earlier identification of neurological deficits, metabolic complications, and respiratory and cardiovascular events. One of the differences between the ICU and the other hospital units is the level of detail in which patients are routinely monitored.

Careful monitoring permits rapid diagnosis of complications and earlier detention of changes in the patient's condition, which assures a better prognosis. A multidisciplinary team of doctors, nurses, physiotherapists, speech therapists, nutritionists and psychologists plays an essential rule in postoperative recovery. This trained team allows recovery with a minimum of sequelae.

81.2 The Neurosurgical Patient in the Intensive Care Unit

81.2.1 Monitoring and Diagnosis of Clinical Complications

The aim of monitoring during the postoperative period is to favour fast recovery and a hospital discharge without complications. In the ICU we mainly monitor the respiratory and cardiovascular system, body temperature, glucose metabolism and water-electrolyte balance.

Respiratory System

Patients submitted to intracranial surgery usually arrive at the ICU still in anaesthetic coma, intubated, and remain under invasive mechanical ventilation until full recovery of consciousness, which will depend on metabolization of the anaesthetics administered for surgery and the presence or not of cerebral injuries after the operation.

The respiratory system must be continuously monitored, specifically the respiratory rate, pulse oximetry and capnography.

The respiratory rate is an important predictor of evolution of the illness. One study observed that the ICU team presented an error of 20% in more than one third of times from direct counting the respiratory rate when compared to counting for objective tracing. In the ICU impedance monitors are frequently used to measure the respiratory rate. Many of these devices use ECG derivations which measure the impedance generated by changes in the distance between derivations due to abdominal-chest movement during breathing.

The pulse oximeter is a non-invasive device that estimates the saturation of hemoglobin for oxygen (SaO_2). SaO_2 and PaO_2 are related through the hemoglobin dissociation curve. The value shown for the oximeter is called peripheral oxygen saturation (SpO_2).

The pulse oximeter (SpO_2) estimates a SaO_2 that is usually within 2% of the difference of the real value as determined by one co-oximeter. Studies show that to maintain a PaO_2 of 60 mmHg, the SpO_2 must be around 92%. A randomized study involving 20,000 patients assigned the subjects to use or not of continuous oximetry during the operative and perioperative period. The authors concluded that oximetry allows the detection of many events of hypoxia and their prompt correction. In seriously ill neurological patients, hypoxia is one of the main mechanisms of secondary brain injury.

The data collected by the Traumatic Coma Data Bank (TCDB) demonstrate that hypoxemia occurs in 22.4% of patients with serious traumatic brain injury (TBI) and that this leads to a significant increase in morbidity and mortality. Jones et al. found that the duration of hypoxemia (SaO_2 <90% for an average duration of 11 to 20 min) is an independent predictor of mortality. These data corroborate the importance of continuous pulse oximetry during the postoperative period after neurosurgery.

Continuous monitoring by capnography measures and generates the curve of exhaled PCO_2. The plateau of the curve is determined by mean alveolar PCO_2, which is in equilibrium with pulmonary $PaCO_2$. PCO_2 measured in the final portion of the plateau is closely correlated to $PaCO_2$. Cerebral blood flow is sensitive to $PaCO_2$. There is an inverse linear relationship between cerebral blood flow and $PaCO_2$. A fall in $PaCO_2$ from 40 to 20 mmHg leads to vasoconstriction and reduces cerebral bold flow by 40%, whereas an increase in $PaCO_2$ to 80 mmHg produces vasodilatation and almost doubles the cerebral blood flow. Hyperventilation causes cerebral vasoconstriction and reduces cerebral blood flow, which could raise the risk of cerebral ischemia. A randomized study found a worse prognosis in patients with serious TBI who had been prophylactically hyperventilated. In conditions of low cerebral complacence, modest rises in $PaCO_2$ increase the cerebral blood volume and can result in accentuated rises in intracranial pressure.

These data indicate that with adequate $PaCO_2$ monitoring iatrogenic cerebral ischemia and worsening of intracranial hypertension can be prevented. Capnography is essential in the neurosurgical patient and PCO_2 must be kept to around 35 mmHg.

Arterial gas analysis and chest X-ray are essential for adjusting the ventilation before and after extubation and diagnosis of any pulmonary complications induced by mechanical ventilation (atelectasis, pneumothorax, pneumomediastinum).

Pulmonary Complications

The development of pulmonary complications significantly contributes to mortality in seriously ill neurosurgical patients and worsening of the neurological evolution. The main pulmonary complications after neurosurgery are pneumonia and atelectasis (17-25% of cases).

Pneumonia. The incidence of pneumonia after craniotomy is 21% (Figure 81.1). The factors contributing to an increased risk of infection are: reduced level of consciousness, use of corticoids, advanced age (>70 years), cardiac insufficiency, cancer surgery (specifically glioma and meningioma), smoking, diabetes mellitus, pulmonary and liver

diseases. The microorganisms most often responsible for pneumonia are Gram-negative bacilli in 50% and Gram-positive bacteria in a small percentage. The mortality rate is high (33-70%).

Atelectasis. Central respiratory depression, injury of the cervical and thoracic spinal cord, hypoventilation because of pain, altered consciousness, bronchial blockage due to mucus plugs, and traumatic pulmonary compression due to pneumothorax, haemothorax and pleural effusion contribute to the formation of atelectasis. It is the main cause of immediate postoperative low fever (24 to 48 hours after surgery). Large areas of atelectasis are responsible for a scenario of serious hypoxemia. Treatment includes manoeuvres of alveolar recruitment (positive end-expiratory pressure [PEEP], increase of the inspiratory time) and physiotherapy. Inadequate resolution and respiratory insufficiency are indications for fibrobronchoscopy.

Figure 81.1. Condensation in left lung base with pleural spill after cerebral tumor resection (Author's personal archive).

Respiratory insufficiency. Respiratory insufficiency is a life-threatening complication after neurosurgery. The neurological causes are the pathologies that determine altered level of consciousness or reduced ventilation. The level of consciousness is related to the loss of the ability to keep the airway open and compromises normal breathing. Reduced ventilation can result from a partial or complete loss of the diaphragm's innervation (injuries of the upper cervical spinal cord) which reduces lung capacity. The pulmonary causes are atelectasis, pneumonia, gastric aspiration, pulmonary thromboembolism, bronchospasm, neurogenic pulmonary edema, and the adult respiratory dysfunction syndrome (ARDS).

In the immediate postoperative period, hypoventilation can occur due to the accumulation of anaesthetics in body fat, leading to renewed sedation. This occurs with halothane and opioids.

Cardiovascular System

Monitoring of mean arterial blood pressure is essential, since hypotension is the leading cause of secondary neuronal injury, and hypertension can lead to bleeding and increase cerebral edema and intracranial hypertension. Automatic non-invasive monitoring of arterial pressure is recommended in patients with hemodynamic stability. This technique has significant limitations in patients who present sudden fluctuations in arterial pressure. It is not indicated for patients in which accurate measuring of arterial pressure is important. The invasive arterial pressure monitoring detects sudden pressure changes and extreme blood pressure levels and facilitates the repeated collection of tests and arterial blood gas analysis. The average arterial pressure must be the value used for decisions in seriously ill patients. In the direct measure of arterial pressure an invasive line is necessary; however, the risk of complications is low. Placement of an invasive arterial pressure (usually in a radial artery) is recommended in the first 24 hours after neurosurgery.

In the immediate postoperative period the average arterial pressure must be kept between values considered normal (80-100 mmHg), while taking into consideration the age group, the nature and extent of the injury, and the previous blood pressure levels of the patient. Invasive monitoring of arterial pressure will continue after 24 hours postoperative in cases which hemodynamic instability is not reached.

The American Heart Association considers continued monitoring with ECG an intervention class I for all patients in intensive care. The incidence of arrhythmias after major surgery is high.

The urinary debit is usually voluminous with the use of mannitol, and blood volume replacement with crystalloids must be intensified to prevent depletion of the extracellular space.

Cardiovascular Complications

Arterial hypertension. Arterial hypertension is frequent in the immediate postoperative period and has been reported in 70-90% of patients. It is due to sympathomimetic stimulation caused by the increase of circulating catecholamines and oxygen consumption. Administration of sodium nitroprusside can be a powerful and safe way to treat serious hypertension. This drug is a cerebral vasodilator but causes a minimum rise of intracranial pressure. Esmolol, a fast-acting beta-blocker, can be used in a similar way, without the risk of increasing intracranial pressure. In patients with chronic hypertension, it seems appropriate to start previous oral anti-hypertensive medication at about half to the two thirds of the previous dose as soon as possible. Frequent rest and sedation reduce the hypertensive condition of a more delayed postoperative patient.

Cardiac complications. Cardiac arrhythmias appear in up to 28% of cases and most often they are supraventricular. Cardiac complications in any patient submitted to surgery may be anticipated thorough preoperative evaluation. The incidence in patients without previous cardiac disease is very low (<0.2%) and the detection of risk factors is of extreme importance. Studies identify risk factors of heart complications in patients not submitted to heart surgery. Evidence of heart attack of the myocardium in last the 6 months, diagnosis of unstable angina, presence of congestive cardiac insufficiency, chest X-ray with signs of pulmonary congestion, valve disease (mainly aortic stenosis), age >70 years, emergency surgery, arrhythmias, and generally unfavourable conditions are the main data to be collected and identified in neurosurgery patients in the preoperative period.

In patients who experience a heart attack of the myocardium in the last 3 to 6 months, the rate of having one again is 30%, whereas in those who suffered a heart attack more than 6 months earlier this rate falls to 5%. Reinfarction occurs in the first 72 hours after surgery, but it can appear until the sixth day after surgery. More than half of these heart attacks are quiet, in which case ECG and serial enzyme dosage are indicated until the sixth postoperative day in patients at high risk. ECG abnormalities are found in 40-60% of patients with subarachnoid hemorrhage due to aneurysm rupture. The most frequent are S-T segment alterations or arrhythmias. A heart attack secondary to subarachnoid hemorrhage has been reported, but it is extremely rare. These ECG alterations can come from injury to the hypothalamus and high levels of catecholamine.

Patients must have their medications optimized during the preoperative period, once 60% decompensated in the first postoperative hours. Left acute cardiac insufficiency can occur after subarachnoid hemorrhage due to aneurysm rupture, mainly in patients with the worst clinical severity.

In patients with heart valve disease, prophylaxis for bacterial endocarditis may be recommended. In those with valve prostheses and under anticoagulation, the therapy should be suspended during the preoperative period. The risk associated with discontinuation of anticoagulant therapy depends on the type of valve, the localization

and factors of associated risks. In patients with only one aortic valve prosthesis and without associated risk factors, the anticoagulant is suspended 3 days before surgery. When the thromboembolism risk is high, intravenous heparin is initiated before surgery with INR <2 and suspended 8 hours before surgery. The TTPA has to be normal 6 hours after heparin suspension. Patients at higher risk of thromboembolism are those with mitral valve prosthesis, atrial fibrillation, previous thromboembolism, ventricular dysfunction, mechanical tricuspid valve or with more than one mechanical valve. A period of 5 to 7 days after-craniotomy is probably a safe break to restart anticoagulation.

Body Temperature

During the immediate postoperative period, hypothermia must be avoided since it causes tremors which increase oxygen consumption, cardiac debit and/or blood pressure. All these alterations favour brain hyperaemia which can contribute to delirium in older patients, difficult to control arterial hypertension and intracranial hypertension. The best way to limit the development of tremors in the postoperative period is to maintain normothermia.

Fever. Fever is very frequent in serious neurosurgery patients due the high risk of nosocomial infections. The role of hypothermia in neuroprotection remains uncertain, but there is consensus that hyperthermia negatively impacts on neurological recovery. Currently it is known that a gradient exists between central body temperature (oesophageal, rectal) and brain temperature. The brain temperature is underestimated, which increases the risk of secondary neuronal injury. An aggressive antithermic treatment for fever and general cooling measures are indicated.

Glucose Metabolism

Metabolic monitoring mainly involves blood glucose control. Glucose measurement every 4 hours is recommended to prevent a neurological catastrophe during the postoperative period. Prospective and randomized studies in critically ill patients have demonstrated that the evolution is better in the surgical group that receives insulin therapy and remains euglycaemic (80-110 mg/dl) than in those with glucose levels between 180 and 200 mg/dl. Hyperglycaemia (>200 mg/dl) worsens the neurological evolution. Hypoglycaemia can lead to irreversible neuronal injury and must be prevented to the maximum. In the postoperative period the objective is to keep the patient euglycaemic (≤140 mg/dl) without a significant increase in the risk of hypoglycaemia episodes.

Electrolyte Control

Much attention must be directed to prevent electrolyte disturbances in the postoperative period. Disturbances occur through alterations between extracellular volume and sodium concentration.

Hyponatremia. Hyponatremia is frequent in seriously ill neurological patients. The measure of serum sodium does not allow to distinguish between hyponatremia associated with hypervolaemia or hypovolaemia. Hyponatremia associated with hypo-osmolality contributes to the increase in intracellular volume which causes or aggravates cerebral edema and intracranial hypertension and with hyperosmolality can lead to cerebral infarction. The main causes of hyponatremia/hypovolaemia in the postoperative period are: diuretic, mannitol, vomiting, diarrhoea and mineralocorticoid deficiency. In these situations, arterial pressure, urinary debit and urinary osmolality can be low, but urea and creatinine will be raised. Replacement with isotonic solutions (physiological saline 0.9%) allows the correction of these electrolyte imbalances. Anoth-

er important cause of hyponatremia is the cerebral salt loss syndrome, which causes the release of natriuretic factors leading to increased diuresis, natriuresis and hypovolemia with normal or raised urinary osmolality. Hyponatremia is corrected by the replacement of solutions with higher sodium concentration (physiological saline 3%). In the presence of hyponatremia in the postoperative period, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is always part of the differential diagnosis, since it demands management in the opposing direction from other aetiologies. This syndrome is caused by the inappropriate secretion of the antidiuretic hormone and is associated with water retention and hypervolemia with high urinary osmolality. The treatment of the SIADH consists of water restriction of 500 ml/day if sodium is <120 mEq/l and 1000 ml/day if sodium is 120-130 mEq/l. If sodium is <115 mEq/l, convulsions or a coma state caused by hyponatremia or in the presence of pathologies in which water restriction is contraindicated (period of vasospasm), a 3% saline solution can be administered.

81.2.2 Prophylaxis of Clinical Complications in the Postoperative Period

Beyond routine monitoring, care postoperative includes the prophylaxis of infection, deep venous thrombosis and upper digestive hemorrhage.

Prophylaxis of Infections

The utility of antibiotic prophylaxis has been widely discussed over the last decades. Controlled studies have finally demonstrated the effectiveness of appropriate antibiotic therapy. Prophylactic antibiotic therapy reduces the incidence of surgical site infections and meningitis during the postoperative period. Anti-staphylococcal agents are studied and recommended. In craniotomies (clean surgeries) the use of cefazolin is recommended in one dose 30 minutes before scalp incision or in special cases of 24-hour antibiotic treatment (ventriculoperitoneal shunt placement).

Prophylaxis of Deep Venous Thrombosis and Pulmonary Thromboembolism

Deep venous thrombosis (DVT) of the lower extremities occurs in 29-43% of neurosurgical patients and the incidence of pulmonary thromboembolism (PTE) is 15%. The risk factors are immobilization for prolonged periods, paralysis of the lower extremities, prolonged surgery (+4 hours), advanced age, neoplasia, direct injury lower limb veins, previous PTE, cerebrovascular disease, use of oral contraceptives, obesity, cardiac congestive insufficiency, hypercoagulability, and pregnancy. Due to the high morbidity and mortality of DVT/PTE, prophylaxis is essential. Some studies confirm the utility of pneumatic compression of the lower limbs before surgery until the patient can walk again. Early mobilization can prevent the formation of venous thrombi. Beyond mechanical support, the use of low-dose heparin or low-molecular-weight heparin is recommended. Low-molecular-weight heparin (enoxaparin 40 mg 1x/d SC, nadroparin 7500 U 1x/d SC) or non-fractionated heparin (heparin 5000 U SC 8/8 hours) initiated 24 hours after the procedure are more efficient in PTE prevention than compression therapy. There is a non-statistically and significant risk of bleeding with this therapy. The American College of Chest Physician places neurosurgery patients in the category of high risk for PTE in the perioperative period. The association of mechanical and pharmacological prophylactic treatments in these patients is indicated.

Prophylaxis of Upper Gastrointestinal Hemorrhage

Neurological patients are at an increased risk of gastrointestinal bleeding or gastric perforation. In an endoscopic evaluation of neurointensive patients, erosions of the gastrointestinal mucosa were seen mainly in patients with secondary intracranial hypertension to brain tumours, TBI or intracranial surgery. In a cohort study of neurosurgical patients in the ICU (excluding TBI) it was observed that 6.8% had gastrointestinal complications in the postoperative period. The majority presented bleeding but a small number evolved with bleeding and perforation. The main risk factors were: SIADH, coma before surgery, postoperative complications, age >60 years, and CNS infections. Corticoids, extensively used in the neurosurgery population, contribute to the formation of gastrointestinal ulcerations. The risk of developing ulcers is twice higher and intestinal perforation can occur in corticosteroid users. In these patients medical prophylaxis of stress ulcers is indicated. Sulcrafate provides efficient prophylaxis without excessively increasing gastric pH (less risk of ventilator-associated pneumonia). However, the difficulty to manage sulcrafate and the reduction in the absorption of anticonvulsants and other drugs delivered by nasogastric catheter make H2 blockers and proton-pump inhibitors the best alternatives for a short postoperative period. Probably, there is no need for pharmacological prophylaxis in patients on an oral diet. In pharmacological prophylaxis ranitine must be used in patients <65 years of age at a dose of 50 mg IV from 8/8 hours or 150 mg OD from 12/12 hours and in those >65 years a dose of 50 mg IV for 12/12h. Omeprazole at a dose of 20-40 mg/d IV or OD.

81.2.3 Monitoring and Diagnosis of Neurological Complications

The neuro-check is a quick neurological evaluation but it does not substitute complete neurological examination. It includes serial recording of the Glasgow Coma Scale (GCS), pupillary size, symmetry and photoreactivity, type of breathing and presence of focal neurological deficits. Any variation in this neurological evaluation must be interpreted as a signal of worsening of the patient and be followed by complete neurological examination and diagnostic and therapeutic measures. The frequency of neuro-check (Table 81.1) changes according to the pathology and clinical evolution of the patient. In the postoperative period, monitoring of the GCS and pupils every 15 minutes until extubation identifies neurological complications in a prompt and effective way. Over the next 6 hours after extubation, a complete neuro-check can be performed every 30 minutes and then every hour up to 24 to 48 hours after surgery. The indications for motoring of intracranial pressure after craniotomy are very varied and controversial.

Intracranial Hypertension

Elevated intracranial hypertension (ICH) causes injury to the brain by compression, herniation and ischemia. It is generally accepted that monitoring and aggressive treatment of ICH can reduce secondary ischemia and improve the neurological evolution. Intracranial hypertension is common after neurosurgery. A retrospective study monitored

Postoperative patient	Glasgow Coma Scale	Pupils	Breathing	Focal deficit
Intubated	Every 15 minutes	Every 15 minutes	-	-
Extubated (first 6 hours)	Every 30 minutes	Every 30 minutes	Every 30 minutes	Every 30 minutes
Extubated (after 6 hours)	Every hour	Every hour	Every hour	Every hour

Table 81.1. **Frequency of neuro-check in the postoperative period.**

514 patients after elective intracranial surgery and verified the presence of ICH in 18.4% of supratentorial surgeries and 12.7% of infratentorial interventions. Of these patients with ICH, clinical deterioration occurred in only 52.8%. The neurological examination does not always allow early diagnosis of hypertension. Hypertension is characterized by chronic headache, nausea, vomiting, reduced level of consciousness and neurological compromise. Some measures to control and prevent hypertension include: headboard elevated to 30 degrees; prevention and treatment of arterial hypertension; treatment for pain, nausea and vomiting; prevention and treatment of tremors; and maintenance of adjusted ventilation and oxygenation. The most common causes of hypertension in the postoperative period are: edema; hemorrhages; cerebral hydrocephalus; pneumoencephalus; and cerebral infarction.

Cerebral Edema

Apart from localization and type of neoplasia, the main focus in the immediate postoperative period is cerebral edema. The development of edema in the immediate postoperative period is associated with manipulation of deep structures and the removal of cerebral tumours. In response to direct trauma from surgical intervention and tissue retraction, there occur relative tissue ischemia, reduction in venous return and reduction in cerebral complacency. Cerebral edema can develop with increased intracranial pressure. The use of the electrocautery increases the local injury and is directly associated with cerebral tissue trauma.

Edema appears 4 to 5 hours after surgery and peaks within 48-72 hours (Figure 81.2). Clinical manifestations correspond to the cerebral area injured. Motor or sensory alterations of the mental state, deficits and paralyses of cranial nerves are common. Transtentorial herniation can occur, worsening the prognosis. Brain CT confirms the diagnosis and excludes such other complications as hydrocephalus and hemorrhage. The tomographic findings are: deletion of ridges; reduction of the size of the ipsilateral ventricle; midline deviation; hypodensity and deletion of the interface between the white and gray matter. After diagnosis with CT, treatment must be initiated. The main objective is to maintain cerebral perfusion pressure (CPP) >60 mmHg and ICP <20 mmHg. The headboard of the bed must remain high (30 degrees) to aid cerebral venous return. Adequate cerebral perfusion pressure is kept by the infusion volume and use of vasoactive drugs. $PaCO_2$ must be kept around 35 mmHg. Hyperventilation ($PaCO_2$ 25-30 mmHg) is indicated when clinical signals of herniation are present. In patients with ICH on mechanical ventilation, sedation is mandatory (benzodiazepines, opioids, propofol). Corticoid administration (dexamethasone in 4 doses every 6 hours up to a dose of 10-40 mg) is recommended for patients submitted to brain tumour resection. The clinical response of cerebral edema to dexamethasone for primary malignant cerebral tumours is less dramatic than for metastasis, and meningomas less than gliomas. In patients with external ventricular derivation

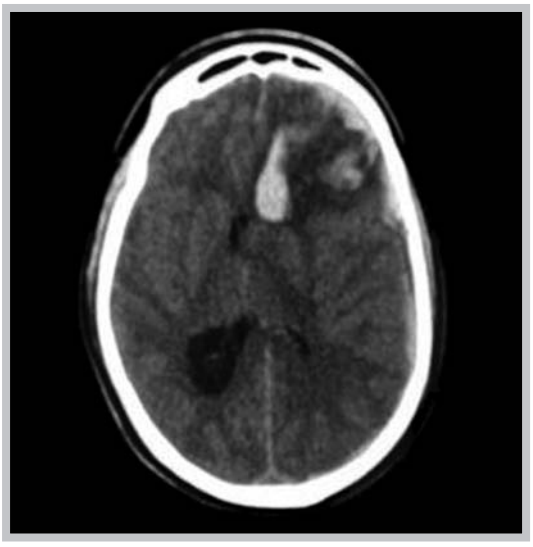

Figure 81.2. **Cerebral edema in the left frontal region with minor bleeding. Immediate postoperative period after tumor resection (Author's personal archive).**

(EVD), cerebrospinal fluid drainage can assist in the control of ICP. The administration of mannitol at a dose of 0,25 to 1 g/kg must be quickly initiated and monitored with serum osmolarity (serum osmolarity kept <320 mOsm). The alternative to this osmotic therapy is hypertonic saline solution in bolus (physiological saline 3 20%), being mainly indicated in patients refractory to mannitol or in the presence of renal function loss. Decompressive craniectomy is indicated in patients with a persistent rise in ICP, despite optimized medical treatment. In the presence of unilateral cerebral edema following cerebral tumour resection, the removal of a great bone flap with dural plastic has had success in reducing ICP.

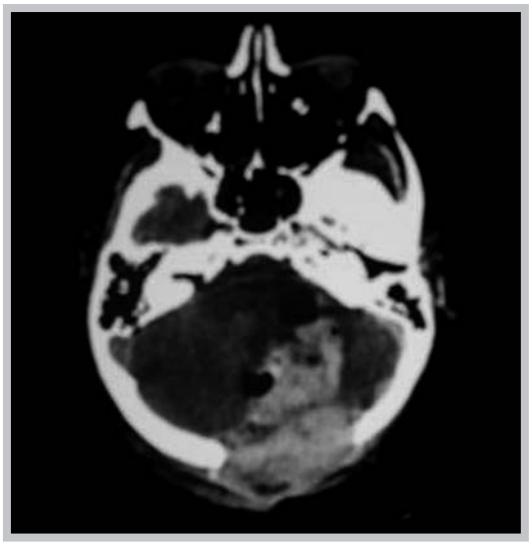

Figure 81.3. **68-year-old woman submitted to posterior tumor resection of the fossa. Deterioration of consciousness (GCS from 15 to 4) during the immediate postoperative period. Emergency CT showing major hemorrhage in the operative stream bed (Author's personal archive).**

Hemorrages

The occurrence of hemorrhage in the immediate postoperative period and the development of epidural, subdural or intraparenchymal haematoma is always a feared complication, because it is a significant and potentially avoidable situation. Accurate estimation of the incidence of haematomas became possible with the advent of tomography in clinical practice. Currently, the incidence of extradural haematoma after neurosurgery varies between 0.9 and 7.1%, whereas the incidence of intracerebral haematoma is of 3.9%. Surgery for ventriculoperitoneal derivation is associated with a very small percentage of bleeding in the surgical site.

The diverse causes associated with this fearful complication are related to the surgical technique and clinical morbidities. Inadequate perioperative haemostasis, inadequate tissue suture, important tissue retraction, abrupt ventricular decompression, direct injury of the cerebral vessels, arterial hypertension and thrombocytopenia. Cerebral tumour resection (resection of malignant tumours) and craniotomy for haematoma draining are associated with a higher incidence of hemorrhage.

Clinical manifestations include chronic headache, new neurological deficit, convulsive seizures, reduced level of consciousness, signs of transtentorial herniation with hypertension, bradycardia and respiratory insufficiency. In patients with bleeding in the posterior fossa, the manifestations are related to the degree of compression of the brainstem and are predominantly related to cardiovascular and respiratory decompensation. The diagnosis is based on head CT (Figure 81.3) and the treatment is emergency surgery for draining the haematoma and relief of intracranial hypertension.

Hydrocephalus

Surgery of the posterior fossa and intraventricular space are often associated with hydrocephalus in the postoperative period. Hydrocephalus can occur in patients with subarachnoid hemorrhage and intracerebral hemorrhage with or without intraventricular extension.

The initial manifestation can be chronic headache or paralysis of cranial nerves, especially cranial nerves III, IV and VI, but also it can present with rapid neurological deterioration.

Ventriculostomy, lumbar puncture and third ventriculostomy endoscopy are all viable methods for handling an acute hydrocephalus.

Ventriculostomy is the most commonly used technique: it can be a heroic measure; it can help to stabilize the patient and gains time for a definitive treatment or time for the base condition to resolve itself and CSF flow to return to normal.

Pneumoencephalus

Pneumoencephalus consists of intracranial air in the following compartments: epidural, subdural, subarachnoid and intraventricular. It is one of the causes of deterioration of consciousness after surgery of the posterior fossa and supratentorial procedures. The risk is higher when the patient is operated in a seated position. Air in the epidural space occurs after surgery involving the skull base where an extensive bifrontal craniotomy is made. Measures in the intraoperative period to prevention the development of pneumoencephalus include closing of the dura mater, reconstruction of the skull base, re-expansion of the intracranial contents and placing a drain in the epidural space. The clinical signals of hypertensive pneumoencephalus generally occur within 2 to 4 days after the operation. Accumulated air causes mass effect and has important clinical repercussion (Figure 81.4).

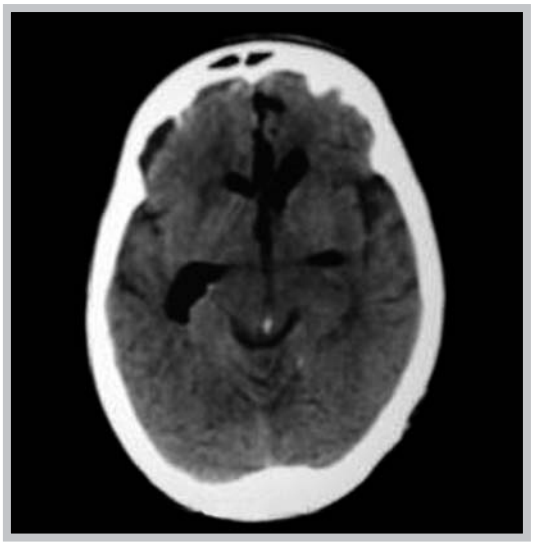

Figure 81.4. **Patient submitted to cerebral tumor resection, with intense chronic headache in the immediate postoperative period but without focal deficit. Emergency CT showing major pneumoencephalus (Author's personal archive).**

The more common clinical manifestations are chronic headache (38%), nausea, vomiting and deterioration of the level of consciousness, with mental confusion or lethargy. It can evolve to coma without focal neurological signals. Hyponatremia is common and convulsive seizures can worsen the situation. Air is evident on the head CT up to 7 days after surgery. Simple pneumoencephalus does not require treatment. In the attempt to promote the reabsorption of pneumoencephalus, some authors suggest keeping the patient with the headboard flat for 48 to 72 hours and with 100% of oxygen. It is thought that ventilation with 100% allows a nitrogen exchange for oxygen of the intracranial air, which is quickly absorbed by the bloodstream. Hypertensive pneumoencephalus must be evacuated (aspiration or catheter placement) with urgency like intracranial haematoma. Surgery can be necessary to repair a skull base fracture or CSF fistula.

Cerebral Vasospasm

The main focus in the immediate postoperative period after clipping of cerebral aneurysm for subarachnoid hemorrhage is the prevention of vasospasm. Up to 70% of hemorrhage cases present vasospasm diagnosed through some complementary examination such as transcranial Doppler (Figure 81.5) or cerebral arteriography (Figure 81.6).

However, clinical vasospasm (cerebral ischemic deficit or cerebral infarction) occurs in up to 35% of patients with hemorrhage and is the leading cause of morbidity and mortality in survivors. The main risk factors of vasospasm are: higher clinical severity, greater blood volume on the CT scan, hypotension, hypovolaemia, hyponatremia, hyperthermia and hyperglycaemia. The use of nimodipine to prevent vasospasm has been vastly

studied. A meta-analysis of 8 studies, evaluating 1574 patients with subarachnoid hemorrhage (Hunt-Hess I to III) evidenced that the use of the nimodipine improves the immediate prognosis, and in 3 months in 27% of cases, reduces the neurological ischemic deficit in 33%, reduces incidence of cerebral infarction on CT in 21%, and reduces the incidence of vasospasm on arteriography in 20%. The recommendation is administration of oral nimodipine at a dose of 60 mg every 4 hours (IV with greater hypotension) for 21 days. From a hemodynamic point of view, it is clear that hypotension and hypovolaemia worsen the prognosis and must be prevented in all patients after subarachnoid hemorrhage. However, there are no data supporting the prophylactic use of HHH therapy (hypertension, hypervolaemia, haemodilution) in patients with subarachnoid hemorrhage without clinical evidence of vasospasm.

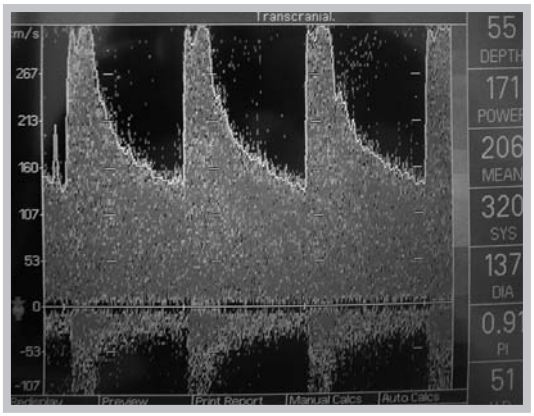

Figure 81.5. **Transcranial Doppler showing severe vasospasm (average speed >200 cm/s) in the right middle cerebral artery.**

Figure 81.6. **HSA Hunt-Hess III. Arteriography showing vasospasm of the basal artery. (Author's personal archive).**

Convulsions

The incidence of early convulsions (first 7days after surgery) varies between 4 and 19% of cases. When late convulsions are considered, the incidence increases up to 70%. They can be focal or generalized. The situations considered at risk for seizure occurrence include:

- Surgery involving the supratentorial compartment: frontal region, parasellar, temporal and parietal. Convulsions after posterior fossa surgery are rare and result from retraction of the supratentorial structures.
- Specific pathologies: cerebral abscesses, cerebral tumours, cerebral arteriovenous malformations, cerebral aneurysm, ventriculoperitoneal shunt, cerebral convulsions before surgery, haematomas, electrolyte alterations, hypoxia, hypoglycaemia.

Patients who do not present a crisis before surgery and submitted to surgery in the supratentorial compartment for some of the pathologies mentioned above must receive an anticonvulsant. Phenytoin is the most widely used anticonvulsant. The loading dose is between 15 and 18 mg/kg before surgery and 5 mg/kg after surgery. In primary cerebral tumours, 75% of convulsions occur with the 3 first months after surgery. Many authors recommend prophylaxis with phenytoin for 3 months. Meningomas are associated with higher rates of convulsions in the postoperative period than other tumours; it has been

suggested that they must be prophylactically treated for 12 months. Some prospective studies concluded that there is no advantage in anticonvulsant prophylaxis in patients with metastatic tumours except in melanoma. Patients who will be submitted to surgery for aneurysm must receive an anticonvulsant only during the perioperative period. Serious TBI must be treated for 1 week. Prophylaxis is effective in the early phase but not in the delayed phase after traumatic convulsive illness.

Convulsions in the immediate postoperative period should arouse the suspicion of haematoma, edema, infarction or metabolic disorders (hypokalemia, hyponatremia, hypoglycemia). Laboratory examinations and skull CT should be obtained to establish a diagnosis of the complications and to plan new surgical intervention, if necessary.

The consequences of convulsive seizures are directly related to the cerebral tissue and systemic effects. The direct effects on the brain include neuronal injury with increased intracranial pressure secondary to the increase in cerebral blood flow. The systemic effects include hypoxia, metabolic acidosis and hyperthermia. This leads to secondary neuronal injury to edematous tissue, creating a vicious cycle that increases the final injury and the recurrence of new convulsive seizures.

81.3 Central Nervous System Infections

Postoperative craniotomy infections are uncommon (incidence around 7%). They include wound infections, osteomyelitis, bacterial meningitis, subdural and epidural empyema and cerebral abscess. Prophylactic antibiotics are effective to decrease infections incidence in clean craniotomy postoperative. Risk factors to infection include diabetes mellitus, immunossupression drugs, craniotomy time, skin disease, drains, an extended surgical time (more than 4 hours) and hemostatic clips. Bacterial meningitis could occur in any intradural surgical interventions and it could be devastating. Bacterial meningitis incidence is around 0.5-0.7% after clean craniotomy. It could be more frequent after external ventricular drainage and in the presence of liquoric fistula. Bacterial meningitis could be as acute and sub-acute presentation, with low-grade fever in the begining. It is suspected in the presence of fever of unknow reason, loss of consciousness and seizure convulsive. Ventriculitis could occur. The diagnostic is confirmed by cerebrospinal fluid (CSF) exam that shows increase white cell count with neutrophil-predominant, low glucose concentration, high protein level and high level of lactate. Prophylatic antibiotic could difficult the diagnostic. When this happens, CSF findings may resemble those of viral meningitis. Microbiological culture of the sample could identify the organism in 70-85% of cases but results can take up to 48 hours to become available. The agents more common are aureus staphylococci, epidermidis staphylococci and gram-negative bacilli. Third-generation cephalosporin and vancomicyn are usually associated to treatment before culture result. Shunt ventricular must be removed.

81.4 Conclusions

This chapter outlines an approach to the postoperative management of the neurosurgical patient. Postoperative care after neurosurgery is a routine situation in the ICU and demands the attendance of specialized team. Here we emphasize the importance of ICU monitoring of neurological complications to minimize morbidity and mortality. Rigorous monitoring of the respiratory system, cardiovascular system, the nervous system, and glu-

cose and sodium metabolism is essential. We discuss the risk factors related to clinical and neurological complications such as cerebral edema, surgical site hemorrhage, convulsions, and pneumoencephalus. Neurological and non-neurological complications are frequent and must be diagnosed promptly to minimize sequelae and allow adequate recovery.

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82 Neurologic Emergencies During Pregnancy

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82.1 Introduction

Complications associated with pregnancy are common, and sometimes require close monitoring in intensive care units (ICUs). Neurologic manifestations during pregnancy can be related to primary involvement of the nervous system, like cerebrovascular disease, or as part of systemic diseases, like preeclampsia. Because of the complexity and importance of functional outcome of the mother and foetus, these complications should be managed in specialized ICUs, where the neurologist and the obstetrician work very closely. An attempt to materialize this idea has been made, and neuroscience intensive care units (NSICU) have been created to meet this goal. Although there are still no data to support this new approach, the idea is becoming more attractive around the world. Here, we present the most common clinical situations for which admission to a NSICU may be a reasonable alternative to a general ICU.

82.2 Pre-eclampsia and Eclampsia

Preeclampsia (PE) and eclampsia (EC) are major causes of maternal and fetal morbidity and mortality, involving 15-20% of pregnancies in the developed countries and even higher rates in the less developed parts of the world. Maternal complications include renal failure, the HELLP syndrome (haemolysis, elevated liver enzymes and thrombocytopenia), liver failure, cerebral edema with seizures and death.

Preeclampsia is defined as the association of newly diagnosed hypertension after 20 weeks of pregnancy and either proteinuria or generalized edema or both. PE can be classified as mild or severe (Table 82.1). Eclampsia refers to the occurrence of seizures during or after pregnancy which are usually preceded by signs of PE. However, up to 38% of EC cases will develop with no prodromic PE [1].

- Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on 2 occasions 6 or more hours apart in a pregnant woman who is on bed rest
- Proteinuria, with excretion of ≥5 g of protein in a 24-hour urine specimen or 3+ or greater in two random samples collected 4 or more hours apart
- Oliguria, with excretion <500 ml of urine in 24 hours
- Pulmonary edema or cyanosis
- Impaired liver function
- Visual or cerebral disturbances
- Pain in the epigastric area or right upper quadrant
- Decreased platelet count
- Intrauterine growth restriction

Table 82.1. Criteria for severe preeclampsia (one or more of the listed.) Adapted from [ACOG Committee on Practice Bulletins--Obstetrics. ACOG Practice Bulletin. Diagnosis and management of preeclampsia and eclampsia. *Obstet Gynecol* 2002; 99: 159-67].

82.2.1 Epidemiology

The incidence of PE is around 5-10% of pregnancies [2], and 1:2000 deliveries for EC, with higher numbers in developing countries. Maternal mortality is 1.8% if EC is present, and this is second only to embolic events [3]. Additionally, 20-50% of obstetric admissions to the NSICU are related to PE [4]. Risk factors for developing PE include: poor nutrition, nulliparity, multiple gestations, maternal age (<18 or >35 years), diabetes, pre-existing hypertension, previous EC, hydatidiform mole, hydrops fetalis, and family history [5].

82.2.2 Pathophysiology

PE is characterized by systemic vascular endothelial dysfunction. It is associated with endothelial damage as well as impaired vascular homeostasis. The decreased amounts of vasodilators like prostaglandin I2 and nitric oxide, as well as the increased amounts of vasoconstrictors (thromboxane A2 and endothelin) found in PE will result in diffuse maternal vasospasm and microangiopathy with increased capillary permeability and tissue edema. That explains why the use of antiplatelet agents (specifically low dose aspirin) during pregnancy has been shown to reduce the relative risk of PE and serious adverse outcome [6,7]. Autoantibodies against angiotensin II type I receptors have been found in patients with PE, a finding that could explain in part the pathogenesis of PE [8]**.** Abnormal placentation and placental hypoxia also play a major role in PE. Recent studies showing overexpression of proteins like soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) contributing to endothelial dysfunction and precede clinical symptoms of PE [9] are becoming the base for the developing of new therapeutic options.

Cerebral pathology shows disruption of the tight junctions and extravasation of fluid into the perivascular spaces, with white matter edema and cortical micro- and macrohemorrhages. Also areas of infarction are seen in the parieto-occipital watershed zones as a consequence of the associated vasospasm [5]. The classic posterior reversible encephalopathy syndrome of PE and EC may be explained by the increased permeability of the posterior cerebrum's blood-brain barrier seen in pregnant rats [1]0.

Eclamptic encephalopathy is believed to be associated with an impairment of cerebral autoregulation since this develops at considerably lower pressures than those reported for hypertensive encephalopathy. This suggests that the autoregulatory curve is shifted to the lower range of pressures (to the left) during pregnancy or that autoregulatory capacity is severely affected [11].

82.2.3 Clinical Presentation

The classic triad of hypertension, proteinuria and edema is not necessarily present in all patients with PE. Atypical presentations of PE include patients with gestational hypertension without proteinuria, capillary leak syndrome (facial edema, ascites and pulmonary edema) with proteinuria but without hypertension and gestational proteinuria alone. Furthermore, PE and EC can present before 20 weeks of gestation, as well as in the late post-partum (>48 hours but <4 weeks after delivery) [12], which makes diagnosis and management even more difficult.

Seizures are the hallmark of EC, and are usually generalized tonic-clonic, but occasionally may have a focal onset (frequently over the face) [13]. Seizures in the late post-partum are only present in 3% of patients with EC [14]. Absence of prodromic PE is variable and seizures can be the first manifestation in up to 60% of patients with EC [15]. Head-

ache, photophobia, visual hallucinations or confusion are also associated with EC. Transitory blindness secondary to cortical ischemia can be seen in 2.3% of patients with EC [16]. Retinal artery vasospasm or retinal detachment is less common. The presence of coma carries a poor prognosis.

82.2.4 Radiographic Features

Most patients with EC will have a normal computerized tomography (CT) of the head [1]7; however, some may present with focal subarachnoid or intraparenchymal hemorrhage, occipital symmetric hypodensities (in patients presenting with cortical blindness) and cerebral edema (focal or generalized) [18].

Low-signal intensities in T_1 and high-signal intensities in T_2-weighted images (with a high diffusion coefficient, i.e., without diffusion restriction) can be seen on magnetic resonance imaging (MRI) of the brain [19]. In early EC, hyperperfusion-induced vasogenic edema without cerebrovascular spastic change can be suggested by MRI perfusion-weighted images obtained by multi-slice FAIR (flow-sensitive alternating inversion recovery) method [20]. These reversible lesions are also seen in hypertensive encephalopathy and posterior leukoencephalopathy syndromes [17].

82.2.5 Management

Management of PE revolves around close monitoring and judicious timing of delivery. It will depend on the evaluation of possible maternal and fetal complications. In general, patients with severe PE or EC should be admitted early to the NSICU, since the course of the disease is unpredictable and can progress rapidly. It is wiser to deliver than to delay once the foetus is between 32 and 34 weeks and can be safely delivered. There is little or no place for conservative management if the patient has developed EC, pulmonary edema, cerebrovascular accident, renal failure or liver injury [21]. The management of these patients in the NSICU is mainly related to management of blood pressure, intravascular volume, intracranial dynamics, and prevention and treatment of seizures.

Blood Pressure Control

The blood pressure (BP) goal should be to keep the systolic <160 mmHg and the diastolic <105-110 mmHg. Invasive BP monitoring is indicated once the patient is in the NSICU. The choice of antihypertensive medication should depend on the physician's experience and familiarity with a particular medication. Drugs that are safe in pregnancy and have been used for the acute management of BP include labetalol, hydralazine and some calcium channel blockers (sustained-release nifedipine and nicardipine).

Intravenous (IV) labetalol is effective in decreasing BP, with a rapid-onset effect and less reflex tachycardia than other drugs. It can be given as a 10-20 mg IV dose, and can be repeated every 10 to 15 minutes, up to a maximum total cumulative dose of 300 mg. Labetalol can also be used as a constant infusion (1-2 mg/min).

Hydralazine has been used extensively in the management of PE, however an old study showed a higher incidence of hypotension with its use [22]. Despite this study, many experts consider the drug as an acceptable antihypertensive. It should be given as 5-10 mg IV doses that can be repeated every 20 to 30 minutes. If a total dose of 30 mg does not achieve optimal BP control, a different agent should be considered.

Nicardipine has been less used for the management of PE. IV administration should be given as continuous infusion starting at 5 mg/h and increased by 2.5 mg/h every 15 minutes to a maximum of 15 mg/h.

Diazoxide has been used alone or in association with hydralazine when adequate BP control was not achieved by a single agent. Miniboluses of diazoxide (15 mg every 3 minutes to a maximum of 300 mg) have shown to be safe and effective in a randomized control trial [23]. The use of immediate-release nifedipine is not encouraged due to its association with excessive reduction in BP with serious cardiovascular outcomes [24].

Nitroprusside is contraindicated in the later stages of pregnancy due to possible fetal cyanide poisoning if used for more than 4 hours; however, it can be considered as a last resort agent to treat severe refractory hypertension.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are contraindicated at all stages of pregnancy because of their teratogenic effect. They also can play an unknown significant role in the pathogenesis of PE [25,26].

Intravascular Volume

Since patients with severe PE are at high risk of developing pulmonary and cerebral edema, overall in the postpartum [27], volume status should be carefully assessed. Total fluid intake should not exceed 80 ml/h [26]. Invasive haemodynamic monitoring can be useful in complicated patients, like those who are unresponsive to antihypertensive therapy, or have developed pulmonary edema refractory to diuresis and acute renal failure [28].

It is important to consider the physiologic changes that pregnancy brings. Maternal blood volume and cardiac output increase progressively through pregnancy, reaching 30-50% above baseline levels by about 28 weeks. Also, systemic vascular resistance and pulmonary vascular resistance are decreased by 20-30% in the near-term patient. During labour, cardiac output increases by a further 10-15%, augmented during contractions by the return of 300-500 ml of blood to the central circulation. Immediately after delivery, there is an increase in preload, producing an increased cardiac output that remains for 48 hours after delivery [29].

Intracranial Dynamics

The management of cerebral edema and elevated intracranial pressure in PE and EC is no different from non-pregnant patients. The role of oxygenation, hyperventilation, correction of hyponatremia, and the use of mannitol or loop diuretics are general measures that can be taken but have not been tested in controlled studies. It is important to mention that mannitol crosses the placenta and causes fetal dehydration, cyanosis and bradycardia (in animal studies); it remains as a FDA category C medication. However, mannitol can be used in life-threatening situations during pregnancy [30] at a dose of 0.25 to 0.5 g/kg of pregnancy maternal weight every 4 to 6 hours intravenously.

The use of pyridoxal phosphate, which promotes GABAergic synaptic activity and normalizes the electroencephalographic (EEG) findings seen in EC [31], has not been studied and remains controversial.

Seizure Management

Magnesium sulphate is the drug of choice to prevent and treat convulsions in women with PE and EC. Magnesium increases the production of prostacyclin, which causes vasodilation, leading to a higher cerebral blood flow and to a short-lived antihypertensive effect. It also blocks the Ca^{++} influx through the NMDA glutamate receptors (pre- and post-synaptically), reducing neuronal excitability [7,32]. It has been shown to decrease the progression from severe PE to EC [33,34], as well as to decrease the risk of abruptio placentae and maternal mortality [33]. A randomized, controlled study also showed the superiority of magnesium sulphate over phenytoin in the prevention of EC in hypertensive pregnant women [35].

Furthermore, patients with EC treated with magnesium sulphate had a 52% lower risk of recurrent seizures compared to diazepam and a 67% lower risk compared to phenytoin in the Eclampsia Trial Collaborative Group [36]. Maternal and infant mortality did not differ. Magnesium sulphate is also more effective than nimodipine for prophylaxis against seizures in women with severe preeclampsia [37].

Although there is no consensus on the optimal magnesium regimen, it is frequently started with a bolus of 4 to 6 g IV over 5 minutes, followed by 1 to 2 g/h IV as a continuous infusion for at least 48 hours post-partum in the case of EC. It can be stopped after 24 hours post-partum if it is used as prophylaxis of seizures in severe PE [38]. The dose should be adjusted in women with renal insufficiency (usually half the dose if serum creatinine is >1.3 mg/dl) [5]. Patients should be monitored in the NSICU for signs of potential magnesium toxicity, which include loss of patellar reflexes, increasing drowsiness, dysarthria, muscle weakness and respiratory depression. If this occurs, serum magnesium levels should be measured (therapeutic levels 4-8 mEq/l), and if they are elevated, magnesium infusion should be discontinued. Calcium gluconate (1 g IV in 10% solution) should be given as antidote in case of impending respiratory arrest. If seizures recur, a loading dose of phenytoin can be tried (18 mg/kg IV at a maximum rate of 50 mg/min).

Termination of Pregnancy

Termination of pregnancy should be decided by obstetricians based on maternal and fetal monitoring. The patient should be hemodynamically stable and seizure free. As mentioned before, there is no benefit to the mother continuing pregnancy once severe PE is diagnosed. If the delivery is done before 32 weeks, steroids are given to promote fetal lung maturity and caesarean section is advised. After 34 weeks, vaginal delivery is preferred [38].

82.3 Hellp Syndrome

The HELLP syndrome is characterized by haemolysis with microangiopathy, elevated liver enzymes and low platelet count. It complicates 2-12% of patients with severe preeclampsia (0.2-0.6% of all pregnancies)2. It is associated with high maternal morbidity but not mortality. Perinatal mortality, on the other hand, ranges between 7 and 20% [39]. The rate of recurrent preeclampsia in patients who had HELLP syndrome is around 20%, whereas the rate of recurrence of HELLP ranges between 2 and 19% [40].

82.3.1 Pathophysiology and Clinical Features

The HELLP syndrome belongs to a group of thrombotic microangiopathy disorders, together with the haemolytic uremic syndrome. The alteration in the maternal-fetal immune balance induces platelet aggregation, endothelial dysfunction and arterial hypertension. Furthermore, excessive activation or defective regulation of the complement system plays a major role in HELLP, leading to enhancing of procoagulant activity and thrombosis [41].

There are no diagnostic clinical features to distinguish HELLP from preeclampsia [40]; most patients present with upper abdominal pain, headache, nausea and vomiting, edema and weight gain, hypertension and proteinuria [2]. Symptoms typically develop during the third trimester, however, second trimester and postpartum presentations are also possible (up to 25%). Shortness of breath and chest pain with no other symptoms have also been described [42]. Some patients can be asymptomatic.

The diagnosis requires the presence of the three laboratory criteria: microangiopathic haemolytic anaemia (schistocytes in blood smear), elevated aminotransferases (AST or ALT >70 U/l), and thrombocytopenia (<100,000 cells/µl). Lactate dehydrogenase (LDH) levels in serum are also elevated.
Computed tomography (CT) of the liver may show subcapsular haematoma, intraparenchymal hemorrhage or infarction or hepatic rupture [43].
Other complications associated with the HELLP syndrome include acute renal failure, disseminated intravascular coagulation, abruptio placentae, the adult respiratory distress syndrome (ARDS), intracranial hemorrhage (intracerebral, intraventricular and retinal [44-46]) and retinal detachment. Ischemic cerebellar strokes have also been reported [47,48]. Cerebral angiography or transcranial Doppler sonography may reveal diffuse vasospasm [43]. Vasogenic cerebral edema has been also reported [49].
It is important to differentiate between the HELLP syndrome and acute fatty liver of pregnancy (AFLP) because they may have the same clinical presentation. AFLP will present more frequently with prolongation of prothrombin time (PT) and activated thromboplastin time (aPTT), hypoglycaemia, and elevated creatinine levels. Patients with thrombotic thrombocytopenic purpura (TTP) will more often have fever than those with the HELLP syndrome [50]. Acute myelogenous leukaemia mimicking the HELLP syndrome has also been described [51].

82.3.2 Management

Management of the HELLP syndrome includes stabilization of the mother (hypertension, seizure prophylaxis), fetal monitoring, and early delivery. Delivery is the only definitive therapy.
Antihypertensive drugs used in HELLP are the same as those used in PE. Prophylactic magnesium sulphate should also be given to prevent seizures. Platelet transfusion is indicated if there is significant maternal bleeding or if the platelet count is <20,000 cells/µl. Plasma exchange with fresh frozen plasma (FFP) could be considered if thrombocytopenia, haemolysis and organ dysfunction persist >72 hours postpartum [52].
The use of dexamethasone in patients with the HELLP syndrome is controversial. Previous studies have shown that dexamethasone is associated with faster platelet count recovery and shorter hospitalization [53]. However, a recent randomized trial showed no benefit of dexamethasone compared to placebo in the resolution of laboratory or clinical parameters, frequency of maternal complications, need for rescue therapy, or length of hospitalization54. Corticosteroids are recommended in patients with less than 34 weeks of pregnancy since they improve perinatal outcome by accelerating fetal lung maturity.
Hepatic hemorrhage without rupture (subcapsular haematoma) is managed conservatively with close monitoring, correction of coagulopathy by transfusion of blood products and consideration of percutaneous embolization of the hepatic arteries. Surgical intervention is indicated if the patient is haemodynamically unstable. Liver rupture is a life-threatening complication that requires aggressive supportive care and immediate laparotomy. Use of recombinant factor VIIa [55] and liver transplantation [56] have also been reported in patients with intractable hemorrhage.

82.4 Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disorder of neuromuscular transmission characterized by varying degrees of weakness and easy fatigability of the skeletal

muscles. Some 85% of patients with MG will have antibodies against the acetylcholine receptor (AchR) in the postsynaptic membrane of skeletal muscles, leading to a reduction in the available receptors and decreased neuromuscular transmission. Precipitants of MG crises include stress, systemic illness, infections, thyroid disorders, use of corticosteroids, surgery with general anaesthesia and pregnancy [57]. During pregnancy, the course of the disease is unpredictable; worsening of symptoms occurs more likely during the first half of pregnancy and postpartum [58].

82.4.1 Clinical Course

The course of MG during pregnancy is unpredictable. Many studies have shown worsening of symptoms in 40% of pregnant women with MG on average [59,60]. However, other studies showed an incidence of only 10-19% of worsening of symptoms, with the majority of patients remaining stable or improving (59% and 22%, respectively) [61,62]. On the other hand, almost all studies agree that most diagnoses of MG and deterioration episodes occur during the postpartum period. In a large Norwegian study, half of the diagnoses of pregnancy-associated MG were made in the postpartum [62]. A Taiwanese study of 12 pregnant women with MG showed that 11 women had clinical deterioration in the postpartum [60]. The highest risk for maternal mortality and clinical deterioration is within the first year after diagnosis, which is why delaying pregnancy for at least 1 to 2 years after diagnosis [63] is recommended. The course in one pregnancy does not predict the course in subsequent pregnancies [61].
Transient neonatal MG, due to the crossing of maternal antibodies through the placenta into the fetal blood, has been reported to be between 10 and 20% [64]. The duration of illness and therapy of women with MG does not correlate with the manifestations of neonatal MG [65]. Preterm rupture of amniotic membranes was also reportedly higher in the MG group [66].

82.4.2 Management

MG crises are usually due to severe dysphagia and aspiration. In the NSICU they could arise after the use of neuromuscular junction blocking medications. The initial manifestations of respiratory failure are mild and can be missed. It is recommended to follow arterial gases and pulmonary function tests. PaO_2 <60 and $PaCO_2$ >45, vital capacity <15 ml/kg and a negative inspiratory force (NIF) of less than -25 cmH_2O are indications for elective intubation and mechanical assistance. Due to decreased pulmonary compliance, plateau airway pressures up to 35 cmH_2O can be tolerated without alveolar overdistension [67]. Most patients with MG will be extubated within 2 weeks [68], however tracheostomy should be considered if this time is longer.
Fetal monitoring such as non-stress tests and fetal breathing can be unreliable in patients with MG since fetal movements can be affected. The use of magnesium in women with preeclampsia and MG is contraindicated due to increased neuromuscular blockade [69]. Patients might experience fatigue during the expulsive phase of labour due to weakness of the striated muscle of the pelvic floor, which could lead to the use of outlet forceps or vacuum extraction. The incidence of postpartum hemorrhage can be higher also. It is recommended to perform close monitoring of respiratory function during labour since fatigue and hypoventilation have been described in patients with MG. Parenteral administration of medications like neostigmine are preferred over oral medications due to errant intestinal absorption. Caesarean sections are performed more frequently in women with MG [66].

The treatment of MG during pregnancy is no different from non-pregnant population, but some considerations should be taken. Acethylcholinesterase inhibitors (neostigmine and pyridostigmine) remain the keystone of treatment. Breastfeeding should be avoided since these medications are excreted with the milk. Corticosteroids should be continued (if they were started before pregnancy) [70], but stress doses are recommended during labour. Other medications, like azathioprine, cyclosporin A and methotrexate should be avoided due to maternal and fetal risks [59,61,62]. Thymectomy during pregnancy has beneficial results [61], even in the incidence of neonatal MG62. Plasmapheresis and intravenous immunoglobulin (IVIG) are effective for MG crisis [71-73] and can be used during pregnancy.

82.5 Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute inflammatory, demyelinating polyradiculoneuropathy characterized by progressive motor weakness, areflexia, and ascending paralysis. Symptoms are preceded by back pain or leg paraesthesias in 50% of patients. Cerebrospinal fluid shows elevated protein levels without cells. Finding prolonged distal latencies and F-waves as well as anti-ganglioside antibodies will strength the diagnosis [74,75].

82.5.1 Epidemiology

The incidence of GBS in the general population is approximately 0.75-2 in 100,000 per year [76]. During pregnancy, the relative risk is low (0.86) but increases during 30 and 90 days postpartum (2.21 and 1.47, respectively), suggestive of a putative hormonal role [77]. This might be explained by the increase of anti-inflammatory Th2 cytokines during pregnancy and the elevation of pro-inflammatory Th1 cytokines in the postpartum [78]. Maternal mortality is not affected by GBS, however, if the onset is during the third trimester, there is a higher risk for respiratory failure which can increase maternal mortality. Recent studies have shown that although ventilatory support was required in 33% of cases, mortality was zero [76]. Fetal survival is close to 96%. There has been only one report of congenital GBS from a mother with GBS [79].

82.5.2 Management

The management of GBS in pregnancy should be done in the NSICU and does not differ from its management in the general population. Supportive care should be offered to patients until muscle strength is regained. The use of plasmapheresis and intravenous immunoglobulins (IVIG) has been studied extensively in general population with GBS but not in pregnant women [80,81]. However, case reports with successful outcomes have been mentioned. Either IVIG alone [82-85] or plasmapheresis alone [86,87] or a combination of plasmapheresis and IVIG (in that order) [79,88,89] was successful in pregnant women.

One of the keys in the management of GBS is close monitoring of respiratory function. Assessment of forced vital capacity (FVC), the ability to cough and to protect the airway should always be considered in these patients. Respiratory failure is usually more insidious than in MG. If FVC is <1.5 l, patients should be admitted to the NSICU, and mechanical ventilation should be started if it is <15 ml/kg.

Autonomic dysfunction is seen in patients with GBS. Dysrhythmias and dramatic blood pressure fluctuations are the cause of admission to the NSICU. Fetal monitoring should

be carried out as indicated, although normal fetal activity is seen even during periods of maximal maternal paralysis.
GBS does not have an impact on uterine contraction and assisted vaginal delivery by vacuum extraction is preferred.
It is important to mention that the risk of venous thromboembolic disease (VTE) is higher in patients with GBS as well as in pregnant women. Thus, pregnant women with GBS should be treated prophylactically with unfractionated heparin or low-molecular-weight heparin. The use of inferior vena cava filters during pregnancy has not been reported, however, temporary filters with later removal have been used in small series of patients [82-85]. The management of VTE with anticoagulation during pregnancy follows the recent guidelines from the American College of Chest Physicians and is discussed in the Stroke section of this chapter.

82.6 Cerebrovascular Disease

The incidence of pregnancy-related stroke is higher than non-pregnancy-related stroke, with an incidence of 34.2 per 100,000 deliveries in one of the largest population-base studies performed in the United States to date [90]. In this study, the risk of stroke in-

Ischemic	• Watershed: severe hypotension, Sheehan's syndrome • Eclampsia: choriocarcinoma • Angiopathies: ▪ Infectious: syphilis, borreliosis, tuberculosis, malaria, Chlamydia pneumoniae, herpes zoster, mycoses ▪ Inflammatory: collagen disorders, granulomatous angiitis of the nervous system, sarcoidosis, Takayasu's disease ▪ Non-inflammatory: dissection, postpartum cerebral angiopathy, Moya-Moya, fibromuscular dysplasia, atherosclerosis, subarachnoid hemorrhage, vascular malformation ▪ Haematologic diseases: protein C, S, antithrombin III deficiency, factor V Leiden, homocystinuria, paraneoplastic coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, sickle cell disease, antiphospholipid antibodies, Sneddon's syndrome ▪ Cardiac or pulmonary disorders: infective or marantic endocarditis, atrial myxoma, fibroelastoma, rheumatic heart disease, mitral valve prolapse, prosthetic valve, patent foramen ovale, amniotic fluid/ fat/air embolism, atrial septal aneurysm, atrial fibrillation, acute myocardial infarct, dilated cardiomyopathy, peripartum cardiomyopathy, hereditary hemorrhagic telangiectasia ▪ Metabolic or channel dysfunction: CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), migraine ▪ Air, fat, amniotic fluid embolism
Intracerebral hemorrhage	Eclampsia, hypertension, cerebral venous and sinus thrombosis (see below), angiopathies (see above), choriocarcinoma, arteriovenous malformation (AVM), aneurysm, bacterial endocarditis, pituitary apoplexy, anticoagulation, cocaine abuse
Subarachnoid hemorrhage	Aneurysm, AVM, eclampsia, angiopathies (see above), choriocarcinoma, cerebral venous and sinus thrombosis (see below), bacterial endocarditis, pituitary apoplexy, anticoagulation, cocaine abuse
Cerebral venous and sinus thrombosis	Hematologic diseases (see above), volume depletion, brain, sinus or mastoid infection, eclampsia, caesarean section

Table 82.2. Causes of stroke during pregnancy.

creased with age (>35 years) and was associated with African–American race, migraine, thrombophilia or thrombocytopenia, smoking, lupus, cardiac disease, sickle cell disease, hypertension (chronic or gestational), postpartum hemorrhage, preeclampsia, transfusion and postpartum infection. Most strokes occurred at the time of delivery or postpartum (41% and 48%, respectively).

Cerebrovascular disease in pregnancy can be caused by three mechanisms: arterial infarction, hemorrhage or venous thrombosis. In one study, out of 16 patients with cerebrovascular disease, 9 had ischemia, 5 had hemorrhage, and 2 had venous thrombosis [91]. Kittner et al. showed that the relative risk of developing a cerebral infarction during pregnancy was 0.7 but increased to 8.7 in the postpartum period. Also, the relative risk of developing intracerebral hemorrhage was 2.5 during pregnancy and increased to 8.7 in the postpartum period [92].

There are different causes for developing stroke during pregnancy (Table 82.2). The hypercoagulable state caused by pregnancy, as well as anatomical changes and the presence of vasculopathy such as postpartum angiopathy, are risk factors that contribute to the development of cerebrovascular disease [93].

The diagnostic workup for stroke in pregnant women is similar that in non-pregnant women, with certain considerations for the radiologic procedures. The use of abdominal shields during CT and digital angiography (especially during the first trimester) will limit radiation exposure of the foetus to an acceptable 2 mRads [94]. Since there are limited studies referring to the exposure of the foetus to iodinated or gadolinium-based contrast (both cross the placenta), it is recommended to use low-osmolality CT contrast agents [95].

82.6.1 Ischemic Stroke

Preeclampsia and eclampsia are considered to be the most common cause of ischemic pregnancy-related strokes, accounting for 25-45% of cases [96]. Furthermore, the risk of ischemic stroke persists beyond pregnancy and puerperium. Women with a history of preeclampsia are 60% more likely to have a non-pregnancy-related ischemic stroke [97]. The risk of stroke is also increased in the adult offspring born from preeclamptic mothers [98].

Elevated blood pressure may play a role in the increased risk of stroke seen in women with preeclampsia. Martin et al. found that 96% of preeclamptic-related strokes had systolic pressures >160 mmHg right before the stroke. In contrast, sustained diastolic pressures >105 mmHg before stroke was not associated with the development of preeclamptic-related strokes [99].

Choriocarcinoma, a trophoblastic tumour associated with molar pregnancy, is another cause of pregnancy-related stroke. Approximately 20% of cases will metastasize to the brain, causing invasion of the cerebral vessels that will lead to local thrombosis and distal embolization or pseudoaneurysm formation and cerebral bleeding. Measurement of beta-human chorionic gonadotrophin in serum should be part of the stroke workup diagnosis in pregnant women, since its levels are markedly increased [100].

Postpartum cerebral angiopathy is characterized by reversible multifocal vasoconstriction of the cerebral arteries101. It presents with sudden headache, photosensitivity, vomiting, altered mental status, seizures and transient or permanent focal neurological symptoms. Transient ischemia, cerebral infarction and intracranial hemorrhage have been reported [102]. Multifocal segmental narrowing of the cerebral arteries, with reversibility and complete resolution after 4-6 weeks is the most common finding on neuroimaging studies [103,93]. Management with the use of systemic steroids [102], as well

as vasodilators, hypervolaemic therapy and cerebral angioplasty [104] has been reported in uncontrolled studies. Although most patients will improve with general measures, few will develop intracranial hemorrhage or progress to maternal death [105].

Paradoxical embolism, based on the presence of patent foramen ovale (PFO) which permits right-to-left shunting of venous emboli into the arterial circulation, has been reported as a cause of ischemic stroke during pregnancy [106]. Antiphospholipid antibody syndrome is a cause of spontaneous abortions, however, transient ischemic attacks and true cerebral infarcts have been reported during pregnancy and puerperium, leading to adverse pregnancy outcomes [107].

Peripartum cardiomyopathy, a type of dilated cardiomyopathy that presents during the last month of pregnancy or within 5 months after delivery, is a well-established risk factor for cardioembolic stroke [108]; and prophylactic anticoagulation is recommended.

Cervical artery dissection, associated with hormonal changes during pregnancy and straining of the arterial wall during delivery [109,110], has been reported in 6-7% of cases of pregnancy-related strokes.

The management of ischemic strokes during pregnancy is rarely done in the NSICU, except in large strokes, with potentially elevated intracranial pressure or need for respiratory and haemodynamic support.

Thrombolysis for the management of acute stroke during pregnancy is controversial. There are no large or controlled studies investigating its efficacy and safety during pregnancy. Reports of individual cases and small series have shown successful outcomes. Teratogenicity has not been reported with its use, but the risk for maternal hemorrhage is high. In a review of off-label thrombolysis for acute ischemic stroke, symptomatic intracranial hemorrhage was described in one of 11 pregnant women [111]. Another review of 172 pregnant women described maternal hemorrhage in 8% of patients after the use of thrombolytics [112]. The risk and benefits to mother and foetus must be carefully considered before using thrombolytics.

The use of aspirin during the first trimester of pregnancy is controversial [113]. Low-dose aspirin (<150 mg/day) appears to be safe during the second and third trimester of pregnancy. This was shown in a large randomized trial involving more than 9000 patients with preeclampsia [114], as well as women with recurrent fetal loss and antiphospholipid antibodies [115]. Low-dose aspirin may also be used for secondary prevention of stroke during pregnancy for high-risk women [116]. The potential risk of aspirin in pregnancy includes maternal and fetal hemorrhage and premature closure of the fetal ductus arteriosus. The use of other antiplatelet therapies like clopidogrel and dipyridamole has not been evaluated sufficiently during pregnancy.

Maternal deaths associated with ischemic events are uncommon, and when they do occur they usually result from secondary hemorrhage [117]. The risk of recurrence in subsequent pregnancies is 2.3% within 5 years, and even higher in patients with stroke of definite cause [118].

82.6.2 Hemorrhagic Stroke

The risk of intracranial hemorrhage (ICH) during pregnancy is higher than in non-pregnant women. Its incidence in the United States, taken from the Nationwide Inpatient Sample (from 1993 to 2002), was 6.1 pregnancy-related ICH per 100,000 deliveries and 7.1 pregnancy-related ICH per 100,000 at-risk person-years (compared to 5.0 in non-pregnant women) [119]. The increased risk of ICH associated with pregnancy was largely attributable to ICH occurring in the postpartum period. These numbers differ from those found in Chinese women, who had a higher incidence of hemorrhagic (65% of pregnan-

cy-related stroke) compared to ischemic stroke [120], with 58% occurring in the prepartum period [121]. Significant risk factors for ICH in pregnant women are advanced maternal age, African-American race, pre-existing hypertension, preeclampsia/eclampsia, coagulopathy, and tobacco abuse [119]. The in-hospital mortality rate for pregnancy-related ICH is around 20% [119], with an average maternal case-fatality of 30% [120]. The risk of ICH in a subsequent pregnancy is unknown [94].

The incidence of subarachnoid hemorrhage (SAH) during pregnancy is 20 per 100,000 deliveries [92], with the most common causes being ruptured cerebral aneurysm and arteriovenous malformations (AVM). Aneurysms are more likely to rupture in the later stages of pregnancy, and up to 6 weeks postpartum [109,122]. Advancing gestational age, haemodynamic and endocrine changes during pregnancy increase the risk of bleeding [122], which makes it difficult to extrapolate results from the non-pregnant population that shows a low risk of bleeding from small or anterior circulation unruptured cerebral aneurysms [123,124]. AVM accounts for almost 50% of all ICHs in pregnant women [125], with 94% occurring during pregnancy and only 6% during labor [122]. Rebleeding during pregnancy occurs in almost 30% of cases [125]. Non-aneurysmal SAH has been reported in the context of pregnancy-induced hypertension and eclampsia also [126].

Women with asymptomatic AVM or aneurysm may undergo correction by embolization, endovascular coiling or surgical clipping. Clipping of the aneurysm can be achieved during any stage of pregnancy and is associated with lower maternal and fetal mortality [94,122]. Endovascular coiling has been reported to be successful [127-129], however, exposure to radiation and contrast material during the first trimester still carries a risk to the foetus and is to be discussed with the patient [123,128].

The management of cerebral vasospasm from ruptured aneurysm does not differ from that in non-pregnant women. Induced hypervolaemia can be achieved with crystalloids or colloids, although there are no data supporting “triple H therapy” in pregnant women. Vasopressors should be used cautiously since they could decrease uteroplacental blood flow. Nimodipine is considered a category C drug by the FDA but it has been used during pregnancy before. Balloon angioplasty has been reported to be successful in eclampsia-related vasospasm [104] but it has not been used in SAH. Delivery is preferred after the aneurysm is secured, but that will depend on the pregnancy stage and viability of the foetus. Before 34 weeks, mother and foetus will need close monitoring until delivery. Vaginal delivery is preferred if pregnancy is at term, but caesarean should be considered on the basis of obstetrical principles with evaluation of risks [130,113].

Treatment of AVMs is the same as in non-pregnant women. However, in patients with high operative risk or inoperable lesions, conservative management should be pursued during pregnancy. Stereotactic radiosurgery and embolization are good options after delivery. Caesarean section is preferred in such cases. Surgery may improve outcome in low-risk surgical candidates and also in comatose patients with large haematomas [125]. Use of external ventricular drainage and intraventricular thrombolysis with r-tPA has been reported in intraventricular hemorrhage caused by Moyamoya disease in pregnant women with relative good outcomes [131-133].

82.6.3 Cerebral Venous Thrombosis

Pregnancy is a predisposing factor for developing cerebral venous thrombosis (CVT). Ischemic strokes caused by CVT have been reported to be 38% in Canada [134] and 39% in Taiwan [135]. The incidence in India is estimated to be between 200 and 500 cases per 100,000 deliveries [136], which is 30 to 50 times higher than in the United States (8.9 cases per 100,000 deliveries) [137]. Most cases occur in the puerperium (73%)

[135,138]. The death rate from all-cause CVT is 2-10%, although mortality is significantly lower for pregnancy-associated CVT [139].
Traumatic damage to the endothelial lining of cerebral sinuses and veins during labour, hypercoagulable states, and stasis of intracerebral blood flow may be the reason for the occurrence of most pregnancy-related CVT [140]. The risk of CVT increases with hypertension, advancing maternal age, caesarean delivery, associated infections and excessive vomiting during pregnancy [141]. Hypercoagulable state (like protein S and C deficiencies, lupus and antiphospholipid syndrome) has been found in 64% of pregnancy-associated CVT [135]. It is important to mention that protein S and anti-thrombin III levels are normally decreased during pregnancy [142], and that their levels should be repeated again after delivery before being attributed as a cause of CVT. Homocysteinaemia has also been associated with CVT during pregnancy [143].
Headache is the most frequent symptom of CVT and occurs in 75-95% of cases. Isolated intracranial hypertension with headache, vomiting and blurred vision (caused by papilledema) accounts for 20-40% of cases of CVT [138]. Post-delivery headache should not be easily attributed to spinal anaesthesia during labour [144], and prompt diagnosis of CVT should be made by magnetic resonance imaging/venography (MRI/MRV), helical CT venography or angiography [145].
Anticoagulation, fluid administration, antibiotics for infection, and measures to reduce elevated intracranial pressure are used in the management of CVT. Anticoagulation is usually given for 6 months in patients with idiopathic venous thrombosis and indefinitely in those with persistent or familial thrombophilic conditions. The use of unfractionated heparin and low-molecular-weight heparin is safe during pregnancy and supported by guidelines [116]. Close monitoring of activated partial thromboplastin time and factor Xa should be maintained, respectively, with the use of these two types of heparin. Because warfarin has teratogenic effects, its use is contraindicated at least during the first 12 weeks of pregnancy. The safety and benefit of anticoagulation, given the high risk of hemorrhagic conversion, has not been evaluated in pregnant women. Studies in the non-pregnant population have shown that anticoagulation is effective, even in patients with hemorrhagic venous infarction [146,147]. An uncontrolled study, showed a mortality benefit of using heparin in pregnancy-related CVT (24% vs. 45% of those who did not receive heparin), with only one fatal hemorrhage in the heparin group [148]. Also, combined intrathrombus r-tPA and IV heparin has been reported in one 9-week pregnant and two postpartum women with good outcomes [149,150]. Prophylactic anticoagulation during subsequent pregnancies is not indicated [145,151].

82.7 Pituitary Apoplexy

Hemorrhage within the pituitary gland is referred to as apoplexy, and ischemic infarction with necrosis of the gland was first described in 1937 by H.L. Sheehan in postpartum women. The exact pathophysiology of Sheehan's syndrome is unknown, but it is thought to be secondary to drastically reduced blood flow to an organ that enlarges in a closed space during pregnancy. It occurs in approximately 1-2% of women with significant post-partum hemorrhage (defined as >1-2 litres of blood and hypovolaemic shock). Asymptomatic pituitary apoplexy (PA) has been found in 10-30% of patients harbouring pituitary tumors [152,153], including patients with prolactin or growth hormone-secreting adenomas and lymphocytic adenohypophysitis [154-158].
There is a vast spectrum of presenting symptoms, ranging from headache and mild visual changes to adrenal crisis, coma, and death. Symptoms result from swelling and ex-

pansion of the hemorrhage, causing compression on nearby structures. Acute onset headache is the most frequent symptom [159]. Visual field deficits, especially bitemporal heteronymous hemianopia are found in 62% of cases of PA. Hypothalamic compression may lead to autonomic dysfunction, deficient thermoregulation and hormonal deficiencies. Involvement of the cavernous sinus and cranial nerves (III, IV, VI and V1 or V2) by lateral extension may lead to different degrees of ophthalmoparesis and pain. Hemorrhagic extension into the subarachnoid space can cause SAH or "chemical" meningitis [153,155]. Sheehan's syndrome presents with panhypopituitarism (hypotension, hypoglycaemia, lactation failure). Altered mental status and coma are seen in 19% of patients. Because this condition can be fatal, rapid diagnosis is important. MRI has shown to be 100% sensitive in the diagnosis of pituitary hemorrhage and adenomas and is considered the test of choice for final diagnosis.

The management of PA should be emergently started. Treatment of common electrolyte abnormalities and corticosteroid replacement (hydrocortisone at stress dosage) should be provided. L-thyroxine should also be given. Diabetes insipidus from compression on the pituitary stalk, hypothalamus or posterior pituitary gland may lead to profound water deficit, so that vasopressin or desmopressin (DDAVP) should be given [159,160]. Neurosurgical consultation for decompression is indicated if involvement of the visual pathway or progression of neurologic signs is present [161]. Bromocriptine is given in neurologically stable patients.

82.8 Status Epilepticus

Most seizures during pregnancy occur in women who already have epilepsy. During pregnancy most women will continue their previous level of seizure control, although 15-30% may experience an increase in seizures [162]. Status epilepticus (SE) occurs in only 1-2% of pregnancies. Pregnancy is not a risk factor for SE in pregnant women without a history of epilepsy [163]. A large prospective registry of antiepileptic drugs and pregnancy showed that 1.8% of pregnant women on antiepileptic drugs had SE, with a similar distribution across all three trimesters [164].

The differential diagnosis for new-onset seizures during pregnancy should be the same as in the non-pregnant population, after eclampsia is excluded, overall during the third trimester. Structural and metabolic changes related to pregnancy may precipitate new-onset seizures. Structural changes include intracranial hemorrhage of multiple types, cerebral sinus thrombosis, brain tumours and ischemic stroke; metabolic causes include hyperemesis gravidarum, hypoglycaemia, acute hepatitis (fatty liver of pregnancy or viral hepatitis), acute intermittent porphyria and infections [162,165]. Herpes encephalitis, the MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), and cavernous angioma have also been describe as causes of SE in pregnancy [166-168].

Pregnancy-induced changes in antiepileptic drug pharmacokinetics are a major factor affecting changes in seizure control in pregnant women with epilepsy, although compliance is also a significant factor. Increased plasma clearance of antiepileptic drugs with advancing gestation, has to be balanced against an increased ratio of unbound free-to-total drug level [169,170]. Therefore, free levels, and not total drug levels, should be checked every month during pregnancy in order to make appropriate changes in the dosage [171].

The effect of SE on the foetus is controversial. It has been related to increased spontaneous abortion and fetal death [172]; however, recent data have reported that only 1/36

pregnancies with SE was complicated with stillbirth, and none was associated with maternal mortality [164].
The treatment of SE should not differ from that in non-pregnant women, with the goal being always to stop electrical and clinical seizure activity early, giving support to the mother and fetus [173]. Intravenous vitamin B6 should be considered, since its levels may be decreased during pregnancy in pyridoxine-dependent epileptics [174,175]. Administration of intravenous antiepileptics should not be delayed because of concerns about teratogenic effects. Medications like phenytoin and valproic acid, with a high protein-bound rate, should be initially administered in lower dose to avoid toxic-free drug levels [176], however, full dosage can eventually be given if seizures continue [177,178]. There are no data about the use of midazolam for SE in pregnancy.
Delivery should be started if there is an obstetrical indication. Neonates should be supported in the neonatal ICU if benzodiazepines or barbiturates were given.

82.9 Management of Intracranial Hypertension During Pregnancy

The management of intracranial hypertension in pregnant women does not differ much from that in non-pregnant patients, apart from special consideration to the potential side effects of the drugs given to decrease intracranial pressure to the mother/foetus unit. Close communication between the obstetrician, the patient's family and the neurointensivist is the key to the best possible outcome.
Unfortunately, none of the various different measures taken to reduce intracranial pressure have been tested in pregnant women; however, there have been some reports of their use in pregnancy, with controversial results [179,180].
General measures like sedation, analgesia, head-of-bed elevation (to 30°), management of hyperthermia and even intubation with assisted ventilation should be considered the ABCs in the management of a pregnant patient in which intracranial hypertension is suspected.
Propofol is the drug of election in pregnant women who require intravenous sedation since it is considered a category B drug. Owing to its very fast onset of action (30 seconds) and short duration (3-10 minutes), it is used broadly in patients who need frequent neurologic exams. Careful monitoring of metabolic acidosis, hyperkalaemia, elevated CPK, triglyceride levels and possible infection is needed with prolonged use.
Etomidate by intravenous infusion has been recommended for sedation by the American Stroke Association guidelines for the management of intracerebral hemorrhage in non-pregnant adults [181]. This can be extrapolated to pregnant women since it is considered a category C drug. However, it is important to consider the potential adrenal insufficiency side effect it causes, which can lead to severe hypotension. Furthermore, previous studies showed increased mortality with etomidate infusion in trauma patients [182].
Benzodiazepines, including midazolam, are considered category D drugs during pregnancy, however, their use has been reported [179]. Although fetal outcomes are poor with its use, it may be used in special circumstances when no other sedatives can be administered.
In terms of analgesia, intravenous morphine and alfentanil are recommended for intracerebral hemorrhage [181]. Both drugs are category C/D in pregnancy and their benefits should be evaluated before being used in pregnant women. Remifentanil, a category C drug, has a very fast onset of action (1-3 minutes) with a short half-life (3-10 minutes).

Moreover, it tends to decrease the needed dose of propofol when used together for sedo-analgesia [183].

Other measures to decrease intracranial pressure are more invasive and include hyperventilation, osmotic therapy, barbiturate coma and hypothermia. Most might be associated with poor fetal outcomes but should be considered in life-threatening situations after discussion with the obstetrician and patient's family.

Hyperventilation is one of the most effective methods available for the rapid reduction of intracranial pressure, however, it has a transient effect (<6 h) and is associated with decreased cerebral blood flow, for which its use has declined considerably over the years. Also, the alkalaemia caused by hyperventilation can lead to a shift in the oxygen-hemoglobin dissociation curve to the left, which impairs the release of oxygen from maternal to fetal blood, causing hypoxemic damage in the fetus [184].

Mannitol is used in intracranial hypertension as an osmotic agent. It reduces cerebral water content, cerebrovascular volume and decreases intracranial pressure. Mannitol is considered a category C drug during pregnancy, crosses the placenta, and can cause fetal dehydration. Animal studies have shown an increase in fetal blood-brain barrier permeability caused by mannitol-induced hyperosmolality [185]. However, mannitol can be used in life-threatening situations during pregnancy at a dose of 0.25-0.5 g/kg of pregnancy maternal weight every 4 to 6 hours intravenously.

Barbiturates in high doses are effective in lowering refractory intracranial hypertension by depressing cerebral metabolic activity, which reduces cerebral blood flow and leads to a fall in intracranial pressure. Barbiturates are considered category D drugs and are contraindicated during pregnancy, however, they still can be used in life-threatening conditions. Infant monitoring in the ICU is recommended after birth if barbiturates were used.

Cerebral temperature is a major factor in ischemic brain damage. Hypothermia ameliorates brain damage by redistributing oxygen and lowering glucose consumption sufficient to permit tolerance to prolonged periods of oxygen deprivation. Furthermore, cooling to 32-34oC can lower refractory intracranial hypertension, but it is also associated with a high rate of complications including pulmonary, infectious, coagulation, and electrolyte problems [186]. Fetal bradycardia is associated with maternal hypothermia, which is usually reversible once normothermia is achieved. Animal studies have shown normal fetal survival after mothers were exposed to temperatures of 20-24°C for 20 minutes [187]. Long-term fetal complications of hypothermia have not been studied yet.

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83 Headache in the Emergency Department: Diagnosis and Management

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83.1 Introduction

Headache is a frequent source of care in the emergency department (ED), where it represents the fifth most frequent cause of consultation, accounting for 1-4% of all visits [1,2], and it is one of the most common reasons for calling the attending neurologist [3]. Nonetheless, most individuals who suffer severe headaches do not use emergency services for evaluation [4]. Most patients have primary headaches (migraine and tension headache), but headache may be a symptom of a variety of life-threatening conditions such as subarachnoid hemorrhage (SAH), intracranial hemorrhage, tumour, encephalitis, meningitis, vasculitis, venous sinus thrombosis and toxic-metabolic syndrome.
Clinical history and thorough clinical examination are useful in most cases to distinguish primary from secondary headache. It is extremely important to know and identify the warning signs that help us to exclude secondary causes. In a patient presenting with headache at the ED, the clinician must quickly determine the correct headache diagnosis and exclude secondary causes, assess the need and type of complementary examinations, including the implementation of the appropriate therapeutic options.

83.2 Primary or Secondary Headache

The most common headaches are called primary, in which there is no structural or metabolic cause explaining the symptoms, i.e., different variants of migraine and tension headache, accounting for over 90% of headache consultations.
We should not forget that, although primary headaches are not symptomatic of severe intracranial injury, pain treatment should not be delayed. The remaining percentage is secondary headaches, where the pain is a clinical manifestation of an underlying structural pathology [5]. In secondary headache, the diagnosis does not depend on headache characteristics, but rather is determined on the basis of the presence of a specific condition, as defined by the International Headache Society, in close temporal relationship with the headache.
Primary headache accounts for 64-98% of non-traumatic causes of ED presentation for headache [5-7]. The fundamental goal of the clinician encountering a patient with headache in the ED is to precisely identify secondary headache that could compromise the patient's life [8] (Table 83.1), especially the so-called dangerous headaches [9].

Primary headache	• Migraine • Trigeminal autonomic cephalalgias • Stabbing headache • Thunderclap headache • Hypnic headache • Headache associated with sexual acitivity or exercise • Cough headache	
Secondary headache	Traumatic	• Subdural/epidural haematoma
	Cerebrovascular disease	• Aneurysmal subarachnoid hemorrhage • Unruptured aneurysms • Stroke • Primary intracerebral or intraventricular hemorrhage • Arterial dissection • Cerebral venous thrombosis • Vasculitis (including temporal arteritis or giant cell arteritis) • Pituitary apoplexy
	Central nervous system (CNS) infections	• Meningoencephalitis (bacterial, viral, mycosis) • Brain abscess
	Non-vascular disease	• Intermittent hydrocephalus (colloid cyst) • Idiopathic intracranial hypertension • Intracranial hypotension (idiopathic or post-puncture) • Intracranial tumours • Chiari malformation • Optic neuritis
	Toxic or metabolic disorders	• Pheochromocytoma • Thyroid disease • Drug-induced • Substance withdrawal • Hypercapnia
	Hypertensive encephalopathy	
	Rhinosino-ocular diseases (sinusitis, acute glaucoma)	
	Secondary to systemic processes	

Table 83.1. **Most common causes of headache treated in emergency services. Modified from [10].**

83.3 Headache History

Clinical history taking is more important in headache than in any other neurological disorder. It is important to establish the location of headache, its intensity, form of onset and precipitating factors. The approach is different when it comes to patients with acute headache of recent onset or when a patient has recurrent episodes of long-term headache [8,10]. With regard to the time of evolution, the headache may be of recent onset or chronic or recurrent. In recent-onset headache, the question of the first episodes of primary headache should be considered, which may hereafter be recurrent, but we must also consider the possibility that it is a secondary headache. Defining the quality of pain is not often possible in the ED setting. Migraine is often hemicranial but it may also

be bilateral. Migraine attacks last longer than 4 hours without treatment. Cluster headache is unilateral and periorbital, accompanied by excruciating pain that typically appears in the classic form at regular intervals, usually 24-48 hours for certain periods (2-3 months) and then remitting during the rest of the year. Its average duration in 15-60 minutes (range 10-180 min) in 65% of patients. Tension-type headache is usually diffuse or arises in different locations.

The onset form and triggers are essential clues to diagnosis, especially when there is abrupt onset of pain [11]. In headache of a sudden onset, the presence of subarachnoid hemorrhage (SAH) must be excluded; it is therefore essential to perform appropriate examinations even if the headache is of short duration, had ceased before reaching the ED, and the neurological examination values are normal. Several prospective studies have shown that among patients with headache of sudden onset (reaching maximum intensity within 1 minute) the cause is an SAH in 11-25% of cases [3-10].

It is important to establish if the headache is triggered by intense physical activity or effort; also this fact leads to a possible diagnosis of SAH. An interesting aspect is so-called thunderclap headache. This kind of headache has a sudden onset, with maximum intensity, is often described by patients as the worst in their life, and precedes, in almost

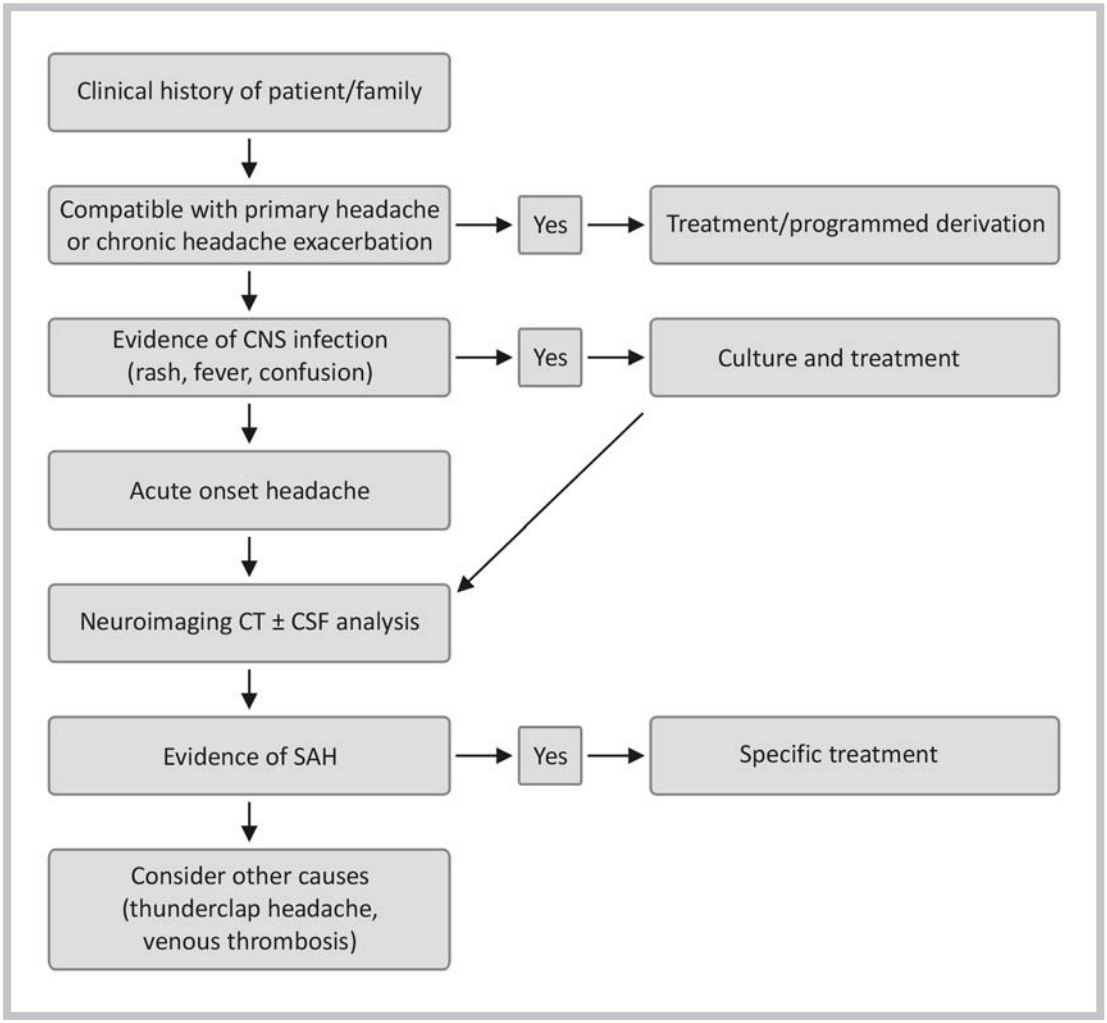

Figure 83.1. **Initial evaluation of headache in the Emergency Department. Modified from [10].**

Figure 83.2. 67-year-old patient with headache as manifestation of temporal arteritis.

half of cases, within a variable time, a SAH [5,9-12].

Although complete agreement is lacking, it is thought that in some cases it may be due to a minor bleeding (warning leak) – the so called "sentinel headache" – or be produced by aneurysmal expansion without rupture. It can be confused with influenza, migraine, sinusitis, etc. [13]. Therefore, urgent examination of normal brain imaging and normal cerebrospinal fluid (CSF) are required to exclude it.

Other cerebrovascular disorders, such as cerebral hemorrhage, cerebral venous thrombosis, malformations and unruptured aneurysms, arterial dissections, angiitis of the central nervous system (CNS), benign angiopathy, reversible hypertensive encephalopathy, certain medications and vasoconstrictors, and pituitary apoplexy can all cause thunderclap headache. Hypertension and hypotension of the CSF, meningitis, encephalitis, and sinusitis can also cause it. Therefore, the diagnosis of primary thunderclap headache is a diagnosis of exclusion. In primary thunderclap headache the headache may recur during the first week. There is no specific treatment; treatment is symptomatic and triptans and ergot should be avoided.

Headache due to increased intracranial pressure (e.g., tumours) runs a course that may be intermittent at first and then permanent. It improves with rest and worsens with Valsalva manoeuvres and effort. Its association with other neurological symptoms (diplopia, paresis, etc.) orients toward a symptomatic nature of headache (Figure 83.1).

One thing to keep in mind is the patient's age. Headache that starts after 50 years of age should lead us consider the possibility of temporal arteritis or other secondary aetiologies (Figure 83.2).

The onset of migraine attacks over age 50 years is very rare because over 90% of patients with migraine suffer their first seizure before the age of 40 years (Table 83.2).

Age at onset	New-onset pain or chronic headache
Type at onset	Acute, subacute or chronic
Duration	Temporal pattern and frequency of attacks
Migraine pain location	Holocranial, facial, occipital
Accompanying symptoms	Nausea, vomiting, phonophobia, photophobia, aggravation with physical activity, autonomic symptoms
Other symptoms preceding or accompanying pain	Photopsia, blurred vision, loss of vision
Pain features	Throbbing, squeezing, burning, stabbing, electric shock
History of headache	Personal/family, similar/different
Precipitating and aggravating factors	Alcohol, food, sleep, menstruation
Treatment	Drugs and dosages previously consumed and therapeutic response

Table 83.2. Headache history.

83.4 Physical Examination

It is necessary to perform complete neurological examination to look for any type of neurological deficit. Vital functions are also important: temperature, blood pressure, pulse, palpation of head and cranial (temporal and neck) arteries, especially in people over 50 years of age, and examination of the neck and shoulders.

Fundus examination is mandatory to rule out the presence of papilledema, a finding characteristic of increased intracranial pressure caused by tumour or venous thrombosis, signs of subhyaloid bleeding (typically associated with SAH) (Figure 83.3).

It is also important the evaluation of meningeal signs and auscultation of possible cervical-cranial murmurs. The presence of fever or rash should lead the physician to con-

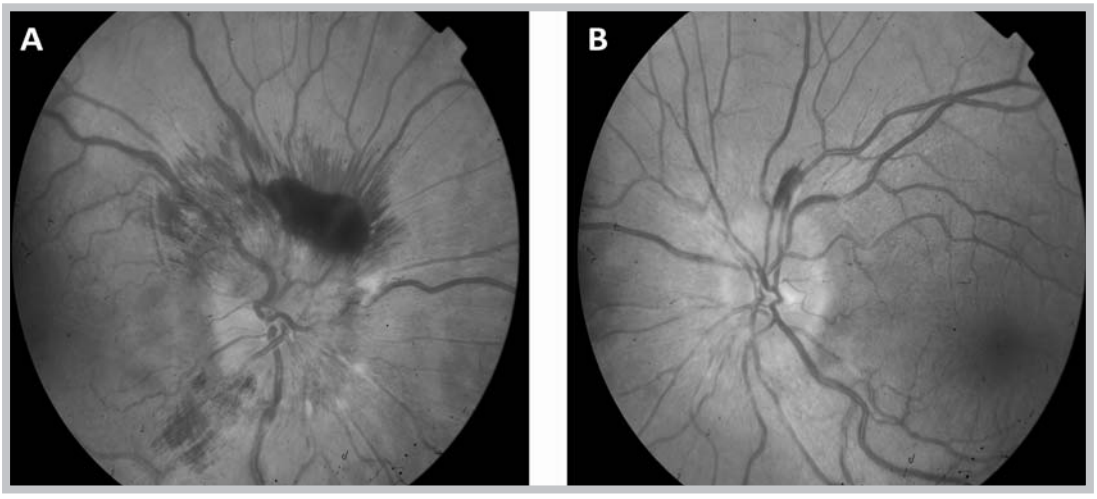

Figure 83.3. **Fundoscopy with bilateral papilledema. Optic disc swelling in a patient with a brain tumor; hemorrhage is also observed.**

- Severe headache, sudden onset
- Recent worsening of chronic headache
- Headache frequency and/or increasing intensity
- Unilateral location, always on the same side (except for cluster headache, paroxysmal hemicrania, occipital neuralgia, trigeminal neuralgia, migraine and other primary headaches consistently unilateral)
- Accompanying manifestations:
  - Conduct disorders or behavioural changes
  - Seizures
  - Focal neurological
  - Papilledema
  - Fever
- Nausea and vomiting not explained by primary headache (migraine) or systemic disease
- Presence of meningeal signs
- Headache precipitated by physical exertion, coughing or postural change
- Primarily nocturnal headache
- Atypical headache
- New headache in patients with cancer or AIDS
- Headache in immunosuppressed patients
- Headache in pregnancy or postpartum
- Progressive headache refractory to treatment

Table 83.3. **Alarm signs in headache.**

sider a diagnosis of meningitis. Blood pressure >120 mmHg diastolic and/or 200 mmHg systolic may cause headache. A unilateral Horner syndrome without symptoms of cerebral ischemia raises the differential diagnosis of arterial dissection and cluster headache. In cervical arterial dissections, it is relatively common that clinical manifestations are restricted to the presentation of neck, face or head pain with no symptoms associated with cerebral ischemia [14].

History taking and physical examination will help to identify the so-called "flags" criteria (Table 83.3) that suggest a secondary etiology [10-15]. The most important warning signs are pain that starts suddenly after physical exertion or Valsalva manoeuvres and has an explosive onset. Other warning signs are the appearance of headache in patients over 50 years of age, abnormal neurological examination, headache with autonomic symptoms or previous visits to the ED for any other symptoms accompanying the headache.

83.5 Risk Stratification. Complementary Studies

An algorithm is structured by assumptions and clinical scenarios that can be a useful tool for ordering and conducting additional tests in the ED.

83.5.1 Analytical Studies

In patients over 50 years of age it is necessary to order a C-reactive protein and erythrocyte sedimentation rate (ESR) test to rule out temporal arteritis. In those under 50 years, analytical examinations are not usually ordered unless there is suspicion of an infectious process or a history of repeated vomiting and dehydration or suspected electrolyte disturbances (at least electrolyte and renal function tests should be ordered).

83.5.2 Neuroimaging

As shown in the algorithm, the decision to obtain an imaging study is based on the clinical history. There are several clear indications, especially when clinical data or findings on examination suggest a secondary headache when pain characteristics do not conform to a primary headache, and especially in the presence of alarm criteria [15-19].

Indications for head CT in the ED	• Acute-onset severe headache • Subacute with progressive worsening • Associated neurological deficit • Papilledema or nuchal rigidity • Nausea and vomiting, fever unexplained by systemic illness • Not classifiable by history • Headache in patients who doubt the diagnosis, in those with marked anxiety or fear of a possible serious intracranial process
Indications for MRI in headache	• Hydrocephalus on cranial CT to reveal obstruction • Suspected space-occupying lesions in the posterior fossa, sella or cavernous sinus • Cough headache, in order to exclude Chiari type I disease • In intracranial hypertension with normal CT, in order to exclude cerebral venous thrombosis • Suspected CSF hypotension headache

Table 83.4. Indications for CT and MRI in headache.

For the assessment of brain parenchyma, the imaging study of choice is an urgent computed tomography (CT), initially without contrast material. On the contrary, if we suspect a Chiari malformation or cavernous sinus pathology, magnetic resonance imaging (MRI) is preferred. It must be remembered that CT has a lower sensitivity in visualizing lesions of the posterior fossa, sella, cavernous sinus, malformations of the occipito-vertebral hinge (Chiari malformation) or in some specific entities that produce headache secondary to CSF hypotension or cerebral vein thrombosis. The sensitivity and specificity of CT for diagnosing SAH (Figure 83.3) are higher than 98% [20].

83.5.3 Study of Cerebrospinal Fluid

Cerebrospinal fluid analysis should be performed if there is clinical suspicion of CNS infection or SAH with inconclusive CT findings. CSF examination is essential in cases of clinical suspicion of SAH with normal CT. Only exceptionally, when puncture is performed in the early phase of bleeding, the CSF may be normal [21]. It is not uncommon that there is suspicion of a SAH after traumatic lumbar puncture with contaminated blood. In such cases, the doubt can be resolved by performing a lumbar puncture in another interspinal space. It may also be useful to perform a differential count on the number of red blood cells per ml among samples from three different tubes, but xanthochromia has much more value and utility for distinguish between traumatic lumbar puncture or SAH [10]. Xanthochromia should be quantified by spectrophotometry, which can persist in more than 70% of cases after 3 weeks. Xanthochromic liquid can also be seen in the presence of protein levels, hyperbilirubinaemia or hypercarotinaemia. Lysis of erythrocytes with the release of oxyhemoglobin, bilirubin and methemoglobin pigments takes place within a few hours of bleeding. Oxyhemoglobin can be detected within 2 hours and hemoglobin in around 10 hours [13,23-25].
In case of suspected meningitis, encephalitis or SAH with normal CT, lumbar puncture is indicated. In general, brain CT should be done before performing a lumbar puncture because of the risk of herniation (and death) associated with the presence of intracranial space-occupying lesions. Liquoral study is not indicated in patients with a brain abscess.

83.6 Secondary Headaches

The constellation of fever, malaise, headache and purulent rhinorrhoea are characteristic of acute sinusitis. Characteristically, pain intensity increases when bending forward and its location varies depending on the sinus involved, being frontal when the frontal sinus is involved, antral with frontal irradiation in case of the maxillary sinus, retro-orbital and midline in case of haemoptysis, and posterior or anterior in case of sphenoid [26].
A new onset of **arterial hypertension** can be a cause of headache; and in pregnant women, blood pressure measurement should be performed at the onset of headache.
The presence of an elevated ESR (>50) in patients over 50 years of age should arouse suspicion of **temporal arteritis**, which is usually present with hemicranial headache with frontotemporal predominance, jaw claudication, constitutional symptoms (asthenia, anorexia, sweating) and visual disturbances that can lead to permanent blindness if corticosteroid therapy is not initiated early. On examination, hardening of the artery, absence of a palpable pulse and pain on palpation can be present. Treatment with prednisone 1 mg/kg/day should be started, with a subsequent tapering down.
Closed-angle glaucoma causes intense pain in the eye and orbit, and vegetative symptoms are often associated with a significant unilateral loss of visual acuity. Physical ex-

amination shows red eyes, median pupil unresponsiveness and increased intraocular pressure. If the headache is associated with neck pain, arterial dissection should be included in the differential diagnosis.

There are also headaches **induced by certain medications** such as nifedipine, nitroglycerin, dipyridamole or sildenafil. Sometimes the headache may be an accompanying symptom or the only symptom of myocardial ischemia. Typically, the headache is triggered by exercise and disappears at rest or after administration of sublingual nitroglycerin [27].

83.7 Headache in Cerebrovascular Disease

Headache occurs at the onset of some nosologic entities of cerebral vascular disease. The one most frequently is associated with headache is SAH (98%), and it may have a prognostic value when there is an arterial aneurysm. It is also frequent in intracerebral hemorrhage and much less often seen in atherothrombotic brain infarction and cardiac embolism.

If the pain is cervical or facial, the underlying process is likely to be dissection pressure. In certain circumstances it is possible that the clinical manifestations are limited to neck, face or head pain, oculosympathetic paralysis associated with ipsilateral Horner syndrome without symptoms of cerebral ischemia, raising the differential diagnosis with cluster headache or a variant migraine.

83.8 Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is due to primary blood extravasation primarily and directly into the subarachnoid space. This distinguishes it from secondary SAH, where the bleeding comes from another location, such as the brain parenchyma or ventricular system. Here we refer to primary SAH. The most common cause (85%) is rupture of an aneurysm, followed by non-aneurysmal perimesencephalic SAH with excellent prognosis (10% of cases), and finally a strange miscellany of other aetiologies (vascular diseases, tumours, etc.) [29].

Although the classic presentation of sudden, intense headache, meningism and focal neurological signs is quite recurrent, it is not unique, and some patients may have other symptoms [30].

Therefore, the degree of suspicion should be high in the presence of an atypical headache (“the worst I have had”, according to patients, very intense or different than usual), especially if associated with any of the following signs and symptoms: loss of consciousness, diplopia, seizures or focal neurological signs.

The existence of a retinal or subhyaloid hemorrhage in this context confirms the diagnostic probability. The most common test is brain CT scan, indicated in an emergency, with a sensitivity of 98% when performed within 12 hours after onset, 93% within 24 hours, and 50% within the week of the episode [30]. There is blood, with a hyperdense area in the subarachnoid space at the convexity or in the basal cisterns. This will allow to identify certain complications (cerebral edema, hydrocephalus, cerebral infarction). If the CT scan is negative, equivocal or the image quality is inadequate, the diagnosis must be confirmed by lumbar puncture. The presence of hemorrhagic CSF is a diagnostic indicator. In case of doubt, the CSF should be centrifuged and examined for signs of subacute hemorrhage, such as xanthochromia and oxyhemoglobin or bilirubin.

Cerebral angiography is still considered the gold standard for diagnosis of cerebral aneurysmal disease. However, this method is invasive and not without neurological and/or non-neurological complications that can be permanent.

Currently, CT angiography or MR angiography are routinely used to search for aneurysms in individuals with a high probability of having them: family members of patients with aneurysms, patients with fibrous dysplasia and polycystic kidney disease. The images are usually of good quality and show the aneurysm size, its neck, and its relationship with the originating and surrounding vessels (Figure 83.4).

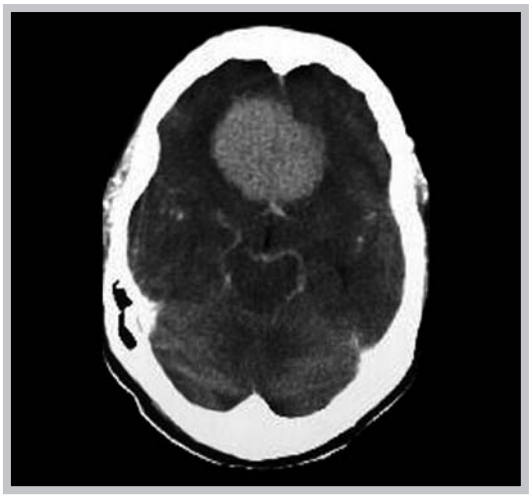

Figure 83.4. **Brain CT with contrast. Frontal meningioma.**

Pituitary apoplexy is a rare entity, clinically characterized by a sudden onset headache followed by vomiting, vision changes, ophthalmoplegia, and decreased level of consciousness [31]. It may be indistinguishable from SAH [32]. The clinical syndrome usually evolves from a few hours to 2 or 3 days. However, stroke may be an incidental finding on tumour resection, subclinical pituitary apoplexy, without prior symptoms.

The incidence varies in different series of surgically treated pituitary adenomas (range, 0.6-9.1%). We believe that MRI, and diffusion and perfusion sequences in particular, add important information for the comprehensive assessment of patients with pituitary apoplexy. MRI not only allows to fully evaluate tumour characteristics and size, but also helps to assess areas of cerebral ischemia and vascular compromission. The most recent application of neuroimaging techniques may be helpful in the correct evaluation of the extent of injury and the decision for early or delayed surgery in these patients.

83.9 Cerebral Venous Thrombosis

Headache is the most common symptom (80-90%) and often present in cerebral venous thrombosis [33]. In this condition, early diagnosis is crucial, given the high probability of recovery when anticoagulant treatment is promptly initiated. It has no specific features, and it's often diffuse with a wide variation in severity.

Around 25% of patients with intracranial hypertension have venous thrombosis. The presentation is usually subacute (days), but it can be acute or chronic. It is a persistent pain that worsens with recumbency and is exacerbated by Valsalva manoeuvres. It's often associated with other signs of intracranial hypertension, focal deficits or focal seizure syndrome.

Migrainous infarction. This entity is defined as one or more symptoms of migraine aura not fully reversible within 7 days, associated with the presence of infarction on neuroimaging studies. It's not always easy to determine if it originates from a migraine attack, especially in patients who have associated vascular risk factors. Its diagnosis is necessary to exclude other causes of stroke by appropriate examinations. Although its mechanism is not fully understood, the epidemiological association between the two entities is unquestionable [34].

83.10 Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) is characterized by increased intracranial pressure without evidence of intracranial pathology. This is a relatively common disease with an incidence of approximately 1-5/100,000 patients/year. It is much more common in obese women of reproductive age, with a male: female ratio of 15:1. Intracranial pressure is high (>200 mmH_2O), as measured by monitoring the epidural or intraventricular pressure or by lumbar puncture. In general, the diagnostic criteria for IIH are based on the symptoms and signs of intracranial hypertension (ICH) and in the absence of laboratory-test abnormalities, including CSF analysis and neuroimaging – preferably magnetic resonance (MR) angiography. Headache is a common symptom of IIH, so that headache associated with IIH is included in the classification of the International Headache Society. However, the characteristics of headache in IIH can be heterogeneous and often present a clinical profile similar to that of some temporary primary headaches. In conclusion, headache associated with IIH presents nonspecific characteristics which can sometimes mimic either primary headache or tension-type headache.
Detailed history taking is essential to search for additional symptoms such as visual disturbances, diplopia, or tinnitus. Fundus examination is mandatory.
The headache must meet one of the following characteristics: daily presentation, a diffuse and/or constant ache (not pulsed) or aggravated by coughing or exertion. It has been observed that about 70% of headache patients have visual disturbances with different characteristics such as blurred vision, decreased visual acuity or visual appearance of scotomas. Less common is the onset of diplopia or cranial nerve VI alterations, which occur in nearly one in three patients with headache. These visual symptoms serve as diagnostic support for suspected ICH [35].

83.11 CSF Hypotension Headache

Intracranial hypotension syndrome is usually secondary to lumbar puncture or trauma. It is characterized by the postural headache associated with low CSF pressure. In healthy humans, the mean CSF pressure is 150 mmH_2O (range 65-200 mmH_2O) in the decubitolateral position. The symptoms of intracranial hypotension occur at pressures <65 mmH_2O.
The brain is held in the cranial cavity and floats on the CSF; the brain's weight in air is 1500 g but only 50 g in the CSF. Therefore, if the volume of CSF is decreased, the

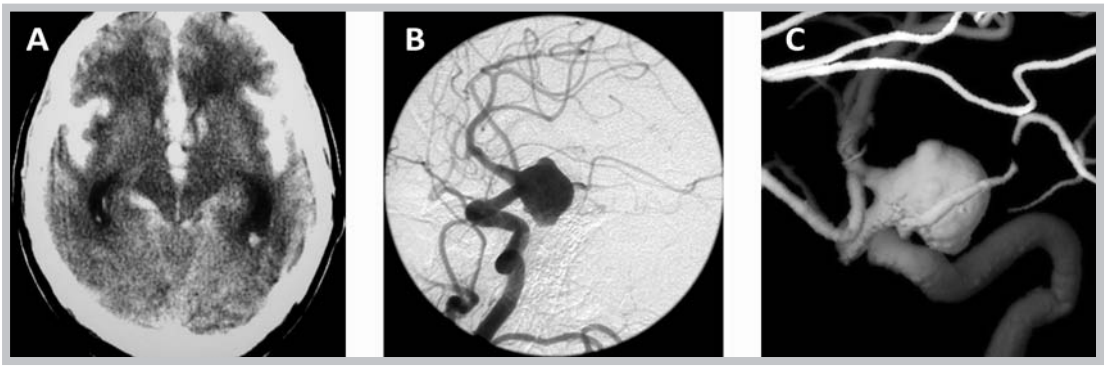

Figure 83.5. **Brain CT without contrast. Angiography and CT neuroimaging study in a patient with massive subaracnoidal hemorrhage and saccular aneurysm.**

brain descends retrocaudal, carrying with it pain-sensitive structures, particularly cranial nerves V, IX and X, and the first three cervical roots. This downward shift is most evident in the standing position, owing to the effect of gravity, and thus worsens the headache. In intracranial hypotension, headache is a constant symptom rather than hypertension. According to the criteria of the International Headache Society, intracranial hypotension can be classified into:

- Spontaneous without evidence of CSF leakage or systemic disease.
- Symptomatic after lumbar puncture (diagnostic myelogram, anaesthesia), trauma (cranial or spinal), postoperative (craniotomy, spinal surgery, post-pneumonectomy), malfunctioning CSF shunt, liquorrhoea, pituitary tumour, systemic disease (dehydration, diabetic coma, hyperpnoea, meningoencephalitis, uraemia, systemic infection).

If there is no clinical history of lumbar puncture, the hypotension should be confirmed by lumbar puncture and CSF pressure measurement. MRI with gadolinium shows diffuse dural uptake (Figure 83.5). MRI is a sensitive technique to locate CSF leakage, but its value has to be established when taking the patient's clinical data into consideration [36].

83.12 Primary Headache Treatment in the Emergency Department

83.12.1 Migraine

Migraine accounts for 37-48% of presentations at the ED for headache. It is characterized by a progressive-onset headache that lasts between 4 and 72 hours, often accompanied by nausea, vomiting, phonophobia and photophobia, and typically worsens with physical activity (Table 83.5).

In general, patients have previously experienced similar attacks and the reason for seeking attention in the ED is that the pain has not responded to usual treatment. According to the International Headache Classification, acute attacks of migraine (72 hours of evolution) of known status is distinguished from the so-called "migraine status", when migraine pain lasts more than 72 hours and is very disabling [5].

Any analgesic or nonsteroidal anti-inflammatory drug (NSAID) may resolve a moderate-intensity crisis, but the most commonly used are oral naproxen or ibuprofen, intramuscular diclofenac 75 mg and intravenous ketoralac (30-60 mg) [37,38].

Criteria	Description
A	At least 5 attacks fulfilling criteria B, C and D
B	Headache attacks lasting 4-72 hours (when not treated or treatment not successful)
C	Headache has at least 2 of the following characteristics: • Unilateral location • Pulsating quality • Moderate intensity or severe pain • Aggravated by routine physical activity (e.g., walking or climbing stairs) or conditions to avoid such activity
D	Pain associated with at least one of the following symptoms: • Nausea, vomiting or both • Photophobia and phonophobia
E	Pain not attributable to another disease

Table 83.5. **Diagnostic criteria for migraine without aura.**

Patients with nausea and vomiting may be given metoclopramide associated with NSAIDs for pain [39,40]. Clinical trials have shown that metoclopramide has, in itself, an analgesic effect on migraine [41].

In an acute migraine of severe intensity that motivates an ED visit, first of all it should be determined whether the patient can tolerate oral medication. If oral medications cannot be given, subcutaneous triptans (sumatriptan) or inhaled (sumatriptan, zolmitriptan) are indicated.

It should be remembered that triptans should not be administered if ergot or other triptans have been recent taken, which are contraindicated in patients with ischemic heart disease, intermittent claudication and uncontrolled hypertension. Sometimes, adequate hydration improves the symptoms.

If the patient is markedly anxious or has sleep disorders, benzodiazepines such as diazepam at low doses (5-10 mg) should be considered, which are often given in combination with NSAIDs intramuscularly (diclofenac and diazepam 5 mg). Chlorpromazine also has an analgesic effect and has been used in patients with migraine of long duration or status migrainosus. It can be administered IV or IM (0.1 mg/kg to 37.5 mg).

Side effects may include drowsiness and hypotension, so that when administered intravenously, it is recommended to administer 500 ml pre-saline solution and inject the medication slowly over at least 15 minutes [42].

In case of status migrainosus or long-lasting migraine, steroids such as dexamethasone or methylprednisolone could be used. Although no clinical trials have confirmed its effectiveness, most experts believe that dexamethasone is the treatment of choice in status migrainosus. The dose is not well established; a 4-20 mg bolus has been admin-

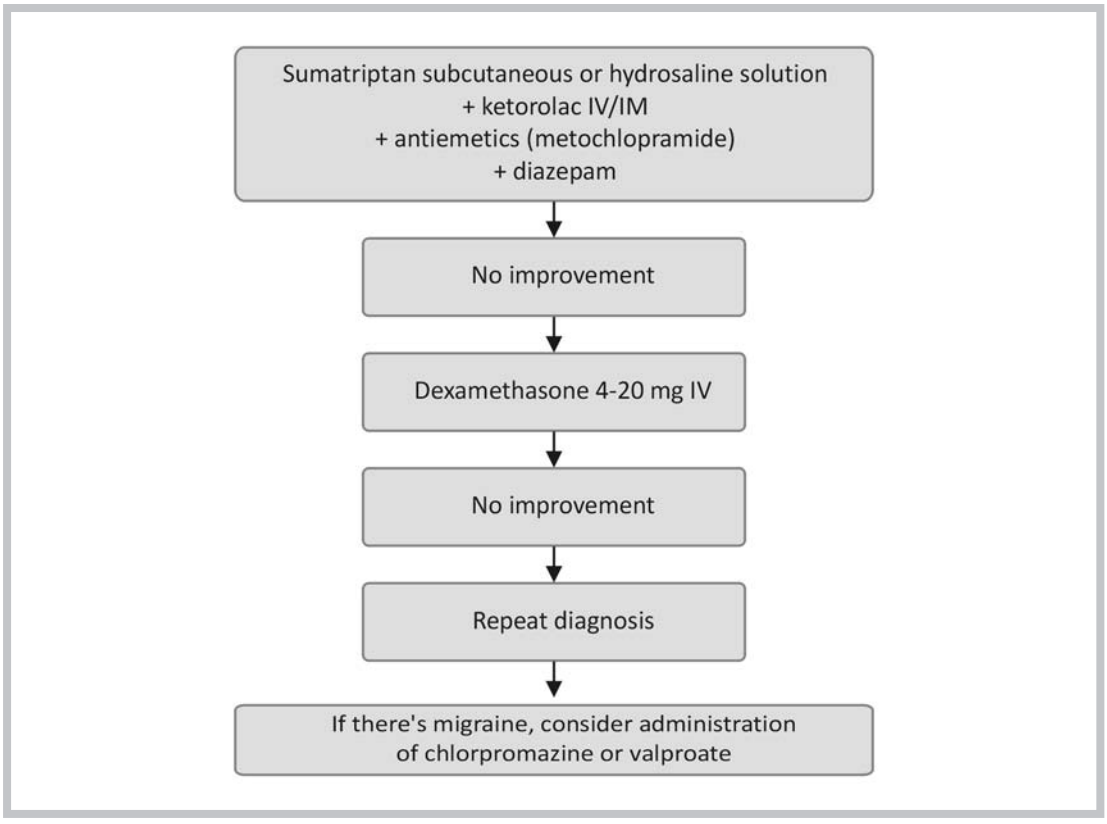

Figure 83.6. **Algorithm for the treatment of migraine and long-lasting migraine. Adapted from [8].**

istered, typically half a dose of 12-16 mg. Methylprednisolone may be administered during pregnancy.
Another possibility in emergency treatment is valproic acid. The doses are slightly lower than those used for treating convulsions and are administered by rapid infusion [43-45]. Therefore, in long-lasting migraine or in status migrainosus, subcutaneous sumatriptan or NSAIDs combined with metoclopramide are recommended. If the headache does not improve, the next step is to administer steroids. If the pain persists, the diagnosis should be reconsidered and, if the diagnosis of migraine is confirmed, chlorpromazine or valproate should be administered [46,47].

83.12.2 Cluster Headache and Other Trigeminal Autonomic Cephalagias

Trigeminal autonomic headache is the most frequent cluster headache. Patients present with a crisis of short duration (generally between 30 minutes and 3 hours), which is accompanied by different symptoms, from autonomic ipsilateral symptoms, to pain (lacrimation, rhinorrhoea, conjunctival injection and/or miosis), and a major state of anxiety. Unlike migraine, cluster headache attacks are accompanying by restless or agitation. Acute treatment is with subcutaneous sumatriptan (6 mg), whose effectiveness has been sufficiently demonstrated, or inhaled triptans, with modest effect, or oxygen [48,49].
Oxygen is effective in about 80% of patients. More than 9 litres per minute of inhaled oxygen should be administered to be effective. Generally, we recommend using 10 l/min high-flow oxygen. Since oxygen masks are normally perforated on both sides, the holes should be covered to increase treatment effectiveness; otherwise a mask a with reservoir should be used. Although the time required for oxygen to be effective is variable, it is generally recommended to apply it for 10-15 minutes.
The long-term approach to these patients should be made by neurologist [50].
SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) is a rare form of paroxysmal headache [50]. Most often it is idiopathic, although there are descriptions of cases secondary to lesions affecting the trigeminal nerve. The differential diagnosis of trigeminal neuralgia (TN) and SUNCT is not always straightforward and, indeed, some authors have expressed doubt that it is really two different entities. It is included within the trigeminal-autonomic headaches in Group 3 of the International Classification of Headache [5]; it is significantly more frequent in males, and the average age at onset is 50 years.
Presentation is defined by at least 20 attacks of unilateral, stabbing or pulsating type pain in the orbital, supraorbital or temporal region, and a duration of 5-240 seconds.
Pain occurs together conjunctival injection and tearing, and the attacks appear with a frequency between 3 and 200 a day. In 47% of cases of SUNCT, a nuisance baseline is described. The pain attacks may be triggered by tactile stimulation in a, trigeminal or extratrigeminal trigger zone [51,52] or by head movements. The pathophysiology involves a central origin, with generally bilateral hypothalamic activation, which disinhibits the trigeminal-autonomic reflex [50,53]. The pain is mediated by the first branch of the trigeminal, while autonomic symptoms derive from activation of the parasympathetic branch of the seventh pair, specifically, the greater superficial petrosal nerve. SUNCT has been reported secondary to posterior fossa pathologies such as strokes, tumours, vascular malformations, morphological alterations or arterial plaques of demyelination. The symptomatic control of SUNCT is usually not simple; while it may respond to antiepileptic drugs such as topiramate or gabapentin, the most effective responses are obtained with lamotrigine.

Nerve infiltration and the use of oxygen or indomethacin are ineffective. The differential diagnosis between SUNCT and NT of the first branch of the trigeminal nerve is quite often difficult. It is accepted that in NT painful episodes are shorter, about 6 seconds on average, respond to analgesic block, and have a refractory period. Autonomic symptoms are not prominent and generally appear during particularly intense and prolonged attacks, and a certain time after the onset of pain.
Good response to the administration of lidocaine has been described [54]. Vascular microdecompression has shown dramatic results in selected patients [55,56].

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Section 10.
Aspects That Shouldn’t Be Forgotten

84 Neurocritical Care for After Endovascular Procedures: Perioperative Management

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84.1 Introduction

Subarachnoid hemorrhage (SAH) is a life threatening critical neurologic illness, most often caused by a ruptured aneurysm that requires rapid diagnosis and critical care [1,2]. This is often preceded by a warning leak [3], such as headache [4]. SAH afflicts about 30,000 patients in the US each year, with higher percentages amongst Asian and Latin American Populations [5]. There is a "golden day" after SAH, namely the initial 24 hours, that are absolutely critical in which occlusion of the aneurysm and correction of physiological derangement must be timely done [6]. However, on a more global perspective, the critical care of SAH is sequential process with different treatment strategies based on the time after SAH. This starts with hemodynamic and airway stabilization, and progresses in a stepwise fashion to the diagnosis of aneurysmal bleed by computerized to-

	Treatments used	Goals
Initial stabilization		
Airway	Oxygen, ventilator	PaO_2=100; CO_2=40
Blood pressure	Nicardipine, labetalol	SBP <140 mmHg
Fluid	Normal saline	Euvolemia
Cardiac function	Fluids, beta blockade	No ischemia, normal cardiac output
Renal function	Fluids, $NaHCO_3$, N-acetyl cysteine	Avoid acute kidney injury
Glucose control	Insulin drip	Normal glycemia, 80-110 mg/dl
Intracranial pressure	Ventriculostomy	ICP <20 mmHg, avoid hydrocephalus
ICU post-coiling		
Blood pressure	Norepinephrine	SBP=120-220 mmHg
Fluid balance	Normal saline	Euvolemia to hypervolemia
Cardiac function	Fluids, beta blockade	No ischemia, normal cardiac output
Renal function	Fluids, $NaHCO_3$, N-acetyl cysteine	Avoid acute kidney injury
Sodium balance	Hypertonic saline, fludrocortisone	Na=138-145 mEq/dl
Glucose control	Insulin drip	Normal glycemia, 80-110 mg/dl
Intracranial pressure	Ventriculostomy	ICP <10 mmHg, clear excess blood from the CSF space
Temperature control	Surface or intravascular devices	T=36-37°C

Table 84.1. Goal directed neurocritical care for SAH.

mography and angiography, occlusion of the aneurysm, treatment of hydrocephalus, treatment of pulmonary and cardiac complications, diagnosis and treatment of vasospasm and treatment of early hydrocephalus. This stepwise treatment paradigm requires a multidisciplinary critical care approach [7,8]. Early endovascular treatment or surgical clipping of aneurysms is critical [9-13], but frequently a large number of critical care problems complicate the post-coiling care of the patient. In this chapter we will focus on the critical care of the post-coiling SAH patient. The goals of treatment are often time-based, and these goals change based on whether the aneurysm is coiled or not. Table 84.1 outlines the overview of the goal-directed neurocritical care for SAH. We will discuss this temporal strategy in sequence.

84.2 Preoperative Stabilization and Critical Care

It is standard practice to admit all SAH patients to an intensive care unit. Prompt attention to the airway and to hemodynamic instability is critical. Ideally, the patient should be admitted to a neurointensive care unit, with nursing staff specially trained to recognize evolving changes in the neurologic examination. Hourly neurologic checks, including measurement of the Glasgow Coma Scale and close attention to changing motor and pupil signs, are the primary clinical monitors to be followed. In addition, routine vital signs and measurement of mean arterial pressure and ICP are initial goals. To be more specific, there are three crisis domains that require goal directed critical care necessary for these patients: 1) cardiac crisis, 2) hyperglycemic crisis, and 3) intracranial pressure crisis. Cardiac crisis typically takes the form of stunned myocardium. This has many names including contraction band myonecrosis, and tako tsubo syndrome. In this cardiac crisis, there is an acute global hypokinesis with congestive heart failure and pulmonary edema. The electrocardiogram typically has widespread symmetric inverted T waves (Figure 84.1), and the troponin values are in the range of 1.0-10 ng/dl. The crisis is not due to coronary artery disease, although some believe that coronary artery vasospasm occurs in conjunction with this syndrome. Reduction in blood pressure, sedation, and fluid balance are typically needed to improve this syndrome. However, hypotension may occur in severe cases, due to cardiac shock, and patients may require inotropic support and mechanical ventilation for stabilization. The syndrome is rapidly reversible and typically lasts for 48-72 hours. In preparation for endovascular treatment, central venous access, arterial blood gas analysis, and hemodynamic support are necessary. The use of continuous infusion of low dose propofol in combination with a narcotic is typically sufficient to induce the level of anesthesia necessary for the endovascular procedure. The use of beta blockade, in the form of metoprolol or a similar agent, may lessen the duration of the cardiac crisis, but not all patients can tolerate this due to hypotension.

Figure 84.1. Example of electrocardiogram.

Hyperglycemic crisis is common acutely after SAH, and are due primarily to catecholamine induced stress. The glucose values typically are in the 200-300 mg/dl range. The severity of hyperglycemia correlates well with the clinical severity of the SAH, with Hunt Hess grades 4-5 hav-

ing the highest blood glucose levels. The degree of hyperglycemia however is an independent predictor of poor outcome, even when severity of SAH is factored in [8]. Hence, immediate evaluation and regularly scheduled glucose checks are needed. In the acute phase of SAH, with the potential for impending brain ischemia, glucose control is advisable, although the exact thresholds are presently unknown. Moderate glucose control with goals of 100-140 mg/dl seem to be a reasonable goal, in the absence of data suggesting otherwise.

Intracranial pressure (ICP) crisis related to acute hydrocephalus is a serious concern after SAH. Patients may develop hydrocephalus resulting in elevation of ICP to values ranging from 30-60 mmHg. Diagnosis is frequently made by computerized tomographic imaging. An example of this is shown in Figure 84.2. Placement of an external ventriculostomy catheter is frequently needed, and should be done before exposing the patient to the supine position for angiography and embolization.

Close attention to fluid balance, with a goal of early euvolemia, is necessary. This can be facilitated by placement of a radial arterial line and a central venous catheter into the subclavian or the internal jugular vein. Measurement of blood pressure and right atrial (RA) pressure allow for prompt control of hypertension and for management of fluid status. These patients often require control of systemic hypertension and volume resuscitation. Before the aneurysm is secured, the mean arterial blood pressure is ideally

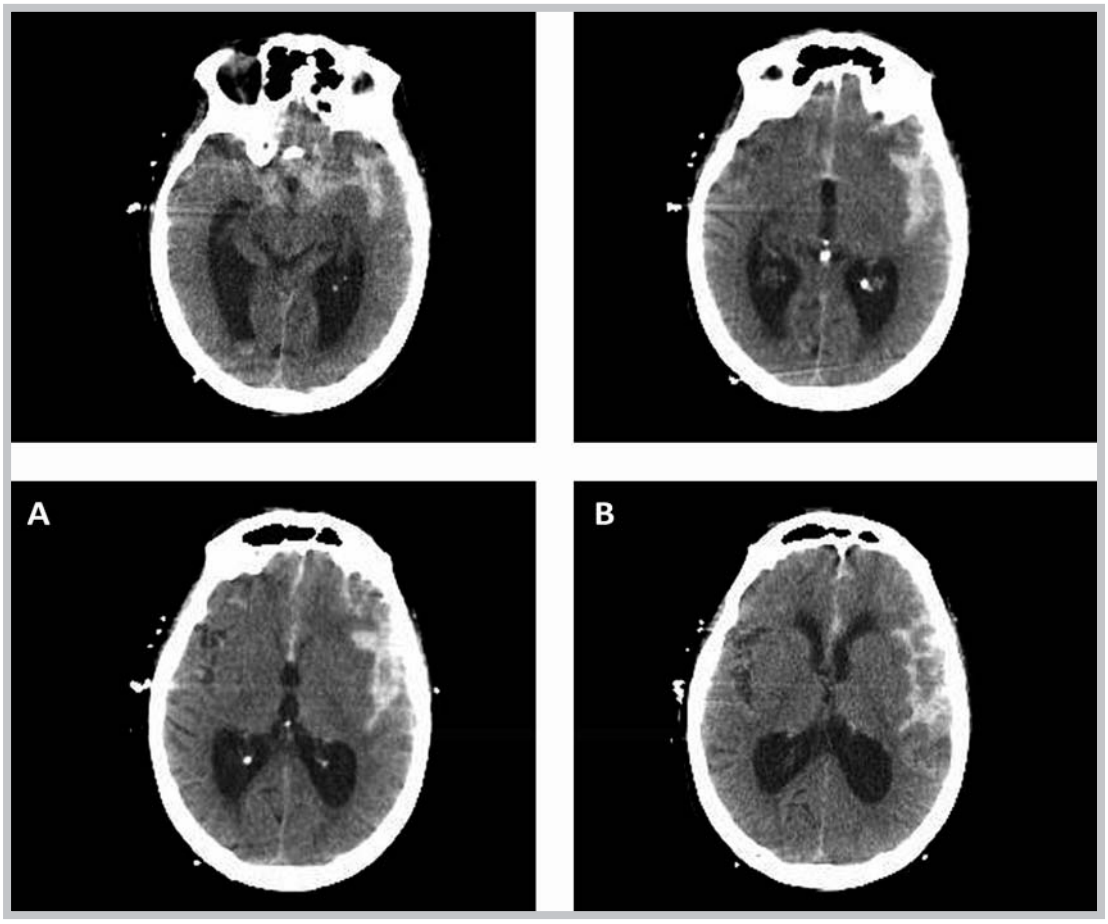

Figure 84.2. **Example of computerized tomographic imaging. Progressive wavelet level: 3-4 (A). Progressive wavelet level: full (B).**

kept at the lower range of blood pressure autoregulation (e.g., 80 to 90 mmHg), and the RA pressure at 5 to 10 mmHg. Agents that are commonly used include intermittent bolus doses of labetalol (10 to 20 mg every 1 hour) or other agents such as nicardipine or hydralazine. Antiadrenergic compounds are usually the most successful in treating the catecholamine-induced increase in blood pressure. If this does not work, then continuous infusions of esmolol or nitroprusside may be needed to control blood pressure. One must consider that reduction in blood pressure may also reduce cerebral perfusion pressure and thereby induce brain ischemia. Thus, if uncertain about ICP, clinicians should maintain the MAP above 90 mmHg to avoid ischemia. Preventing acute kidney injury is also an important consideration, given that patients are exposed to radiologic contrast agents. While there is no consensus about how best to prevent acute kidney injury, several options have been demonstrated to be of benefit [14]. Pre-angiography hydration and the minimum dose of intravenous contrast are the two most critical elements to prevent acute kidney injury during angiography. The use of N-acetylcysteine, sodium bicarbonate infusions, and acetozolamide have been advocated by many to be useful. In a randomized controlled trial, Merten et al. demonstrated that the use of sodium bicarbonate in the maintenance hydration fluid resulted in less contrast-related acute kidney injury.

84.3 Critical Care During the Endovascular Procedure

Until recently, the critical care of patients during the endovascular therapy has not received much attention. Important considerations during the procedure include adequate airway protection and oxygenation, sedation, blood pressure management, and management of ICP. Airway protection may be attained through the use of elective endotracheal intubation. If the patient is somewhat somnolent or has a preoperative Hunt and Hess grade of 3 or worse, then endotracheal intubation is indicated. Oxygenation and airway protection are further facilitated by adequate sedation. Sedation that can be easily adjusted and is rapidly metabolized is most useful and permits the interventional team to examine the patient intermittently if needed. Agents that fullfill these requirements include short-acting benzodiazepines, such as midazolam and propofol. Additionally short-acting inhalational agents may be used. A caveat that should be kept carefully in mind is that all of these agents may reduce blood pressure and consequently reduce cerebral perfusion pressure if autoregulation is impaired, which is often the case. Thus, close monitoring of blood pressure and supplemental use of vasoactive agents may be necessary to avoid adverse reductions of blood pressure.

Similar concerns of hemodynamic support and adverse cardiac responses to sedatives and anesthetics should be kept in mind during the intervention. Cardiac arrhythmias are well known to occur early after SAH, and they require prompt attention. Below, we consider several possible cardiopulmonary complications that may first arise during interventional treatment. A minimum of cardiac and central venous pressure monitoring has been our standard for making prompt diagnoses of such difficulties. Airway and respiratory support, with maintenance of the airway and normal carbon dioxide through endotracheal intubation and mechanical ventilation is critical.

Measurement of ICP and cerebral perfusion pressure is an important aspect of critical care during the endovascular treatment. A ventriculostomy permits drainage of CSF and subarachnoid blood, and it is the preferred method for acute management of changes in ICP, without the use of hyperventilation or diuretics (i.e., mannitol) [15]. These latter two methods of reducing ICP have adverse side effects, such as brain ischemia from hy-

perventilation or hypovolemia from mannitol-induced diuresis. These are best avoided in the acute phases of SAH. ICP should be maintained in a normal range of 15 to 20 mmHg. This range should permit adequate perfusion pressures while the risk of aneurysm rerupture is avoided. The latter may occur owing to unintentional overdrain-age of CSF or sudden changes in ICP. Thus, with use of the ventriculostomy, the drainage point should be set to a water level between 15 and 20 cm so that sudden declines in ICP are avoided. In addition to monitoring the acute angiogram and embolization treatment, the clinicians should monitor ICP during papaverine infusion and angioplasty for vasospasm, because they both have been associated with increased cerebral blood volume and increases in ICP. Finally, monitoring ICP can provide guidance as to the adequacy of sedation and blood pressure in the setting of a comatose patient who is unable to be adequately examined.

84.4 Post-procedural Neurocritical Care

84.4.1 Treating Medical Complications

Recently, Solenski and colleagues [16] have shown that medical complications after SAH are responsible for additional morbidity and mortality (approaching 40%), nearly equal to the primary neurologic morbidity. The attributable death rate caused by medical complications is approximately 23%. Thus, early assessment of arterial blood gases, chest radiograms and airway stability, and continuous pulse oximetry are required for the appropriate treatment of these patients. Indeed anticipation of full ventilator support during the period of aggressive intravascular volume therapy should be anticipated and the family and medical consultants informed and educated about this issue.

Acute pulmonary edema and hypoxemia are nearly universal in SAH [17]. This is because of neurogenic pulmonary edema and is not to be related to hypertensive, hypervolemic, and hemodilutional (HHH) therapy or fluid overload. Initial widened alveolar-arterial PO_2 gradients, pulmonary edema, and respiratory distress occur acutely in more than 80% of patients and lead to prolonged hospital stays and increased costs. In addition to the acute cardiac insufficiency, there seems to be a neurogenic origin for this hypoxemia that is out of proportion to cardiac failure or fluid overload. The need for aggressive maintenance of intravascular volume in euvolemic or hypervolemic states elicits the subtle pulmonary dysfunction and triggers fulminant pulmonary edema. Treatment of acute pulmonary edema may include the use of dobutamine [18], gentle diuresis, and augmented positive end-expiratory pressure (PEEP).

Early cardiac dysfunction, including diffuse contraction band necrosis and segmental wall motion abnormalities, occurs in a sizable minority of SAH patients. [19] The dysfunction is caused in large part by neurogenic sympathetic overactivity as well as by the surge in systemic catecholamines. Several reports of cardiac arrhythmias in the acute stages of SAH exist. The occurrence of arrhythmias and wall motion abnormalities predisposes the patient to decreased cardiac output and thus reduced cerebral perfusion. This cardiac dysfunction is often reversible but can give rise to early pulmonary and cardiovascular insufficiency. If doubt arises as to the function of the cardiovascular system or the pulmonary function, prompt evaluation with a right heart catheterization or echocardiogram should be entertained.

In addition, evaluation for concurrent myocardial ischemia or pneumonia should be performed. Management of these complications encompasses many common means (i.e., antibiotics) with the caveat that volume depletion and diuresis should be minimized in

patients who have primary ischemic injury or in whom vasospasm or reduced cerebral perfusion pressure exist. In the latter situation, a relative compromise in tolerating excessive pulmonary edema may be necessary to ensure adequate perfusion of the brain. Contrary to typical intensive or cardiac care protocols, hydration rather than diuresis is the goal.

Hyponatremia is a frequent complication after SAH. This is likely due to cerebral salt wasting. Replenishment with hypertonic saline and supplemental mineralocorticoid administration, typically with fludrocortisone, is necessary, in order to maintain sodium in the normal range, 138-145 mEq/dl.

Avoid of fever is a very important feature as well. Fever can exacerbate neurologic damage, and has been linked as an independent factor affecting poor neurologic outcome [20,21]. The use of surface cooling devices or intravascular cooling devices has become commonplace. The goal temperature is typically 36-37°C, with strict avoidance of any fever. The use of antishivering protocols is critical to implementing this control and avoiding unnecessary metabolic challenges to the patient [22]. Medications such as buspirone, and meperidine are important adjunctive agents that limit the extent of shivering and thereby facilitate the positive effects of cooling.

84.4.2 Treating Neurologic Complications

Often, obstructive hydrocephalus occurs within the first few hours after SAH. It can be life threatening because of brain-stem compression and occlusion of large as well as smaller penetrating blood vessels. Deterioration of the level of consciousness early after the primary event is the most common presentation. The use of a ventriculostomy for ICP measurement and drainage of CSF should be performed on an individual basis for acute hydrocephalus, based on the severity of clinical neurologic dysfunction and the CT scan appearance of trapped temporal horns or obliterated basilar cisterns. Several reports suggest a beneficial effect of ventriculostomy to relieve hydrocephalus and to improve patient outcome [15,23,24]. The use of ventricular drainage is a usefull early test of possible neurologic viability and chose operative candidates in whom neurologic improvement occurred after CSF drainage. Thus, the ventriculostomy may serve as both a therapeutic device as well as an indicator of which severe-grade patients should be aggressively treated.

Many have found that early drainage or lavage of the CSF space decreases the incidence of vasospasm after SAH [25] and that the infusion of thrombolytic agents may aid in this process with the timing of such intervention usually after the aneurysm has been secured. However, sudden drainage of CSF may precipitate rerupture of the aneurysm, mainly because of the transmural pressure across the aneurysm wall exceeding the intraventricular pressure. Thus, caution must be exercised during placement of a ventricular drain and during draining of fluid. One must limit the amount of CSF drained and the equilibrium CSF pressure at which the fluid drains. A practical approach is to drain CSF if the ICP exceeds 20 mmHg until the aneurysm is occluded. The drain is set at a 15 to 20 cm height such that the intraventricular pressure does not drop below this value during the draining process. Thus, one may avoid excessive ICP or dangerous hydrocephalus while avoiding unintentional aneurysm rerupture.

Rehemorrhage after the primary event is the most worrisome initial neurologic complication. Kassell and co-workers [9,11] have shown that early operative management decreases the risk of rehemorrhage and improves outcome. In most centers, early clipping of the aneurysm or endovascular treatment occurs within 24 to 48 hours after rupture. Subsequent intensive care unit care then makes use of neurologic monitoring, especially

the neurologic examination, ICP monitoring, transcranial Doppler ultrasound, and continuous EEG [6,26]. These techniques are used in a complementary fashion to detect and treat vasospasm and other neurologic complications such as seizures. Refinements in the application of these techniques and the use of hypervolemic-hypertensive-hemodilutional therapy offer the hope of decreasing the morbidity from vasospasm and improving the outcome [6].

In summary, the prompt recognition of SAH and the acute management of neurologic and medical problems is necessary to prevent additional morbidity and to maximize the neurologic recovery of patients suffering from SAH.

84.4.3 The Use of Neurologic Monitoring

One of the hallmarks for neurocritical care is the use of specific neurologic biomarker monitoring instruments to detect delayed cerebral ischemia, seizures, and other forms of neurologic deterioration [6,26]. Continuous EEG monitoring has the potential to detect vasospasm-related cerebral ischemia [1,6]. Several quantitative parameters, namely the percent alpha variability (PAV) and the alpha/delta ratio are sensitive indicators of cerebral ischemia. A typical example of the serial changes in cEEG PAV are seen in Figure 84.3. PAV detects vasospasm before more conventional measures, such as the transcranial Doppler ultrasound, CT angiography, or the clinical exam. In our hands, we use PAV as an early indicator of cerebral ischemia, and will induce hypertension while awaiting confirmatory testing, even if the neurologic exam is unchanged.

Cerebral microdialysis is another important neurologic monitor for the detection of vasospasm-related cerebral ischemia. The principal findings on microdialysis with ischemia are: 1) a reduction in brain glucose and 2) an increase in the lactate/pyruvate ratio. Several groups have demonstrated utility in using cerebral microdialysis for this type of monitoring.

Similarly brain tissue oxygen monitoring ($PbtO_2$) is a regional tissue monitor that indicates the balance of oxygen delivery and oxygen consumption in the brain. This monitor is capable of detecting reductions in the combination of cerebral blood flow and oxygen content [27].

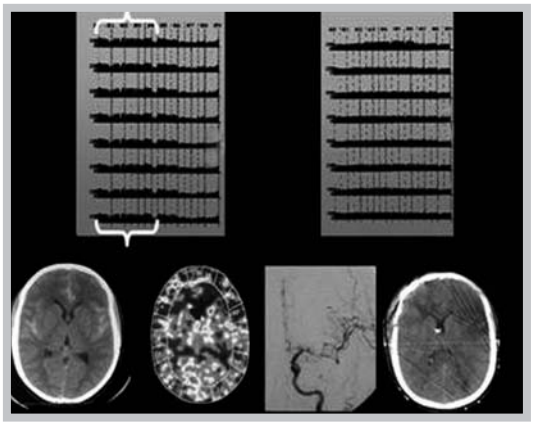

Figure 84.3. **A typical example of the serial changes in continuos EEG PAV.**

84.5 Conclusions

The acute management of aneurysmal SAH requires a comprehensive approach entailing acute critical care and stabilization, occlusion of the aneurysm, and intensive care management of acute neurologic complications. The development of endovascular treatment of aneurysms has added an important, less-invasive treatment to the regimen available in treating aneurysms. An integrated approach of providing critical care before, during, and after the occlusion of the aneurysm is an important concept that should be the goal. Debate and controversy remain regarding which aneurysms are best

suited to endovascular treatment or to surgical treatment; an evolving experience and clinical trials will provide further guidance. Nonetheless, some aneurysms may require both surgery and endovascular treatment [19]. Finally, close neurologic observation and directed specialized monitoring techniques are required for providing directed critical care in the acute period after SAH.

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85 Neurological Complications of Heart Surgery

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85.1 Introduction

Heart surgery is one of the most frequent procedures in developed countries. However, although the number of patients subjected to valve surgery has remained virtually unchanged over the last few years, coronary vascularization procedures are still rising. Recent progress in surgical techniques, anesthetic procedures and intra- and post-operative monitoring techniques have made it possible to operate older patients with greater comorbidity whilst reducing the morbidity/mortality related to the surgery itself. However, peri-operative complications that affect the central nervous system (CNS) can still be considered common, with relatively high morbidity and mortality rates, significant personal, family and social impact, and a high consumption of health resources. The most frequent complications arising from heart surgery are mainly focused on ischemic stroke, confusion syndromes and neuropsychological abnormalities.
In spite of the fact that neurological complications affecting the CNS are the most common and important, it is not uncommon that peripheral nervous system (PNS) involvement, mainly plexopathies and neuropathies, occurs after heart surgery (Table 85.1).

Location	Neurological complications
Central Nervous System	• Ischemic stroke • Hemorrhagic stroke • Epileptic seizures • Coma • Encephalopathy • Confusion syndrome • Neuropsychological dysfunction
Peripheral Nervous System	• Brachial plexopathy • Cubital neuropathy • Phrenic neuropathy • Intercostal neuropathy • Femoral neuropathy • Anterior ischemic optic neuropathy

Table 85.1. Most frequent neurological complications in heart surgery.

85.2 Complications of the Central Nervous System

85.2.1 Epidemiology

Those studies that assessed the incidence of CNS complications during the peri-operative period of heart surgery have found widely varying results. This is most probably due, amongst other factors, to differences in the surgical technique used, prior patient comorbidity, anesthesia time, length of follow-up, variations in terms used to define complications, neuroimaging techniques used and the retrospective or prospective nature of the study. Indeed, the peri-operative existence of a neurological dysfunction has

been defined in various ways, using terms such as "encephalopathy", "delirium", "confusion", "agitation", "stroke", "alteration of memory", with no uniform criteria having been used or, at times, established to define them. In this context, in an attempt to unify the criteria used to evaluate the neurological complications following coronary revascularization, the so-called Multicentre Group for the study of Perioperatorive Ischemia proposed classifying them as follows:

- Type I: Focal lesions, including stroke, confusion syndrome, transient ischemic attack, stupor, and coma.
- Type II: Cognitive dysfunction, memory deficit, and convulsive seizures.

It is estimated that the incidence of ischemic stroke following coronary revascularization surgery is between 1.5% and 5.2% and increases for valve replacement surgery and other invasive open surgery procedures. Approximately 60% of strokes occur during the first two days of the post-operative process, and virtually of them during the first nine days. During the first few weeks following surgery, the rates of encephalopathy and neuropsychological dysfunction vary between 3% and 79%.

85.2.2 Risk Factors

Table 85.2 highlights the main risk factors for the development of neurological complications during the peri-operative period of heart surgery.

Atherosclerosis of the ascending aorta. This is possibly the most important risk factor for developing type I and II neurological complications following heart surgery. The incidence of cerebrovascular disease in patients with aortic atherosclerosis is 8.7%, compared to 1.8% in other patients. A correlation has been observed between the severity of aortic atherosclerosis and the risk for developing cerebrovascular disease; this is 3% in patients with moderate involvement and 4.8% in those with severe atherosclerosis (>5 mm).

History of cerebrovascular lesion. This is an independent risk factor that increases the possibility of suffering a new cerebrovascular event by 8.5% and which worsens prior symptoms by up to 35%. The need to maintain anticoagulant treatment after some heart surgery procedures and heparinisation during extracorporeal circulation may favor the hemorrhagic transformation of previous cerebral infarctions.

Carotid stenosis. The existence of a stenosis greater than 80% is associated with an 11-18.8% higher risk of suffering from ischemic stroke, encephalopathy or a neuropsychological abnormality following myocardial revascularization. This increase may be due to a reduced perfusion distal to the stenosis or thromboembolic complications.

Elderly age. An age of 70-75 years or older is also an independent risk factor for the development of some kind of cerebrovascular complication following heart surgery, as it is associated with a higher probability of presenting atherosclerotic lesions in the aorta, carotid and intracranial arteries.

High blood pressure is an independent risk factor for the development of both type I and type II neurological complications.

- Elderly age
- Diabetes mellitus
- High blood pressure
- Atherosclerosis of the proximal aorta
- Carotid and/or intracranial artery atherosclerosis
- History of cerebrovascular disease
- Heart failure
- Severe or moderate left ventricular dysfunction
- Post-operative atrial fibrillation
- History of unstable angina or recent myocardial infarction
- Peripheral arteriopathy
- Kidney failure
- Prior lung disease

Table 85.2. **Risk factors for the development of neurological complications of the central nervous system in heart surgery.**

Diabetes mellitus and intra-operative hyperglucemia are also risk factors, especially in women.
Heart function. The existence of low cardiac output (pre- or post-operative), the presence of atrial or ventricular thrombi, the development of post-operative arrhythmias and a history of coronary disease or unstable angina increase the risk of type I and II neurological complications.
Type of surgery. Closed surgery techniques, such as coronary bypass, entail less risk than open heart surgery procedures (valve replacements). The use of intermittent aortic clamp and intra-aortic contrapulsation ballon are independent risk factors for type I neurological complications.

85.2.3 Etiopathogeny

The fundamental etiopathogenic mechanisms of neurological complications in the patient subjected to heart surgery involve cerebral embolism and hypoperfusion.

Cerebral Embolism

Cerebral embolism is the main mechanism involved in producing neurological complications that occur during the peri-operative period of heart surgery, especially in interventions with extracorporeal circulation.
Depending on the origin and nature of the emboli, the cerebral complications produced may, in general terms, be due to thromboembolic or atheroembolic phenomena, or gas embolism. Emboli may derive from atherosclerotic, generally ulcerated, lesions of the aortic arch or supra-aortic trunks, mural thrombi, from the cardiopulmonary bypass circuit, pre-existing cardiac lesions (hypofunctional ventricle, atrial dilatation), calcified valves or be generated by post-operative arrhythmias (atrial fibrillation). The neurosonological studies performed to date have revealed that aortic handling maneuvers, especially clamping and declamping (the origin of more than 60% of emboli detected), are the main causes of rupture of the atheroma and subsequent formation of emboli. Ischemic lesions may also occur days after surgery as the activation of coagulation factors in operated patients promotes a state of hypercoagulability and the formation of thrombi on stenotic arteries, with the subsequent development of thromboembolic phenomena. Conversely, gas emboli enter the arterial circulation after being generated in arterial cannulation sites, open heart chambers or arterial anastomoses and they are the most frequent emboly type detected during extracorporeal circulation.
Macro- and microemboli can be differentiated on the basis of their size (diameter greater or lesser than 200 microns). Macroemboli are usually produced in relation to rupture of the atherosclerotic plaque and mainly cause focal neurological deficits of greater or lesser severity upon occlusion of median and large calibre arteries. Microemboli (comprised of fibrinoplatelet aggregates, atheromatous detritus, lipids, air, etc.) usually affect “borderline” vascular areas between the medial and posterior cerebral artery or the medial cerebral artery and the anterior cerebral artery. Sometimes, microemboli may produce lesions that are similar to those of hypoperfusion and evolve with clinical symptoms of neuropsychological dysfunction, confusion syndromes or give rise to lacunar syndromes.

Hypoperfusion

The second mechanism implicated in the origin of peri-operative neurological complications is hypoperfusion. Cerebral hypofusion may be due to the existence of low blood flow, arterial hypotension, hypovolemia or incorrect positioning of the aortic cannu-

la. It is favored by the coexistence of prior intra- or extracranial arteriopathy or by a low availability of collaterals from the Willis polygon. Cerebral circulation has self-regulation mechanisms where cerebral blood flow (CBF) is kept virtually constant under a mean blood pressure margin between 30 and 100 mmHg. In addition to the pressure (arterial or from the extracorporeal circulation pump) and flow characteristics (normally lower than physiological flow during extracorporeal circulation), CBF depends on other factors such as the acid-base equilibrium, hypoxemia, arterial pCO_2 or the anesthetic technique used. These self-regulation mechanisms mean that elderly patients with high blood pressure, diabetes or a history of cerebrovascular disease keep the self-regulation curve shifted to the right. A mean blood pressure that would be suitable in other circumstances may result in a state of hypoperfusion as a result of insufficient CBF, thus meaning that these patients would require higher perfusion pressures than the normal population. In addition to contributing by themselves to hypoperfusion, a low mean blood pressure and reduced blood flow result in a lower ability to dissolve and fragment circulating microemboli, thereby increasing the risk of infarction in borderline areas, as well as neuropsychological complications. Hypoperfusion secondary to insufficient perfusion pressure, either intra-operative or during the immediate post-operative period, may be the cause of multiple bihemispheric ischemic lesions with subcortical predominance.

Clotting Disorders

The need to maintain a state of anticoagulation during the procedure in some procedures of heart surgery may result in cerebral hemorrhagic complications. This is particularly significant in elderly patients, where the presence of silent vascular lesions and the coexistence of atherosclerotic arteriopathies, such as amyloidosis, is more frequent.

Systemic Inflammatory Response

It should also be taken into account that the significant inflammatory response that generally arises during cardiopulmonary bypass could, at times, lead to conditions ranging from lung dysfunction to temporary multiple organ failure. Although no direct causal relationship between a systemic inflammatory response and neurological damage has been demonstrated, it is possible that this contributes to its development and progress, especially neuropsychological abnormalities.

85.3 Most Common Central Nervous System Complications

The clinical CNS manifestations that may present in a patient who has undergone heart surgery cover a range of possible signs and symptoms, which will depend on the location, number and kind of lesions produced. Among the main neurological complications, the following entities and syndromes should be considered (Table 85.1).

85.3.1 Ischemic Stroke

Early strokes, which are present during the first few hours of surgery, are the most frequent complication and have been attributed to intra-operative emboli or as a consequence of hypoperfusion states. When stroke symptoms occur later, the most frequent cause is cardiac arrhythmia (especially atrial fibrillation) or detachment of aortic atheroma. Initially, patients who have suffered stroke take longer to recover from the anesthesia.

Patients with hemispheric infarctions will present contralateral weakness or hemianesthesia, hemianopsia, aphasia or hemispatial neglect. Cerebellar infarctions may evolve with vertigo, nausea, vomiting, dysarthria, vertical nystagmus and ataxia. Infarction in the brainstem will give rise to cranial nerve paralysis and motor or sensory deficits that vary according to the location and size of the lesion. Infarctions in the protuberance may lead to "locked-in syndrome", which should be differentiated from coma. These patients present quadriplegia, bilateral facial paralysis, anarthria and paralysis of the horizontal gaze, but comprehension and vertical eye movements are preserved.

Hypoperfusion-related cerebral infarctions typically affect borderline areas, limiting regions whose irrigation depends on two or three vascular areas. The most commonly affected areas are those located between the medial and anterior cerebral arteries and the medial and posterior cerebral arteries. Infarctions in the borderline area between the anterior cerebral artery and the medial cerebral artery produce contralateral hemiparesia, which mainly affects the arm, and transcortical motor aphasia if the dominant hemisphere is affected. Bilateral infarctions in this same area may very characteristically produce bilateral involvement of the proximal musculature of the upper limbs ("man-in-the-barrel syndrome"). Infarctions in the borderline area between the medial and posterior cerebral arteries may cause sensory, visual-field or language deficits. Bilateral infarctions, which are produced by either hypoperfusion or embolism, may produce a reduction in the level of consciousness or similar brainstem lesions.

85.3.2 Hemorrhagic Stroke

The presence of cerebral or subarachnoid hemorrhage has occasionally been reported following congenital cardiopathy procedures and in heart transplant recipients. The pathophysiological mechanism proposed for these cases is the rupture of small arteries as a result of increased CBF or because of clotting disorders, especially in patients with vascular risk factors, cerebral arteriopathy or silent vascular lesions. Patients with endocarditis also present an increased risk of intracranial hemorrhage during heparinisation, which is performed during the cardiopulmonary bypass. This risk may be minimised using an extracorporeal circulation circuit that allows to reduce systemic heparinisation.

85.3.3 Epileptic Seizures

Epileptic seizures have been documented in 0.6-3.5% of operated heart surgery patients. They are generally a manifestation of cortical infarctions and may evolve into epileptic status in cases of serious metabolic abnormalities (hyponatremia, hypoglucemia), hypoxia and associated pharmacological toxicity (lidocaine, procainamide).

85.3.4 Coma

The coma state occurs as a complication of focal lesions (ischemic or hemorrhagic) in the brainstem, hemispheric lesions with compression of the brainstem because of edema, global cerebral hypoperfusion, convulsive state and serious metabolic abnormalities. Patients in coma as a result of diffuse anoxic brain damage usually will be affected by myoclonus and convulsions (Lance-Adams myoclonic encephalopathy) with uncertain prognosis. Clinical evolution to a persistent vegetative state may be observed in patients with long-term global cerebral ischemia.

85.3.5 Confusion Syndrome

This should be suspected in patients with slow recovery from anesthesia or who, once awake, present a state where agitation, disorientation and visual hallucinations alternate with a reduced level of consciousness, generally stupor. Confusion syndrome in heart surgery patients occurs between 3% and 32% of patients, especially those with previous psychiatric disease, alcohol consumers or with prior cerebrovascular disease. The clinical symptoms of encephalopathy may arise following metabolic abnormalities (liver, kidney or thyroid failure) as a manifestation of right parietal infarctions or because of diffuse cerebral dysfunction of ischemic origin. This situation can improve spontaneously or evolve toward different degrees of neuropsychological dysfunction or death.

85.3.6 Neuropsychological Dysfunction

This mainly consists of attention deficit, difficulty concentrating, memory alterations, changes in character, altered executive functions, etc. It appears in 50-70% of patients during the first week of the post-operative period and remains in 30-50% at 6 weeks and 20-40% at 6 months and 1 year post-surgery. Despite appearing to be a transitory and reversible abnormality, long-term follow-up studies suggest that up to 42% of patients present neuropsychological dysfunction at 5 years.

Short-term cognitive abnormalities (from the first week up until 1 year post-op) mainly imply changes to memory and visuospatial skills. They are usually transitory and reversible deficits. Their etiology is multifactorial and is related to hypoperfusion and the release of microemboli during extracorporeal circulation, although it is possible that, especially during the first few days, there is an underlying effect of the drugs used during anesthesia, sedation and analgesia.

Long-term cognitive abnormalities have been observed in longitudinal studies at one and five years post-intervention. The main impairment occurs to psychomotor reactivity, whereas verbal learning and memory remain unchanged. It cannot be ruled out that the subcortical damage which appears in the long-term may be due to the presence of vascular risk and comorbidity rather than the effect of surgery.

85.4 Diagnosis of Central Nervous System Complications

The diagnosis of neurological complications in a patient who has undergone heart surgery should include a case history and neurological examination, as well as cerebral neuroimaging techniques, epiaortic ultrasound, neurosonological studies and the determination of biochemical markers.

85.4.1 Case History and Neurological Examination

All patients who will undergo heart surgery should have a detailed history aimed at the investigation of vascular risk factors and history of neurological and, especially, cerebrovascular disease. Patients should be examined before and after the intervention in order to identify new signs not present in prior examinations. Early neurological examination following surgery should be exhaustive and especially thorough in those patients with risk factors as they are the ones with the highest probability of presenting neurological complications. It is recommended to perform a neuropsychological assessment during

the post-operative period, especially after day 3-5 to avoid an effect of the anesthesia and sedatives. The Mini-Mental State Examination has been proposed as a screening element, and batteries of neuropsychological test should be reserved for those patients with specific dysfunctions (visuospatial abnormality, change in character, etc.).

85.4.2 Neuroimaging Techniques

Neuroimaging techniques should be performed on those patients with symptoms of neurological dysfunction following surgery. Computed tomography (CT) has been the standard imaging technique for the initial and urgent assessment of the patient following heart surgery for many years due to its ability to detect hemorrhage in the hyperacute period, ischemia-related parenchymatous abnormalities, and its more widespread availability in a hospital setting.

However, given the known limitations of CT, brain magnetic resonance (MR) enables very small lesions to be identified, can perfectly determine the regions of posterior circulation and has a high sensitivity for the detection of ischemic lesions and edema, even in their early stages. Multimodal MR, which includes the use of diffusion-perfusion sequences and gradient echo, has a high capacity and reliability for studying the location, number and size of ischemic lesions, the detection of hemorrhages and their parenchymatous complications, such as cerebral edema. By identifying potentially recoverable ischemic tissue (mismatch), MR also facilitates the selection of patients who are candidates for therapeutic interventions, such as mechanical extraction of the thrombus. The diffusion sequences (Figure 85.1) also detect silent infarctions and enable the prognostic utility in patients with post-surgical infarctions and neuropsychological dysfunction to be assessed. Although MR is a technique of choice due to its high diagnostic efficacy, it is contraindicated in the presence of pacemakers and Swan-Ganz catheters. Valve displacement or heating of the ferromagnetic material or the valvuloplasty ring are potential risks that should be studied on a case-by-case basis [www.mrisafety.com]. Performing a brain MR during the patient's pre-operative assessment, especially in those patients with multiple vascular risk factors, also helps to establish a risk profile as silent ischemic lesions can be detected.

85.4.3 Epiaortic Ultrasound and Neurosonological Study

Epiaortic ultrasound is a highly sensitive technique that can be used to determine the severity of atherosclerosis of the ascending aorta, which is one of the main risk factors for the development of neurological complications. It has been demonstrated to be superior to manual palpation and transesophageal ultrasound and is used for intra-operative diagnosis of aortic atherosclerosis.

A carotid color Duplex scan is a necessary tool for both the screening of at-risk patients and diagnosing a post-operative arterial occlusion. Carotid stenosis is a risk

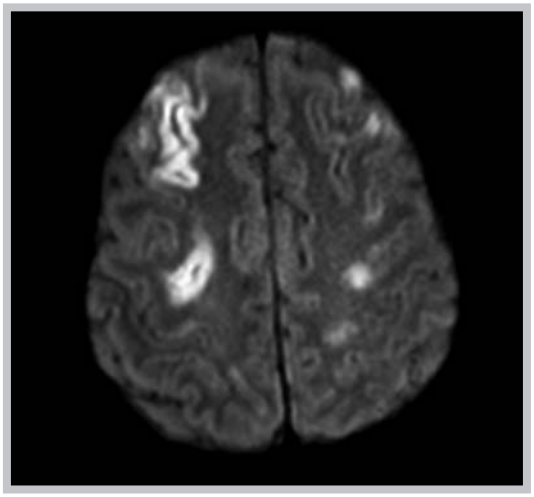

Figure 85.1. **Cerebral magnetic resonance, diffusion sequences, axial plane. Ischemic lesions in borderline areas in both brain hemispheres following heart surgery.**

factor for the development of neurological abnormalities as it is both a source of emboli and because it contributes to cerebral hypoperfusion in low flow situations. Guidelines of the American Heart Association propose performing a carotid eco-Doppler for patients with stenosis of the anterior descending artery, peripheral vascular disease, smokers, a history of transient ischemic attack (TIA) or previous stroke, carotid murmur or aged older than 65 years.

Transcranial Duplex monitoring during cardiopulmonary bypass has shown the existence of microemboli (documented in the form of HITS – High-Intensity Transient Signals) and could be useful for monitoring cerebral perfusion during surgery.

85.4.4 Biochemical Markers of CNS Complications

The quantification of various substances released following a hypoxic-ischemic cerebral lesion could be a marker for brain damage. Although the concentration of several substances in both serum and the cerebrospinal fluid has been studied (brain-specific CPK, adenylate cyclase, neurospecific enolase, myelin basic protein, S-100 β, etc.), their clinical utility has not been demonstrated. An association has recently been found between pre-operative serum concentrations of anti-NMDA anti-receptor antibodies and the subsequent development of neurological abnormalities, although this requires further confirmation.

85.5 Treatment of CNS Complicacions

The therapeutic direction for heart surgery complications in the CNS can be focused on three aspects: preventive treatment, neuroprotective treatment during surgery and treatment of neurological complications.

85.5.1 Preventive Treatment

A pre-operative assessment reduces the risk of neurological damage by enabling pre-existing modifiable risk factors to be identified and treated. An optimum control of blood pressure, glycemia and heart and kidney function prior to surgery reduces the risk of suffering a subsequent neurological complication. Because of their etiopathogenic importance, carotid stenosis and aortic atheromatosis require special consideration.

Carotid stenosis. Carotid endarterectomy performed prior to, or together with, myocardial revascularization is usually recommended in patients with symptomatic carotid stenosis or in asymptomatic patients with carotid stenosis (unilateral or bilateral) greater than or equal to 80%. This intervention reduces mortality and the risk of developing ischemic stroke after heart surgery.

Aortic atheromatosis. When the aorta presents a thickness above 3 mm, it is essential to choose the area to perform the clamping, aortic cannulation and proximal anastomosis of the aortocoronary grafts carefully, or even consider revascularisation surgery without extracorporeal circulation. No benefit of pre- or intra-operative endarterectomy has been demonstrated.

85.5.2 Neuroprotective Treatment

Protection of the CNS during heart surgery includes pharmacological and non-pharmacological measures.

Non-pharmacological measures

In procedures with extracorporeal circulation, temperature, acid-base balance and blood pressure are related to the risk of development of CNS abnormalities:

- **Temperature** of the cardiopulmonary bypass. Systemic hypothermia reduces cerebral metabolism (7% for each Celsius degree) and has a protective effect against transitory ischemic attacks. Moderate hypothermia is normally used in both closed-chamber procedures that require extracorporeal circulation (32°C) and open procedures (28°C). The beneficial effects of hypothermia disappear when reheating of the system begins. Hyperthermia, with temperatures over 41°C, increases cerebral metabolism, denatures proteins, and facilitates gas embolism, therefore this process should always be performed very gradually.
- **Acid-base equilibrium**. Hypothermia alters the acid-base balance and as a consequence affects CBF. The main techniques to regulate the acid-base balance during hypothermia are alpha-stat and pH-stat. In alpha-stat, measurement of the pH and CO_2 is performed directly in blood at 37°C, whereas in pH-stat this is performed using values adjusted for the patient's current temperature. The use of pH-stat requires the addition of CO_2 to the circulation during the hypothermic phase of cardiopulmonary bypass, thereby increasing the risk of embolization. Acid-base regulation by means of the alpha-stat technique is recommended as it preserves cerebral self-regulation and reduces the risk of embolization and subsequent neuropsychological abnormalities.
- **Blood pressure**. The majority of patients tolerate mean blood pressures to between 50 and 70 mmHg during extracorporeal circulation well. However, elderly and hypertensive patients will require higher values as their cerebral self-regulation curve is shifted to the right. Hypotension should be avoided during the procedure as this causes cerebral hypoperfusion, less clearance of circulating microemboli and a higher risk of cerebral ischemic lesions and the development of neuropsychological abnormalities.
- **Surgical position**. Placing the patient in the Trendelemburg position seems to reduce the risk of gas embolization, especially during open chamber procedures.
- **Intraoperative monitoring**. Transesophageal echocardiography enables the detection of permeable oval foramen, thrombi in the left atrium in patients with atrial fibrillation, air retention in open chamber procedures, mural thrombi in the left ventricle, thrombosis in the valve prosthesis, valvular vegetations, dissection of the proximal aorta and atherosclerosis of the aorta to be detected, thus allowing the risk of neurological complications to be reduced. Epiaortic ultrasound can also help to locate the most ideal place to perform aortic clamping, thereby reducing possible disruption of the atheroma.
- **Kind of surgery**. Coronary revascularization surgery, which is performed without extracorporeal circulation, is less invasive and reduces the complications of cardiopulmonary bypass. This technique requires a careful positioning and very close cardiac monitoring. The heart rate needs to be controlled pharmacologically (under 75 beats/minute) to reduce the movement of the heart in the surgical field and reduce myocardial consumption during the procedure. A reduction in ischemic stroke has been observed in high-risk patients treated with this kind of surgery, although its influence on the risk of neuropsychological complications is debatable.

Pharmacological Measures

Strategies for pharmacological protection attempt to interfere with the metabolic cascade that occurs during and after cerebral ischemia in order to prevent or delay cell death. NMDA receptor antagonists, calcium and sodium channel blockers, antioxidants,

complement inhibitors, magnesium sulfate, leukocyte adhesion inhibitors, barbiturates, amongst other agents, have been studied. Although several drugs have shown neuroprotective effects in experimental models of both focal and global ischemia, none has demonstrated clinical efficacy in humans. Patients treated with aprotinin, a non-specific serine-protease inhibitor, to reduce bleeding during heart surgery seem to present a lower incidence of infarction in the post-operative period. The possible neuroprotective effect of citicoline is currently being assessed in a double-blind placebo-controlled clinical trial in patients with cerebral infarction. Citicoline could be of great use in patients undergoing heart surgery given its excellent safety profile.

85.5.3 Treatment of Complications

Ischemic Stroke

Patients who present a cerebral infarction during the peri-operative period are not candidates for endovenous thrombolytic treatment as their use is specifically contraindicated up to 14 days later due to their high risk of hemorrhage. Despite this limitation, intra-arterial treatment and mechanical thrombolysis are two possible therapies that could be applied in selected patients. Intra-arterial thrombolytic treatment during the first 4.5 hours of symptom onset has been administered to patients with ischemic stroke 2-9 days post-surgery, with high recanalization rates and no significant side effects being documented. Mechanical extraction of the embolus (MERCI system) has been successfully applied to selected patients with a therapeutic window of up to eight hours.

As in all cases of cerebral ischemia, oxygenation, blood pressure, glycemia and body temperature should be monitored and corrected, just as for any other patient who has undergone an ischemic stroke, but taking the underlying heart disease and the surgery performed into account. Hypoxia in patients with saturations below 92% should be treated. Low blood pressure should be avoided and treated posturally, with fluid therapy and, if necessary, low doses of phenylephrine. High blood pressure during the acute phase of stroke is usually reactive and tends to reduce spontaneously over the next few days, therefore blood pressure values need not be “normalized”. In principle, the general treatment criteria established for acute phase ischemic stroke, which are covered in another chapter of this book, should be followed. Isotonic fluids can be administered to prevent dehydration, although a volume overload that may worsen the cerebral edema and heart failure should be avoided. Hyperglycemia is an independent predictor of worse neurological evolution, therefore it should be controlled early and glucose-containing solutions should be avoided. Hyperthermia is also an independent predictor of worse neurological evolution, therefore it should be treated vigorously using physical measures and antipyretics (paracetamol).

Anticoagulation therapy with unfractionated or low molecular weight heparin has not been shown to be beneficial for the acute treatment of atherothrombotic or hypoperfusion-related stroke and increases the risk of systemic complications such as hemopericardium. Anticoagulation therapy should be considered in the case of stroke with a demonstrated and persistent cardioembolic source by weighing up the risk/benefit ratio. The use of platelet anti-aggregants (acetylsalicyclic acid) following coronary revascularisation surgery has been shown to be safe and effective as it improves the prognosis of the infarction.

Hemorrhagic Stroke

Attempts should be made to normalize the abnormal coagulation status and the general treatment protocol for acute phase stroke should be followed.

Confusion Syndrome and Post-anoxic Encephalopathy

Confusion syndrome and post-anoxic encephalopathy should be treated vigorously and the underlying causes that may trigger them, especially reversible metabolic abnormalities, corrected. Post-anoxic myoclonic encephalopathy may be treated with piracetam at high doses (up to 24 g/day); valproic acid can be associated according to the response. Atypical neuroleptics should preferably be used for patients with acute confusion syndrome; benzodiazepines should be avoided if possible.

Epileptic Seizures

The cause should be treated whenever possible, and symptomatic treatment with antiepileptic drugs (carbamazepine, oxcarbazepine, gabapentin, levetiracetam, etc.) should be administered. Endovenous levetiracetam or valproic acid according to protocol, instead of phenytoin, is recommended in the case of status epilepticus.

Neuropsychological Dysfunction

Cognitive rehabilitation is recommended and, depending on the intensity and kind of deficits detected, specific treatment by specialized personnel should be considered.

85.6 Complications of the Peripheral Nervous System

Post-operative complications that affect the CNS are highly relevant from the clinical point of view because of their prognosis and risk of disabling sequelae. In contrast with the severity of these complications, little attention has been paid to neurological abnormalities that affect the peripheral nervous system, thus meaning that they are frequently underdiagnosed. However, it is estimated that 2-15% of patients who have undergone heart surgery present post-operative brachial plexopathies and 1-30% neuropathies affecting the phrenic or intercostal nerves.

85.6.1 Brachial Plexopathy

This may occur as a consequence of traction of the brachial plexus, its compression between the clavicle and the first rib with sternal retraction, and during dissection of the internal mammary artery. It manifests clinically as pain, motor weakness, paresthesias and decreased osteotendinous reflexes in the upper limb. Paresthesias are more frequent in the fourth and little fingers and may also present upon compression of the cubital nerve in the elbow. Weakness in the extensor muscle of the second finger of the hand and the small abductor muscle of the thumb differentiates plexopathy from cubital neuropathy.

85.6.2 Phrenic Nerve Neuropathy

The incidence of phrenic nerve neuropathy has been estimated at between 1% and 30% of patients, although its frequency has decreased significantly in the last few years. Lesion of the phrenic nerve occurs upon application of ice to cool the heart, a procedure that is used increasingly infrequently. Patients who present bilateral dysfunction of the phrenic nerve require prolonged mechanical ventilation. Most make a full recovery during the first year.

85.6.3 Intercostal Neuropathy

Dissection of the internal thoracic artery may be associated with a lesion of the anterior intercostal nerves. Intercostal neuropathy evolves clinically with paresthesia and "burning pain" in the sternal region and the left anterolateral region of the thorax. Symptoms are usually partially or fully reversible, although patients may require up to two years to recover.

85.6.4 Femoral Neuropathy

The production of a femoral neuropathy following insertion of an intra-aortic balloon as a result of local trauma, vascular occlusion or formation of pseudoaneurysms has been reported.

85.6.5 Optic Neuropathy

Visual impairment due to ischemic optic neuropathy is rare and occurs as a result of embolism in approximately 0.1% of heart surgery patients.

85.7 Diagnosis and Treatment of Complications of the PNS

Diagnosis is based on clinical data, and symptoms usually remit once the acute phase is ended and the general condition improved. Most lesions occur because of reversible disruption of the myelin sheath (neurapraxia) and usually have a good prognosis, therefore early rehabilitation is recommended. If symptoms do not improve within three weeks of evolution, electroneurography and an electromyogram should be performed to assess damage to axons and to locate the site of the lesion. Administration of vitamin B12 may be useful in both cases. In case of dysesthesias or painful hyperalgesia, treatment with carbamazepine, oxcarbazepine or gabapentin, amongst other drugs, is indicated.

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86 Neurogenic Cardiopulmonary Injury

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86.1 Introduction

The occurrence of neurogenic pulmonary edema (NPE) in patients with acute and severe cerebral injuries has been noted since the beginning of the 20th century.
The first cases were reported in epileptic patients with uncontrollable seizures and, during the First World War, in soldiers with severe cerebral trauma, NPE has been better studied in cases of aneurysmal subarachnoid hemorrhage (aSAH).
Neurocardiogenic damage has been also described in various neurological and neurosurgical pathologies, with the most significant studies being performed in patients with aSAH. The resulting cardiomyopathy is known as tako-tsubo or apical ballooning syndrome. Its identification was facilitated by the routine use of echocardiography, which allows its non-invasive diagnosis and a more detailed study of its incidence and evolution.
The biomedical literature regarding pulmonary and cardiac damage related to severe acute cerebral diseases usually differentiates NPE from neurogenic cardiomyopathy even if these complications can frequently coexist in the same patient. For didactical reasons, we will maintain this division in this Chapter, specifying when the possible interaction between cardiac and pulmonary diseases can influence therapeutic decisions in a considerable way.

86.2 Neurogenic Pulmonary Edema

86.2.1 Causes and Incidence

NPE consists of an increase in interstitial and alveolar liquid which occurs as a direct consequence of an acute damage of the central nervous system. It can occur as a complication of every acute event that affects the brain, the brainstem or the spinal cord at cervical level. Its causes include, among the others, aSAH, traumatic brain of cervical spinal cord injury, cerebral or cerebellar intraparenchymal hemorrhages, ischemic stroke, encephalitis and status epilepticus [1]. Intracranial hemorrhages in general, and aSAH in particular, are the most frequent causes.
Data about NPE incidence in patients with aSAH differs accross studies. This occurs due to the different criteria used for its definition and because of the different populations analyzed. While evidence of pulmonary edema has been demonstrated in more than 70% of fatal cases of aSAH studied with necropsy, the incidence is between 8% and 23% when clinical criteria are considered [1-5]. It is more frequent in patients with severe clinical presentations (Hunt and Hess grades IV and V), or with extensive bleeding (Fish-

er grades 3 and 4) and it is possible that the risk of this complication is greater after rupture of posterior circulation aneurysms [1,3].

86.2.2 Pathophysiology

Traditionally, it is postulated that NPE may be a consequence of an excessive adrenergic discharge which leads to pulmonary vasoconstriction and a rapid increase in pulmonary capillary hydrostatic pressure. The resulting pulmonary and systemic vasoconstriction would cause an transitory but dramatic increase in hydrostatic pressure in the capillary vessels of the pulmonary circulation, causing an alteration in the Starling force and consequently leading to fluid leakage into the alveolar space [6,7].
Undoubtedly, other physiopathological pathways mechanisms may be involved, such as pulmonary capillary vessel damage and activation of the inflammatory response, with consequent increase of the permeability of the hemato-alveolar barrier. This may explain the high protein content in the alveolar fluid observed in experimental models of NPE and in patients with this complication [6,8]. The endothelial damage of pulmonary capillary vessels can be caused by the increase in hydrostatic pressure described, by a direct effect of sympathetic hyperstimulation, or by an acute inflammatory response related to the cerebral damage.

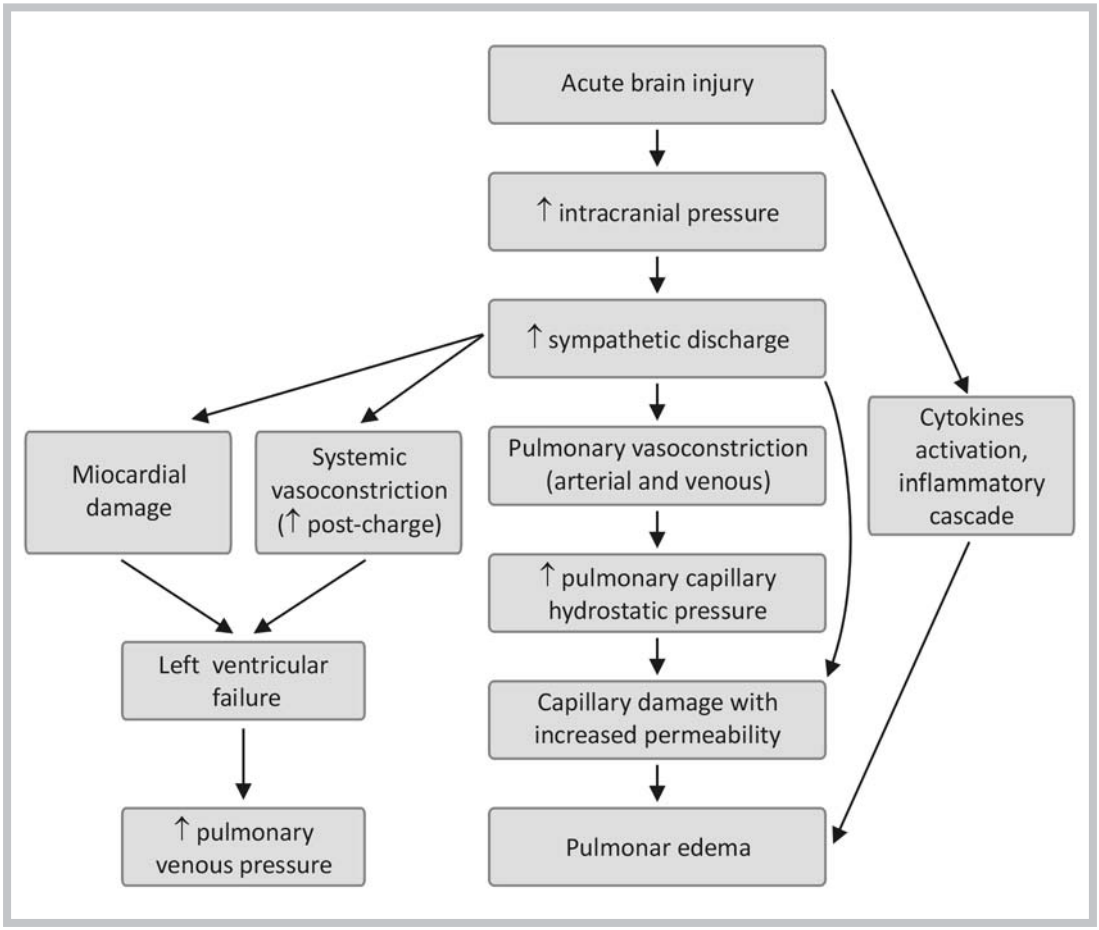

Figure 86.1. Pathophysiology of neurogenic pulmonary edema.

Another element that can contribute to the NPE is the degree of cardiac dysfunction from left ventricular failure. The sudden increase in left ventricular pressure related to the dramatic rise in afterload caused by adrenergically-induced arteiral hypertension can exacerbate the pulmonary hypertension and produce more alveolar edema [9]. In my experience, it can be difficult to discriminate between the two components, neurogenic and cardiogenic, of acute pulmonary edema in neurocritical patients.
Figure 86.1 summarizes the basic concepts regarding NPE physiopathology.

86.2.3 Diagnosis

There are no pathognomic signs which allow the identification of NPE. Its semiology is similar to all the other cases of acute pulmonary edema (dyspnea, hypoxemia, crackles on pulmonary auscultation), but signs of left ventricular failure are frequently absent (absence of cardiac gallop).
Chest films show bilateral pulmonary opacities, corresponding to an increase of interstitial and alveolar liquid (Figure 86.2). Pulmonary infiltrates can resolve rapidly with adequate therapeutic management. In the absence of coexisting cardiac injury, the electrocardiogram does not show major changes and central venous pressure is normal. Although it would be expected to find highly elevated pulmonary capillary wedge pressure, it is not so uncommon to find those pressures within relatively normal range [5]. This is probably due to the fact that the increase in pulmonary wedge pressure is severe but temporary. As a consequence, the pressure can be normalized by the moment the pulmonary hemodynamic measures become available.
The differential diagnosis should include, as in all the patients with acute hypoxemia, ventilator-associated pneumonia, aspiration pneumonitis, atelectasis, acute pulmonary embolism and cardiogenic edema from acute cardiac failure [2,4].
Furthermore it is useful to keep in mind that some hypoxic patients during the acute phase of aSAH can show relatively normal findings on chest X-ray, but this does not exclude the possibility of a of ventilation-perfusion mismatch caused by an increase of intrapulmonary liquid [5]. Once that the other causes of hypoxemia have been excluded, it is appropriate to consider these cases of cryptogenic hypoxemia as possible less severe cases of NPE.

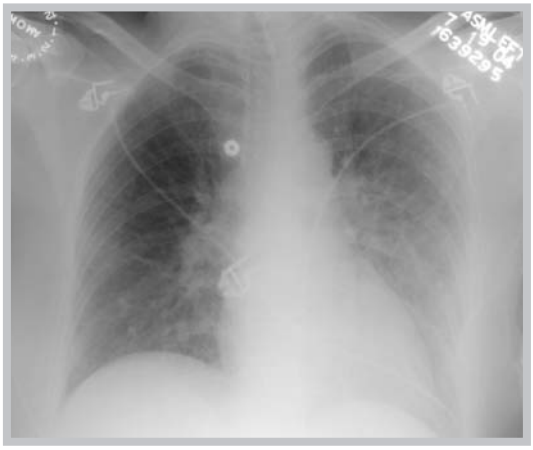

Figure 86.2. **Chest X-ray findings in a case of neurogenic pulmonary edema.**

86.2.4 Treatment

The treatment of NPE is based on the control of the acute neurological disease, with special attention to the reduction of intracranial pressure, and on providing ventilation support to improve hypoxemia [1].
Even if pulmonary complication can be fatal, the majority of deaths in these cases occur as a consequence of the primary cerebral injury. Serial assessment of neurological status and, when indicated, continuous monitoring of intracranial pressure and cerebral perfusion pressure are essential to treat these patients effectively.

Temporary endotracheal intubation and sedation are usually recommended. Some less severe cases can be managed with non-invasive ventilation, but the high levels of positive end-expiratory pressure (PEEP) necessary to treat the hypoxemia may not be well tolerated when are administered via BiPAP mask. Usually PEEP values between 10 and 15 mmHg should be used in cases of severe or moderate NPE. In general, these levels do not compromise cerebral perfusion [10], but the effect of PEEP in the intracranial and cerebral perfusion pressures should be evaluated in each single case. Hyperventilation can be necessary to achieve a fast control of the intracranial hypertension, but prolonged hyperventilation and hypocapnia (PCO_2 <30 mmHg) should be avoided because the resulting cerebral vasoconstriction can cause ischemia. On the other side, permissive hypercapnia, which can be considered an adequate ventilation technique in other cases, is not indicated in the majority of patients with NPE because it can result in worsening of the intracranial hypertension. Ventilation in prone position can be a particularly advantageous option in some patients, and in my opinion should only be performed in patients with severe, refractory hypoxemia [11]. Undoubtedly, these patients should be adequately monitored to ensure that intracranial pressure does not increase when the patient is placed in prone position. The administration of nitric oxide by inhalation should be considered with caution before being prescribed, because its use can increase the risk of hemorrhagic by compromising platelets function.

In patients with intracranial hypertension and NPE, the use of mannitol should be preferred to the administration of hypertonic saline solutions. To decrease the intracranial pressure, the induction of serum hyperosmolarity can accelerate the resolution of pulmonary edema [12]. Pharmacological neuromuscular paralysis can be useful to attain a better control of the intracranial pressure and may be necessary to optimize ventilation and oxygenation. Decompressive craniectomy is a valid option in refractory cases.

The hemodynamic therapy should be ideally guided by echocardiography and, sometimes, pulmonary catheterism. In most cases, bedside echocardiography obviates the need for pulmonary catheterism. When cardiac function is compromised, the use of inotropic drugs can be efficacious. Dobutamine, milrinone, and dopamine (in moderate doses) are valid options. Depending on the systemic arterial pressure, vasodilator drugs (e.g. nicardipine or clonidine), or less frequently vasoconstrictors (e.g. norepinephrine) may be necessary. It is recommended to avoid the use of beta-blockers in all the cases where there is evidence or suspicion of severe heart failure. However, in less severe cases I tend to favor the use of moderate doses of a beta-blocker to prevent additional adrenergically-induce myocardiac injury. Diuretics, such as furosemide, can be used to decrease the preload and they can be administered in combination with mannitol. Once hypoxemia has been corrected, it is very important to remember that in patients with aSAH it is neither necessary nor recommended to maintain the intravascular space contracted, due to the negative effects of hypovolemia on the risk of cerebral ischemia from vasospasm [2]. Once the NPE has resolved, there is no contraindication in these patients for the induction of hemodynamic augmentation therapy (induced hypertension and moderate hypervolemia) if they develop symptomatic vasospasm.

86.2.5 Prognosis

The occurrence of NPE has been associated with worsened functional prognosis, particularly in patients with aSAH [1-3]. This association may be explained by the greater severity of the primary neurological insult in those patients who develop MSE as a complication. Patients with NPE or other acute oxygenation problems often need more prolonged hospitalization in the intensive care unit [5]. However, NPE is eminently treatable and it usually resolves within 24-48 hours with adequate therapy [1].

86.3 Neurogenic Acute Cardiomiopathy

86.3.1 Features, Causes and Incidence

Different cardiac derangements can occur in association with cerebral diseases, including electrocardiographic changes, elevation of cardiac enzymes and transient left ventricular dysfunction. While the majority of these canges are not specific, there is a characteristic form of neurogenic cardiomyopathy known as tako-tsubo or apical ballooning syndrome [13]. This cardiac disorder is usually caused by acute physiological (e.g. in the case of intracranial hemorrhages) or emotional (e.g. "voodoo death") stressors, hence the alternative denomination of "stress-induced cardiomyopathy" [14].

The most frequent electrocardiographic changes are seen during repolarization: T waves inversion (known as cerebral T waves), increase of the QTc interval, and appearance of U waves (Figure 86.3).

ST segment elevation can be confused with acute myocardial ischemia. Tansient Q waves that do not follow the standard evolution of ischemic cases can occur, but are less frequent. These changes were initially described in patients with aSAH and these are the patients in whom they are most often observed in clinical practice. On the basis of the criteria used to define them, the incidence of EGC abnormalities reported in different studies varies, but it is usually accepted that they occur in 40-70% of aSAH cases [13]. The incidence is lower, but nonetheless elevated (15-40%), in patients with ischemic stroke [13].

Cardiac arrhythmias are frequent too. Benign arrhythmias are most common, but fatal arrhythmias can occur. The spectrum of possible arrhythmias includes atrial or ventricular extrasystole, supraventricular tachycardia, torsade de pointes and ventricular tachycardia or ventricular fibrillation [13,15]. In ischemic strokes, the compromise of the insula increases the risk of ventricular arrhythmias and sudden death [16,17]. Whether the side of insular involvement affects this risk is still under discussion [16,17].

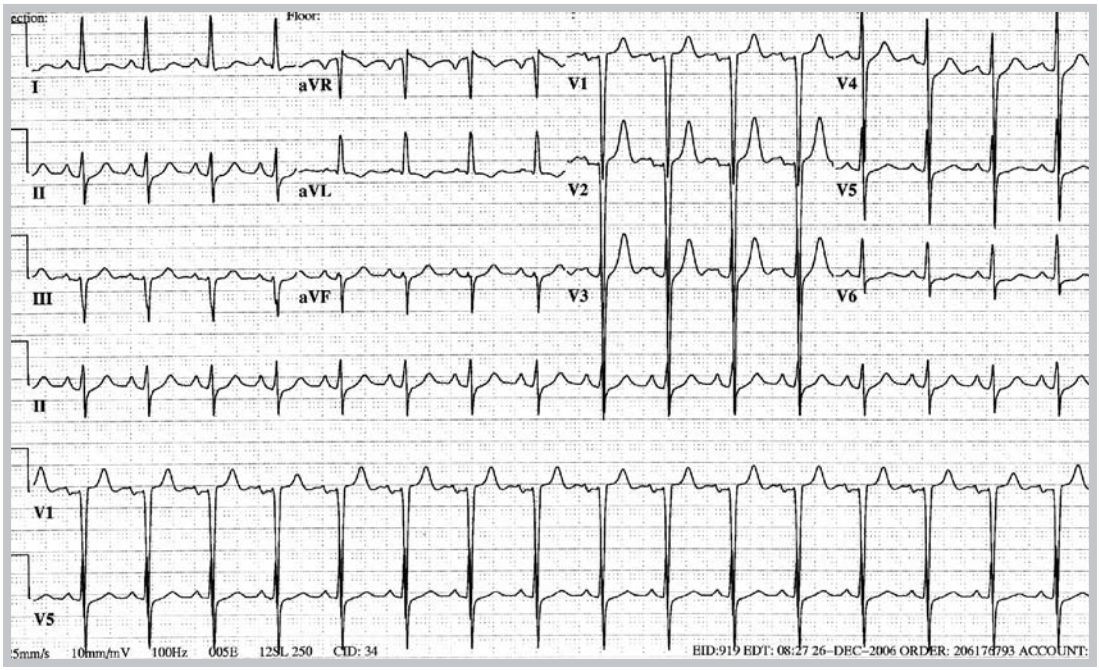

Figure 86.3. Example of electrocardiographic changes in a patient with subarachnoid hemorrhage.

Elevation of cardiac enzymes is frequent in patients with cerebrovascular events, especially if they are severe. Elevated cardiac enzymes can also be seen in patients with seizures, encephalitis, or brain trauma. The levels of both CK-MB and troponin can increase [13,18]. Characteristically they reach a peak during the first day and start declining over the following 1 to 4 days. They correlate with electrocardiographic and echocardiographic changes, but not with coronary disease [19]. Blood levels of brain natriuretic peptide (BNP) are usually increased in patients with electrocardiographic abnormalities [20].

Neurogenic cardiomyopathy can exhibit characteristic echocardiographic features. Regional abnormalities in ventricular motility do not respect the distribution of one coronary artery. Most often involve the apical and septal ventricular segments become akinetic or hypokinetic with relative preservation or hyperkinesis of the basal segments [21]. The resulting appearance of the heart on the ventriculogram explains why this condition has been named tako-tsubo cardiomyopathy ("Tako-tsubo" is the Japanese name for octopus traps that fishermen still use to catch octopus) or apical ballooning syndrome. Yet, atypical echocardiographic patterns can also occur [22]. This kind of cardiomyopathy is more frequent in post-menopausal women suffering of severe aSAH [14,19,23]. In patients with ischemic stroke, this pathology is much more frequent in women with stroke and insular damage [24]. Ejection fraction of the left ventricle decreases suddenly after the cerebral event, but returns to normal over the following 4 weeks [13,14,23]. It can be associated with acute pulmonary edema and can require hemodynamic support.

86.3.2 Pathophysiology

Acute neurogenic cardiomyopathy is thought to be caused by the injury of myocardial fibers and terminal nerves due to a massive sympathetic discharge [13,14,25,26]. This pathophysiological explanation is supported by the reports of apical ballooning in after infusion of cathecolamines [27]. In patients with SAH-related cardiac dysfunction a state of sympathetic denervation with normal myocardial perfusion has been demonstrated [25]. The pathological correlate is contraction band necrosis (also known as myofibrillary degeneration or coagulative myocytolysis) that occurs in proximity of sympathetic nerve terminals and does not respect the boundaries of coronary artery territories [13].

86.3.3 Diagnostic Evaluation

All patients with acute cerebral injuries should be managed in intensive care units, ideally dedicated units with neurological expertise, and be kept on cardiac telemetry. The initial evaluation should include an electrocardiogram, a chest X-ray and cardiac enzymes in all the cases, and a transthoracic electrocardiogram in patients with pulmonary edema, hypotension, or other manifestations of cardiac dysfunction. Furthermore it is prudent to perform an echocardiogram in postmenopausal women with severe aSAH even if there are no signs of cardiac failure, because these patients are at high risk of developing stress-induced cardiomyopathy. In patients with echocardiographic changes compatible with neurogenic cardiomyopathy, it is not necessary to evaluate the coronary circulation. In these cases it is advisable to repeat an echocardiogram after 1-2 weeks to reassess the ventricular function. Pulmonary catheterization is only necessary in cases of refractory shock. Figure 86.4 highlights a diagnostic algorithm to be considered when acute neurocardiogenic injury is suspected.

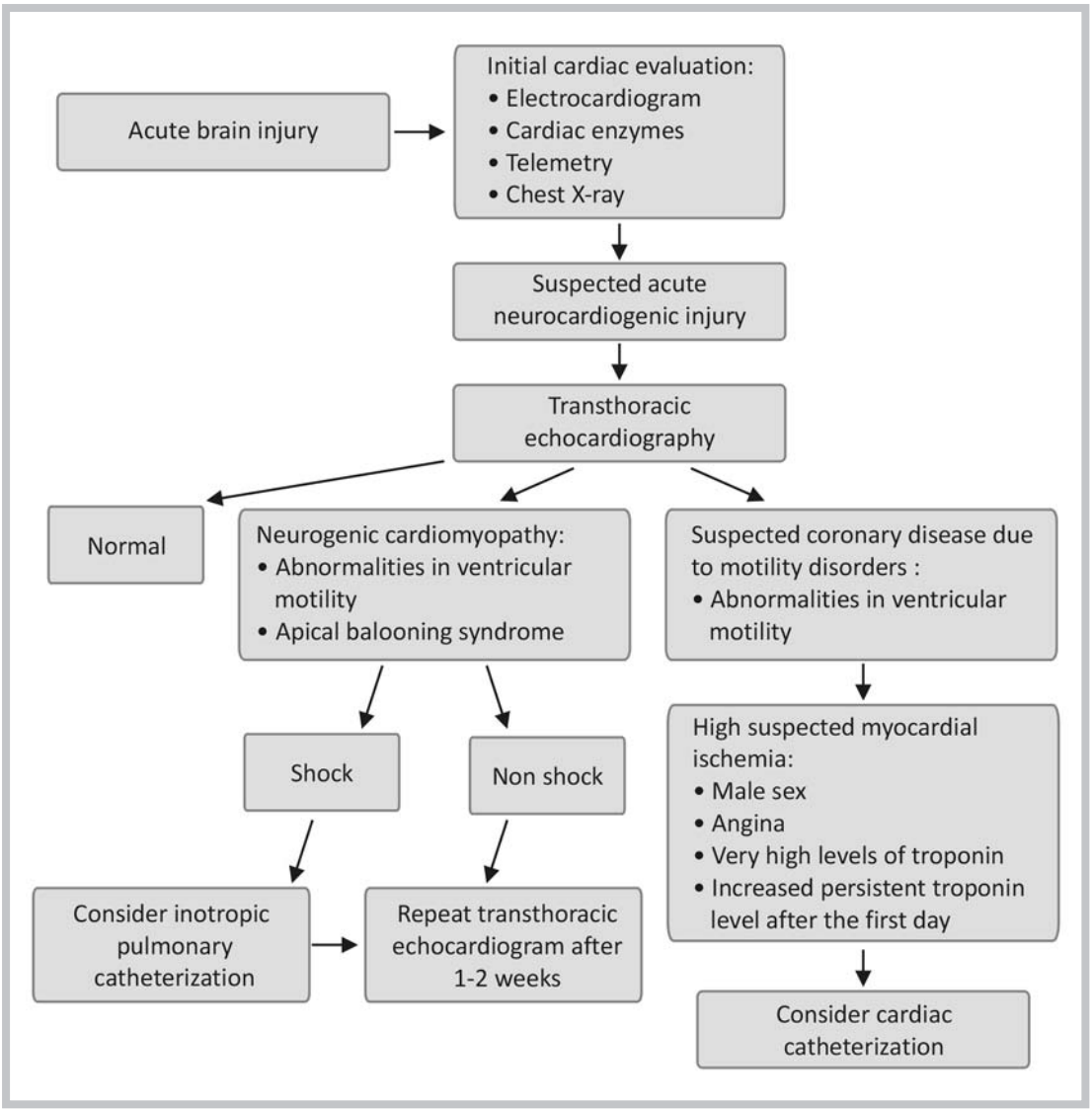

Figure 86.4. **Evaluation and management of patients with suspected acute neurogenic cardiomyopathy. Modified from [14].**

86.3.4 Treatment

The main tenets of treatment of acute neurogenic cardiomyopathy are hemodynamic support and cardiac rhythm monitoring. It is preferable to use inotropic drugs instead of pure vasopressors in case of hypotension. Diuretics such as furosemide are necessary when cardiogenic pulmonary edema is present. Arrhythmias should be treated as in other cases. In patients with prolonged QTc interval it is particularly important to avoid or correct any degree of hypokalemia and hypomagnesemia. In patients with aSAH and vasospasm who still have depressed cardiac function, therapeutic options include inotropic drugs, insertion of an intra-aortic balloon pump, and intra-arterial techniques, such as angioplasty or selective infusion of calcium channel blockers [13,14].

The prophylactic use of beta-blockers in patients at high risk of acute neurogenic cardiomyopathy can be useful, but more studies are needed before it can be recommended.

86.3.5 Prognosis

Although the cardiac dysfunction is reversible [28], most studies have shown that the presence of elevated troponin levels and electrocardiographic changes are associated with worse prognosis in patients with aSAH, intraparenchymal hemorrhage and ischemic stroke [18,29,30]. Available data is insufficient to determine if this correlation could be a direct consequence of cardiac damage or a surrogate marker of more severe acute brain disease.

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87 Acute Hydrocephalus in the Neurointensive Care Unit: Etiology, Diagnosis and Treatment

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87.1 Introduction

This chapter describes the etiology, diagnosis and management of acute hydrocephalus, a common cause of neurological impairment and intracranial hypertension in neurocritical patients. Various disease entities may lead to hydrocephalus. Special emphasis will be devoted to the use of intraventricular catheters or drains in the management of acute hydrocephalus, as well as the use of catheters or lumbar drain. Complications from their use will also be discussed. A brief review of the intracranial hypertension syndrome is given.

87.2 Intracranial Hypertension

The intracranial hypertension syndrome comprises a variety of disease entities. The neurological diseases making up this syndrome may originate in the brain parenchyma or abnormalities in cerebrospinal fluid flow or cerebral blood volume (Table 87.1).
The clinical manifestations of intracranial hypertension are not specific. The etiology of this syndrome has a broad differential diagnosis. Diagnosis is based mainly on suggestive symptoms and signs (see next section), together with brain imaging studies including computed axial tomography (CAT) and cerebral magnetic resonance imaging (MRI). In patients with a level of consciousness of <9 on the Glasgow Coma scale (GCS), invasive monitoring of intracranial pressure is justified. The ideal tool to monitor the pressure is an intraventricular catheter (when the lateral ventricles are dilated enough for appropriate catheter insertion). The use of such catheters facilitates intracranial pressure measuring and relieves pressure by draining cerebrospinal fluid (CSF).

Brain parenchyma	Hematoma, tumour, brain abscess, brain edema
Cerebrospinal fluid	Hydrocephalus
Cerebral blood volume	Hypertensive encephalopathy, cerebral vasodilatation secondary to systemic hypotension, fever, dehydration in patients with abnormal brain compliance

Table 87.1. **Neurological diseases making up intracranial hypertension syndrome.**

87.3 Acute Hydrocephalus

The hydrocephalus syndrome is characterized by an increase in CSF volume. Two groups of causes of hydrocephalus are distinguished: 1) increased production of CSF and 2) reduced reabsorption or obstruction of normal CSF flow. In neurological/

Obstructive hydrocephalus	• Tumours
	• Primary intraventricular hemorrhage:
	  ▪ Hypertensive hemorrhage
	  ▪ Primary vascular abnormality
	• Secondary intraventricular hemorrhage:
	  ▪ Trauma
	  ▪ Subarachnoid hemorrhage
	  ▪ Parenchymal hemorrhage with ventricular extension (Figure 87.1)

Communicating hydrocephalus	• Suppurative meningitis • Subarachnoid hemorrhage (subacute/chronic) • Intraventricular hemorrhage (subacute/chronic)

Table 87.2. **Types of hydrocephalus.**

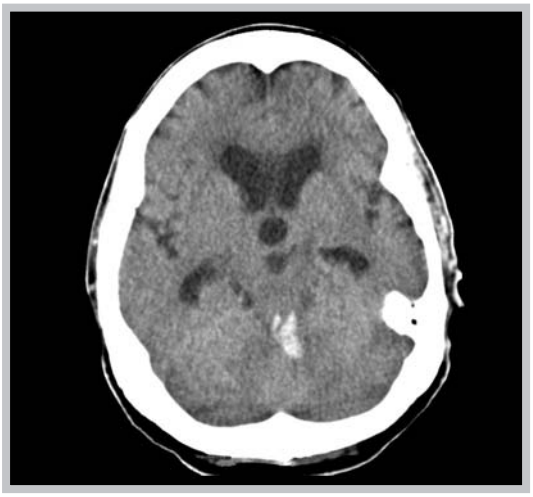

Figure 87.1. **Brain computed tomography of a patient with intraventricular hemorrhage of cerebellar origin and associated hydrocephalus.**

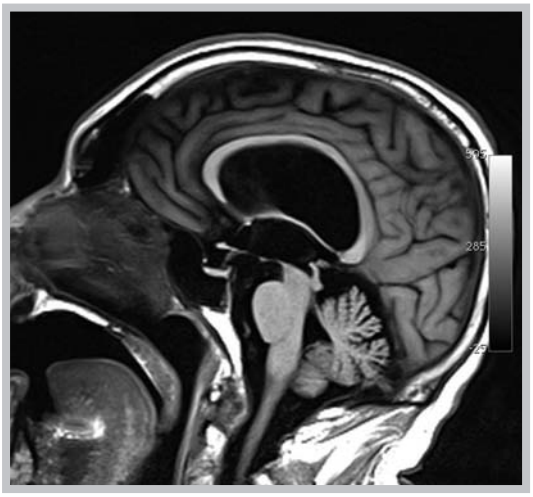

Figure 87.2. **MRI (sagittal section) of patients with hydrocephalus associated with aqueduct stenosis.**

neurosurgical intensive care, acute hydrocephalus is most often caused by a reduction in reabsorption of CSF or an acute obstruction of normal CSF circulation.

The clinical presentation is not specific; characteristic symptoms and signs include: elevated intracranial pressure, reduced consciousness, nausea and vomiting, occasional signs of meningeal irritation due to mechanical traction of the meninges. In advanced stages, lower limb motor weakness with pyramidal signs is frequently found on neurological examination. Papilledema is common in advanced stages. Although the syndrome of intracranial hypertension is simple to identify and familiar to most medical professionals in neuroscience, it is frequently superimposed over an underlying cause: subarachnoid hemorrhage, intracerebral hemorrhage, midline shift with "trapped ventricles", and brain tumours among others. Seeking the causes of this complication in high-risk patients presenting with an unexplained decrease in consciousness is therefore essential. The degree of risk is stratified according to risk factors. Imaging studies such as CT of the brain are needed to confirm the diagnosis. Nuclear magnetic resonance (NMR) is the most appropriate study for obtaining a more accurate anatomical definition (Figure 87.2). Additionally, although of limited use, scales such as the bi-caudate index (size of the frontal caudate ventricles divided by the diameter of the skull at that level) can provide objective values for monitoring patients.

87.4 Treatment

In addition to treating the underlying disease, the emergency treatment of acute hydrocephalus syndrome involves placement of an external ventricular drain (EVD [1,2] via ventriculostomy or intraventricular catheters (IVC).

The most common indication for catheter insertion is a reduced level of consciousness in patients with a radiographic diagnosis of acute hydrocephalus. A description of techniques for external ventricular drainage is beyond the scope of this chapter. The reader is referred to the references listed at the end of this chapter. In general, after insertion of the IVC, the necessary connections are completed (Figures 87.3 and 87.4).

The IVC is connected to a 3-way valve. One line is connected to the drainage chamber, the second to the IVC, and the third to a pressure transducer. Intracranial pressure (ICP) can only be measured after closing the valve to drain the chambers. This will produce a single column of liquid in contact with the membrane transduction.

Management of the IVC will vary depending on the etiology of acute hydrocephalus; however, some general principles are valid and deserve to be discussed:

- The use of an external ventricular drain for acute hydrocephalus is an emergency procedure and can potentially prevent permanent loss of neurological function. However, it is a temporary measure until definitive treatment is identified and instituted.
- The initial goal of ventriculoperitoneal shunting (VPS) is to control intracranial hypertension. However, excessive drainage of CSF should be avoided for the following reasons:
  - Superior cerebellar herniation syndrome [3]. Cerebellar tissue can be pulled along a caudorostral vector, compressing the structures related to the anatomy of consciousness (rostral brainstem and thalamus). This complication ensues from a pressure differential between the different ventricular structures.
  - Re-bleeding from re-rupture of vascular malformations such as aneurysms, arteriovenous malformations, or hypertensive bleeding; this results in a sharp reduction in

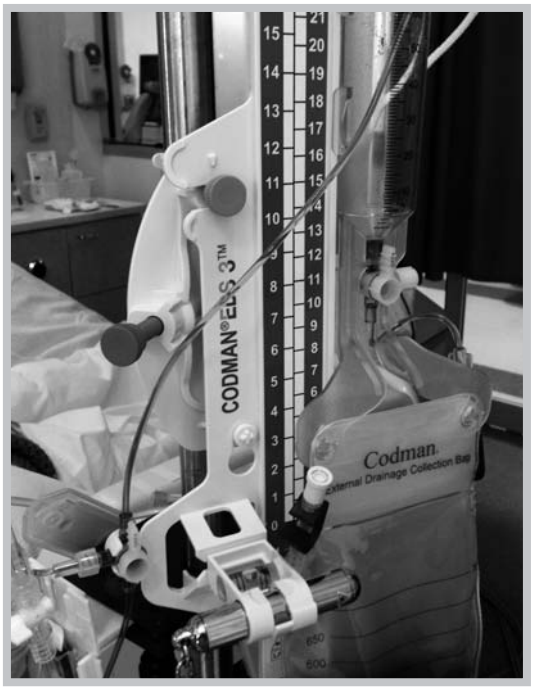

Figure 87.3. Ventricular drainage system.

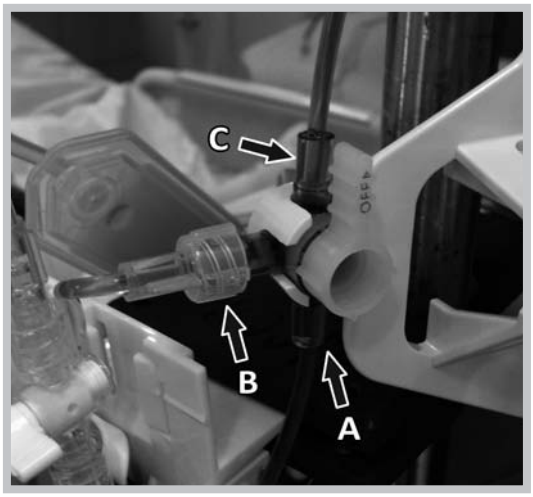

Figure 87.4. Three-way valve with the patient connected (A) to the transducer (B) and the reservoir (C).

transmural pressure due to the hemostatic mechanism that serves for acute or "buffering".

- If the cause of acute hydrocephalus requires surgery (e.g., brain tumour), such treatment should be instituted when the patient has been stabilized. If the cause of acute hydrocephalus requires acute surgical procedures, EVD management varies depending on the natural history of the underlying disease. Once it is determined that the patient requires chronic artificial CSF drainage, a ventricular shunt system will be inserted.

87.5 Intraventricular Catheter Management

In general, the decision to begin discontinuing VPS depends on the following variables:

- Stable neurologic patient.
- Normalization of intracranial pressure.
- Reasonable expectation of normalization of CSF physiology and anatomy, based on the patient's clinical course and knowledge of the natural history of the underlying disease.
- Neurological examination to monitor clinically appropriate response to the discontinuation process.

Once the patient meets these requirements, the "pop-off", or the elevation of the reservoir chamber of the ventriculostomy system, is gradually elevated. Generally, when the pop-off is low (<10 mmHg), CSF drainage may be high (>200 cc/24 h). Pop-off elevations of 5 mmHg every 24 hours is a common practice. The neurological examination, intracranial pressure (ICP) and volume of CSF drained in 24 hours will be taken into consideration. If the neurologic examination and ICP remain stable, the pop-off should be raised every 24 hours to 15-20 mmHg.

At these levels, if drainage is <200 cc/24 h in association with normal ICP values and the neurological examination is stable, pop-off elevations of up to 20 mmHg are recommended. At this level, the drain is clamped, and the neurological examination and ICP are monitored for 24 hours. If these parameters are stable, the drain can be removed. A brain CT study is recommended before removing the drainage system. This recommendation is justified if there is a need to compare ventricular size before and after removing the IVC in case of future clinical deterioration.

If during this process the patient demonstrates neurological impairment, the pop-off must be reduced or the IVC must be reopened. Other causes of encephalopathy should be studied concomitantly, such as metabolic processes, fever, subclinical seizures, and so on. CT can help determine the cause of deterioration. Clinical response to ventricular drainage in this scenario is, however, essential to determine its cause.

87.6 Management of the Catheter or Lumbar Drain

A lumbar drain is a catheter inserted under aseptic conditions in the intervertebral space (L4-L5). The technique involves the use of a Tuohy needle through which the drain is inserted cephalic into the spinal subarachnoid space. This type of CSF drainage is feasible only in cases of communicating hydrocephalus or when elevated ICP is diffuse, in the absence of pressure gradients between cranial compartments. Subsequent management, following the principles described above in the management of IVCs, depends on the

underlying disease [4,5]. This kind of management of acute hydrocephalus or intracranial hypertension (below), though limited to certain diseases, is interesting because it is less invasive than IVC and the implicit risk of brain damage, especially bleeding. The risk of infection persists for the duration of use of these drains.

87.7 Complications

Infections:

- Prophylactic antibiotic therapy is restricted to a dose of antibiotics with activity against Gram-positive bacteria before insertion of ventriculostomy drains impregnated with antibiotics [6].
- Parenchymal hemorrhage in the ventricular drain tract.
- Subdural hematoma, a complication of excessive drainage of CSF.

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88 Chronic Subdural Hematoma: A Forgotten Entity in Neurocritical Care

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88.1 Introduction

The first description of this entity dates back to 1857 when Virchow termed it "internal hemorrhagic pachymeningitis". Years later, he established the relationship between trauma of subdural veins or "bridging veins'' and the onset of chronic subdural hematoma (CSDH), then named "subdural hemorrhagic cyst". Since then, trauma has been recognized as one of the major risk factors for the development of CSDH.
Classically, CSDH has been considered benign. In our experience, this assumption is far from reality because CSDH can cause various complications with a mortality that, in some recent studies, has been estimated to be 15%. Current opinion in the neurosurgical community considers hematoma evacuation essential in the treatment of symptomatic patients. Opinions differ, however, on other therapeutic options, including the most convenient surgical technique, approach of recurrences or peri-operative management.

88.2 Definition

Chronic subdural hematoma (CSDH) is a subdural blood accumulation surrounded by a newly formed membrane located between the dura mater and the arachnoid space. Generally it manifests clinically 3 weeks after a triggering event that can be or not evident or identifiable. Subacute subdural hematoma develops between 3 and 20 days after the precipitating event. Its form of presentation, clinical features, and treatment are similar to those of CSDH.

88.3 Epidemiology and Risk Factors

The incidence of CSDH is near to 1.7 per 100,000 individuals per year. Mean age at presentation is 63 years. Its incidence is 7 times higher after age 70 years and is expected to increase with longer life expectancy. Age is one of the most important risk factors because the aging process brings two changes related to the development of CSDH. On the one hand, the increased fragility of the bridging veins make them more susceptible to rupture even after minor trauma and on the other side there is a remarkable increase in the subdural space available for the accumulation of collections due to generalized cerebral atrophy. A history of trauma can usually be elicited in 50-70% of cases. Often, such

trauma was minor and in many casesa history of accidental fall, without a direct impact to the head is present. Approximately one quarter of patients is under anticoagulation treatment and 5-10% have a history of epilepsy or alcohol abuse.
Table 88.1 lists predisposing factors for the development of CSDH.

- Age
- Head trauma
- Epilepsy
- Alcohol
- Hemorragic diathesis/coagulopathy
- Oral anticoagulant therapy
- Antiplatelet therapy
- Hemodialysis
- Intracranial hypotension (lumbar puncture, cerebrospinal fluid [CSF] derivations or shunts)

Table 88.1. Risk factors.

88.4 Pathophysiology

From an anatomopathological point of view, within 24 hours after the accumulation of blood in the subdural space, caused by either trauma or another factor, the hematoma is invaded by fibrin and fibroblasts originating from the dura mater. One week later, a membrane forms on the external surface of the hematoma and increases progressively, allowing fibroblasts to invade the hematoma, with the development of a thin internal membrane. The latter process ends after 3 weeks. The hematoma is then liquefied by phagocyte activity and can follow two paths:

- Spontaneous absorption of the hematoma, thus solving the problem, or
- Progressive growth of the hematoma, resulting in CSDH.

Two hypotheses try to explain the growth of hematoma. In 1932 Gardner, studying experimental models, postulated the osmotic theory, based on the premise that fluid from plasma of neoformation vessels of the dural surface or CSF is attracted into the subdural space through osmotic gradient created by the breakdown of blood products of the acute hematoma. This phenomenon is facilitated by the semipermeable nature of the subdural hematoma membrane. This theory was later confirmed by the studies of Zollinger and Gross. In an experimental study, Glover et al. showed that corticosteroids decrease the permeability of the CSDH membrane to proteins, thus decreasing the size of hematoma. Nevertheless, some evidence exists to refute this theory. Gitlin analysed the total ratios between albumin, gammaglobulins and proteins in the subdural liquid and the plasma and found that the concentrations were remarkably greater in the subdural fluid. This fact cannot be attributed to the lysis of erythrocytes because of the lack of these proteins, suggesting that albumin comes from the newly formed vessels of the membrane of the subdural hematoma.
Additionally, Rabe et al. highlighted that albumin marked with iodium^{131}, administered intravenously, appears quickly in the subdural collection. Weir compared the osmolality of the subdural hematoma fluid, venous blood, and cerebrospinal fluid and found no significant difference between them.
The most widely accepted theory sustains that “bleeding recurrence” is the main reason for hematoma growth. Magnetic resonance imaging (MRI) or computed tomography (CT) show different densities of the hematoma. Clots of different ages, consistencies and stages are often encountered at surgery.
This theory was reinforced by Ito et al. who infused red cells marked with 51 Cr-labelled and studied their concentration in a fluid obtained during craniotomy performed between 6 and 24 hours later. They estimated that new hemorrhages contributed on average to 6.7% of the hematoma content. The authors also proposed that hematoma has a high fibrinolytic activity that contributes even more to the increase in its size.
Several anatomopathology studies have explained this aspect better, demonstrating structural alterations in the capillaries of the membranes of the hematoma that can

favour the continuous passage of small amounts of blood towards the interior of the hematoma (Figure 88.1).

Recent studies have demonstrated that the hematoma content is characterized by elevated levels of cytokines and endothelium-derived growth factors that can contribute to the formation and development of membranes, and considerable amounts of inflammation mediators and fibrinolytic factors that can concur in the genesis of hematoma. Therefore, it seems that the hematoma itself is responsible for its chronic evolution.

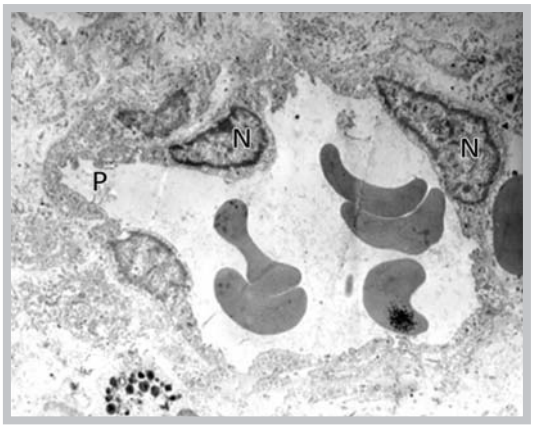

Figure 88.1. **Electronic microscopy showing the external membrane of a chronic subdural hematoma. An ample hair light (l) with erythrocytes is visible within its interior (EC), a thin layer of endothelial cells rests on a discontinuous basal membrane (X 5000).**
N = nucleus
P = protrusion

Since CSDH develops in the atrophic brains of adults of advanced age, the intracerebral pressure (ICP) usually remains within normal limits or rises slightly. Positron emission tomography (PET) studies that evaluated changes in metabolism and cerebral blood flow (CBF) are contradictory. Ikeda found a local reduction in CBF in hemiparetic patients. Ishikawa demonstrated an increase in cerebral oxygen extraction in the hemisphere adjacent to the hematoma, accompanied by a marked reduction in CBF and cerebral metabolic oxygen rate ($CMRO_2$) mainly in the frontal and temporal lobes and in the basal ganglia.

Recently, Yamada et al. observed a small bilateral reduction in CBF and $CMRO_2$, while oxygen extraction, cerebral blood volume, and cerebrovascular reactivity remained stable. All the altered variables stabilized within 4 weeks after hematoma evacuation. This period is shorter (average 3 days), in patients in which the symptoms reverse.

88.5 Clinical Features

The diagnosis of CSDH requires a high degree of suspicion. Due to its multiple forms of presentation, it is known as “the great imitator”. The commonest onset form is an altered mental state (50-70%). Delirium, confusional states, psychotic symptoms or alterations in behaviour are some of the symptoms that often can lead to the wrong diagnosis of psychiatric diseases or dementia.

In less than half of cases consciousness is impaired, varying from confusion to coma. Near to 60% of patients present with focal neurological deficits characterized by a location contralateral to the hematoma, slow evolution, and fluctuations (appearance and disappearance). Sometimes the symptoms are similar to those of a brain tumour patient with signs of elevated ICP such as migraine, vomiting and hemiparesis. Convulsions are infrequent, except in patients with a history of previous seizures. If they do occur, they are almost always associated with large collections. Other manifestations, although less common, include: gait and position disturbances, ataxia, akinesia, rigidity or extrapyramidal syndromes. In some cases, the hemiparesis may be ipsilateral to the hematoma; this can be explained by displacement and compression of the brainstem against contralateral tentorium.

88.6 Role of Neuroimaging Studies in Diagnosis

The neuroimage of election is CT scan because it is not invasive, it is rapid and low cost; in addition, it also allows the evaluation of other intracranial structures. CSDH has a dynamic nature, therefore requires considering this aspect due to the characteristics of the collection change with the time. During acute phase, the hematoma is hyperdense in relation to cerebral parenchyma due to the presence of fresh blood.

In 40% of acute cases, the density can be mixed with hypodense areas. This finding could be due to the fact that bleeding is so recent that part of the blood is not yet coagulated or because of the presence of CSF originating from the arachnoids.

With time, lysis of the collection takes place, so that the hematoma becomes as dense as the cerebral tissue (isodensity). In the chronic phase, beyond the third week, the collection begins to be reabsorbed, so that the hematoma acquires a hypodense aspect. Nevertheless, remembering the concepts explained in the paragraph on pathophysiolo-

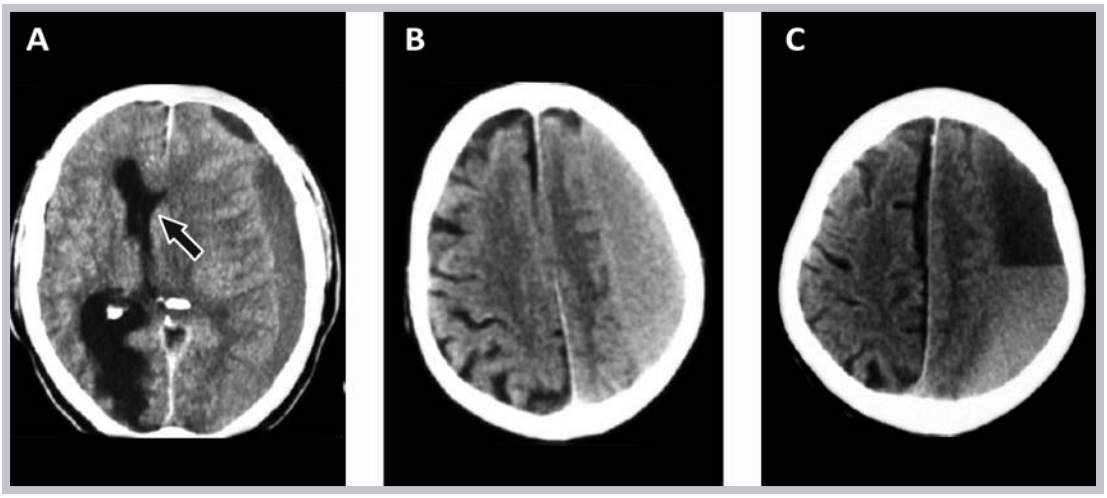

Figure 88.2. (A). Hypodense subdural hematoma with marked midline shift (arrow). (B). Isodense hematoma. (C). Hematoma with mixed density.

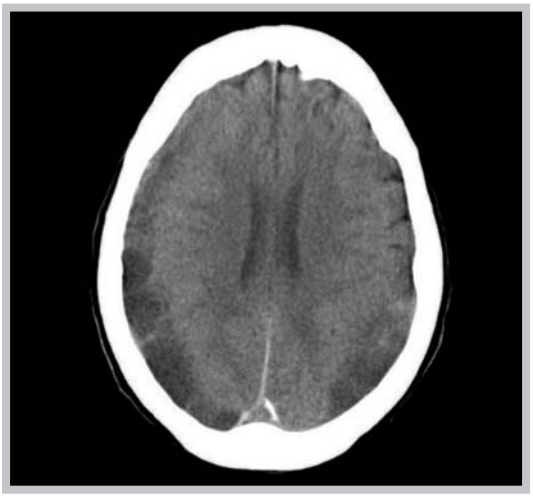

Figure 88.3. Bilateral subdural hematoma with isodense areas.

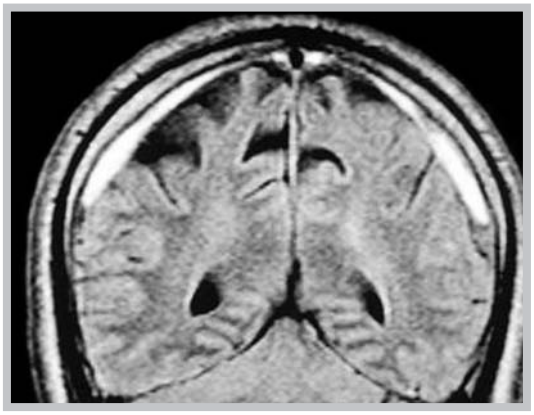

Figure 88.4. T1-weighted image of CSDH.

gy, continuous microhemorrhages can produce sometimes a collection with heterogeneous aspect sometimes with mixed areas with different densities due to precipitation of fresh blood in the declivities (Figure 88.2).

Generally, identifying a hematoma is easier when it appears as a hyperdense. The difficulties arise with isodense collections. In such cases, mainly in non trained eyes, it's very important the analysis of other structures, such as the median line, lateral ventricles and the sulcus between cerebral circumvolutions which often are displaced, compressed or absent, respectively. Another source of confusion is the finding of isodense images after recent trauma. This can be related to very low hemoglobin levels. Bilateral hematomas, usually don't produce midline shift, but may lead to medial compression of both ventricles, resulting in a narrow, elongated ventricle that can suggest a diagnosis of isodense hematoma (Figure 88.3). In such cases, misdiagnosis may be avoided by injecting contrast material, that reinforce internal membrane of the hematoma, cortical sulcus and vessels.

MRI can be especially useful in patients with isodense hematoma without impairment of other cerebral structures or in those cases with hematoma localized at the vertex, the base of the skull or posterior fossa. In addition, MRI allows the identification of small or transversally oriented collections. CSDH is hyperdense on T1 and T2 sequences, reflecting acute bleeding within a chronic collection. On T1 images it can be isodense (Figure 88.4).

88.7 Treatment

88.7.1 Surgery

Chronic subdural chronic hematoma is a surgical emergency, although conservative treatment has been successful in some cases. There is nearly unanimous agreement among neurosurgeons that hematoma evacuation is the gold standard mainly in symptomatic cases or when the thickness of the collection is >1 cm (on the tomograph scale); nevertheless, consensus on the surgical technique is lacking. Two recent surveys in Canada and the United Kingdom support this affirmation. Different options exist. Here we will list them, without entering into a detailed description.

- Twist-drill craniotomy. If the drainage orifice is small and drainage is not left, the index of recurrence is increased.
- Burr hole trephination (two or three), for which irrigates normal saline solution and causing the washing of the collection, until the collection is washed out, giving the brain time to re-expand. A closed drainage system can be left, but some still prefer the technique of "last points".
- Conventional osteoplastic craniotomy, with extirpation of the external membrane of hematoma. Deep membrane is not extirpated, because is attached to the brain and may damage it.
- Neuroendoscopic treatment
- Terphination, making a great hole, through which washing is introduced.

Data from evidence-based medicine do not allow to establish standard treatment guidelines for the surgical treatment of CSDH. Neither trials nor information exist that demonstrate which type of management is better, even if some recommendations are possible; all have a low level of evidence (C):

- Both burr hole trephination and twist-drill craniotomy are safe methods.
- Burr hole trephination has a better treatment/complication ratio and lower recurrence rates than twist-drill craniotomy.

- Conventional osteoplastic craniotomy and burr hole trephination have lower recurrence rates.
- Closed drainage systems reduce the risk of recurrence without increasing the risk of other complications.

88.7.2 Neurointensive Care

Although the treatment of CSDH is generally surgical, almost 20% of cases can resolve spontaneously, principally due to a collections of lower size. If one decides to wait, it is essential to closely monitor the state of consciousness, performing neuroimaging (CT or MR) at the minimum sign of neurological deterioration. Perioperative management doesn't differ from the management of other neurocritical illnesses, except for some controversial aspects that we will analyze below.

Position of the Head: 0 or 30 Degrees?

In medicine in general, and intensive care in particular, there are dogmas that are handed down from generation to generation, even with the lack of solid scientific evidence. One of these controversial topics is how the head should be maintained after CSDH evacuation. Several opinions among neurosurgeons exist. Some advocate a horizontal (0 degrees) head position, others an elevated position, and still others suggest alternating the positions throughout the day. Advocates of the horizontal position base their rationale on "physical reasons", because, in theory, this position diminishes the potential space (which can be increased by the cerebral atrophy that accompanying ageing) where hematoma could develop. In addition, horizontal position annuls the effect of the gravity, improves cerebral perfusion and favours cerebral expansion due to vigorous transmission of arterial compression waves within cerebral parenchyma,. Finally, the horizontal position theoretically improves the drainage of subdural collections.

Some neurosurgeons systematically elevate the head to 30 degrees. It is well known, and it has been previously discussed in other chapters of this book, that elevating the head favours the reduction of intracerebral pressure (ICP), facilitating the venous drainage of the brain. Additionally, remember that two theories try to explain the growth of subdural hematoma: the osmotic theory and the theory of recurrent bleeding. Both these components disappear, at least hypothetically, when the head is elevated because the necessary pressure gradient for the development of the osmotic theory diminishes and the action of gravity decreases the intraluminal pressure from the neoformation vessels of the external membrane of the hematoma that originate recurrent bleeding. Other no less important reasons support the choice for head elevation. Gastrointestinal system of the neurocritically ill patients does not work correctly, becoming paralyzed or slowed down due to cerebral damage or side effects of the drugs commonly administered (e.g., morphine, fentanyl, diphenylhydantoin, noradrenaline, etc.). In addition, the use of acid blockers such as omeprazole and lanzoprazole, or blockers of the acid secretion of the stomach like ranitidine, elevate the pH, thus favouring the growth of microorganisms, mainly Gram-negative species. Also, the lower oesophageal sphincter, whose main function is to prevent gastric reflux, doesn't work properly. All these aspects can augment the risk of continuous microaspirations, which is one of the main risk factors in the pathogenesis of ventilation-associated pneumonia. This risk remarkably decreases when the head of the bed is raised to 30 degrees or more.

In conclusion, there is no consensus on head position during the postoperative period. Nakajima reported that the rate of recurrence is the same for both positions, whereas Miele et al. found no differences in the rate of expansion or in the recurrence of hematoma.

Corticosteroid Therapy: Yes or No?

Anecdotal series, with a small number of patients, or single case reports suggest a favourable effect of corticosteroid therapy in conservative treatment. The rationale for the use of corticosteroids in CSDH lies in its capacity to decrease the permeability and its antiangiogenic properties over the subdural clot membrane, both mechanisms derived from experimental studies and very few clinical studies. Data obtained from a retrospective series suggests that dexamethasone (4 mg every 8 hours) is at least a feasible and safe option in the management of CSDH, however, no evidence for their efficacy exists since the studies were not validated in large-scale populations or in randomized controlled trials.

Anticonvulsants

Seizures as presentation form of CSDH are rare with reported rates around 6%. During postsurgical period the data reported are contradictory. The incidence of seizures appears to be inversely related to the population size. In a small series of 50 subjects, the estimated incidence was 32%, whereas the average rate was 3 and 0.3% in two studies involving 568 and 1439 patients, respectively. Since all the reported studies were retrospective, the systematic use of anticonvulsants cannot be recommended. We use anticonvulsants agents in the following circumstances:

- History of epilepsy.
- Previous utilization of anticonvulsants drugs.
- Convulsions as a presenting form of CSDH.

If the patient is already efficaciously treated with anticonvulsants, the same therapeutic scheme should be continued.

Antibiotics

Although most neurosurgeons or neurointensivists prescribe antibiotics, the best timing, dosage, administration route and therapeutic options are still unclear. From an infectious point of view, the wounds produced by techniques to evacuate CSDH are considered “clean” because they do not produce trauma, tissue damage, potentially do not invade or penetrate contaminated systems such as the digestive, respiratory or genitourinary. If the conditions of surgical asepsis are followed, the use of IV cephazoline 1 g during induction of anesthesia in a single dose is recommended.

88.7.3 Postsurgical Complications

Despite ongoing advances in surgical techniques, postsurgical outcome has remained unchanged. The main reasons for deterioration during the postoperative period are complications associated with hematoma evacuation. This is the reason for which the intensivist must learn to recognize them early for take all necessary measures for their quick and favourable resolution.

The complications rate is >20%, with **recurrence of hematoma** the most frequent one. The incidence of recurrences is 8-45% depending on the series analyzed, and the main risk factors are patient age and the anatomical characteristics of the collection and the membrane. It is often difficult to differentiate between the residual liquid of the surgery and the liquid caused by re-accumulation of the hematoma from recurrent bleeding. This last possibility must always be taken into consideration especially in patients who do not improve or deteriorate during the postsurgical period. In such cases, the drainage debit should be monitored, paying attention to the occurrence of abrupt increases or decreases. If any of the described situations occur quickly, a CT must be performed to reveal the presence of mixed or elevated density collections.

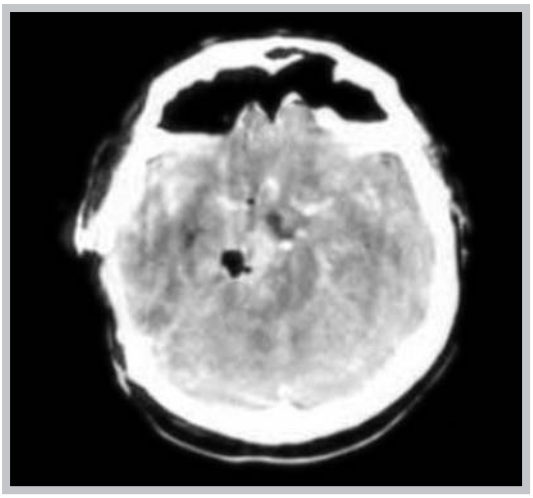

Figure 88.5. **Hypertensive pneumoencephalus in the anterolateral region of the frontal lobes with cerebral edema.**

Occasionally, in approximately 8% of cases, **air is entrapped in the subdural space**. This is favoured by the slow re-expansion of an atrophic brain, chronically compressed by hematoma. Air accumulation can be prevented by maintaining the head horizontal, irrigating the cavity with saline solution to promote slow drainage together with residual hematoma. Nevertheless, and even with preventive measures, the entrapped air can sometimes increase the pressure, causing mass effect and neurologic deterioration. Another important factor that contributes to mass effect is that the volume of the entrapped air increases as the body temperature rises. When entrapped air provoke mass effe, this situation is referred as **hypertensive pneumoencephalus**; this risk should always be taken into consideration because it is a surgical emergency that requires immediate intervention (Figure 88.5).

A lethal complication, fortunately rare, is the development of **intracerebral hemorrhage** (Figure 88.6). McKissock in 1960 was the first to describe a patient who deteriorated suddenly and died after hematoma evacuation. The autopsy revealed bleeding in the brainstem. Since this report, other reports and case series have been published. The reported incidence is around 4-5%. Several theories have attempted to explain this phenomenon but the most consistent one is that the sudden decompression following evacuation of the hematoma is related to a significant increase in cortical cerebral blood flow in blood vessels that have lost their autoregulation. This hypothesis is not sufficient to explain the bleeding that occurs distant from the surgical site, so other factors must be considered, such as coagulopathy, hypertension, amyloid angiopathy, direct damage to the vasculature as a result of displacement, etc.

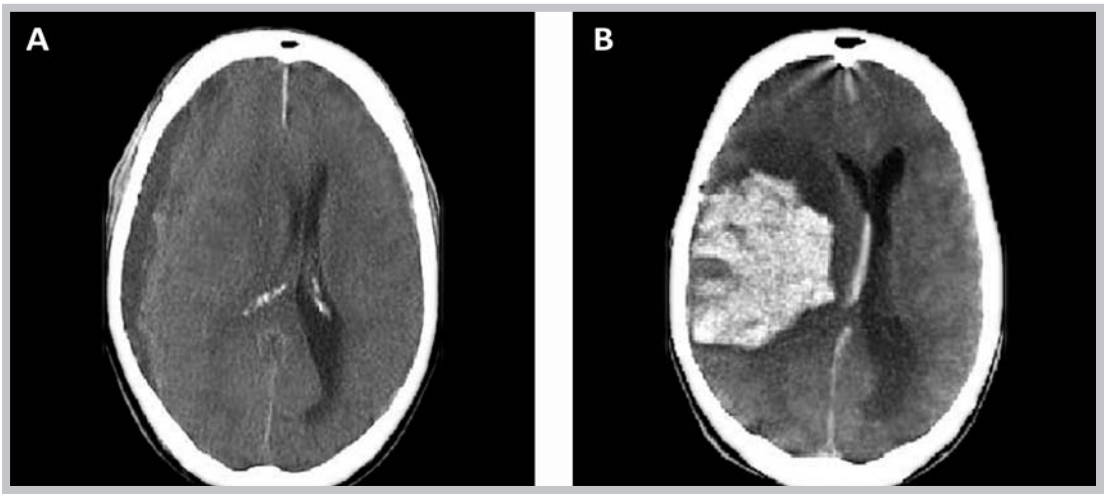

Figure 88.6. **Intracerebral hematoma after evacuation of a hypodense CSDH.**

In the first three days after surgery, the intracranial hypertension syndrome can occasionally occur; its substrate is cerebral edema. This does not usually cause major problems because the standard measures for the management of elevated ICP are normally sufficient to handle this situation.
Other postsurgical complications (approximately 10% of cases) are reversible delirium, or confusional state caused by intracranial hypotension or the onset of seizures.
Other complications are infections, which, although rare, cover a wide spectrum from wound infection to subdural empyema. They are described in detail in another chapter of this book.

88.8 Prognosis

Several predictors of outcome has been described. The preoperative state of consciousness has been found to be of greater significance in different case series. Markwalder devised a scale that allows classifying the degree of clinical deterioration. Multiple CT findings can be associated with preoperative conditions and postoperative recovery of the state of consciousness, including: degree of cerebral atrophy, presence of hydrocephalus, pneumoencephalus, levels of sedimentation, and hematoma density. Interestingly, there is no relationship between hematoma volume, degree of impaired consciousness and/or outcome.

Grade	Description
0	Neurologically normal
1	Alert and orientated: absence of mild symptoms such as headache, or mild neurological deficit such as reflex asymmetry
2	Drowsy or disorientated, or variable neurological deficit such as hemiparesis
3	Stuporous, but responding appropriately to noxious stimuli, several focal signs such as hemiplegia
4	Comatose with absent motor responses to painful stimuli, decerebrate or decorticate posturing

Table 88.2. Markwalder Scale.

There is no consensus on the influence of age on prognosis. Since CSDH mainly affects the elderly, it is unclear whether age *per se* or the presence of concomitant comorbidities are the true prognostic factors.
The reported mortality is 0-38% depending on the population studied, with an average of 16%. Approximately 75% of patients return to their previous activities and 15% remain with severe disabilities.

88.9 Conclusions

Erroneously considered benign, CSDH is a disease of the elderly. Trauma is the most frequent etiology, but there is a trigger event in half of cases. Clinically, it can take various forms and can mimic many other situations or neurological disorders. Computed tomography is the complementary method of choice for diagnosis and monitoring of this patient group. The state of consciousness is key to predicting prognosis. It is a surgical emergency, with a postoperative complications rate of up to 20%. Morbidity and mortality are directly related to age; nevertheless, outcome is very good when CSDH is not underestimated and is managed in a multidisciplinary approach.

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89 Intoxication With Central Nervous System Depressant Agents

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89.1 Introduction

Patients with CNS depressant intoxication often constitute a toxicological emergency. The most common cause of intoxication in adults is attempted suicide, followed by accidental causes, mainly in children.

Given the severity of the emergency that this type of drug can cause, it is critical to correctly evaluate the problem, with adequate patient interview, physical examination and complementary methods. The aim is to reach a presumptive diagnosis, understanding the most likely etiology and start specific treatments immediately.

This chapter provides a practical guide to the management of patients entering an emergency department intoxicated with central nervous system (CNS) depressant agents.

89.2 Development

When patients with altered state of consciousness enter the emergency department, we should always consider possible exposure to CNS depressant agents because this condition requires rapid diagnosis and treatment.

- Alcohol
- Benzodiazepines
- Barbiturates
- Opioids
- Phenothiazines
- Butyrophenones
- Anticonvulsants
- Tricyclic antidepressants
- Others
- Antihypertensives (beta-blockers)
- Calcium channel blockers
- Digitalis
- Vinyl chloride
- Methaqualone
- Chloral hydrate

Table 89.1. Main drugs with CNS depressant activity.

Questions	Answers
What did you take?	Identification of the generic name of the substance involved, the composition of the product containing it, and its presentation
How much did you take?	Evaluates the extent of intoxication in order to start immediately the appropriate treatment
When?	It's the latency time: the time of ingestion to the time patient presents at hospital or onset of symptoms
How?	Evaluates the administration route of the poison
Where?	Know where it happened (it helps when you do not know what the patient has taken)
Why?	To better understand the intoxication

Table 89.2. Questions for the diagnosis of intoxication.

Many various drugs have CNS depressant activity (Table 89.1); therefore, family history of the patient is extremely relevant because it can yield data on the medication administered to the patients, their availability, and so on. All these aspects are useful in the analysis of intoxication cases (Table 89.2).

Few signs and symptoms are special features and, on the contrary, are often similar to those presented by other diseases such as infectious disease, stroke, coma, etc. A thorough physical examination is essential to search for meaningful data (Table 89.3).

Toxicological screenings are limited and not always available in all emergency departments; therefore, available laboratory tests should be performed, such as acid-base status, electrolytes, glucose, urea, white blood cell count, hematocrit, creatine, lactic acid, anion gap, and urine sediment.

The electrocardiogram (ECG) is an inexpensive, quick means to obtain objective information on intoxication etiology and severity. Rarely will ECG alone provide guidance to establish a precise etiologic diagnosis; however, together with findings from history, epidemiology, vital signs, characteristics of the skin, eyes and peristalsis, the ECG has a fundamental diagnostic value. CNS depressants can cause rhythm disturbances in cardiac conduction, often with PR interval prolongation, QRS widening, QT prolongation, and atrial and ventricular arrhythmias.

The physical examination will disclose signs that can help in the diagnosis: vital functions (blood pressure, heart rate, pulse), skin and mucosa colour, smell of the expired air and the vomit or clothes, body temperature, and breathing pattern.

Patients intoxicated with CNS depressants may have different levels of altered consciousness. This is of great clinical importance, because it represents the key point to understand whether the clinical features are related to a structural cause (stroke or subdural hematoma) or to a toxic/metabolic cause (intake of psychiatric drugs, opioids,

Clinical features	Suspected substance	
Miosis, bradycardia, nystagmus, ataxia, coma, hypoglycemia, hypothermia, ethyl breath	Alcohol	
Muscle hypotonia, drowsiness, stupor, coma, seizures, cardiorespiratory depression, hyporeflexia, ataxia, hypothermia	Benzodiazepins	
Nystagmus, somnolence, cardiorespiratory depression, hypotension, slurred speech, hypotonia, ataxia, dysarthria, hypothermia, miosis, flaccid coma	Barbiturates	
Sensory depression, bradypnoea, coma, seizures, spasticity, hyperreflexia, bradycardia, constipation, hypotension, hypothermia, miosis	Opioids	
Arrhythmias, hypotension, hypothermia, sensory impairment, oculocephalic crisis spasmodic torticollis, hypertonia, myoclonus, ataxia, orolingual dyskinesia	Phenothiazines	
Convulsions, sensory depression, extrapyramidal symptoms, anticholinergic symptoms, arrhythmias, hypotension, hypothermia	Butyrophenones	
Hypotension, hypothermia, tremor, hyperreflexia, dysarthria, coma, convulsions, sensory depression, anticholinergic symptoms, arrhythmias	Tricyclic antidepressants	
Nausea, vomiting, myoclonus, mydriasis dysarthria, nystagmus, ataxia, diplopia, blurred vision, respiratory depression	Carbamazepine	Anticonvulsants
Arrhythmias, hypotension, nausea, vomiting, seizures, tremors, nystagmus, vertigo, mydriasis, dysarthria mental confusion, ataxia diplopia, blurred vision	Phenytoin	

Table 89.3. **Clinical signs of CNS depressant intoxication.**

Manifestations	Toxic/metabolic coma	Structural coma
Pupils	Not modified	Modified
Oculocephalic manoeuvre	Maintained	Altered
Papilledema	Rare	Frequent
Motor system	Usually not compromised	Usually compromised
Vital signs	Highly altered	Not highly altered

Table 89.4. **Differences between "structural" and "toxic/metabolic" manifestations of coma.**

hydrocarbons, alcohol, hyperosmolar coma). Therefore, a quick and easy way to orient toward the etiology is to analyze three parameters: pupils, equal and reactive to light; eye position at rest and response to challenging manoeuvres; motor response to painful stimuli. In disorders caused by CNS depressants the first function affected is usually breathing followed by pupillary reflexes. In contrast, pupillary reflexes are altered earlier when the disorder is due to a structural cause (Table 89.4).

89.3 Treatment of the Most Frequent Types of Intoxication With CNS Depressants

Prompt treatment of clinical picture caused by the toxic agent and successful patient management are key to management. Evaluation will follow the ABCD scheme:

- **A**: Airway management, ensuring airway patency and preventing aspiration.
- **B**: Breathing, evaluating respiratory function and adequate ventilation.
- **C**: Circulatory control, restoring or maintaining hemodynamic status.
- **D**: Neurological assessment, followed by measures to prevent absorption of toxic mechanisms, promote elimination of the substance involved, and antagonize the toxic effect of the substance, if possible using specific antagonists.

89.3.1 Preventing Absorption of the Toxic Agent

Gastric Decontamination

If there was an oral intake and the dose has a potential toxicity, vomiting should be induced or gastric lavage performed within the first 2 hours after the accident for liquid and toxic, and within 6 hours for solids, provided that the patient is conscious.

Vomiting

Vomiting is caused by pharyngeal stimulation or administration of syrup of ipecac (15-30 ml in adults and 15 ml in children), followed by approximately 250 ml of water. If this treatment is not effective within 20 minutes, it should be repeated by stimulating the jaws. If vomiting fails, gastric lavage should be performed in order to decontaminate and prevent the absorption of ipecac. This treatment should not be performed in children <6 months of age or in patients in coma or with convulsions. We do not use this method, because evidence for its use is controversial.

Gastric Lavage

A nasogastric tube of the largest possible diameter should be used. The patient is placed in the Trendelenburg position with the head turned to the left, while inserting the na-

sogastric tube. First, the stomach contents should be allowed to flow spontaneously. Then normal saline solution or water should be administered (volume ≤10-15 ml/ kg in children and 200 to 400 ml in adults), repeating lavage cycles until the instilled liquid is equal to the removed one. The liquid should never be introduced under pressure never exceeding the capacity of the stomach, which would otherwise cause opening of the pylorus and rapid passage of toxic substances into the duodenum. The lavage liquid extracted will be collected in wide mouth jars for analysis and forensic toxicology.
Gastric lavage may be performed at any age and even in unconscious patients after tracheal intubation and airway protection.

Administration of Absorbent Substances

Activated carbon, also called activated charcoal, acts by adsorption to form non-absorbable macromolecules. The dosage is 15-30 g in children and 50-100 g in adults, dissolved in 100-150 ml of water or a carbonated drink.
For toxic enterohepatic circulation, activated charcoal, which may start up to 12 hours after ingestion, is indicated in multiple doses, every 4 hours at a dose of 0.50 g/kg, followed by administration of a cathartic. This is contraindicated in case of paralysis, obstruction or perforation of the ileus or in comatose patients without airway protection.

Facilitate Elimination

Intestinal decontamination. Once the toxic agent is adsorbed, its passage through the digestive tract should be accelerated by the administration of purgatives. The most commonly used is milk of magnesia (magnesium hydroxide solution 8%). The dosage is 13-30 ml in children and 60 ml in adults every 4 hours, until the colour of coal deposition. Other cathartics used are sodium sulphate or magnesium: 30 g in 250 ml of water for adults, with a maximum of three doses, and 70%sorbitol solution, 50-70 ml every 4 hours.
Oleose purgatives, solbitol and salite solutions are not recommended for pediatric use because of the risk of causing severe electrolyte alterations. The administration of cathartics is contraindicated in patients <1 year of age or in patients with diarrhoea, evidence of intestinal obstruction, bleeding, perforated viscus or peritonitis, electrolyte alterations, dietary sodium restriction, and renal failure for magnesium sulphate.

Purification Methods

The vast majority of toxins are eliminated with the urine. Adequate hydration ensures normal elimination mechanisms.
Forced diuresis promotes the elimination a copious flow of urine (5-10 ml/min or 500 ml/h) through the provision of sufficient fluids intravenously, and, depending on the pKa of the toxic agent, at changing urinary pH by the administration of alkalizing substances such as sodium bicarbonate (1-2 mEq kg in dextrose solution 5%) in order to raise the urinary pH to 7.5-8, or acidifying substances such as chloride ammonium or sometimes ascorbic acid (the latter are currently under review for their high risk/benefit ratio).
Other methods that can be used in specific cases include: peritoneal dialysis, hemodialysis, hemoperfusion, exchange transfusion, and plasmapheresis.

89.3.2 Benzodiazepine Intoxication

Treatment:
- Perform ABCD.
- Keep the patient under observation for at least 8 hours, then evaluate if he/she is conscious and if his/her psychiatric condition is stable.

- Suspend oral administration.
- Endotracheal intubation, according to neurological status, before starting decontamination of the gastrointestinal tract.
- Supplemental oxygen according to patient's condition.
- If the patient is conscious, vomiting can be induced.
- Gastric lavage 2 hours after ingestion, with saline solution (200 ml in adults, 10 ml/kg in children) until liquid runs clear.
- Activated charcoal can be started up to 4 hours after ingestion, 1 g/kg in 100-150 ml of water or carbonated drinks.
- Administer saline cathartic: The cathartic should be administered after the first dose of charcoal and repeated within 4 hours at the same dose if no catharsis is obtained, taking care not to repeat the carbon until an effective catharsis is obtained.
- The known antidote for benzodiazepines is flumazenil. Its use is recommended in cases of coma and respiratory depression secondary to the use of benzodiazepines. Flumazenil administration may involve risks for patients with hypotension, arrhythmias or hemodynamic instability; furthermore, it can cause seizures in patients with a history of epilepsy, increased intracranial pressure, concomitant ingestion of tricyclic antidepressants, anticonvulsants or cocaine, and benzodiazepine withdrawal syndrome in addicted patients. The use of flumazenil is unnecessary in most cases and can be associated with high risks, so it should be restricted to selected cases. Its effect begins within 1-2 minutes after the first dose and persists for 1-5 hours, depending on dose and type of benzodiazepine involved. The initial dose is 0.2 mg IV (0.01 mg/kg for children), and if no response is obtained, 0.3 mg bolus (up to a maximum of 3 mg in adults and 1 mg in children) can be administered.
- Psychiatric evaluation in cases of suicide.

89.3.3 Phenothiazine Intoxication

Treatment:

- Perform ABCD.
- Vomiting can be induced If the patient is conscious.
- Gastric lavage with saline 200 ml in adults 10 ml/kg in children until liquid runs clear.
- Administer activated charcoal 1 g/kg in 100-150 ml of water or carbonated drinks.
- Administer saline purgatives.
- If extrapyramidal symptoms are present, administer biperiden 0.04 mg/kg IM every 30 min until response (maximum 4 doses). An alternative is to administer diphenhydramine 1 mg/kg IM or IV (max 50 mg).
- In case of seizures, administer diazepam 5-10 mg IV (children: 0.2-0.5 mg/kg); if necessary, add a loading dose of diphenylhydantoin.
- Specific treatment is required in case of cardiac arrhythmias.

89.3.4 Anticonvulsants Intoxication (Phenytoin, Carbamazepine, Valproic Acid)

Treatment:

- Perform ABCD.
- Hospitalize the patient.
- Continuous monitoring for 24 hours
- Suspend oral administration

- Vomiting can be induced if the patient is conscious.
- Gastric lavage with saline 200 ml in adults 10 ml/kg in children until liquid runs clear.
- Administer activated charcoal starting 12 hours after ingestion, 1 g/kg in 100-150 ml of water every 6 h for 48 h or until recovery of consciousness. Closely monitor the state of ileus, because of the anticholinergic effects of the drug.
- Provide cathartic. The cathartic should be administered after the first dose of charcoal and repeated at the same dose if no bowel movement is observed within 4 h, taking care not to repeat the activated carbon until an effective catharsis is obtained.
- In case of seizures or agitation, benzodiazepines (diazepam 5 mg in adults, 0.1-0.3 mg/kg in children) or phenobarbital (15 mg/kg maintenance dose 5 mg/kg) should be administered. Do not administer drugs such as phenytoin or antipsychotics such as haloperidol and group I antiarrhythmics, which increase the risk of cardiac toxicity and decrease the threshold of seizure.
- Specific treatment for cardiac arrhythmias is required.
- Psychiatric evaluation in cases of attempted suicide.

89.3.5 Barbiturate Intoxication

Treatment:

- Perform ABCD
- Gastric lavage and induced vomiting should be performed if the patient is conscious. If sensory depression exists, endotracheal intubation prior to gastric lavage should be done, considering that aspiration is a cause of high mortality.
- Activated charcoal should be administered every 4 h, followed by saline purgatives.
- Monitor cardiovascular status, with special control of blood pressure and eventual shock treatment.
- Serial controls of the internal environment.
- Alkalinize urine with sodium bicarbonate.
- Force diuresis.
- If the dose of barbiturate is very high or there is kidney failure, peritoneal dialysis or hemodialysis should be performed.

89.3.6 Tricyclic Antidepressant Intoxication

Treatment:

- Perform ABC.
- Perform continuous cardiac monitoring and ECG.
- Vomiting can be induced if the patient is conscious.
- Gastric lavage with 0.9% saline solution, until the stomach contents are cleared out (after intubation if consciousness is impaired).
- In this particular case, administer a cathartic (5 ml/kg oral mannitol) before activated carbon because reduced peristalsis can lead to intestinal obstruction. If mannitol is not available, magnesium sulphate should be administered (30 g in adults and 250 mg/kg in children). If in the following 4 h the effect is not obtained, an additional dose of cathartic should be administered.
- Once you have verified the presence of peristalsis, administer activated carbon (1 g/kg in 100-150 ml of water by nasogastric tube), repeating the administration every 6 h for 4 doses, verifying that catharsis is obtained before the second dose. Keep in mind that these drugs have enterohepatic circulation, so carbon administration must be repeated serially for 24 and 48 h.

- Management of seizures with benzodiazepines, diazepam 5-10 mg IV (children dose 0.2-0.5 mg/kg). Do not use phenytoin because it causes sodium channel blocker poisoning.
- If agitation is present, sedation with benzodiazepines is possible. The use of antipsychotics such as haloperidol is associated with an increased risk of cardiac toxicity and reduced seizure threshold.
- Specific treatment in cardiac arrhythmias is required.

89.3.7 Intoxication With Opioids And Their Derivatives

Decontamination of the gastrointestinal tract is performed in cases of oral overdose. It is not useful in cases of intravenous or inhaled ingestion.
Treatment:

- Perform ABCD.
- Naloxone is administered at a dose of 0.4-2 mg up to 10 mg IV.
- Due to the drug's short half-life, continuous infusion at a rate of 0.4-0.8 mg/h should be administered to prevent recurrence of symptoms. In children the dose is 0.01 mg IV, repeated every 2 to 3 min up to 2 mg total.
- Do not induce vomiting because of risk of aspiration or seizures.
- Gastric lavage with saline 200 ml until liquid runs clear (in children 10 ml/kg).
- Activated charcoal 1 g/kg in 100-150 ml of water by nasogastric tube.
- Magnesium sulphate at normal doses.
- If seizures are present, administer diazepam (0.2-0.5 mg/kg). If seizures are uncontrollable or recur, consider the use of phenytoin.
- If hypotension is present, administer intravenous fluids.
- Naloxone may be associated with pulmonary edema, thus requiring mechanical ventilation and positive end-expiratory pressure (PEEP).

89.3.8 Ethanol Intoxication

In a patient with a history of ingesting ethyl alcohol, the presence of other diseases should be checked, such as head or spinal cord trauma, postictal states, infections, or drug intoxication.
Treatment:

- Perform ABCD: The patient intoxicated with ethyl alcohol should be managed on the basis of the clinical state of intoxication and the presence of respiratory, metabolic, gastrointestinal or traumatic complications. In such cases, the patient should be hospitalized or referred to a higher level of care.
- Maintain body heat by physical means.
- If agitation is present, haloperidol should be administered in adults (5 mg per h in adults and 0.01-0.1 mg/kg in children; maximum dose 0.5 mg total).
- Aspiration of gastric contents through a nasogastric tube after intubation is indicated in patients entering an extremely intoxicated comatose state after acute and massive intake of ethanol.
- The use of activated charcoal is indicated when there is the suspicion of co-ingestion of other substances that can be absorbed by activated carbon.
- Administer 100 mg of thiamine IV slowly to patients suspected of alcoholism or malnutrition to prevent or treat Wernicke-Korsakoff syndrome.
- In patients with hypoglycemia, dextrose 0.25-0.5 g/kg IV should be administrated, with periodic monitoring of blood glucose, in the absence of hypoglycemia the patient can be hydrated with normal saline solution.

- If vomiting is present, administer metoclopramide at standard doses.
- In alcoholic patients with hypomagnesemia, magnesium sulphate 2 g IV should be administered.
- Hypokalemia and hypophosphatemia should be corrected.
- 11.In patients with hepatic encephalopathy, lactulose 30 ml per os should be administered.
- In patients with high clinical or radiological suspicion of aspiration, broad-spectrum antibiotics (clindamycin or ampicillin + ceftriaxone sulbactan) should be administered.
- In patients with severe ethanol intoxication, hemodialysis can be performed, although in most cases it is unnecessary.

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90 Study and Treatment of Neurological Compromise in Collagenopathies and Vasculitis of the Central Nervous System

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90.1 Introduction

Vasculitis is a clinical entity and pathology caused by inflammation of the blood vessel walls. It affects the small, medium and large vessels, as well as a number of organs, which results in the diversity of its clinical manifestations. Vasculitiis may be primary to the CNS or secondary to different systemic diseases such as collagenopathies, infectious processes, tumours, drugs, etc. An overview of the types of vasculitis affecting the CNS is given in Table 90.1.

90.2 Clinical Presentation

Patients with systemic vasculitis of the CNS initially present with general symptoms such as fever, myalgias, arthralgias and asthenia, together with those related to organs pref-

		Granulomatous	Non-granulomatous
Isolated vasculitis of the CNS		Large vessels	Medium and small vessels
Systemic vasculitis affecting the CNS	Primary	Large vessels (aorta and branches) Medium vessels (visceral vessels) Small vessels	Temporal arteritis Takayasu disease Nodous polyarteritis Kawasaki disease Wegener's disease Schönlein-Henoch purpura Churg-Strauss syndrome Polyangiitis
	Secondary	Viral, bacterial and mycotic infections Collagen diseases (SLE, Sjögren syndrome, Behçet disease, sclerodermia, dermatomyositis) Drugs: amphetamines, cocaine, oral anticonceptives Tumours: leukemia, lymphoma and glioma	

Table 90.1 Classification of vasculitis.

Temporal arteritis	Granulomatous arteritis of the aorta and its branches that mostly affects the external carotid. Thickening is often observed with signs of pain and tumefaction of the temporal artery. It usually affects patients older than 50 years and is frequently associated with rheumatic polymyalgia. Anemia, increased erythrosedimentation rate and alkaline phosphatase are frequent in the laboratory
Takayasu arteritis	Granulomatous inflammation of the aorta and its branches. It generally affects women between 20 and 40 years of age. The clinical picture depends on the involved branches of the aorta, which may present with hemispheric ischemic symptoms, subclavian steal syndrome, lower limb claudication, renal or mesenteric ischemia
Kawasaki disease	Arteritis affecting the small, medium and large vessels associated with mucocutaneous lymph node syndrome. The coronary arteries are frequently involved, causing aneurysms. This disease was described only in patients up to 20 years old
Wegener's granulomatosis	Granulomatous inflammation affecting the respiratory tract and necrotizing vasculitis of the small, medium and large vessels. In the CNS it usually presents with ischemic phenomena. It is often accompanied by necrotizing glomerulonephritis
Churg-Strauss syndrome	Granulomatous inflammation with abundant eosinophils affecting the respiratory tract and necrotizing vasculitis of the small and medium vessels. A respiratory illness characterized by bronchospasms and hypereosinophilia is frequently present

Table 90.2. **Clinical characteristics of the main types of vasculitis affecting the CNS.**

erentially involved in a particular type of vasculitis; for example, purpura, subcutaneous nodules, pneumonitis, nephropathy, etc. Neurological manifestations include: headache, convulsions, signs of focal compromise, cognitive deterioration, altered state of consciousness, involuntary movements, and cranial nerve deficits. The main clinical features of primary and secondary vasculitis affecting the CNS are listed in Table 90.2.

90.3 Complementary Studies

Laboratory findings in vasculitis may be nonspecific and related to the systemic inflammatory response, as in anemia, leukocytosis or leukopenia, elevated C reactive protein, accelerated erythrosedimentation rate, increased fibrinogen, etc. The most frequent alterations related to the involvement of specific organs include: increased blood urea nitrogen (BUN), creatinine, proteinuria and hepatic enzymes. A complementary serum study may provide information concerning the pathogenesis of the disease. The presence of hypocomplementemia is strongly suggestive of a disease mediated by immunocomplexes, such as systemic lupus erythematosus (SLE). The main autoantibodies present in the different vasculitis syndromes are mentioned in Table 90.3.
The electroencephalogram (EEG) is nonspecific and the findings may only be observed in the presence of slow waves or

Antibodies	Vasculitic syndrome
Antinuclear antibodies	Systemic lupus erythematosus Sjögren syndrome Mixed connective tissue disease Dermatomyositis
Anti DNA	Systemic lupus erythematosus
Anti Sm	Systemic lupus erythematosus
Anti P	Systemic lupus erythematosus
Antineutrophil cytoplasmic antibody (ANCA)	
C-ANCA	Wegener's disease
P-ANCA	Microscopic polyangiitis Churg-Strauss syndrome
Anticardiolipin antibodies	Antiphospholipidic syndrome

Table 90.3. **Antibodies and vasculitis syndromes.**

isolated spike waves or generalized in patients presenting with clinical convulsions.

Computed tomography (CT) offers little return for the study of vasculitis in the CNS, with a sensitivity of <50% in the detection of lesions. Magnetic resonance imaging (MRI) seems to be more useful, although its sensitivity and specificity are unknown. Vascular lesions in these patients tend to be multiple and with a hemorrhagic component. Diffusion sequences and T_2-weighted gradient echo are useful for the visualization of hemispherical strokes, as well as those in the trunk or cerebellum (Figure 90.1).

Angiography is useful in the detection of lesions in medium and large vessels. However, when smaller sized branches are affected, and generally with distal compromise of the middle cerebral artery, digital angiography is the method of choice, with a sensitivity and specificity of 50% for the detection of characteristic lesions in the shape of rosary beads (Figure 90.2).

In systemic vasculitis with repercussions in the CNS, the involvement of different organs generally allows for diagnosis, while in primary vasculitis of the CNS cerebral biopsy and leptomeninges are considered the gold standard by most authors. The lack of clinical signs with the high specificity and low efficiency of complementary studies would require a cerebral biopsy when a diagnosis of primary vasculitis of the CNS is suspected.

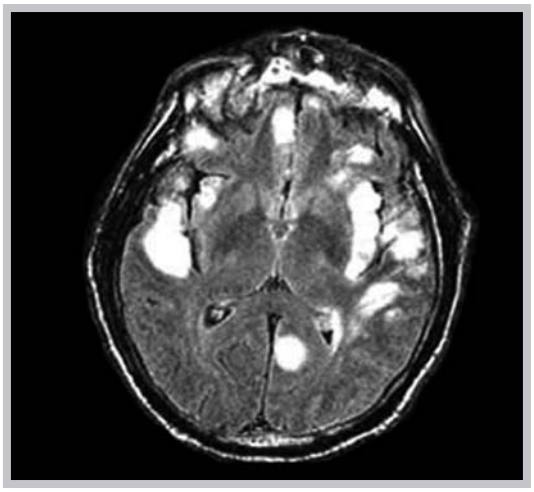

Figure 90.1. Magnetic resonance imaging with multiple lesions hyperintensitive in diffusion-weighted, sequences.

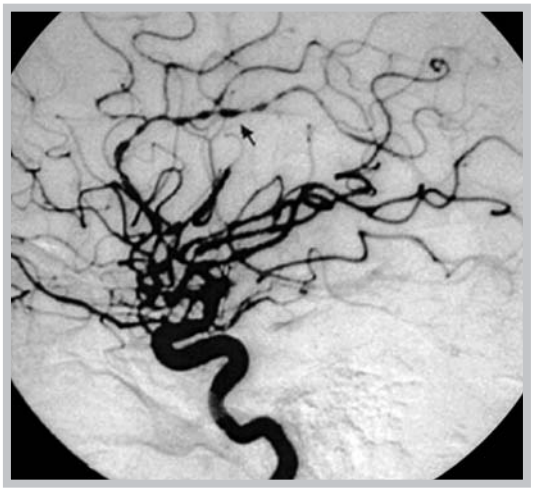

Figure 90.2. Digital angiography with lesions in the shape of rosary beads (arrow).

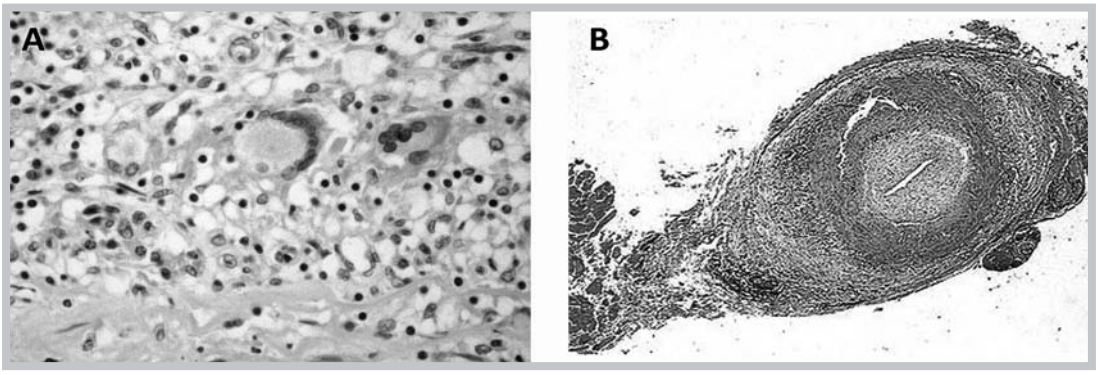

Figure 90.3. Two different patterns of vasculitis: necrotizing granulomatsis in large vessels and nongranulomatosis lymphocitic vasculitis of the small vessels.

In a study by Alrawi et al. only 36% of patients suspected with vasculitis of the CNS were anatomopathogically confirmed, while the remaining 64% had either another disease or the biopsy was not diagnostic. Two patterns have been described in vasculitis: necrotizing granulomatosis in large vessels and nongranulomatous lymphocytic vasculitis of the small vessels (Figure 90.3).

90.4 Pathogenesis

Different immunological mechanisms that are not mutually exclusive are involved in the pathogenesis of the inflammation and damage of the vascular wall. The most common is caused by the formation of immune complexes, as in serum disease. Attachment of immunocomplexes to the vascular wall induces adherence and activation of the complement cascade, with immune amplification through the release of cytokines, the consequent expression of adhesion molecules in their membranes, and the release of their lysosomal products, with damage to the endothelium and other components of the vascular wall. Other mechanisms involved in vascular damage include: anticellular endothelial and antilysosomal antibodies and the creation of a cellular type of immune response with the formation of granulomas.

90.5 Differential Diagnosis

It is worth noting here that there are illnesses that are not classically considered as vasculitis but that share anatomopathological features with it, such as:

- Severe hemorrhagic encephalomyelitis with perivenular inflammatory infiltrates, such as in demyelinating diseases and vascular wall necrosis.
- Reversible posterior leukoencephalopathy where there is an opening of the narrow endothelial unions due to toxic or secondary hemodynamic changes.
- Inflammatory changes in atherothrombotic disease.

The main differential diagnoses of vasculitis of the CNS are summarized in Table 90.4. Figure 90.4. reports a flow-chart for the management of these patients.

Metabolic diseases	• Mitochondriopathies • Organic aciduria
Ischemic lesions	• Hemoglobinopathies • Antiphospholipidic Syndrome • Hemodynamic stroke • Cardioembolic stroke • Venous stroke
Demyelinating inflammatory lesions	• Multiple sclerosis • Sarcoidosis • Subacute sclerosing panencephalitis • Acute hemorrhagic encephalomyelitis • Acute dissemimated encephalomyelitis
Infectious lesions	• Cerebritis • Granuloma • AIDS
Tumoural lesions	• Langerhans cell hystiocytosis • Primary lymphoma of CNS
Non-inflammatory vasculopathies	• Moya Moya Syndrome • Fibromuscular dysplasia • Reversible posterior leukoencephalopathies

Table 90.4. Differential diagnosis of CNS vasculitis.

90.6 Treatment

The medical profile of isolated vasculitis of the CNS or in a systemic context, once infectious tumoural and toxic causes are

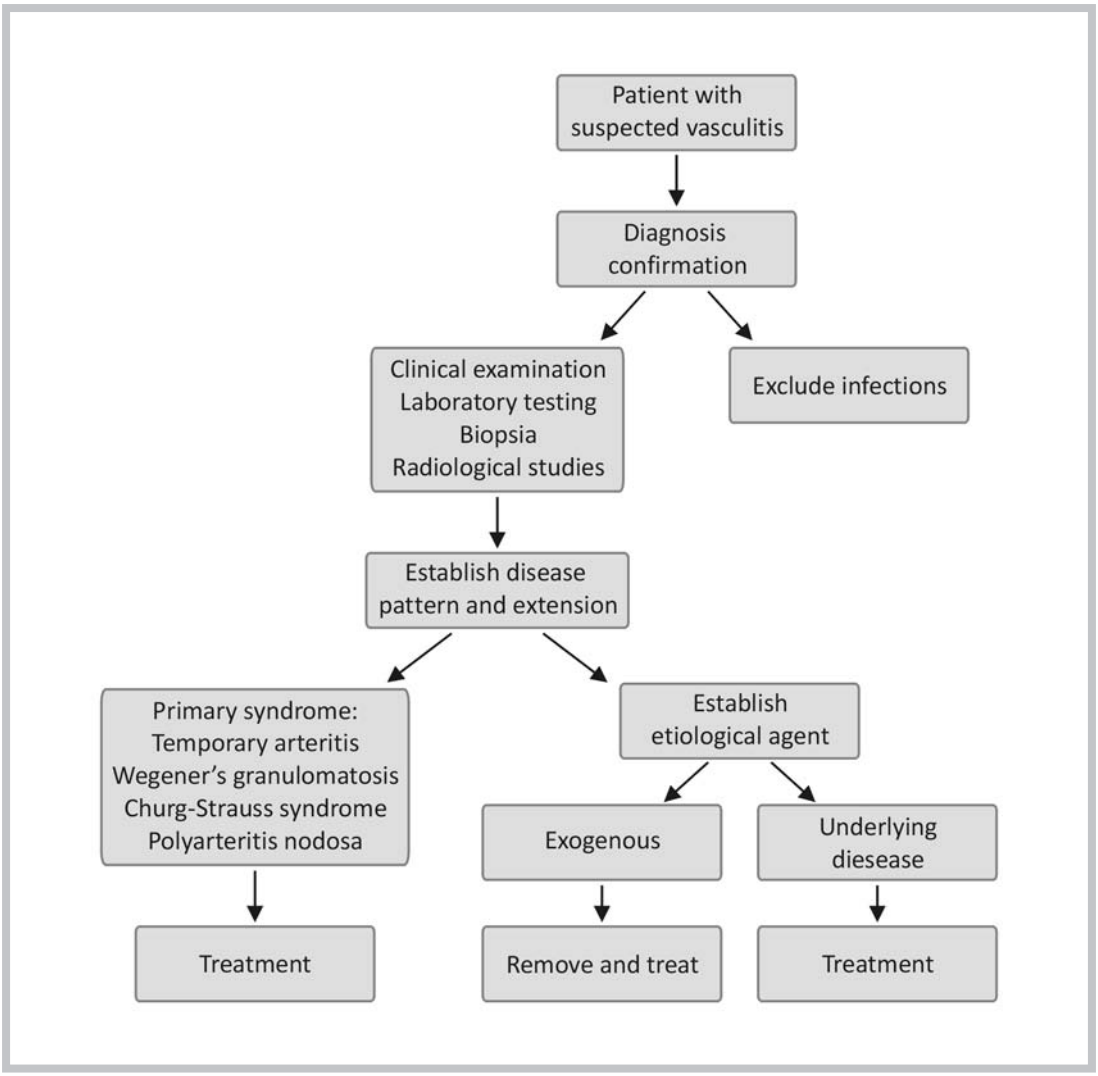

Figure 90.4. **Flow chart for the management of a patient with suspected vasculitis.**

ruled out, requires rapid immunosupressive treatment. In isolated vasculitis of the CNS, there is little experience, as only isolated cases have been reported. Pulsed methyprednisolone therapy may be initiated; when there is no favourable clinical response, treatment with intravenous cyclophosphamide can be initiated. In Kawasaki disease, intravenous administration of standard human gamma globulin has been widely accepted, in a single dose of 3 g/kg within the first 10 to 12 days of onset of the illness. This reduces the incidence of coronary complications. Schönlein-Henoch purpura generally requires no treatment and is self-limited in time.

When CNS involvement is significant, pulsed methylprednisolone therapy may be used. Necrotizing vasculitis, such as systemic panarteritis, Wegener's granulomatosis, the Churg-Strauss syndrome and Takayasu arteritis usually require the administration of combined corticoids and immunodepressants. In systemic vasculitis a certain degree of effectiveness with biological drugs, such as etanercept, inflixomab and rituximab recently been reported. The therapeutic use of antithrombotics is controversial, although certain groups use aspirin in patients at risk of thromboembolic phenomena.

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91 Management of Acute Movement Disorders

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91.1 Introduction

This chapter describes the main acute movement disorders, their clinical manifestations, causes and treatment. Drugs represent the most frequent etiologic factor and are the cause of the neuroleptic malignant syndrome and serotoninergic syndrome. A section of this chapter is devoted to emergencies secondary to Parkinson's disease, including the parkinsonism hyperpyrexia syndrome, acute psychosis and the emergencies derived from deep brain stimulators.

	Rigidity	Parkinsonism	Dystonia	Chorea-balism
Drugs	Neuroleptic malignant syndrome Serotonin syndrome	Parkinsonism-hyperpyrexia (See Table 91.2)	Acute dystonia caused by neuroleptic drugs	Phenytoin, carbamazepine, tricyclic antidepressants, estrogens, cocaine, baclofen, trazodone, anticholinergics
Degenerative diseases			Laryngeal dystonia in multisystem atrophy	Parkinson's disease
Idiopathic			Laryngeal dystonia in adduction, status dystonicus	
Infections	Rabies, tetanus	Mycoplasma, encephalitis lethargica	Encephalitis lethargica, retropharyngeal abscess	
Toxic agents	Strychnine	See Table 91.6		
Metabolic disease	Hypocalcemia	Central pontine and extrapontine myelinolysis		Hypoglycemia Hyperglycemia
Autoimmune diseases	Stiff man syndrome		Anti-NMDAR encephalitis	Sydenham chorea Antiphospholipid syndrome Lupus erythematosus Hashimoto's encephalopathy Paraneoplastic syndrome
Psychiatric diseases	Lethal catatonia		Pseudo-dystonia	
Hereditary diseases	Hyperekplexia, malignant hyperthermia	Dystonia Parkinsonism with rapid onset		
Diseases in children			Atlantoaxial subluxation	

Table 91.1. **Major presentations of acute movement disorders and their causes.**

Movement	Drug (frequent)	Drug (non frequent)
Chorea	L-Dopa	Phenytoin, carbamazepine, tricyclic antidepressants, estrogens, cocaine, baclofen, trazodone, anticholinergics
Myoclonus	SSRIs	Tricyclic antidepressants, lithium, MAO-I, carbamazepine, penicillin and cephalosporins, cocaine, opioids, amantadine, bromocriptine
Tremor	Neuroleptics, valproate, alcohol, sympathomimetics	Opiates, immunosuppressants, OAD, antibiotics and antivirals, anticonvulsants, antiarrhythmics, corticosteroids, amiodarone, thyroxine
Dystonia	Neuroleptics and L-Dopa	Dopamine agonists, phenytoin, carbamazepine, SSRIs, tricyclic antidepressants, cocaine
Parkinsonism	Neuroleptics	Flunarizine, cinnarizine, tricyclic antidepressants, tacrine, carbamazepine, phenytoin, valproate, lamotrigine, MPTP

Table 91.2. **Drug-induced acute movement disorders.**
MAO-I = monoamine oxidase inhibitors
MPTP = 1-methyl-4-phenyl-1.2.3.6-tetrahydropyridine
OAD = oral antidiabetics
SSRIs = selective serotonin reuptake inhibitors

Acute parkinsonism, various forms of acute dystonia, chorea, myoclonus acute ballism are also described. Finally, a section on movement disorders presenting as a stroke is provided.
Movement disorders requiring emergency care comprise neurological diseases with an acute or subacute onset in which the predominant clinical presentation is movement disorder, and in which an error in diagnosis or treatment can lead to significant morbidity and even mortality [1,2]. They account for a small percentage of urgent neurological consultations and may have very different etiologies (Table 91.1), among which are those secondary to drugs (Table 91.2). They can be classified according to the presenting signs and symptoms: rigidity, parkinsonism, dystonia, chorea or ballism and myoclonus.

91.2 Syndromes Presenting With Stiffness

Stiffness is the presenting symptom of neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, stiff-person syndrome, and lethal catatonia (Table 91.3). Other diseases can also manifest with rigidity, including infectious diseases such as tetanus or rabies, strychnine poisoning, hypocalcemia, and inherited diseases such as hyperekplexia.

91.2.1 Neuroleptic Malignant Syndrome

The neuroleptic malignant syndrome (NMS) is induced by drugs exerting an antidopaminergic effect, in particular the classic neuroleptics such as haloperidol or chlorpromazine. NMS can also be caused by an antiemetic such as methoclopramide and antihistamines such as promethazine [3,4]. It occurs in 0.2% of cases after the administration of atypical antipsychotics (olanzapine, clozapine, risperidone, quetiapine, and aripiprazole).
Its occurrence may be favored by the co-administration of lithium to any of the listed drugs. It is more common in young men using slow-release preparations and is favoured by dehydration. This is an idiosyncratic reaction that occurs within a few weeks after the start of the treatment or after an increase in the dosage; it is characterized by severe

Process	Serotonin syndrome	Neuroleptic malignant syndrome	Acute akinesia syndrome – hyperpyrexia	Malignant hyperthermia	Lethal catatonia
Medication	Serotoninergic drugs	Dopaminergic antagonists	Suspension of dopaminergic drugs	Inhalatory anesthesia	
Onset time	<12 h	1-3 days	1-3 days	0.5-25 h	1-3 days
Constants	Hypertension, tachycardia, tachypnoea, hyperthermia (>41.1°C)	Hypertension, tachycardia, tachypnoea, hyperthermia (>41.1°C)	Hypertension, tachycardia, tachypnoea, hyperthermia (>40°C)	Hypertension, tachycardia, tachypnoea, hyperthermia (>46°C)	Hypertension, tachycardia, tachypnoea, hyperthermia (>40°C)
Pupils	Midriasis	Normal	Normal	Normal	Normal
Skin	Diaphoresis	Pallor, diaphoresis	Anhidrosis	Spotted, diaphoresis	Diaphoresis
Intestinal motility	Increased	Normal or decreased	Decreased	Decreased	Normal or decreased
Muscle tone	Increased, especially in lower limbs	Lead pipe stiffness	Increased, plus severe akinesia	Rigidity like "rigor mortis"	Increased with catatonic signs and akinetic mutism
Reflexes	Hypereflexia, clonus	Hyporeflexia	Normal	Hyporeflexia	Normal
Mental state	Agitation, coma	Stupor, coma, mutism	Confusion, stupor, coma	Agitation	Stupor, coma, mutism

Table 91.3. **Major clinical features of different processes that occur with stiffness.**

Process	Specific treatment	Standard treatment
Serotonin syndrome	• Cyproheptadine, starting dose 12 mg followed by 2 mg/2h • Chlorpromazine 50-100 mg IV	• Suspend precipitating drug • Administration of intravenous fluids • Cool body with physical measures • Monitor urine output and treat renal failure (dialysis), if any • Treat acidosis, if any • Institute life-support measures with a respirator, if necessary
Neuroleptic malignant syndrome	• NGT dopamine agonists (bromocriptine, amantadine or levodopa) • Apomorphine SC or rotigotine SC • Dantrolene 25-80 mg/8 h	
Acute akinesia syndrome – hyperpyrexia	• NGT dopamine agonists (bromocriptine, amantadine or levodopa) • Apomorphine SC or rotigotine SC • Dantrolene 25-80 mg/8 h • Treatment of intercurrent infections	
Malignant hyperthermia	• Hyperventilate with oxygen 100% • Dantrolene 2.5 mg/kg bolus, then repeat 2 mg/kg every 5 min after infusion 1-2 mg/kg/h • Treat hypercalcemia and arrhythmia	
Lethal catatonia	• Lorazepam IV • Daily ECT (10 sessions)	

Table 91.4. **Treatment of various processes that occur with stiffness.**

ECT = electroconvulsive therapy

NGT = nasogastric tube

SC = subcutaneous

muscle rigidity, altered level of consciousness and dysautonomia, with fever, sweating, tachycardia, tachypnoea, and fluctuations in blood pressure.
Some studies show an elevation in creatine kinase (CK) as a result of rhabdomyolysis caused by stiffness and which can lead to renal failure secondary to myoglobinuria.
There are two pathophysiological hypotheses: a central mechanism that blocks dopamine in the striatum (stiffness) and hypothalamus (dysautonomia), and a peripheral mechanism that alters muscle fibre contractility due to alterations of the membrane of the sarcoplasmic reticulum.
Treatment consists of suspending neuroleptics (Table 91.4), general life-support measures (hydration and mechanical ventilation if necessary), administration of dopaminergic drugs such as bromocriptine at a starting dose of 2.5 mg/8 h orally (nasogastric tube) and increasing it to 5 mg/8 h after 2 days. Subcutaneous apomorphine or transdermal rotigotine patches may also be administered. Dantrolene at a starting dose of 25 mg/24 h with further increases to 25 mg/12 h or 1-10 mg/kg intravenously may be used in severe disease. Electroconvulsive therapy should be considered in psychotic patients. If untreated, the mortality rate is estimated to reach 20% and the causes of death are pulmonary embolism, aspiration pneumonia and renal failure.

91.2.2 Serotonin Syndrome

The serotonin syndrome is a potentially life-threatening adverse drug reaction that may occur following serotonin-acting drug administration. It has an incidence of approximately 14-16% of patients taking overdoses of selective serotonin reuptake inhibitors (SSRIs), but it may also occur after the use of other drugs with serotonergic action (Table 91.5).
It is clinically characterized (Table 91.3) by altered mental status (delirium, anxiety, hypervigilance, akathisia), autonomic hyperactivity (diarrhoea, sweating, tachycardia, hyperthermia, mydriasis) and neuromuscular disorders (myoclonus, tremor, hyperreflexia, rigidity). The onset of symptoms is usually rapid, occurring within minutes to hours after taking the medication. Laboratory findings consist of metabolic acidosis, rhabdomyolysis, increased CK, kidney failure, and even disseminated intravascular coagulopathy (DIC) [5]. Idiopathic serotonin syndrome is not a reaction but rather a predictable consequence of excess serotonergic activity of the serotonin receptors of the central nervous system (CNS) and peripheral nervous system, resulting from drug abuse interactions or voluntary ingestion as a suicide attempt. The activation of 5-HT2A receptors contributes mainly to the manifestations of the serotonin syndrome. Treatment (Table 91.4) consists of removing the precipitat-

Class	Drug
Serotonin reuptake inhibitors	SSRIs, tricyclic antidepressants, dextromethorphan, dextroamphetamine, cocaine, meperidine, opioids (except morphine)
Serotonin metabolism Inhibitors	MAO-B Inhibitors (selegiline), MAO-I antidepressants
Agents that increase serotonin synthesis	L-tryptophan
Agents favouring the release of serotonin	MDMA (ecstasy), amphetamines, cocaine, fenfluracina
Serotonergic agonists	Sumatriptan, ergotamine, buspirone
Agents favouring nonspecific serotonergic activity	Lithium, electroconvulsive therapy

Table 91.5. Drugs that can cause the serotonin syndrome.
MAO-I = monoamine oxidase inhibitors
MAO-B = monoamine oxidase B
MDMA = 3,4-methylenedioxymethamphetamine
SSRIs = selective serotonin reuptake inhibitors

ing agent, life support, control of agitation, hyperthermia and autonomic instability. In some cases, discontinuation of the offending medication or medications, and offering supportive measures are sufficient to resolve symptoms within 24 hours. In other cases, other measures, such as benzodiazepine administration, should be added. Physical restraint should be avoided because it can cause rapid clinical deterioration. In moderately and severe cases, 5-HT2A antagonists such as cyproheptadine should be administered at a starting dose of 4-8 mg orally, followed by a maintenance dose of up to 8 mg/6 h. It can be administered only orally and by nasogastric tube. When hyperthermia is >41ºC, neuromuscular paralysis with nondepolarizing agents and tracheal intubation may be required. Antipyretics have no role in the management of hyperthermia since it is not the hypothalamus that is involved but rather the muscle activity. Succinylcholine should be avoided because of the risk of arrhythmia, together with the hypercalcemia that occurs with rhabdomyolysis. Drugs such as bromocriptine, propranolol or dantrolene are not recommended.

91.2.3 Malignant Hyperthermia

This serious disease with a genetic component is an autosomal dominant disorder with variable penetrance due to a mutation of the ryanodine receptor on the long arm of chromosome 19 [6]. Mutations of this receptor cause an alteration in calcium homeostasis, with an increase in muscular calcium and sustained muscle contraction which, in turn, leads to a state of hypermetabolism with lactic acidosis, hypercapnia and hyperthermia. It is triggered by inhaled halogenated anesthetics and depolarizing muscle relaxants. Clinical manifestations (Table 91.3) may appear in the operating room or several hours after anesthesia. The most common early sign is tachycardia, followed by muscle rigidity, masseter spasm, and tachypnoea. Metabolic and respiratory acidosis also develop. Elevated temperature is a late sign, together with arrhythmias, cyanosis, hypotension, hyperkalemia and rhabdomyolysis. Treatment (Table 91.4) consists in hyperventilating the patient with 100% oxygen, administering dantrolene (2.5 mg/kg bolus every 5 min followed by 1-2 mg/kg/h infusion), reducing body temperature with physical measures, treating the acidosis with sodium bicarbonate, monitoring urine output, and treating arrhythmias.

91.2.4 Lethal Catatonia

This syndrome has various causes and usually occurs in the context of psychiatric illness; it may be triggered by nervous system infections, hyperthyroidism, lupus, toxic, trauma, etc. It usually occurs in young people and its relationship with NMS is unclear. It's characterized by insomnia, anorexia, catatonic motor excitation, confusion, dysautonomia (sweating, tachycardia and changes in blood pressure), hallucinations, echolalia, echopraxia, stare, fixed postures, mutism, rigidity, intense and high fever (Table 91.3). It has been speculated that its physiopathology is related to an involvement of dopaminergic transmission. Treatment consists of life support with intravenous lorazepam; electroconvulsive therapy is the treatment of choice(Table 91.4) [3].

91.2.5 Stiff Person Syndrome

This syndrome can have an acute or subacute onset and is characterized by the appearance of pain and muscles spasm of the lumbar paraspinal, abdominal and lower ex-

tremities, resulting in an exaggerated lumbar lordosis, which can cause fractures, joint subluxations or abdominal hernia. It is associated with generalized hyperreflexia. Contractures can occur spontaneously or after auditory or sensory triggers and disappears during sleep. Neurophysiological studies suggest that it is a central continuous motor activity. It is accepted that there is an idiopathic paraneoplastic variant of stiff person syndrome (SPS), another variant is associated with focal encephalitis, and a syndrome of rigid limbs. At least half of patients have antibodies against glutamic acid decarboxylase (GAD) and anti-gephyrin antibodies. The efficacy of intravenous immunoglobulin therapy has been demonstrated in some forms of SPS [7].

91.3 Emergency in Parkinson's Disease (PD)

91.3.1 Parkinsonism-hyperpyrexia Syndrome (PHS)

Also called malignant syndrome or NMS-like syndrome, it occurs in patients with long-standing Parkinson's disease admitted to hospital for surgery or intercurrent process that involve a significant reduction in antiparkinsonian medication. It can also occur in other akinetic-rigid syndromes other than PD. It's characterized by the sudden onset of extreme akinesia with increased body temperature (Table 3). Other clinical manifestations that may occur spontaneously are stiffness, decreased level of consciousness (from light drowsiness to coma), autonomic alteration with tachycardia, fluctuating blood pressure, lack of perspiration, ileus, or vocal cord paralysis. In addition, there is an elevation of CK secondary to rhabdomyolysis and that can lead to renal failure. Disseminated intravascular coagulation (DIC) is the most serious complication and carries a high mortality. Not all patients show all clinical signs [8].
Diagnosis is based on clinical manifestations. In addition to levodopa dose reduction, other triggers may be the change in one agonist for another, infection, elevated environmental temperature (heat stroke) causing dehydration, or changes in the distribution of levodopa due to changes in nutrition (i.e., initiation of enteral nutrition). Sometimes a sudden decline occurs as a consequence of antiparkinsonian treatment suspension (the so called "superoff effect"). Underlying the pathophysiology may be acute dopaminergic hypotransmission in the hypothalamus, nigrostriatal system and mesocortical dopamine system. There is also an individual susceptibility. Post-mortem studies have found hypothalamic necrosis.
Treatment consists in its early detection and the administration of fluids (2500-3000 ml/24 h) with electrolytes and glucose, vitamin B1, physical and pharmacological measures against hyperthermia, treating infection if diagnosed, and antiparkinsonian treatment reinstated as soon as possible by nasogastric tube if there are problems with swallowing (Table 4). Bromocriptine, amantadine or apomorphine injection can also be used. If the stiffness is severe, it may be necessary to use dantrolene at doses of 80 mg/day intravenously.

91.3.2 Acute Psychosis

Clinical manifestations of psychosis in PD consists of visual hallucinations, often stereotyped, and persecutory or jealousy delirium. Hallucinations and delirium can be accompanied by intense agitation, confusion and sleep disturbances which alter the quality of life of patients and their caregivers. Psychosis is related to antiparkinsonian treat-

ment. Its onset is not only due to dopaminergic dysfunction but also other neurochemical changes. It has been suggested that hallucinations are due to early mesolimbocortical receptor hypersensitivity not purely related to the degeneration of serotonergic or cholinergic mechanisms [9].
When acute psychosis is suspected, triggers such as infections and metabolic or structural brain processes should be investigated. If psychotic symptoms are mild, you should try to simplify the treatment by reducing or suspending antiparkinsonian drugs added to levodopa, such as amantadine, selegiline, dopamine agonists and catechol O-methyltransferase (COMT) inhibitors. If, despite these changes, the symptoms persist, it may be necessary to reduce levodopa, and, if this is not enough, atypical neuroleptics such as clozapine, quetiapine, or aripiprazole should be administered. Cholinesterase inhibitors have proved effective in cases of PD with dementia. As a therapeutic alternative to neuroleptics, ondansetron, and 5HT3 antagonist have been also proposed.

91.3.3 Emergencies in Patients With Deep Brain Stimulators

Deep brain stimulation is a therapeutic alternative in selected patients with PD. This treatment may cause complications leading to emergency complications that the general neurologist should be familiar with; however, the patient should be referred to a specialized centre in these circumstances [10].
Among the surgical delayed complications we can list deep vein thrombosis and pulmonary thromboembolism, together with any surgical procedure involving prolonged bed rest. In addition, local infections can occur because of: accumulation of serous fluid in the surgical bag housing the stimulator; problems with the implanted material such as electrode displacement or breakage, or cable infection or necrosis in the subcutaneous track. Additionally, the generator may be disconnected because of inadvertent contact with a strong magnetic field, thus producing a sudden worsening of parkinsonian symptoms. This can also happen if the neurostimulator batteries are depleted (they typically last about 5 years). In both cases, in which a negative effect induced by a recent change in the parameters of the neurostimulator is suspected, consultation with neurologists expert in the management of its programming system will be necessary.
Complications consequent to brain stimulation are the appearance of choreic or ballistic movement disorders due to stimulation of the subthalamic nucleus. Psychiatric disorders may also occur, such as apathy or cognitive impairment, anhedonia, euphoria or hypomania, which have been associated with stimulation of the medial and ventral areas of the subthalamic nucleus. The stimulation of neighbouring fibres of the internal capsule can produce pseudobulbar symptoms, such as dysphagia, dysarthria and inappropriate crying.
The neurostimulator produces electrical interference with the electrocardiogram (ECG), the electroencephalogram (EEG), and metallic interference with computed tomography (CT). These effects should be considered when a patient with a neurostimulator enters the emergency room for other medical problems.

91.4 Acute Parkinsonism

The incidence of acute parkinsonism is very rare. It may be caused by infectious agents such as mycoplasma or drugs such as amphotericin B. Metabolic disorders such as central pontine or extrapontine myelinolysis can produce acute parkinsonism. This dis-

- Methanol
- Cyanide
- Herbicides: rotenone and paraquat
- Heroin
- Manganese
- Mercury
- Carbon monoxide
- MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
- Plants of the *Annonacea* family, especially *Annona muricata* (corossol, soursop)

Table 91.6. **Toxic agents that can cause parkinsonism.**

ease occurs as a result of osmotic alterations (e.g., in the context of correction of hyponatremia secondary to hyperemesis) and can be found by magnetic resonance imaging (MRI) of cranial hyperintense lesions in the striatum that can be reversed, together with parkinsonism. There is a rare hereditary disease with linkage in a region of chromosome 19, called dystonia-parkinsonism, in which symptoms may occur acutely or subacutely with parkinsonism and dystonia of orofacial muscles. The onset of parkinsonism by accidental consumption or addiction to various drugs is documented in the literature (Table 91.6) [11].

Lethargic encephalitis occurred in epidemics in the early 20th century as encephalitis with involvement of the basal ganglia, mainly producing parkinsonism and psychiatric and sleep disorders. In recent decades, there have also been reports of encephalitis whose pathophysiology is poorly understood. There is no clear evidence of infectious agents invading the nervous system, although lymphocytosis is found in the oligoclonal bands of cerebrospinal fluid. MRI findings may not show alterations or signal changes in the midbrain and basal ganglia. In recent cases, steroids have been used with good clinical response, with complete recovery of the patients in many cases [2].

91.5 Acute Dystonia

91.5.1 Drug-induced Dystonias

Within this group, the most frequent cause of consultation in the emergency department are the dystonias secondary to drugs. Young people often develop this disease during the first hours or days after taking drugs such as antipsychotic dopamine antagonists (haloperidol) or antiemetics (clebopride or metoclopramide), antidepressants, SSRIs, norepinephrine or cocaine. They can also appear after the use of atypical antipsychotics [12].

Other drugs such as rivastigmine or interferon alfa-2b may occasionally cause acute dystonic reactions. The clinical manifestations usually consist of focal craniocervical dystonia, which often occurs in the form of torticollis, but can be as trismus, lingual protrusion, oculogyric crises, pharyngeal or laryngeal dystonia, blepharospasm and even axial and limb dystonia. It occurs in 30-40% of young psychotics who started treatment with antipsychotics. It seems to be dose-related. AIDS patients with immunodeficiencies are at higher risk. In such patients, dystonic reactions have been reported after treatment with other drugs such as intravenous immunoglobulins. Treatment consists of intravenous anticholinergic drugs such as Akineton® (biperiden) 5 mg IV or IM or Cogentin® (benztropine) 1-2 mg; the dose may be repeated if symptoms do not improve; it is appropriate to continue the treatment a few days then orally.

91.5.2 Acute Laryngeal Dystonia

Another reason for urgent consultation is acute laryngeal dystonia or Gerhardt's syndrome, a sporadic idiopathic dystonia in which a laryngeal spasm occurs by dystonia in

adduction of the vocal cords during inspiration, with the potential risk of airway obstruction. The clinical manifestation is a respiratory stridor that yields to sleep. This rare entity is confirmed by fibroscopy and treatment involves the injection of botulinum toxin into the thyroarytenoid muscle [2].
Patients with multiple system atrophy may also present with stridor caused by altered abduction of the vocal cords due to dystonic spasms of the thyroarytenoid muscles (adductors), abductor muscle weakness and neurogenic posterior cricoarytenoid muscle atrophy. This serious symptom can cause sudden death. Treatment consists of applying continuous positive airway pressure (CPAP) (non-invasive passive ventilation), botulinum toxin or tracheostomy.

91.5.3 Dystonic Storm

Dystonic storm (or status dystonicus) is a serious emergency that can occur in patients with primary or secondary dystonia. The symptom is the appearance of severe dystonic spasms involving painful generalized hyperthermia, rhabdomyolysis with the risk of acute renal failure, anarthria, respiratory failure and dysphagia with the risk of pneumonia by bronchoaspiration. Status dystonicus shares many aspects with status epilepticus. Precipitating factors may be the same for both: trauma, surgery, infection, fever and rapid introduction or withdrawal of a drug. The optimal treatment strategy is still unclear. Only in rare cases are oral medications (haloperidol, tetrabenazine and pimozide) effective. Midazolam and short-acting and short half-life benzodiazepines can be used as first-line therapy (30-100 mg/kg/h). If they fail, propofol (0.3-3.0 mg/kg/h) can be administered.The general therapeutic measures consist of hydration to prevent acute renal failure,analgesia, ECG monitoring, respiratory monitoring and admission to the intensive care unit, if necessary. As in status epilepticus, general anesthesia is sometimes necessary, and neuromuscular blockade by curaring agents. infusion of intrathecal baclofen or functional surgery may be needed in patients with degenerative diseases [13].

91.5.4 Anti-NMDAR Encephalitis

The encephalitis associated against the N-methyl-D-aspartate receptor (NMDAR) is a multistage illness that progresses from psychosis, memory and language deficits, seizures, catatonic features associated with abnormal movements and autonomic and breathing instability [14]. Oro-lingual-facial dyskinesias are the most characteristic abnormal movements but other types might occur simultaneously or alternate with limb and trunk choreoathetosis, oculogyric crisis, dystonia, rigidity and even opisthotonic postures. Autonomic manifestations include hyperthermia, tachycardia or bradycardia, hypertension or hypotension, hypersalivation, urinary incontinence and erectile dysfunction. Hypoventilation requiring ventilatory support may occur. Seizures develop at early stages of the disease that may overlap with abnormal movements. Antibodies against NMDAR have a pathogenic role as they cause a reversible decrease of synaptic NMDAR. This disorder predominantly affects children and young adults and it can occur associated or not to a tumour (usually an ovarian teratoma). Treatment consists of tumour resection, if it is present, and immunotherapy (corticosteroids, intravenous immunoglobulinor plasma exchange). Sometimes a second line treatment with cyclophosphamide or rituximab is necessary. More than 75% of all patients have a substantial recovery.

91.5.5 Pseudo-dystonic Emergency

Sometimes an atlantoaxial subluxation or a retropharyngeal abscess in children may presented as a stiff neck which can also occur in cases of spinal cord and posterior fossa tumours. Among these emergencies, we may include psychogenic movement disorders that usually consist of motley and flowery movements that have an acute onset. It is important to consider this diagnosis to avoid unnecessary examinations, but the differential diagnosis can sometimes be difficult and the patient should be kept under observation.

91.6 Acute Chorea-Ballism

Ballism and chorea are part of the same spectrum of motor impairment. Proximal ballism may be associated with chorea in the distal extremity and can transform into chorea. Ballism or chorea with acute presentation are usually due to structural lesions of the nervous system which are usually ischemic but sometimes related to other processes of different nature (infections, autoimmune diseases, hypoglycemia or other metabolic disorders) [2]. Chorea may be the manifestation of a paraneoplastic disease and its acute or subacute onset may be the reason for visiting the emergency room. It's generally accompanied by other symptoms of encephalopathy, and imaging tests findings are usually characterized by signal changes in the basal ganglia. It is associated with lung carcinoma, small cell lung carcinoma and anti-Hu or anti-CV2 syndrome.

91.7 Myoclonus

Myoclonus or asterixis is the clinical manifestation of metabolic encephalopathy of liver failure or kidney failure. Myoclonus may be part of serotonin syndrome. Opiate intoxication and their withdrawal can be accompanied by myoclonus. Treatment with lithium, tricyclic antidepressants, imipenem and cefuroxime may cause cortical action myoclonus. Focal brain lesions of various etiologies (infectious, vascular, etc.) can cause focal myoclonus [15].

91.8 Movement Disorders in Stroke

The presentation of stroke as a movement disorder is rare and occurs in 1% of cases. The most common movement disorder secondary to stroke is hemiballism hemichorea, followed by hemidystonia. Ischemic lesions affecting the globus pallidus or the midbrain may cause acute parkinsonism, stroke of the putamen may cause dystonia, and stroke in the subthalamic or caudate nucleus usually presents with chorea-ballism. Thalamic infarcts may produce different movement disorders depending on the thalamic nuclei involved. Damage to the ventral anterior nuclei can cause myoclonic dystonia (Figure 91.1) and a "thalamic hand", with isolated dystonic posture with pseudo-ataxic movements after injury in the ventral intermediate nucleus (VIM) and ventral posterior nucleus, respectively, and postural and action tremor after injury to the VIM, and impaired thalamocortical connectivity. The most common etiology of strokes that occur with a movement disorder is small vessel disease, but the possibility of a cardioembol-

Figure 91.1. **Sequence of photographs showing involuntary movements in a patient with acute thalamic stroke, with flexion and external rotation of the lower limbs and eversion of both feet (myoclonic dystonia).**

ic origin in thalamic infarcts should be considered. Most of these movement disorders that appear in the acute phase are transient and resolve spontaneously within the first days or weeks.

Involuntary motor phenomena with varied presentation have been reported in ischemic lesions of the brainstem. They can range from small amplitude movements similar to myoclonus to shaking of the limbs and even the trunk, which are often intermittent and can be triggered by painful stimuli. Their frequency is unknown, but they usually occur in extensive lesions of the brainstem usually related to acute basilar occlusion [16]. The pathophysiology is uncertain and the most likely is the corticospinal tract ischemia. Recognition of these movements, and consequent measures for quick diagnosis and treatment, are important because they may suggest the formation of a basilar occlusion.

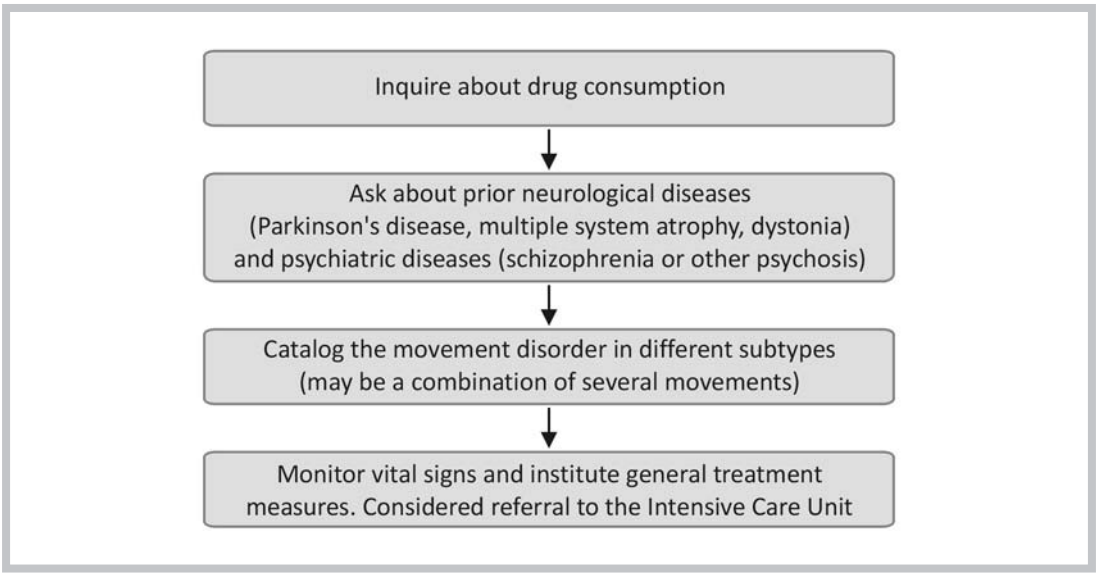

Figure 91.2. **Algorithm for emergency management of acute movement disorders.**

91.9 Conclusions

In patients accessing the emergency room with a movement disorder of acute onset, clinical manifestations and etiology may be various. In such cases we must evaluate the autonomic disorders that may accompany the clinical features and establish the therapeutic measures that can sometimes require ICU admission (Figure 91.2).

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92 Physiotherapy: An Essential Tool in Neurocritical Care

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92.1 Introduction

Currently, there is a worldwide trend to create specialized intensive care units (ICU). According to two reports (2001 and 2006) by the Royal College of Physicians of London, intensive care management of patients suffering from stroke (cerebrovascular accident [CVA]) appears to reduce hospitalization, degree of sequelae and mortality [1]. In Brazil, especially in private health services and large cities, it is not uncommon to find within the same hospital highly specialized facilities for the care of cardiac, surgical, and transplant patients. And among who benefit most from this segmentation are neurological patients. A neurological ICU may be operated within a general ICU or at a separate location. What defines it is not the physical space but rather the technology resources available for monitoring and treating diseases of the brain, coupled with human resources specialized in neurointensive care [2], including the physiotherapist.

Until recently, neurological disorders in the acute phase were treated with a passive therapy. The patients were kept alive but sedated, with treatment aimed solely to maintain clinical stability until the disorder spontaneously regressed. With the advent of scientific and technological medicine, therapy has become more active: neurological changes and blood metabolism are rigorously monitored so that early intervention can be instituted and undesired consequences avoided or minimized [3]. A typical example is thrombolytic therapy in ischemic stroke.

Worldwide, although neurological diseases are not a leading cause of mortality, the incidence of stroke and traumatic brain injury (TBI) is increasing as is the number of survivors with disabilities.

From a functional standpoint, neurological patients, such as those recovering from TBI, have severe limitations that significantly impair their quality of life, in addition to the psychosocial and financial burden on both the family and society [4]. The clinical manifestation of nervous system diseases is closely related to the site or sites of injury and their respective extension [5]. Therefore, it is essential to understand the nature and complexity of the entire nervous system in relation to the interventions by the multidisciplinary team member to ensure that such treatment is safe, effective and not harmful. The physiotherapist has an important role in the intensive care of the neurologically ill owing to the risk of respiratory complications, the frequent need for mechanical ventilator assistance, and the presence of motor deficits, among others. The physiotherapist plays an active part in assisting patients; this work requires continuous training and improvement, as well as collaboration with doctors, nurses, nutritionists and other team members.

Preventing complications, restoring function and improving the neurological functional status of patients in order to achieve the greatest degree of independence are among the goals of physical therapy in neurointensive care. The rehabilitation process begins

in the ICU and views the patient as a whole individual, taking an approach that does not isolate the neurological system, but rather integrates it with other systems, adjust treatment to the course of illness and recovery to obtain better results.
Hence, it is not advisable for the therapist to work solely according to a protocol. This does not mean ignoring treatment protocols; protocols are important for guiding a group of professionals in the conduct of day-to-day treatment, avoiding hasty decisions and therapeutic abuse. On the other hand, neurointensive physiotherapy, treatment and pre-defined goals can ignore the fluctuating clinical conditions commonly described by patients in the acute neurological phase which requires a more refined therapeutic approach.
Some studies report that respiratory physiotherapy in critically ill patients can bring about undesirable consequences, such as impaired oxygen transport resulting from the adverse effects on venous return, cardiac output and systemic blood pressure. In theory, respiratory physiotherapy applied to the patient's chest, increases intrathoracic pressure [7,8]. This, in turn, leads to decreased venous return, and both can impair cardiac filling, resulting in increased intracranial pressure [9,10]. On the other hand, cardiovascular effects are indeed observed in hypovolemic patients, and the possible temporary increase in intracranial pressure is not reflected in brain injury when cerebral autoregulation is preserved. In practice, physiotherapy and motor rehabilitation need to be informed by the monitoring of brain energy metabolism, for example, as tools to guide the intensity, duration and type of interventions that can be applied to the patient at a given moment.
There are still few studies in neurointensive physiotherapy that add to scientifically based evidence. This does not diminish the importance of physical therapy or that it is not practiced; instead, clinical trials in this segment are lacking. In general, scientific research investigating the technical resources and the activities of the physical therapist in neurointensive care require more rigorous methodological design. We need measures of the expressive point of view of monitoring neurological status and the sample size, as in any study design, with the aim to improve physiological outcomes and clinical outcomes such as achieving a lower incidence of pneumonia, shorter duration of mechanical ventilation and hospitalization, among others.
Thus, in the following pages we will discuss physical therapy in acute-stage neurological patients hospitalized in an ICU.
Finally, there is a popular saying in neurointensive care that says: «If you cannot help, at least do not hinder.» In other words, there is little or nothing you can do to reverse the damage from the primary neurological injury, but incorrect therapeutic management of neurological patients in the acute phase may worsen secondary injury, increasing the degree of disability.

92.2 Neurointensive Vision for Physical Therapy

92.2.1 Characteristics of Neurointensive Patients

The most frequent reasons for admission to a neurointensive ICU are: head trauma, stroke, spinal cord trauma, brain surgery (mainly tumour resection and clamping of aneurysms), among others.
The clinical picture is often characterized by prolonged hospitalization and mechanical ventilation, frequent need for tracheostomy due to immobility and bed restriction. This condition is usually associated with pulmonary complications.
In this context, the appropriate management and support of physical therapy will include: assessment of dysfunction, monitoring, and neurointensive physiotherapy.

Assessment of Dysfunction and Monitoring

The importance of evaluation and monitoring of dysfunctional neurointensive patients resides in the early detection of clinical abnormalities which can be reversed before permanent sequelae ensue. The neurological workup is usually extensive and thorough. In the ICU, the assessment should be rapid and encompass level and content of consciousness, pupil assessment and motor response patterns (muscle tone, reflexes and strength), as well as adequate monitoring of cerebral blood flow and metabolism.

Monitoring of respiratory function will examine the rates of gas exchange and respiratory mechanics (Table 92.1), facilitate the evaluation of pulmonary complications such as hypoxemia and hypercapnia. Both may increase the damage to the airway adjacent to primary lesions, the so-called twilight zone of brain injury.

Oxygenation	• Oxygen saturation (arterial and peripheral) and the ratio of partial pressure of oxygen over the fraction of inspired oxygen (PaO_2/FiO_2) • Pulse oximetry
Ventilation	• Partial pressure of carbon dioxide • Capnography
Mechanical breathing	• Compliance • Lung resistance • Intrinsic PEEP (particularly when the minute ventilation as a therapeutic strategy needs to be increased)

Table 92.1. **Evaluation of gas exchange and respiratory mechanisms in neurointensive care.**

During assessment, the physical therapist will observe the chest and monitor radiological changes, which will guide the diagnosis and monitoring of potential lung disorders, besides the need for physical therapy interventions.

Assessment of cardiovascular function will check for heart rate (HR) and mean arterial pressure (MAP). Continuous electrocardiography (ECG) can identify common cardiac arrhythmias in acute neuropathy [12], and changes in MAP can be correlated to intracranial hypertension. In some acute situations, physical therapy may be contraindicated.

In emergency situations, evaluation is performed concurrently with the basic manoeuvres recommended for the initial treatment of neurological and neurosurgical patients. The team must be integrated and well-trained in order to preserve life. Therapeutic priorities follow the sequence: A – Airway maintenance; B – collateral ventilation/oxygenation; C – circulation; and D – the deficit. Also, further investigation should be performed as soon as possible.

In the neurological workup, the therapist must be properly trained to assess the following parameters.

Parameter	Response observed	Score
Eye opening	Spontaneous eye opening	4
	Verbal stimuli	3
	Painful stimuli	2
	Missing	1
Best verbal response	Oriented	5
	Confused	4
	Profanity	3
	Incomprehensible sounds	2
	Missing	1
Best motor response	Obeys commands	6
	Locates painful stimuli	5
	Nonspecific withdrawal	4
	Decortication	3
	Decerebrate	2
	Missing	1

Table 92.2. **Glasgow Coma Scale (GCS). Teasdale and Jennett (1974) [13], subsequently modified by Jennett et al. (1977) [14].**

92.2.2 Content and Level of Consciousness

The level of consciousness is the degree of behavioural warning the individual shows

that can be determined by the level of response given by the patient to external stimuli. The Glasgow Coma Scale (GCS), devised by Teasdale and Jennett in 1974, [13], initially totalled 14 points and was subsequently amended in 1975, with the addition of 1 point for a total of 15 points. It is used to monitor the level of consciousness after TBI according to the following scores: ≤8 (severe coma); 9-12 (moderate coma); and 13-15 (mild coma) (Table 92.2).

Parameter	Score
Anxious, agitated or restless	1
Cooperative accepting ventilation, oriented and peaceful	2
Sleeping, response to discrete auditory and tactile stimuli	3
Sleeping, minimal response to auditory and tactile stimuli	4
Responds only to painful stimuli	5
No response to painful stimuli	6

Table 92.3. Ramsay Sedation Scale [16].

Besides being used to monitor the patient during the acute phase, ECG is also applied as an index of neurological prognosis. This scale has a positive predictive value of 80-90% for assessing prognosis, with 10-20% of patients who may have an incorrect prediction of their prognosis [15].

Frequently been used in the ICU to evaluate the degree of sedation in neurological patients is the Ramsay scale [16] (Table 92.3). The neurophysiologic responses to verbal, visual, tactile, and proprioceptive stimulation depend on the ascending activating reticular formation and cerebral cortex.

Since the contents of consciousness are the sum of all cognitive and affective functions of humans, such as language, praxis, memory and gnosis, they depend on the function of the cerebral cortex [17] and should be evaluated by asking simple questions concerning the patient's orientation in time, place and person. According to the answer, consciousness is classified as directed or disoriented. At first, the patient may respond to questions coherently or be unable to answer even after being prompted. Some clinical conditions such as hypoxemia and hypercapnia aggravate the state of disorientation and should be rectified immediately once detected.

Pupils

Pupillary examination will evaluate pupil diameter, symmetry and light reflexes (Table 92.4); abnormalities in pupillary size and reactivity may be indicative of structural damage extending from the thalamus to the bridge.

Since some pupil changes can alert to the need for urgent therapeutic intervention, they should be monitored several times a day and during physiotherapy. Complications such as intracranial bleeding and cerebral edema may cause increased intracranial pressure and/or brain herniation, resulting in changes of the pupils, which can vary rapidly from isocoria to anisocoria or mydriasis and non-reactivity of one or both pupils. In such situations, early intervention can determine the patient's prognosis.

Parameter	Classification	Characteristics
Diameter	Miotic	<2 mm
	Mydriatic	>5 mm
	Average fixed	4 to 5 mm, fixed in the light
Symmetry	Average fixed	4 to 5 mm, fixed in the light
	Isocoria	Symmetrical
	Anisocoria	Asymmetric
	Discoria	Abnormally
Reactivity	Photoreactive	Contraction on light stimulus
	Non reactive	No reaction to light stimulus

Table 92.4. Pupillary assessment.

Patterns of Motor Response

Brain lesions can produce pathological patterns of motor response; those most frequently observed in the ICU are:

- Decortication: posture of adduction and flexion of the elbow, wrist and finger flexion of the upper limb, as well as hyperextension, plantar flexion and internal rotation of the lower limb. These changes are suggestive of dysfunction in the deep supratentorial regions of the internal capsule.
- Decerebrate: posture of adduction, extension and hyperpronation associated with upper limb extension and plantar flexion of the lower limb, suggestive of high spinal cord injury, above the red nucleus, extending to the diencephalon.
- Paresis: partial inability to perform voluntary movements. It may consist of several deficits, such as loss of selective motor control of balance, righting reactions, primitive reflexes and sensitivity, as well as the presence of abnormal muscle tone.
- Plegia: the total inability to perform voluntary movements, including deficits that can result from injury to the pyramidal tract, extrapyramidal system, cerebral cortex (premotor, primary motor and somatosensory) and the cerebellum. Depending on the extent and severity of injury, the patient presents a clinical picture of paralysis with spasticity, hyperreflexia or hyporeflexia (sagging).

But among the abnormal reflexes, the one most frequently encountered in clinical practice in the ICU is the plantar cutaneous reflex which, when positive (Babinski sign), indicates a loss of pyramidal function which can be transient depending on the patient's condition.

92.2.3 Brain Hemodynamics

Brain hemodynamics is characterized by a balance of the intracranial components (brain tissue, blood and cerebrospinal fluid [CSF]) being able to tolerate small increases in volume without changing intracranial pressure (ICP). Therefore, an increased volume in one or more components will be accompanied by a decrease in others. However, when there is damage that interferes with brain compliance, even minor expansion of the intracranial content can significantly increase ICP, contributing to the loss of cerebral autoregulation.

Monitoring brain hemodynamics includes the evaluation of cerebral metabolic and circulatory function. The coupling of these functions depends on the mechanisms of cerebral autoregulation. Thus, cerebral autoregulation is the brain's ability to maintain blood flow constant regardless of variations in blood pressure, while satisfying the brain's metabolic demands.

The conditions that lead to augmented aerobic metabolism increase the production of carbon dioxide, responsible for vasodilation and appropriate increased microcirculatory cerebral blood flow. In contrast, anaerobic metabolism, concomitant with a reduction in carbon dioxide, mediates vasoconstriction and flow reduction.

Cerebral blood flow can be calculated by the formula: CBF = CPP / CVR (CBF = cerebral blood flow, CPP = cerebral perfusion pressure, CVR = cerebral vascular resistance). The normal CPP range is 60-95 mmHg. For monitoring CPP, Langfitt and colleagues (12) proposed calculating the difference between MAP and ICP, i.e., CPP = MAP – ICP (MAP = mean arterial pressure, ICP = intracranial pressure).

Thus, maintenance of MAP, generally >100 mmHg in adults, helps to ensure adequate CPP. The parameter of normal peak is <10 mmHg in adults, whereas peaks ≥20 mmHg characterize intracranial hypertension (ICH).

The adequacy of cerebral blood flow to meet metabolic demand can be used to monitor cerebral of oxygen extraction (CEO_2).This represents the true and most important parameter of proportionality between CBF and oxygen consumption. CEO_2 is understood as the difference between oxygen supply and consumption, estimated in clinical practice, the difference between the arterial and venous saturation of oxygen (the latter is obtained from the jugular bulb catheter). Normal values for CEO_2 are 33% for adults, with a range of variation of approximately 24 to 42%. Values above and below normal represent hyper-or low flow in cerebral oxygen consumption, respectively.
These notions of brain hemodynamics guide the team in physiotherapy management and clinical or surgical treatment which require the coupling of neurological function, cardiovascular and respiratory diseases.

92.3 Physical Therapy

92.3.1 Respiratory Therapy

Techniques and Resources of Respiratory Therapy

Respiratory therapy aims to minimize the retention of endobronchial secretions and maximize ventilation and oxygenation (18). When performed during mechanical ventilation, respiratory therapy helps to adjust ventilation parameters, weaning and extubation. The use of noninvasive mechanical ventilation is increasingly reported in the literature [19].
Respiratory complications are more frequent in neurocritically ill patients: pneumonia, acute respiratory failure, neurogenic pulmonary edema and atelectasis [20]. Under these conditions, physiotherapy techniques use protective strategies of mechanical ventilation to minimize the symptoms and degree of lung injury [21,22].
Respiratory therapy may promote a temporary rise in intrathoracic pressure and consequent reflex in cerebral hemodynamics and intracranial pressure [9]. Therefore, patients should be approached with special care for each of the techniques applied at the time of therapy.

Bronchial Hygiene

Chest physiotherapy is included most ICU treatment protocols in the developing countries. Its role is quite varied, depending on location and tradition of service, level of education, training and experience, and especially the patient characteristics.
In some ICUs the physical therapist will evaluate and monitor all patients daily while in others, the service is performed only upon request. This helps to determine the character of its action, intervention and outcomes.
The features and therapeutic techniques in respiratory therapy include the following.

Stimulation of Cough

Stimulation of cough is a common technique to treat respiratory complications resulting from the accumulation of secretions, especially in patients with cognitive impairment (no response to verbal commands) and those with high spinal cord injury, in whom paralysis of the trunk and abdomen muscles reduces the ability to generate effective cough. In such patients, there is a close relationship between motor level and peak expiratory flow during cough [23]. Jaeger and colleagues [24] studied the efficacy of three methods of cough stimulation in patients with high spinal cord injury. The methods in-

volved coughing without manual assistance, with assistance from the therapist, and abdominal electrical stimulation. The effectiveness of the technique was measured by peak expiratory flow. Electrical stimulation-induced cough was more effective than manually assisted cough; however, abdominal electrical stimulation is not a common practice in the ICU.

Inducing coughing is undesirable in patients with increased intracranial pressure. It is contraindicated because it leads to an increase in intrathoracic pressure, decreasing venous return, thereby increasing cerebral blood flow. However, when cerebral autoregulation is preserved, intracranial pressure returns to normal levels immediately after the procedure, demonstrating adequate compliance of the nervous system. Under such conditions, cough can be used as a resource during bronchial hygiene therapy.

Endotracheal Suction

A constant concern in neurological patients is the aspiration of pulmonary secretions because this can negatively affect the cerebrovascular status by increasing intracranial pressure. Therefore, brain damage can ensue not only from the primary trauma but also secondarily to reduced oxygen to the brain as a result of cerebral edema, ischemia and increased intracranial pressure.

Tracheal aspiration refers to the effective removal of endotracheal secretions, aseptically through a suction system. Airway access for the procedure can be achieved by two methods or systems: open and closed. The first is the most widespread and routinely used in clinical practice. It involves disconnecting the patient from mechanical ventilation for the aseptic introduction of a the probe for aspiration. The second system refers to a multi-use probe enclosed in a plastic cover which is connected to an endotracheal tube and ventilator circuit, allowing aspiration without interrupting mechanical ventilation.

Considering the secondary respiratory complications of neurointensive patients in the acute phase, the closed system seems to be more advantageous as it allows continuation of mechanical ventilation and maintenance of positive end-expiratory pressure (PEEP), thus reducing the partial pressure of oxygen in arterial blood (PaO_2) and increased partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and minimizing the risk of contamination and respiratory infections.

With either system it is recommended that the patient be adequately sedated to avoid psychomotor agitation and be properly positioned (supine rise from 35 to 40°). There is no consensus in the literature on performing this procedure in the presence of impaired cerebral compliance. Some authors suggest the use of lidocaine diluted in 0.9% saline solution directly into the tracheal tube or intravenously administered [25,26].

Bruyas (1981) and Thiesen and colleagues (2005) [9,27], at the time of endotracheal aspiration, reported a significant increase in ICP due to stimulation of the cough reflex, which increases intrathoracic pressure and therefore decreases venous return, interfering directly with brain metabolism. Some authors have recommended adequate sedation combined with topical anesthesia and neuromuscular blockers in order to avoid psychomotor agitation and stimulation of the cough reflex, and thus effects on ICP and CPP and MAP [25,28-30].

The aspiration time should not exceed 15 / 2 to prevent hypoxemia; the suction pressure should not exceed 120 mmHg or the suction flow rate 16 l/min to avoid mucosal trauma. Intratracheal instillation of 0.9% saline solution, while feeding, can be used with caution to thin thick bronchial secretions and plugs, as saline instillation may trigger a reflex cough and Valsalva manoeuvre, significantly increasing the ICP [31].

Aspiration should be performed only when pulmonary auscultation reveals rales, the mechanical ventilator display indicates increased peak inspiratory, deterioration of oxygenation demonstrated by a drop in oxygen saturation, and when the movement of se-

cretions is audible during respiration. The technique should not be performed at regular intervals because the risk of routine aspiration outweigh its benefits [31].

Despite its being a widely used procedure in neurological patients, endotracheal suctioning is associated with complications including, hypoxemia, changes in partial pressure of carbon dioxide, tracheal mucosal injury, increased intracranial pressure, hypertension, bradycardia and arrhythmias. It can also result in damage to the mucosa and mucociliary system, which is usually operator-dependent, the amount of pressure used, and the establishment of this procedure as a routine [32].

Another study suggested that hyperventilation and hyperoxygenation performed before tracheal aspiration can avoid significant changes in cerebral hemodynamics [33]. Hypoxemia is one of the most significant complications in neurological patients, since the magnitude of the decline of PaO_2 and oxygen saturation (SaO_2) and increased partial pressure of carbon dioxide ($PaCO_2$) can trigger bradycardia, coronary vasoconstriction and supply blood to the tissues, causing cerebral ischemia, worsening the prognosis.

There is consensus [34,35] that additional oxygen can be administered in ventilated neurological patients during tracheal aspiration procedures.

Conventional Manoeuvres

Conventional physical therapy manoeuvres include compression, vibration, locking and unlocking chest manoeuvres, postural drainage, tapping and ventilatory patterns. These manoeuvres can also be used in neurological patients. However, some care must be observed.

In the study by Thiesen et al. [9] effects were observed of conventional physiotherapy manoeuvres on cerebral perfusion pressure and intracranial pressure in head-injured patients, with peaks of up to 30 mmHg. The authors concluded that the manoeuvres did not significantly affect cerebral perfusion pressure. Of the manoeuvres studied, tracheal aspiration led to an evident increase in ICP, which returned to baseline 1 minute after the procedure. It is understood that in patients with preserved cerebral autoregulation, the return of ICP to baseline values is rapid, without generating unwanted effects in CPP, so that tracheal aspiration can be performed if necessary.

Chest physiotherapy manoeuvres tend to increase intrathoracic pressure by increasing lung volume. They are indicated in the treatment of alveolar collapse because elevated $PaCO_2$ causes vasodilation, with a consequent increase in cerebral blood flow and ICP. Therefore, in situations where alveolar collapse is accompanied by hypercapnia, one of the benefits of chest manoeuvres is to reduce $PaCO_2$.

Thoracic Manoeuvres

Manoeuvres of manual chest physiotherapy (chest compression, locking and unlocking manoeuvres, thoracic breathing pattern, directed or contralateral) for the reversal of alveolar collapse tend to increase intrathoracic pressure by increasing lung volume and warrant caution in these patients. Often the failure is responsible for the increased intracranial pressure owing to increased $PaCO_2$, which is responsible for vasodilation and the consequent increase in cerebral blood flow. Therefore, the increase in lung volume resulting from re-expansion manoeuvres may be beneficial in treating alveolar collapse by reducing $PaCO_2$, even if some degree of intracranial hypertension is generated, especially when cerebral autoregulation is preserved.

Alveolar Recruitment

Alveolar recruitment has been indicated for the treatment of alveolar collapse observed in the acute respiratory distress syndrome (ARDS), where hypercapnia can be tolerated.

In patients with neurological injury alone, the ventilation strategy will differ from those previously mentioned because it seeks to achieve greater control of the amounts of CO_2 in arterial blood. Therefore, in patients with concomitant brain injury and severe respiratory failure there is a conflict in the therapeutic principles that guide ventilatory support. Studies investigating with the effect of positive end-expiratory pressure (PEEP) on ICP have been inconsistent [10,36-38]. Shapiro and Marshall [38] reported increased ICP after using 4-8 cmH_2O PEEP and decreased CPP in 50% of cases. In contrast, Frost [36] observed no peaks with the use of high PEEP.

Importantly, another study found a significant reduction in CPP during PEEP only in patients with low central venous pressure (CVP), suggesting the deleterious effect of hypovolemia during ventilation with PEEP [37]. Some authors have suggested that PEEP may cause a significant increase in ICP only in patients with low-compliance brains [38-40].

For these reasons, it is of fundamental importance to join the efforts of the multidisciplinary team in therapeutic decision making, taking into account the risk-benefit ratio for patients where hypoxia is a major risk factor for complications after injury or brain surgery.

Despite the many studies, mostly experimental, on alveolar recruitment manoeuvres, few clinical trials have investigated the effects of these manoeuvres in acute respiratory failure in neurological patients. Studies by Huynh and Wolf [41,42] concluded that PEEP of up to 15 cmH_2O did not lead to a drop in CPP nor an increase in ICP in patients after neurosurgery.

In another study evaluating 43 patients after severe neurological injury with respiratory failure and undergoing recruitment manoeuvres using pressures up to 60 cmH_2O for 30 seconds, there was a deterioration in cerebral hemodynamics, with increased ICP and decreased CPP. Since the authors noted an improvement in blood oxygenation, they recommended routine use of this manoeuvre.

Muscle Training

Recent studies have addressed the complications of mechanical ventilation in the short term, such as reducing the mass and contractile properties of respiratory muscles. In a study by Capdevila and colleagues [44], 48 hours of mechanical ventilation were sufficient to reduce respiratory muscle strength by around 20 to 30%, the ability to generate strength, fatigue resistance and atrophy of type IIa and IIb fibres of the respiratory muscles in rats. Also, Hering and colleagues [45], in a study in pigs with oleic acid-induced lung injury, found that mechanical ventilation in 80% of cases reduced blood flow to respiratory muscles in comparison to spontaneous breathing, despite improvement of the oxygenation index.

These factors contribute to our understanding that suppression of spontaneous breathing during mechanical ventilation in patients with primary or secondary neuromuscular disorders adversely affects respiratory muscle activity, impairing the removal of ventilatory support.

In this case, the muscle training has a key role in the permanent removal of mechanical ventilation [46]. Stiller and Huff [47] reported that training the muscles of the neck and upper chest in ventilator-dependent quadriplegic patients may improve the vital capacity and allow the ventilator to be disconnected for longer periods.

The use of abdominal weight and load resistance muscle training in 11 patients with complete cervical lesion showed significant differences in forced vital capacity, maximum voluntary ventilation, and maximal inspiratory pressure. However, there was no difference between the two techniques studied by Derrickson and colleagues [48].

In other neuromuscular disorders, muscle training can also improve strength and endurance, as reported by McCool and Tzelepis [49]. The authors reviewed seven studies on

muscle training, involving a total of 75 patients whose training regimen included the use of inspiratory resistance load and isocapnic hyperpnoea. The patients with lower neuromuscular disorders showed significant increases in muscle strength and endurance. Patients with more severe disorders were retainers of carbon dioxide, where there was little change in muscle strength or endurance. No adverse effects were reported in these patients.

Besides the effects on the performance of respiratory muscles, muscle training appears to improve lung function and reduce dyspnoea, as in cases of myasthenia gravis and multiple sclerosis [50]. In such patients, we observed a reduction in periods of pulmonary exacerbation, improved exercise tolerance, cough effective, and less need for mechanical ventilation. In addition, the type of tracheal access must be considered because these patients remain under prolonged mechanical ventilation. Some studies comparing very early tracheostomy intubation with mechanical ventilation reported that tracheostomy assists in weaning from mechanical ventilation and decreases the incidence of infections due to easier suctioning the airways, and generates greater degree of comfort, better mobility, communication and power for the patient [18].

92.3.2 Motor Assessment

Recommended instruments for the assessment of neurological patients in the ICU.

The aims of physiotherapy assessment and intervention in neurological and neurosurgical patients in the ICU are to detect and identify complications, making a detailed assessment of the degree of function and weaknesses. Standardization of physiotherapy assessment and intervention in neurological and neurosurgical patients supports decision making in line with the best scientific evidence and available resources.

Objective clinical assessment will require reliable and valid scales that are appropriate to what we want to measure, that establish a baseline before starting treatment, and that allow us to record the degree and duration of response to treatment. Evaluation includes careful measurement, accompanied by judicious assessment of the results, which will help to create an appropriate intervention plan and permit its modification according to the patient's specific needs.

The goal of rehabilitation is to reduce the level of disability, reaching the maximum of functional independence, participation and integration in social and economic life. To measure the achievement of these objectives, rehabilitation must have assessment tools to objectively quantify the level of disability which a patient presents at a given time and to measure changes that occur prospectively in rehabilitation treatment. The use of rating scales helps to prioritize areas where we must act in the planning of rehabilitation and then allows us to compare the effectiveness and efficiency of treatments.

Physiotherapy assessment and intervention in critically ill patients is aimed at early identification of deficits secondary to the injury, providing timely interventions to existing or emerging gaps, preventing or reducing the risk of further complications, and promoting well-being to facilitate recovery in relation to mobility, health, and preservation of the patient's social role.

Prolonged immobilization, lack of active movement, impaired sensation and proprioception, and altered level of consciousness lead to deficits in aerobic capacity, muscle performance, joint mobility, and integumentary and sensory integrity, which must be identified and treated early to ensure the quality of care and the necessary continuity of care during all phases of the disease.

The American Physical Therapy Association (APTA) [51] has recommended specific criteria for intervention and monitoring the use of testing and measurement.

Deficit	Tests and measures
Impaired aerobic capacity	• Cardiovascular symptoms and signs • Pulmonary symptoms and signs • Evaluation of physiological response to postural changes • Brain monitoring
Impaired respiratory muscle performance	• Maximum static pressures (PI_{max} and PE_{max}) • Nasal pressure sigh
Impaired muscle performance	• Strength, endurance and muscle strength in functional activities
Impaired joint mobility	• Goniometry
Impaired alertness/attention and cognition	• Glasgow Coma scale (GCS) • Rancho Los Amigos Levels of Cognitive Functioning (LOCF) • Mini Mental test
Impaired integumentary integrity	• Braden scale
Impaired ventilation	• Auscultation • Arterial blood gases • Pulse oximetry • Capnography • Pulmonary symptoms (dyspnea)
Impaired breathing	• Breathing pattern • Cough • Assessment of dyspnoea • Phonation • Auscultation • Parameters of mechanical ventilatory support
Impaired gas exchange	• Arterial blood gases • Pulse oximetry
Deficits in integrity reflexes	• Tendon reflexes • Ashworth Scale (muscle tone)

Table 92.5. **Tests and measures to evaluate the most common deficits in neurological patients in the ICU.**

Tests and measures are essential resources for evaluation; they identify deficits, functional limitations and disability, allowing the selection of interventions and the documentation of changes in patient status so that the scope of outcomes which are the endpoints of the intervention can be indicated.

In the ICU, tests and measures should be selected and applied according to the patient's clinical condition, so that dynamic process deficits and limitations can be interpreted and identified. Depending on the state of consciousness, the tests can measure clinical and hemodynamic status and deficits (Table 92.5).

Some authors recommend evaluating the effectiveness of rehabilitation using scales such as the Cognitive Functioning Scale, the Rancho Los Amigos Scale, the Barthel Index, the Mini Mental Test, and the Disability Rating Scale (DRS) [52,53].

Scales for assessing functionality at the beginning and end of rehabilitation intervention that may demonstrate its effectiveness include the scales described below.

Rancho Los Amigos Scale

The **Rancho Los Amigos scale (Levels of Cognitive Functioning Scale [LOCF])** measures the level of patient response and functional capacity. Its name comes from the rehabilitation hospital where it was created, the Rancho Los Amigos in California. The LOCF scale is based on the patient's reaction to external stimuli and to the environment. The scale consists of eight different levels, and each patient will progress through the levels

with starts and stops, progress and plateaus. Irdesel et al. [54] investigated in 30 patients with head trauma admitted to the ICU of the School of Medicine, University of Uludag, complications observed during a rehabilitation program in the acute phase, its relationship with functional status, and the factors that influence rehabilitation outcome. The rehabilitation program consisted of postural rehabilitation, joint mobility exercises and breathing exercises. All patients were assessed with the scales of the Functional Independence Measure (FIM) and the LOCF upon entering the ICU and at discharge. Improvement was measured in terms of functional outcomes and levels of disability. The most frequent complications were pneumonia (46.7%), atelectasis (43.3%), anemia (40%), and meningitis (30%). The authors found that levels of functionality decreased with an increasing number of complications and concluded that rehabilitation plays an important role in the recovery of patients with head trauma and that the reduction in the incidence of complications and improved levels of functionality can be achieved with rehabilitation programs. They suggested the need for long-term studies with a large number of patients to obtain accurate data on factors associated with rehabilitation outcomes.
The following is a brief summary of the components of the LOCF:

- Level 1. No response: The patient is apparently in a deep sleep and there is no response to stimuli.
- Level 2. Generalized Response: The patient does not react consistently and without purpose to the stimulus. The answer is not specific and is delayed.
- Level 3. Localized Response: The patient responds to a particular stimulus but not consistently, can follow simple commands, but is slowed. He or she can be aware of their body, because it reacts to situations of discomfort, with a response to some people but not others.
- Level 4. Confused and agitated response: The patient has greater activity but the ability to process information is severely affected; demonstrates strange and purposeless behaviour, incoherent and/or inappropriate speech. Euphoric or hostile. Selective attention is nonexistent. The patient requires maximum assistance in self-care.
- Level 5. Unclear, inappropriate, not stirred: The patient appears alert and responds to simple commands; has appropriate responses to complex orders; is alert to the environment, with a high degree of distractibility and is unable to focus attention on specific tasks; uses poor language; has important memory impairment, lack of initiative to perform tasks without direction; can perform self-care activities with assistance.
- Level 6. Unclear, appropriate: The patient has goal-directed behaviours under external guidance, follows simple commands and remembers tasks related to self-care and responds appropriately to situations.
- Level 7. Automatic response, appropriate: The patient is independent in protected environments and needs supervision in the community.
- Level 8. Replies with purpose, appropriate: The patient is alert and able to integrate past and present events. Although there are consequences for cognitive-behaviour and functioning in the community.

Functional Independence Measure scale

This global ordinal scale for functional assessment (mobility and self-care) is useful in making decisions about the effectiveness of interventions. Several studies have used the FIM to investigate treatment outcome in self-care, transfers (mobility) and locomotion [55-57].
The FIM uses a 7-point ordinal scale to rate 18 items describing 6 functional areas. The scores measure the weight of care required, wherein high FIM scores represent high lev-

els of independence. Four of these areas: self care, sphincter control, mobility and locomotion factors are measured with 13 items and include motor function. The other two areas, social cognition and communication, are measured with 5 items and relate to the cognitive sphere. The total FIM score is obtained by adding up the scores for the 18 items (Table 92.6).

Level	Description
1	Total assistance; subject contributes <25% of the effort or is unable to do the task
2	Maximal assistance; subject provides less than half of the effort (25-49%)
3	Moderate assistance; subject still performs 50-74% of the task
4	Minimal assistance; subject requires hands-on help only (performs >75% of the task)
5	Supervision
6	Modified independence, subject requires use of a device but no physical help
7	Complete independence

Table 92.6. **Functional Independence Measure (FIM) Scale.**

Barthel Index

The Barthel Index (BI) is a measure of the level of independence in activities of daily living (ADL) [1]. It is the best known, studied and internationally disseminated scale for the assessment of ADLs. ADLs are a set of primary activities of the individual, aimed at self-care and mobility, which provide elementary autonomy and independence and allow the person to live without needing continued assistance from others; these include such activities as eating, bowel control, toileting, dressing, bathing, transferring.

The Barthel Index evaluates 10 areas of ADLs (eating, transferring between the chair and bed, grooming, toileting, bathing, moving, climbing stairs, dressing and undressing, bowel and urine control).

Level	Description
0-20	Total dependence
21 60	Severe dependence
61-90	Moderate dependence
91-99	Slight dependence
100	Independence

Table 92.7. **Barthel Index.**

The total score ranges between 0 and 100, where zero indicates total dependence in ADLs and 100 indicates mobility and independence. The interpretation suggested by Shah et al. (1989) on the BI score is described in Table 92.7.

The Barthel Index is the gold standard test for measuring ADLs; its conceptual validity has enabled studies to demonstrate its predictive ability in relation to duration of hospitalization, overall functional outcome, and the ability to live and participate in the community.

Disability Rating Scale (DRS)

The DRS was designed for assessing patients with moderate or severe TBI (Table 92.8).

The DRS total score ranges from 0 (no disability) to 29 (extreme vegetative state), so the lower the score, the better the patient's functional status [58].

One of the advantages of the DRS is that it allows tracking an individual in a coma until his or her return to the community. The first three items in the order of the DRS ("eye opening", "communication skills"

Level of disability	Score
None	0
Light	1
Partial	2-3
Moderate	4-6
Moderately severe	7-11
Serious	12-16
Very severe	17-21
Severe	22-24
Vegetative state	25-29

Table 92.8. **Disability Rating Scale.**

and “motor response”) are a slight modification of the Glasgow Coma Scale (GCS) [13] and reflect the level of impairment. The cognitive abilities “Food”, “Toilet” and “Go potty” reflect the level of disability, as a “level of functioning.”

92.3.3 Effects of Prolonged Bed Rest

Beyond dispute are the deleterious effects of prolonged bed rest for patients in critical condition. Physical deconditioning and alterations in various systems, secondary to prolonged immobilization in bed are common problems in mechanically ventilated patients with acute respiratory failure, contributing to prolonged hospital stay.

Prolonged immobilization, systemic inflammatory response, poor nutritional status, and the frequent use of drugs such as neuromuscular blockers and corticosteroids contribute to the development of debilitating diseases and neuromuscular disorders. Patients exposed to prolonged periods of immobility often experience pain and changes in mood, compromising their functional capacity [59].

Nava and Ambrosina [60] reported that prolonged bed rest results in decreased muscle mass and muscle capacity for aerobic work; they also noted that patients may progress to polyneuropathy or myopathy of critically ill patients, causing major muscular weakness in approximately 95% of patients up to 5 years during follow-up. The effects of prolonged bed rest in critically ill patients have dramatic effects on the functionality and quality of life related to health. Critically ill patients remain in the supine position for long periods of time, whereas healthy humans change their position approximately every 11.6 minutes during sleep, a phenomenon described as minimum physiological requirement for mobility. Prolonged bed rest can give rise to deleterious effects in the cardiovascular/pulmonary, integumentary, skeletal muscle and others despite repositioning every 2 h [61]. In the ICU, the patient remains for long periods of bed rest, where inactivity and immobility themselves have deleterious physiological effects, including atelectasis, pressure ulcers and increased susceptibility to aspiration and pneumonia.

Prolonged bed rest and immobility predispose to collapse of the peripheral units, resulting in decreased lung volume. The literature reports atelectasis as a common respiratory complication in neurological or neurosurgical patients, associated with low lung volumes, prolonged standing, inadequate cough and accumulation of secretions. The effect of immobility is greater in the elderly and patients with chronic diseases, including congestive heart failure and chronic obstructive pulmonary disease [62]. Some studies report the occurrence of polyneuropathy of critical patients in more than 50% of patients requiring mechanical ventilatory support for more than 7 days [63-65].

Since 1944, the effects of prolonged bed rest have been documented, including bone decalcification, muscle atrophy, dizziness and even fainting when patients start some light activity after prolonged periods of rest [66]. An editorial published in *The Lancet* in 1969 highlighted the damaging effect that prolonged bed rest has on the mechanisms that maintain circulatory homeostasis when passing to the standing position, suggesting that the root causes of an increased tendency toward motion sickness as seen in tilt table tests were insufficient venous return and, consequently, inadequate ventricular diastolic filling and decreased muscle tone, which was consistent with the work of Levine and Lown [67]. The editorial also specified that «the consequences of symptomatic postural hypotension (weakness, instability and tendency to dizziness in orthostatic position) are not specific to a particular disease and are experienced by many patients and healthy individuals after short periods of bed rest».

Table 92.9 illustrates the effects of prolonged bed rest [68]. Recently there has been a growing interest in initiating early mobilization of ICU patients under mechanical venti-

lation. Research in this field is still emerging, but studies indicate that early mobilization in critically ill patients is safe, feasible and associated with short-term benefits. Despite the theoretical advantages that physical therapy offers to address this problem, the evidence is not very strong, yet, in regards to the benefits of early initiation of physical therapy in the ICU [69].

Needham [70] conducted a systematic review of 24 studies involving ICU patients hospitalized with sepsis, prolonged mechanical ventilation and multiple organ failure. The author reported that 46% of 1421 patients in one study had neuromuscular dysfunction associated with prolonged use of mechanical ventilation and longer ICU stays. The review also cited numerous studies, highlighting the physical changes caused by prolonged bed rest, such as loss of muscle strength and changes in heart function. The researcher also based his comments and observations on his experience with patients in the medical ICU at Johns Hopkins Hospital, which has developed a rehabilitation program for ICU patients. The review concluded that the routine use of sedation and prolonged bed rest in ICU patients could cause prolonged residual neuromuscular complications and significant physical impairment of function and quality of life long after leaving the hospital.

Muscular system	• Muscle atrophy • Muscle weakness • Decreased tolerance to exercise • Insulin resistance • Decreased ATP • Decreased protein synthesis • Orthostatic hypotension • Phlebothrombosis
Skeletal system	• Osteoporosis, joint ankylosis, fibrosis
Musculoskeletal system	• Increased resting heart rate • Decreased stroke volume • Cardiac muscle atrophy
Respiratory system	• Decreased vital capacity • Decrease in maximal voluntary ventilation • Altered cough mechanism
Gastrointestinal system	• Constipation • Anorexia
Genitourinary system	• Decreased glomerular filtration • Increased diuresis • Hypercalciuria
Endocrine system	• Glucose intolerance • Altered circadian rhythm • Decreased parathyroid hormone • Increased plasma renin activity • Increased secretion of aldosterone
Metabolism and nutrition	• Increased excretion of nitrogen • Increased excretion of calcium • Increased excretion of phosphorus
Integumentary system	• Pressure ulcers • Edema • Subcutaneous bursitis
Psychosocial	• Depression • Decreased functional capacity

Table 92.9. **Effects of prolonged bed rest.**

Porta et al. [71] conducted a prospective study in 66 patients with respiratory failure and requiring ventilatory assistance for more than 48 or 96 hours. The study compared the effects of implementing a physical therapy program with the effects of general training of upper limb support, which consisted of ergometer cycle training. The study confirmed the benefits of physical therapy in critically ill patients and showed that adding upper limb exercise increases exercise tolerance and reduces dyspnoea and fatigue.

Hodgin et al. [69], in their study surveyed 984 U.S. physical therapists in order to determine the use of physical therapy in the recovery of critically ill patients. The authors concluded that in the United States, physical therapy is performed in ICU patients during recovery from serious illness, however, the frequency and type of physiotherapy varies significantly based on the type of hospital and clinical setting, and 87% of interventions involved stroke patients.

Korupolu et al. [72] reviewed important aspects to consider in the early mobilization of ICU patients, including safety, feasibility, potential benefits, possible obstacles, and resources. The article also highlighted the future directions for this field, including research and potential adjunctive interventions to improve neuromuscular performance resulting from prolonged bed rest after major diseases.

Below are some strategies in evidence-based interventions and the recommendations and conclusions the studies made regarding the effect of prolonged bed rest in neurointensive patients.

Continuous Rotational Therapy

In the supine patient, the abdominal contents push the diaphragm cephalad, resulting in decreased functional residual capacity, with alveolar collapse in dependent areas. Regardless of the mechanisms involved, hypoxia causes atelectasis and hypoventilation, creating a vicious cycle that complicates the clinical course.

Among the intervention strategies to prevent and/or treat atelectasis and pneumonia associated with prolonged bed rest is continuous rotational therapy (CRT) or kinetic therapy and positioning. CTR refers to the use of specialized beds that rotate the patient on its longitudinal axis to a maximum angle of 60 degrees to each side continuously; the slower rotation speed prevents the stimulation of the vestibular apparatus. CRT prevents the closure of dependent airways, reduction of lung compliance, atelectasis, accumulation of lung secretions and secondary infection [73] to these complications.

CTR can be achieved by using a rotational platform bed (movement therapy) or a bed mattress with compartments that inflate and deflate beds (oscillatory) [74].

Some authors have examined the beneficial effects of rotational therapy. Waldmann et al. [75] conducted a meta-analysis to analyze the effect of rotational therapy in the prevention and/or treatment of respiratory complications in critically ill patients. From their search of the literature published between 1987 and 2004 they analyzed 15 studies which reported on the types of beds but very little about the rotation parameters, for example, grade, pause time, and the amount of time per day; however, the meta-analysis suggested that rotational therapy decreases the incidence of pneumonia but has no effect on the duration of mechanical ventilation.

Powers et al. [76] suggested performing rotational therapy with rotation of 40 degrees or more for at least 18 hours a day. The article mentioned that the most suitable patients for rotational therapy present oxygenation index, PaO_2/FiO_2 (P/F ratio) <300 mmHg, FiO_2 >0.5 or PEEP >10 cmH_2O and patients at risk of developing the acute respiratory distress syndrome (ARDS) (septic shock, multisystem organ failure, trauma, and aspiration). The exclusion criteria in the study were the use of rotational therapy in patients without ventilatory support, except for those with spinal cord injury, patients with agitation refractive to sedation, patients incompatible with the specifications of the bed, patients

with uncontrollable diarrhoea and postoperative cardiac surgery. Criteria for discontinuing CTR were: a significant improvement in the P/F ratio, FiO_2 <0.4, increased mobility, uncontrolled shaking, extubation, and ability to walk, patients not more than 5 days on CRT, and patients who could not tolerate CTR for 18 h/day.

Culpepper Swadener et al. [77] investigated the impact of CRT in patients considered at high risk for pulmonary complications, using a tool that predicts patients at risk of nosocomial pneumonia. The tool comprises a list of 12 items, each assigned a score of 1, where 5 indicates that the patient is at high risk for developing pneumonia. Patients who received CRT were divided into two groups: one group started early CRT (n=49) and the other group received late CRT. The results of the study showed that early initiation of CRT, within 48 hours when the patient meets the criteria defined for treatment, significantly reduced the need for care and the total cost of ICU stay. The study excluded neurological patients requiring high FiO_2 for short periods of time to increase cerebral oxygenation, and not by lung involvement. Patients with unstable spinal cord injury, long bone fractures requiring traction, and some patients with head and neck boards were not considered for CRT.

Although the CTR is not used in our unit, it should be considered as a useful tool in the prevention and treatment of pulmonary complications; however, this implies extensive knowledge of the technology, development of a clinical protocol by professionals, and its application on the basis of a judicious assessment to define the correct indication.

Positioning

Positioning is the use of body position as a technique for specific treatment in the ICU. It can be used for physiological purposes: to optimize oxygen transport, increase lung volume, decrease breathing effort, minimize cardiac work, improve mucociliary clearance, and improve ventilation/perfusion [78]. Due to its immediate and direct effect on oxygen transport, therapeutic positioning can be considered a noninvasive intervention that promotes arterial oxygenation. Routine mobilization of critically ill patients at least every 2 hours has become a standard of care. However, there is not an objective assessment regarding compliance with this standard on a regular basis.

Krishnagopalan et al. [79] conducted an observational, longitudinal prospective study to determine whether ICU patients were repositioned every 2 hours. The results showed that, on average, 49.3% of the observed time, patient position was unchanged for more than 2 hours. Only 2 of 74 patients (2.7%) had their position changed every 2 hours. The authors concluded that most patients did not receive critical position changes every 2 hours, which warranted a reassessment of the care of critically ill patients.

Although repositioning critically ill patients seems logical, little data that supports its clinical effectiveness have been published.

In critically ill patients, physical therapists who perform positioning consider the need for selecting and applying specific body positions based on evaluation, chest radiography, and hemodynamics of the patient, always seeking physiological improvement.

The choice of positioning (sitting, lateral, prone, bipedal), time and frequency are the result of clinical reasoning, based on the evaluation of factors contributing to cardiopulmonary failure and response to intervention.

In patients with acute brain injury, special consideration must be taken such as keeping the head and neck properly aligned to promote venous return and/or monitor the position chosen so that it does not interfere with brain monitoring. Depending on hemodynamic conditions and the state of consciousness, the patient's progress and goals of the intervention, several positions can be used.

In critically ill patients, the orthostatic and/or sitting position is used to improve lung volume, reduce breathing effort, and decrease the risk of aspiration. The sitting position restores ventilation-dependent lung regions, preventing intra-abdominal pressure interfering with lung volumes.

The supine position helps improve ventilation/perfusion, redistributes alveolar edema, and improves functional residual capacity in patients with ARDS.

The lateral decubitus position improves the ventilation-perfusion relationship in patients with unilateral disease. Stiller et al. [80] compared various physiotherapy techniques in patients with acute lobar atelectasis, and concluded that with the involved side up and the bed in a horizontal position atelectasis improved when hyperinflation was combined with secretion suction, which was checked radiologically. Thomas et al. [81] conducted a survey of physiotherapists and nurses in three Australian ICUs and inquired about the rationale, objectives, type, frequency, duration, positioning used, and the perception of risks that may hinder implementation of effective positioning. Fifty-nine (83%) of the respondents agreed that there was an accepted norm in relation to the duration of 2 hours in position changes in ventilated patients. Of these respondents, 51 (86%) agreed that this standard is only met "over 50% of the time" by 34 (47%) ICUs. The study concluded that physiotherapists and nurses are aware of the practice of evidence-based positioning according to the indications and the potential risk factors, but it also recognized that educational strategies are needed to improve the type and frequency of positioning in the ICU.

Compression Stockings

In ICU patients, factors such as prolonged standing and/or intraoperative vasodilation can reduce blood flow in the veins and cause venous stasis. Among the factors contributing to the development of venous thromboembolism is damage to the vessel wall, reducing blood flow velocity, and increased blood coagulability known as Virchow's triad [82]. Endothelial vasodilation can overstretch the tunica media and cause damage to the innermost layers. In the presence of venous stasis, these lesions attract activated platelets, clotting factors and other thrombogenic damaged tissues. The interaction of these factors, coupled with trauma and immobility, increase the risk of blood clots in the venous system. This disorder usually occurs in the deep veins of the legs, called deep vein thrombosis (DVT).

Given this situation, there are a number of proposals for prophylaxis, including anticoagulants such as low-molecular-weight heparin and mechanical methods such as compression stockings and intermittent pneumatic compression devices, which are instruments that generate intermittent uniform or graded forces to facilitate emptying of the veins.

The combination of anticoagulant and mechanical methods to prevent DVT has been shown to have additive effect in patients undergoing elective abdominal surgery, coronary artery bypass surgery, and neurosurgery [83].

The effectiveness of early ambulation and lower limb exercises in preventing DVT has not been fully proved, although it is generally believed that the stasis caused by prolonged bed rest plays a key role in the pathogenesis of thrombosis [84]. The simplest method of prevention is early ambulation for muscle contraction in the leg muscles to minimize venous stasis.

The most common mechanical methods in routine use to eliminate venous stasis are graduated elastic compression stockings (GECS) and intermittent pneumatic compression (IPC) with boots or leggings. Compression stockings exert pressure on the applied areas, enabling the venous valves (responsible for proper circulation) to close again and work correctly.

Compression stockings prevent DVT by acting on three etiologic factors: venous stasis, vascular damage and coagulation. External compression reduces the cross-sectional area of the leg and increases blood flow velocity in both the superficial and deeper veins. This increase in blood velocity and decrease in venous stasis reduce the risk of thrombus formation by compressing the dilated vein walls, reducing local contact time and concentration of coagulation agents. Graduated compression stockings are designed to exert greater compression at the ankle (about 18 mmHg) than in the thighs (8 mmHg) to create a pressure gradient favouring venous return.

There are few reports on the use of compression stockings specifically in neurointensive patients; however, given the reported benefits, this prophylactic measure is commonly used in ICU patients with factors risk for DVT.

There are no absolute contraindications to the use of compression stockings. Relative contraindications and risks are associated with skin conditions (burns, skin lesions, presence of orthopedic devices), the presence of peripheral arterial disease or peripheral neuropathy. Excessive pressure exerted by an improper stocking or edema may decrease skin blood flow, causing problems in tissue oxygenation.

It is necessary to take into account some considerations for the appropriate use of compression stockings:

- Select the proper size and height according to the manufacturer's recommendations.
- Evaluate the skin conditions.
- Assess perfusion.
- Monitor leg edema.
- Check that there are no folds that can restrict blood flow.
- Remove the stocking and monitor the skin condition. Although there is no evidence on the optimal frequency to provide skin care, expert opinion suggests that it should be done at least once a day.
- Family and/or caregiver education on the indications for stockings, proper placement, skin care and the need to monitor and control edema.

Still undefined is the length of compression stockings. Thigh-length stockings are more difficult to place, more expensive and less tolerated than knee stockings; however, most studies have been conducted using long stockings.

Some authors suggest and confirm the benefits of applying graduated pressure to activate venous outflow. Graduated pressure is defined as the application of different pressure levels, applying higher pressure to the ankle and lower pressure to the most proximal area. Intermittent pneumatic compression (IPC) provides intermittent inflation that prevents venous stasis in the leg and appears to stimulate the endogenous fibrinolytic system. Sequential compression gradients (e.g., pressure of 20 mmHg on the thigh, 30 mmHg on the calf and 35 mmHg on the ankle, applied sequentially for 12 seconds), produce an increase of 240% in the rate of blood filling in the veins. By way of comparison, single-chamber leggings, inflated to 35 mmHg over the calf for 12 seconds, produce a 180% increase in the venous blood filling rate. Intermittent pneumatic compression with inflatable leggings is seldom used in the ICU, probably it is cumbersome and can only be applied to one patient at a time [85].

Some authors assume that the incorrect application of IPC devices, described in 23% of patients in an ICU and 52% of patients in intermediate care wards, can be a frequent cause of failure in this way to prevent DVT [86].

Complications and side effects of IPC are scarce; they may cause occasional discomfort and should not be used in patients with evidence of peripheral vascular ischemia of the legs.

IPC devices should be applied in the immediate preoperative, intraoperative and early postoperative periods and until the patient is able to walk.

Physiotherapy Intervention Strategies in Neurological and/or Neurosurgical ICU Patients

Rehabilitation in patients with diseases or injuries of the peripheral or central nervous system should be approached as a comprehensive intervention that begins in the acute phase and continues during the period of maximum recovery; early physiotherapy intervention in the ICU is widely supported by the literature [87].

Franckeviciute et al. [88] suggested considering: tolerance to physical activity, autonomic nervous system condition, hemodynamic changes and states of attention, cognition and perception.

Prolonged immobilization, lack of active movement, impaired sensation and proprioception, and altered level of consciousness among others, cause deficits in aerobic capacity, muscle performance, joint mobility, and integumentary and sensory integrity. These must be identified and treated early to ensure quality of care and ensure adequate monitoring during all phases of the disease.

What follows is physiotherapy interventions on the most common deficiencies in patients with acute brain injury.

Joint mobility and muscle performance can be compromised by prolonged bed rest, causing contractures secondary to altered muscle tone, poor mobility, skin wounds, heterotopic ossification, decreased muscle strength, deep vein thrombosis and other complications.

O'Sullivan et al. [89] proposed physiotherapy interventions in ICU patients, with the results evaluated by the LOCF Scale (Levels of Cognitive Functioning) and taking into account the scale's various different levels (Table 92.10).

There are several approaches to the management of neurological sensorimotor problems, including traditional therapy (passive, active assisted, and active exercise), the compensatory approach (promote overuse of the parts involved to compensate functional loss, facilitation skills, and facilitate normal movement patterns to evaluate progress in function), and models based on new motor control theories (movement emerges from the individual's interaction with the environment and the task), and the technique of mobilizing the nervous system [90].

All approaches will include proper bed positioning with the following objectives:

- Establish basic strategies of movement in bed.
- Promote adequate bronchial hygiene.
- Avoid changes in muscle tone.
- Avoid complications in the integumentary system.
- Promote body symmetry.
- Provide adequate proprioceptive stimuli.
- Promote awareness of the affected side.
- Relieve pain.
- Provide comfort.

In the ICU, in order to ensure proper positioning and promote and maintain proper alignment in bed, the therapist must create educational strategies for the nurse, the caregiver and the patient's family. It is

- Improve functionality and level of alertness
- Reduce the risk of secondary complications
- Improve motor control and postural control
- Increase tolerance to activities and positions
- Improve joint integrity and mobility to promote functionality
- Educating caregivers and family about the diagnosis, intervention, physical therapy, goals and results
- Coordinate care with all team members
- Modulate tone
- Improve strength in the patient
- Maintain integrity and joint mobility
- Reduce the risk of secondary complications
- Increase tolerance for activity
- Educating patients, caregivers and family about the diagnosis, prognosis, intervention in physical therapy and results
- Coordinate care with all team members

Table 92.10. Goals of physiotherapy intervention.

Position	Head	Scapula	Trunk	Superior members	Inferior members
Supine	Midline with slight flexion Roll parallel to head to prevent lateral flexion and rotation	Place a small roll under scapula affected to maintain proper alignment Shoulders levelled at all levels	Symmetrical Pelvis level Place pillow under hips to promote weight-bearing	Shoulder in slight abduction and external rotation Elbow slightly flexed; avoid hyperextension of elbow Forearm pronated Wrist in neutral or slight extension Fingers relaxed and abducted	Knees slightly bent. To do is put a roll in the lower third of the thigh. If the patient has increased tone level adductors and internal rotators of the hip should a pillow should be placed in the middle of both lower limbs Foot or ankle boots or splints
Lateral recumbency on affected side	Place two pillows over head to prevent shortening of neck on affected side and ensure proper alignment	Protraction shoulder with scapula in abduction. Avoid having patient bear weight on shoulder	Trunk line	Place pillow under affected forearm to facilitate hand-eye and hand-hand contact	Place a pillow in the middle of the lower limbs. The affected leg is in slight flexion of hips and knees
Lateral position on the healthy side	Place one pillow over his head to promote proper alignment	Scapula in abduction	Trunk line	Affected upper limb: shoulder in neutral, elbow bent, forearm pronated, wrist and fingers slightly extended, abducted and slightly extended. Supported on a pillow under upper limb	Place pillow in the middle of the lower limbs. Affected leg in slight flexion of hips and knees

Table 92.11. **Proper positioning in bed in patients with acute brain injury.**

generally believed that the supine position exacerbates extensor spasm. According to Davies [91], when this position cannot be avoided, the therapist must develop strategies to minimize undesirable effects, with the use of rolls, pillows and wedges to increase the regularity of movements and stretching of the limbs.

The lateral position can be used to break flexor or extensor synergy [92]. Ways to position the patient supine, lateral decubitus on the healthy side and on the affected side to promote proper alignment and positioning are given in Table 92.11.

Depending on the overall conditions of patient, intervention often focuses on traditional therapy. Intervention strategies in traditional therapy will aim to maintain joint mobility, postural responses that normally modulate the tone and provide adequate proprioceptive stimulus.

To achieve these goals, joint mobility exercises can be performed in bed to prevent contractures, avoid deep vein thrombosis and, possibly, lower muscle tone and promote changes in sensory stimulation.

Joint mobility exercises include passive exercises of the trunk, scapula, pelvis, rib cage, upper limbs and lower limbs. Neck mobility should be done gradually, slowly and within

the short range, preventing flexion with the head bent forward so as to avoid increasing intrathoracic pressure and elevation of ICP.

Scapular and pelvic mobilization can be performed when the patient is using diagonal, lateral, scapular, and pelvic techniques with proprioceptive neuromuscular facilitation (anterior elevation, posterior elevation and subsequent depression, previous depression). The technique of initiating rhythm is used with the aim to improve the ability to initiate movement and to provide proprioceptive stimulation. This technique starts with passive exercise and progresses to active and active-assisted exercises, according to the state of consciousness and cooperation, until the patient has adequately integrated movement.

Mobilization of the upper limbs should begin by mobilizing the shoulder girdle at different levels while paying attention to the mechanics of the glenohumeral joint, otherwise joint pain and joint instability can ensue, leading to shoulder pain or subluxation. Wilches et al. [90] suggest the implementation of such measures as follows:

- Support the shoulder in a position that maintains normal scapulohumeral orientation in bed in patients with hemiplegia; when positioned in lateral recumbency, the affected side should be protected against the scapula from non-weight bearing directly on the shoulder; and when in lateral decubitus on the healthy side, positioning should support the upper member engaged to prevent tensile forces from luxating the shoulder.
- Use the savanna motion to move the patient in bed, avoiding traction on the upper limb.
- Range of joint motion (ROM) exercises should not exceed 90° in flexion and abduction of the shoulder unless there is good rotation of the scapula and external rotation of the humeral head.
- Provide support to the upper limb to counteract gravity in the semisitting or sitting position.

For mobilization of the lower extremities, it is essential to maintain a range of motion of all joints with emphasis on maintaining ankle mobility, which can be limited by changes in muscle tone and effects of gravity that produce shortening of the plantiflexors in the muscles and Achilles tendon. According to Williams and colleagues [93], a shortened muscle and no movement can cause stiffening due to increased tissue inside.

Cameron M et al. [94] investigated in 22 patients the changes associated with contracture formation in a population with stroke (CVA) in the acute phase. The presence of contractures was assessed by quantifying the resting posture, resistance to passive motion and passive range of motion, followed by initial assessment; measurements were taken at 4, 8, 20 and 32 weeks. The group able to perform some functional movement (8/22) improved upper limb function while the group unable to make any functional movement (14/22) suffered changes associated with the onset of wrist contractures. The authors concluded that patients more susceptible to the formation of contractures were those who showed no signs of improvement in early functional recovery (2-4 weeks after the event).

Preserving the integrity of the ankle and foot is very important for maintenance of joint mobility because these joints are essential for carrying out functional activities such as transfers, sitting, positioning in the wheelchair, standing and walking. Integrity can be preserved by sustained muscle stretching (about 30 seconds), with continuity, frequency (at least twice a day), and performing a preset number of repetitions according to patient response to ensure benefits (e.g., 3 sets of 6 repetitions).

Muscle stretching should be performed slowly so as not to create a stretch reflex and inhibit neural response. The effect of long slow stretching is not entirely clear, although it varies depending on how long the muscle stays stretched. It seems that it is influenced

by the neural components of muscle through the Golgi tendon organs and muscle spindles, and the long-term structural components by the number and length of the sarcomeres [95].

Importantly, other strategies, depending on the patient's condition, also facilitate stretching, e.g., mobilization of soft tissues, and techniques including motion sequences to establish relationships between segments, such as the Feldenkrais, and from the Bobath concept, the use of inhibitory reflex positions.

Exercises with the patient out of bed, using a chair or table as support for standing, if the clinical condition allows, can mobilize segments such as the pelvis, ribcage and shoulder girdle, with the patient lying partially and moving only on one plane.

92.3.4 Splints

The effects of prolonged rest, unconsciousness, and an altered muscle tone can increase the risk of muscle contractions. Stokes et al. [92] suggest that a low score on the Glasgow Coma Scale (GSC <9) and signs of decerebration identify patients at risk of developing contractures, such as signs of shortening which do not improve with intervention or the inability to assume the standing position due to the motor impairment secondary to injury.

It is important to assess the degree of motor impairment and establish an appropriate diagnosis to prescribe the use of splints. This represents an economic cost to the family that can be avoided if the patient quickly recovers mobility or appropriate assistance is given when the patient will actually require splints.

Joint integrity can be maintained with bed rolls, pillows, wedges, footboards, hands and ankles specifically engaged when the motor deficit is not very clear, and with splints when the patient has a well-established motor deficit as in those with spinal cord injury (SCI).

Clinical practice guidelines on splinting adults with neurological dysfunction (ACPIN, 1998) [96] identified a lack of research in this area, making it almost impossible to adopt an attitude based on the evidence on the use of splints. Splints allow stretching with little long-term strength. Improperly designed splints can cause pressure ulcers and tissue damage, so it is important that after the application of splints, the therapist assesses proper joint alignment and continuously checks for the presence of pressure zones. The therapist should teach the nursing staff and family and/or caregiver to apply the splints correctly, to identify pressure signs, and the time of use.

The time needed to prevent contractures remains debatable; the literature indicates a range from 30 minutes to 6 hours [97,98].

Prophylactic splints, braces or pressure corrective splints or serials can be used in patients with multiple risk factors as identified above. Barnard et al. [99] reported a reduction in the overall level of spasticity after using splint boots. Robichaud and Agostinucci [100] speculated that this effect could be due to a reduction in the signals from proprioceptive and thermal receptors due to splint placement. They indicated that a total contact brace promotes an even distribution of pressure and heat, reducing the excitability of alpha or gamma motor neurons of the spinal cord.

Pressure splints or inflatable splints [101] can be used in the ICU, taking into account the patient's socioeconomic status and knowledge of the indications, contraindications and benefits thereof.

A pressure splint consists of two orally inflatable plastic sleeves designed for upper and lower limbs. They are used for modular sensory stimulation and muscle tone in the affected side. A correctly placed pressure splint not only helps to reduce spasticity as a passive

instrument but, as a more dynamic aid, it plays an active role in achieving better results. The splint can be placed for applying pressure for a period of at least 20 minutes to 1 hour maximum. Pressure splints can be combined with joint mobility exercises and techniques to modulate muscle tone. The splint applies pressure to the arm by placing the shoulder in external rotation, elbow, wrist and finger extension, and thumb abduction.

Corrective or serial splints are used to increase range of motion in the presence of contractures. Two common designs are cylindrical and gutter serial splints. The advantage of drop-shaped braces is that you can encourage active movement while function is not altered.

A systematic review by Mortenson et al. [102] reported that, the level of evidence available to date does not consider serial splinting as an adjunctive therapy to improve functional mobility. The recommendation for future research should include sensitive measures of levels of function, activity and participation according to the International Classification of Functioning (ICF). However, in this very review it was felt that the use of splints improves passive range of motion and decreases spasticity.

Singer et al. [103] in their descriptive study looked at patients with moderate to severe brain injury (GCS ≤12) and assessed ankle dorsiflexion and muscles activity in plantiflexion. The occurrence of contracture was defined as a maximum passive range of motion ≤0 degrees of dorsiflexion with the knee extended on at least two measurements. The study identified ankle contracture in 40 of the 105 patients. Contraction was determined in 23 patients with a physical therapy program that included stretching and prolonged motor re-education. Additional treatment with splints and botulinum toxin to correct persistent contractures was performed in 26 cases.

Other authors evaluated the use of serial casts in 16 patients to determine the short-term benefit of correction of equinovarus ankle after brain injury and concluded that the use of serial splinting seems to be effective in reducing deformity, at least in the short term.

In the ICU a footboard can be designed to ensure adequate alignment of the feet and hands. They can be created by the physiotherapist or occupational therapist using plaster bandages and then laminated with cotton, ensuring that both the upper and lower limbs remain in functional positions. For the lower limbs it is important to maintain the ankle in a neutral position, while the hand should be positioned to the wrist in slight extension (45°), the thumb and fingers slightly flexed and abducted.

Another alteration that can lead to reduced joint mobility and muscle performance is impaired muscle tone secondary to neurological injury, which will result in a lack of adequate voluntary control of movement and musculoskeletal complications that can alter biomechanical movements, subsequently reducing levels of function and independence. It is believed that therapeutic movement and altering the alignment of body parts are able to indirectly influence muscle tone in other areas. For example, movement of the trunk and shoulder girdle can aid in bending the arm [91,104].

The patient's position should be noted as it can provide an indication of normal, increased (spasticity or rigidity) or decreased (flaccid or hypotonic) muscle tone. Tone is assessed by passive movement of the limbs and trunk through the normal range of motion with the patient relaxed. Among the most frequent alterations is muscle spasticity, a motor disorder characterized by a speed-dependent increase in muscle tone, which can cause pain, limited joint motion and difficulty with care. The early onset of spasticity often causes clubfoot in adults with acquired brain injury and may limit the achievement of rehabilitation goals.

Irdesel et al. [105] in their study reported that spasticity was present in 23.4% (7/27 patients), contracture in 10% (3/27) of those with head trauma admitted to the ICU of the School of Medicine, University of Uludag, after an early rehabilitation program.

There are different techniques recommended by root sensory stimulation that can be used to facilitate or inhibit muscle tone, depending on the stimulus and the way it is applied. For example, ice quickly applied over the muscle facilitates its activation; conversely, it inhibits activation if applied for prolonged periods. The neutral temperature (body) is considered inhibitory for hyperactivity of muscle tone. Vibrations can also be used to facilitate or inhibit muscle activity. High-frequency vibration tend to facilitate muscle activation, whereas low-frequency vibration often inhibits muscle activity. Similarly, a quick stretch facilitates muscle activation due to the stretch reflex, while prolonged stretching (manually or using boots, splints or braces) decreases the levels of activity. A quick touch or tapping also facilitates muscle activation, while slow touches are considered inhibitory.

Techniques that activate joint receptors can also be used to facilitate muscle activation in patients with neurological disorders. One aproximation consists of joint-to-joint compression that can be applied manually or by weight bearing. Technical manual traction applied over a joint can also facilitate muscle activity. Changing the patient's position may also be suggested as a technique to alter muscle and postural tone. The assumption is that placing the patient in certain positions can alter muscle length and postural tone and changes in reflex activity. For example, positioning the patient supine can facilitate extensor tone, while the flexor tone is facilitated when the patient lies prone; placing the patient in lateral position is often used to inhibit the effect of the asymmetric tonic neck reflex (ATNR) and to facilitate bilateral symmetrical neck position [106].

During physiotherapy in patients with acute brain injury, the therapist provides stimulation in various ways. When passive movement activities are carried out in patients who are not under the influence of sedatives and muscle relaxants, the therapist should explain what is being done, so that the execution of the activity fosters the patient orientation. It is important to maintain direct communication, thus orienting the patient in time, place and person, via tactile, auditory and visual stimulation.

Sensory stimulation increases alertness and produces movement. It is assumed that overstimulation can be provided in a controlled manner, with a balance of multisensory stimulation and rest, as well as activation and stimulation of the reticular system resulting in a general increase in alertness.

Stimulation is more effective when administered in short treatment sessions (15 to 30 min). Stimuli should be presented first in an orderly fashion in one or two ways at a time, to prevent overstimulation.

Auditory, visual, olfactory, tactile and vestibular stimulation are all important. According to Ada et al. [107], ICU patients are burdened by high dependency and a plethora of interventions that involve handling and movement. Therefore, it may be necessary to limit sensory stimulation instead of increasing rest periods, for example, by using eye patches to maintain normal daily rhythms. It is important to share with the patient's family and friends the concept of controlled sensory stimulation in promoting recovery.

Later, when the patient's hemodynamic conditions permit and under proper monitoring, stimulation can progress to assisted active exercises, assisted-resistance sets and free sets (with mild resistance held between 3-4 seconds) using different techniques and diagonal neuromuscular facilitation of proprioception in patients with SCI. In patients with hemiplegia different intervention approaches include the Bobath technique, the technique of relearning motor, motor control, Brunnstrom technique, Margaret Johnston, Rood and Perfetti cognitive therapeutic exercises, among others.

The patient and nursing staff should be taught the proper way to mobilize the patient in bed, how to place the patient in the upright sitting position. The activities in the bed should be preceded by some preparation with the patient sitting on the edge of the bed with his or her feet flat on the floor or on a surface to activate the trunk muscles while

sitting or standing, which decreases the base of support and places a greater demand on the muscles, promoting greater functionality and independence in the patient.
During the activities in bed, patients recovering from post-stroke hemiparesis should be taught how to change position from supine to lateral decubitus on the healthy side and the affected side, as well as lateral position on the healthy side and the affected side in the sitting position and vice versa so that they can carry out activities such as half-bridging and bridging exercises that help to facilitate co-contraction around the hip and weight bearing on the limb, thereby increasing the patient's functional independence.
In patients with high spinal cord injury (quadriplegic), the family or caregiver should be taught how to properly use sheet movement and how to make bed transfers. If the patient has a high or low paraplegia, training should start with the acquisition of different positions in bed to achieve functional independence using bed or mat activities as proposed by the proprioceptive neuromuscular facilitation technique.
It is important that patients with neurological disorders start sitting and standing early. The sitting position is essential to maximize therapeutic function, reduce positions held, prevent skin pressure ulcers, maintain joint mobility, decrease pain and promote patient socialization. When the aftermath of the injury is severe, the sitting position can be achieved with a wheelchair adapted to the patient's needs, depending on the type, level and severity of the injury.
Facilitating the adoption of the standing position favours the maintenance of muscle length, reabsorption of calcium, intestinal peristalsis, tone, and modulation of the activation of extensor activity. To be most effective, it must be an action that allows dynamic changes in pitch [108]. Markham [109] and Brown [110] agree that the standing position alters muscle tone through the vestibular system, being an important source of excitatory influence to the extensor muscles.
Bohannon et al. [111] suggest that when taken daily, the standing position can preserve muscle tone and reduce the frequency of spasms, thus maintaining joint range.
The ICU patient may be placed in a standing position if hemodynamic conditions permit, using a stretcher or table and standing or leaning with adequate monitoring.
All possible strategies to prevent the onset or complications of deficits in joint mobility and muscle performance should be guided by clinical reasoning-oriented and achievement of patient function and independence.

92.3.5 Technical Mobilization of the Nervous System

Neural mobilization belongs to a group of techniques that have attracted renewed interest, sparked, among other reasons, the growing body of scientific literature that is reviewing and updating the reliability and validity of these procedures and the involvement of the nervous tissue as a source of pain in pathological processes of the musculoskeletal system.
Mobility is the coupling of the nervous system with mechanical systems that determine the quality and range of motion of the musculoskeletal system. The nervous system, like other somatic structures (muscles, tendons, capsules, etc.), may suffer from disease processes affecting its elasticity and mobility, as well as generating symptoms which manifest themselves often with characteristics similar to those generated by other somatic structures.
Orthopedic manual physical therapy has developed and extended the practice of elongation of the nervous system and various treatment techniques for mobilizing nerve tissue and its adjacent structures.

The nervous system and connective tissue sheaths, like other soft tissues, benefit from mobilization and therapeutic criteria applied by elongation.

Movement in one part of the body causes movement of the nervous system. This fact is used as a tool for the diagnosis and treatment of many orthopedic problems. An injury to any body structure can hamper the nervous system's mobility and elasticity, which are essential features of normal body movement. Butler [112] stated that the clinical consequences of an altered biomechanics of the nervous system are recognized and that many disorders attributed to musculoskeletal sources originate or have a significant component in an adverse natural tension.

The connection between movement of the nervous system and symptoms demonstrated in orthopedic patients can be explained by the fact that the nervous system may suffer physical injury that jeopardizes neural and connective tissues. The disorder can be extradural, intradural or both. The nerve is usually in contact with various tissues, called neural containers or mechanical interfaces adjacent to tissue. Pathological phenomena include bleeding, swelling or scar tissue, or splints and perhaps hypertonic and stiff muscles.

The injury may be in the blood supply to the nerve, the nerve itself or the axoplasmic flow (axonal transport). The nervous system consumes 20% of the oxygen present in the arterial circulation, which is necessary for impulse conduction [113]. An increase of 8% in the normal length of a nerve reduces blood flow, and an increase of 15% will result in the complete occlusion of blood flow [114]. Blood vessels in the spinal cord and peripheral nerves have a length and extra-anatomical organization, responsible for movement and normal blood flow [115].

According to Butler [112], alteration of nerve function begins at pressures of 30-40 mmHg. In a healthy person, the pressure in the carpal tunnel with the wrist joint in neutral position reaches 30 mmHg and 100 mmHg with the wrist in flexion, which suggests that a person with hemiplegic flexor spasticity in the wrist joint will have abnormal pressure on the median nerve. The symptoms often seen in the hemiplegic hand may arise, besides other causes, from impaired axonal transport.

It is possible that some of the physiological changes seen in the hemiplegic person are due to spasticity (mechanical interface) that influences the axonal flow. The axoplasm displays thixotropic properties, meaning that it flows better when kept in motion [116].

The neural mobilization technique involves movements not only in joints and muscles but also in the nervous system. Following surgery, the physiotherapist should include: movement of the distal parts in all movements made during treatment, mobilization of the nerve itself and trunk motion, strengthening movement of the nervous system and influencing the sympathetic chain.

Before starting the intervention it is important to make a proper assessment and take into account the following recommendations:

- Treatment progress and movement should be slow because the nervous system is delicate and superficial in some areas.
- The joints should be kept well aligned during each movement.
- Pay attention to the effect of all movements over the body as a whole.
- Special care must be taken when handling unconscious or insensitive patients.
- Nerve pain may appear after a few hours after the nerve has been irritated.
- It has been shown that the frequent repetition of the Stretch Straight Leg Raise technique (resembling a hamstring stretch with hips flexed and knee extended) even in healthy people can cause symptoms such as headache, nausea and a feeling of floating. One possible explanation may be that the exercise pressor reflex (EPR) moves the sympathetic chain.

Rolf [74], Davies [117,118] and Simionato et al. [119] all described signs of neural tension in the Guillain-Barré syndrome. From the authors' experience it appears that the effect of motion on the nervous system can also be applied to CNS lesions. When studying patients with hemiplegia, spinal cord injury or cerebral palsy, it is often observed that the range of motion of a body part is altered by the passive movement of another distant part of the original motion [117]. According to Davies [118], clinical experience shows that there is a loss of movement of neuraxial and peripheral nerves after head injury. This loss results in abnormal postures, increased resistance to movement and loss of selective movements of the trunk and extremities.

Currently, there are no scientific studies or evidence of the effect of neural mobilization in the treatment of patients in intensive care. Knowledge in these patients is insufficient to explain the physiological effect of treatment; however, considering the proposals of the technique, neural mobilization could be used with caution in patients in the acute neurological phase, as long as the neurological changes are stable, the patient is conscious, and no acute disease process is present. Under constant re-evaluation, passive mobilization of the nervous system may be appropriate in selected patients.

92.4 Prognosis

Despite the care directed to ICU patients, it is observed that neurological lesions can have serious sequelae. Given this situation, research has attempted to determine the factors that affect the clinical course and several therapeutic modalities have been suggested and implemented in some segments of rehabilitation. The vast majority of these studies use the Glasgow Outcome Scale (GOS) created by Jennett and Bond in 1975 [14] to monitor patients according to physical sequelae, cognitive and social measures.

Other factors considered in the prognostic evaluation of these patients include: age, pupillary changes and GCS at hospital admission, type of neurological injury, and complications associated with neurological injury such as intracranial hypertension, pneumonia, hypoxemia, and hypotension pressure among others.

Several published studies have correlated therapy after brain injury with the sequelae presented by patients with TBI throughout its evolution. Early identification of secondary brain injury is essential for patients because it can be prevented or minimized with appropriate therapeutic management, thus reducing its influence on the ultimate prognosis of the individual.

92.5 Types of Sequelae

Consequences of head injury can be classified as physical, behavioural, cognitive and medical [120]. The physical sequelae are proportional to the area affected and the degree of injury, and include paresis/plegia, the deficits following cranial nerve injury, post-traumatic epilepsy and headache, as well as combinations of cerebellar and pyramidal signs and asymmetric pyramidal signs and bilateral extrapyramidal signs.

The behavioural sequel are related to changes in the patient's relationship with the environment after brain injury: the damage resulting from neurological impairment in the cortical area of the brain, brainstem, hypothalamus, thalamus, prefrontal and limbic system. These behavioural changes may result from the primary lesion or arise as a side effect, or even, as an exacerbation of pre-existing personality disorders, which can lead

to poor social adjustment, making it difficult to return to activities of daily living (ADLs) [121].

Cognitive sequelae include changes in memory, especially with regard to pre- and post-trauma conditions, as well as difficulties in maintaining attention and concentration [122].

The medical sequelae include those resulting from metabolic, neuroendocrine, cardiovascular, gastrointestinal, respiratory and blood disorders. Hawk [123,124] noted that pneumonia was present in 59.2% of patients (16/27) and 49% of cases (49/100), respectively. This delayed complication is related to a worse prognosis.

Jennett and Plum [125] also reported two other types of disabilities: 1) a persistent vegetative state characterized by reduced responsiveness when awake with no evidence of cortical function; and 2) the socioeconomic sequelae directly related to the epidemiology of TBI, the largest segment composed of persons in their most productive years of life and who are generally responsible for maintaining their families. Hence, the social and economic burdens are carried by the patients and their families.

Added to these burdens, patients often have symptoms that may persist for weeks or months after injury, such as headache, dizziness and incoordination, even in the absence of physical deficits [126].

Finally, the management of patients has evolved markedly in recent decades, especially in the pre-hospital and ICU settings, with faster and more efficient action to improve survival.

Upon admission, immediate care is considered crucial to minimize damage and improve the prognosis of patients, including complete evaluation with imaging studies such as computed tomography (CT) to diagnose the type of injury and its extent. In a simplified manner, CT findings have been classified as focal lesions or diffuse injury, depending on the area affected and its extent. According to the type and degree of involvement, these lesions can be post-trauma prognostic indicators [127-129]. Another classification of CT was developed by Marshall et al. [130] in order to increase the ability to predict patient outcome after TBI, and which is also used in combination with the Glasgow Outcome Scale (GOS) for the same purpose.

92.6 Prognostic Index

There are several factors that can be considered as an index of prognosis after head injury, including the following.

Age: a factor determining the prognosis; the elderly were found to have the worst prognosis of 122 patients after injury [131,132].

Changes in pupil reactivity and the GCS score at the time of initial evaluation are efficient in determining the prognosis: the lower the GCS score and the longer the time spent in a coma, associated with pupillary changes (anisocoria, decreased or absent reflex to light stimuli), the greater the number of patients with worse outcome, high rate of morbidity and late mortality [128,129,131-135].

Type of injury: considering that CT findings may be predictors of prognosis after TBI, patients with diffuse lesions are more likely to have with a worse prognosis compared to those with focal lesions [134].

Presence of complications observed during hospitalization such as hypotension, hypoxia, intracranial hypertension and pneumonia are described in the literature as indicators of poor prognosis, with high rates of morbidity and mortality for patients after TBI [131,138-142].

Surgical intervention is a therapeutic resource for some complications after brain injury [143]. However, outcome after surgery in relation to prognosis remains controversial [144-146].

Change in memory: the vast majority of patients have memory impairment following neurological injury, particularly after TBI. These changes and their recovery are discussed by Katz and Alexander [122], who report that early diagnosis, age and severity of the trauma are the most influential factors in the recovery of post-traumatic amnesia.

Change in behaviour: there are reports that patients may develop behavioural changes after injury [121,147]. Such changes may interfere with social reintegration and are more often identified by family members than by patients. Novack et al. [148] found that cognitive and memory changes seen after TBI improved greatly after 1 year, and that motor sequelae were most responsible for the limitations of the patients. However, these results were only partially consistent with other studies in which such changes interfered with social reintegration [122,123,129,135-137].

The brain is responsible for many higher functions, including cognitive abilities, thinking, behaviour and motor skills. Therefore, the impact of brain injury in the lives of patients and their families can be devastating, whether personal, social, monetary, or a combination thereof.

With regard to therapeutic perspectives, much has been invested in management and treatment; however, they incur high costs for public and private health services, not all of which guarantee the multidisciplinary care (medical, nursing, physiotherapy, psychotherapy, occupational therapy, etc.) necessary to achieve maximum rehabilitation in each case.

Along this line, Mata et al. [149] conducted a study to assess the quality of life after TBI, and found that the quality of life of TBI patients declined from 96.6% (before injury) to 57.5% during the 2 years after injury. And the fall was correlated with age, severity of injury and quality of life.

92.7 Final Considerations

The improvement in the prognosis of neurological patients, clinical and surgical, in recent years, has been due mainly to advances in intensive care. The widespread use of rigorous clinical monitoring, guiding therapeutic interventions in cardiac and neurological functions, allows the therapist to predict the degree of attention patients require not only in mechanical ventilation, but also in the prevention of respiratory and neuromuscular failure. These precautions minimize pulmonary complications, provide early intervention, and contribute to a better prognosis after brain injury.

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93 Nursing Care of the Patient With Acute Brain Injury

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93.1 Introduction

In the past 30 years great progress has been made in the treatment and outcomes of brain injury. For example, the overall mortality from severe traumatic brain injury (TBI) fell from 36% in 1980 to almost half in specialized trauma centres in recent years. But the belief that this improved outcome may be due to technological advance alone is not entirely true. Monitoring of intracranial pressure and cerebral oxygenation provides us with more physiological information for making decisions; however, most care measures, rather than modify the results, depend on very simple and common manoeuvres such airway control, prevention of hyperthermia and hypotension, and strict monitoring of blood glucose among others.
Growing scientific evidence supports the fact that specialized units with doctors and nurses trained in neurological/surgical intensive care have a great impact and favourable effect on clinical outcomes [1].

93.2 Pathophysiology of Acute Brain Injury

To understand better what happens during acute injuries of the central nervous system (CNS) we must differentiate between primary and secondary injury.
The **primary insult** or injury is the physical damage that occurs at the moment of injury. This injury is already established at the time of admission to hospital and we can do little about it (Table 93.1).
In contrast, **secondary brain injury** (Table 93.2) involves a series of processes that may have been induced directly or not during the initial injury or may be the result of different situations (often iatrogenic) that occur later. Sometimes the effects associated with secondary injury may have extracerebral origin. Cerebral edema, metabolic disorders, calcium toxicity, cytotoxic injury, inflammation or apopto-

- **Trauma:** contusion, concussion, laceration, intra or extra axial hemorrhage
- **Ischemic:** global (anoxia, cardiac arrest) or regional (vasospasm, thrombosis, embolism)
- **Inflammatory:** meningitis, encephalitis, abscess
- **Compressive:** tumours, edema
- **Metabolic:** encephalopathy (hepatic, renal), drugs, electrolyte disturbances

Table 93.1. Mechanisms of primary insult.

- **Hypoperfusion:** global (intracranial hypertension, significant decrease of mean arterial pressure); regional (vasospasm, edema, hyperventilation)
- **Hypoxia:** systemic hypoxia, regional hypoperfusion, increased oxygen consumption (fever, seizures, etc.)
- **Reperfusion injury:** free radical generation, cytokines, prostaglandins
- **Release of excitatory amino acids:** glutamate, aspartate
- **Electrolyte or acid-base disorders:** hyper-or hyponatremia, acidosis, hyper-or hypoglycemia

Table 93.2. Mechanisms of secondary insult.

sis are examples of processes that are initiated as a result of traumatic injury and evolve over time, with worsening of prognosis.
Other secondary insults can result from alterations in other organ systems. Episodes of hypotension, hypoxia, hyperglycemia, hypercapnia, for example, double and sometimes triple the morbidity and mortality of patients with neurological injuries, regardless of the type of injury or its initial severity.
In general, the initial damage cannot be reversed, whereas secondary injury is often preventable or reversible. In patients with acute brain injury, great care should be focused on avoiding or at least minimizing secondary insults. This is the real challenge for the treatment team.
When analyzing the data objectively, it is clear that the causes of the decline in mortality from trauma in the past 20 years have been the ability to decrease the influence of secondary insults to the injured brain.

93.3 Nursing Care of the Neurocritically Ill Patient

One way to improve team work and quality of care is with the application of standards and protocols. Furthermore, clinical practice guidelines save nursing time. Much has been written on this aspect and on the importance and prevalence of some actions over others; however, there is consensus among experts that written protocols greatly reduce the probability of error, promote the uniqueness of criteria between care team members, and reduce morbidity and mortality rates.
In 2005, Jean Louis Vincent [2] proposed a mnemonic for remembering the most important aspects in the daily care of critically ill patients. These criteria are basic and take on special importance in the neurocritical patient.
FAST HUG. Each letter making up this mnemonic represents an issue that directly influences the evolution and prognosis of the patient, supported by evidence from numerous systematic reviews. Vincent adds that we give our patients “a quick hug at least once a day.”

93.3.1 F: Feeding (Food)

The early onset of enteral nutrition is a key component in the care of critically ill patients as it increases mesenteric blood flow, maintaining intestinal mucosa integrity and promoting gastrointestinal motility and peristalsis. Since the brain is unable to store glucose, its primary source of energy, it depends on a constant supply from the cerebral circulation to maintain basal metabolism. When glucose levels decrease significantly, brain cells become dysfunctional and die.
At the same time, promoting proper bowel function in patients with acute brain injury prevents the increase in intra-abdominal pressure and the consequent increase in intrathoracic pressure and ICP, and reduces the risk of sepsis related to the translocation of intestinal bacteria.
Nutritional replacement should begin at an early stage, i.e., within 24-48 hours after brain injury [3-5]. It takes 2 to 3 days to gradually increase the power to reach the necessary requirements. Patients with TBI should receive all of their caloric requirements at day 7 after brain injury [6]. The enteral is preferable to the parenteral route because of the lower risks for the patient. If gastric feeding is not tolerated within 48 hours post-injury, post-pyloric feeding beyond the ligament of Treitz should be initiated [7]. If enteral feeding is not possible or not tolerated, parenteral nutrition should be started [8]. There is no consensus on continuous or bolus feeding, but the latter method is more physio-

logic and increases the probability of distension of the administered volume. All strategies should be considered to manage the nutrients in the optimal amount (e.g., use of enteral tubes of small caliber, use of gastric residual volume threshold greater or not measuring the same).

93.3.2 A: Analgesia

Pain has a negative impact on physiological and psychological recovery. For this reason, adequate pain treatment is essential in the management of critically ill patients. The neurocritical patient feels pain not only because of the underlying disease but also because of the routine procedures received, for example, changes in decubitus, aspiration of secretions, blood sampling, wound healing, and catheter implantation. Episodes of pain significantly increase ICP. In the awake patient, pain is evaluated on graphic scales (visual analog scale [VAS]), usually consisting of a straight line with "no pain" at one end and "maximum pain" at the other, on which the patient marks the level of pain experienced. For sedated patients, in which analgesia tends to be underutilized, it is important to evaluate the physiological equivalent of somatic pain, for example: facial expression, movement and posture can be clear indicators of pain. Among physiological signs, tachycardia, hypertension, or tachypnoea require adjustment of analgesic dose or its utilization, if not being administered.
Continuous infusion of analgesic drugs or regularly administered doses (extra dose or "bailout" when required) are more effective than bolus doses "as needed", which can lead to time intervals without coverage. The indication "as needed" should be eradicated from our mind. Intravenous administration allows faster, more accurate titration according to the needs of the patient. We must remember the side effects of opioids: respiratory depression, constipation, gastroparesis, hypotension, and hallucinations. Adequate but not excessive analgesia coverage must be provided. Furthermore, the fact that a patient cannot speak does not mean that he or she does not have pain. Overanalgesia is just as undesirable as underanalgesia.

93.3.3 S: Sedation

Both insufficient and excessive sedation may have deleterious effects on patient outcomes. Pain and anxiety can increase or exacerbate secondary brain insult by increasing cerebral oxygen consumption and ICP. In contrast, excessive sedation can cause respiratory depression and hypotension, both of which are associated with pneumonia, prolonged duration on mechanical ventilation and stay in the intensive care unit (ICU).
Two strategies to manage sedoanalgesia in the ICU have been proposed: one entails sedation protocol directed by nurses, and the other daily interruption of sedation. The intent of both strategies is to individualize and optimize the management of sedation (adjust the level of sedation to an individual target), minimize oversedation and its complications by preventing the accumulation of analgesics and sedatives (tachyphylaxis). Although it seems easy to increase the sedative dose to keep the patient adapted, quiet and calm, excessive sedation is associated with serious complications, including the risk of venous thrombosis, reduced intestinal motility, hypotension, reduced oxygen extraction capacity, inhibition of the protective reflexes of the airways, shortness of clearance of secretions, increased risk of polyneuropathy due to immobility, prolonged mechanical ventilation and ICU stay, with increases in hospitalization costs.
Both strategies have been associated with significant reductions in the duration of mechanical ventilation and ICU stay. The daily interruption strategy has additional advan-

Score	Designation	Description	Exploration
+4	Combative	Combative, violent, immediate danger to staff	Observe the patient
+3	Very agitated	Aggressive attempts to withdraw tubes and catheters	
+2	Agitated	Frequent and purposeless movements, "struggle" with the fan	
+1	Restless	Anxious but not aggressive or vigorous movements	
0	Alert and calm		
-1	Somnolent	Not fully alert but remains (≥10 seconds) awake (eyes open and track) to the call	Call the patient by name and say "open your eyes and look at me"
-2	Mild sedation	Wakes up briefly (<10 seconds) to the call with eye tracking	
-3	Moderate sedation	Movement or eye opening to the call (but with eye tracking)	
-4	Deep sedation	No response to the call, but movement or eye opening to physical stimulation	Encourage the patient by shaking his shoulder or rubbing over the sternal region
-5	Unanswered	No response to voice or physical stimuli	

Table 93.3. **Richmond Agitation Sedation Scale (RASS) for the assessment of sedation in critically ill patients.**

tages, including less psychological distress at discharge (post-traumatic stress disorder) and a lower rate of complications related to mechanical ventilation such as pneumonia and venous thromboembolism. The daily suspension sedation protocol is not indicated in all patients, so its appropriateness must be evaluated in each case, for example, sedoanalgesia should not be suspended until a patient in the acute stage of brain injury, with unstable ICP values or curves, low intracranial compliance or hemodynamic instability, is stabilized. Therefore, these situations should be evaluated individually. In such patients, continuous titration of sedation is preferable.

If the patient cannot be ventilated and is receiving the maximum dose of analgesia and sedation, he or she can be assessed with the use of muscle relaxants. Neuromuscular blockade should be used only when strictly necessary and for the shortest time possible.

Objective assessment of sedoanalgesia with a validated measurement scale is recommended. It must be done systematically by trained personnel. In recent years we have developed powerful tools to assess sedation. Assessment scales with high validity and reliability include the MASS, SAS and RASS scoring systems. The Sedation-Agitation Scale (SAS) and Richmond Agitation Sedation Scale (RASS) (Table 93.3*)* are easy to use and remember, which facilitates their acceptance by the ICU staff. While the RASS has the highest sensitivity and specificity, the most important aspect is its regular utilization, making day-to-day adjustments and recording the results.

It is recommended not to use deep sedation (RASS <-2) routinely. Sedation levels will differ for each patient and should be adapted to their condition and time of evolution. As a general rule, we recommend a RASS score between 0 and -2 [9].

93.3.4 T Thromboembolism Prophylaxis

The options for the prevention of deep vein thrombosis (DVT) in neurological/neurosurgical patients include both mechanical and pharmacological interventions.

Mechanical therapy carries fewer risks. Sequential compression devices should be used when heparin is contraindicated [10] or as an adjuvant. We recommend graduated compression stockings or intermittent pneumatic compression stockings, unless a lower extremity injury prevents their use. Their use should be continued until the patient can walk. Studies have found no changes in mean arterial pressure, ICP or central venous pressure (CVP) with the initiation of sequential pneumatic compression devices; however, lower extremity injury may prevent or limit their use. Elastic bandages or stockings have not demonstrated clear advantages in the prophylaxis of DVT. Those that have demonstrated an advantage, albeit with low levels of prevention, are known as graduated compression stockings which compress more in the calf region and less towards the root of the thigh. Any decision regarding the use of these therapies for the prevention of DVT must weigh the efficacy and risks of the proposed intervention. Heparins should be indicated from the third day if there are not contraindications and Low Molecular Weight Heparins (LMWH) are better than unfractionated. The formal recommendation is LMWH and intermittent pneumatic compression stockings.

93.3.5 H: Head (Head Elevation)

Several studies have shown that raising the head to 30-45° from the horizontal plane can reduce the incidence of gastro-oesophageal reflux and nosocomial pneumonia in mechanically ventilated patients. In patients with additional acute brain injury, raising the head from the horizontal to 30° facilitates venous drainage of the brain, decreases ICP, while cerebral perfusion pressure (CPP), cerebral blood flow (CBF) and global or regional cerebral oxygenation are not affected [11]. Elevation of the head of the bed >30 degrees may exacerbate intracranial hypertension if intra-abdominal pressure is elevated, therefore, it's not recommended without contemporaneous ICP monitoring.
Elevating the head of the bed may decrease CPP by decreasing arterial pressure, so patients should be euvolemic before raising the bed.
Despite available evidence and recommendations, this simple strategy does not have the expected response of the critical care team although it is an inexpensive measure.
It is important to remember that we are talking here about the semi-sitting position and not only maintaining the head raised. To reduce the likelihood of gastro-oesophageal reflux, staff must ensure that the entire trunk is inclined. This requires continuous postural corrections because even sedated patients tend to slide toward the foot of the bed. The semi-sitting position should be maintained in all patients unless there are express contraindications (for example, neurocritically ill patients with postoperative subacute or chronic subdural hematoma should be positioned flat in bed).
Moreover, patients should always have the head in a neutral position to prevent rotation to the right or the left and neck hyperflexion and hyperextension, which would otherwise increase ICP due to alterations in venous drainage [12].

93.3.6 U: Stress Ulcer

Although still discussed, proton pump inhibitors IV are recommended, beceuse they not develop tolerance, are easy to administer, produce a costant inhibition of acid secretion for 24 hours, and are well toletated in case of renal dysfunction. They should be used until you can start a good nutrition enteral caloric intake, then should be discontinued. Prevention of stress ulceration is especially important in patients with respiratory failure, clotting abnormalities, under steroid therapy, or with a history of peptic ulcer because of increased risk of developing gastrointestinal bleeding related to stress. All guidelines recommend early enteral nutrition as a cornerstone in the prevention of stress ulceration.

93.3.7 G: Glycemia Control

Elevated blood glucose levels are associated with poor outcome in critically ill patients. This point has also been demonstrated in several acute neurological diseases such as stroke and head injury.
After the publication of a widely cited article by van der Berghe et al. [13] reporting a decrease in morbidity and mortality in surgical ICU patients who received continuous insulin infusion to maintain a blood glucose level between 80 and 110 mg/dl, many critical care units implemented the routine use of this therapeutic approach.
Less clear is the effect this practice has on patients with acute brain injury, especially since only 4% of patients in this study had a primary neurological condition as a reason for ICU admission. In such patients, even an accidental short period of hypoglycemia

Causes of elevated ICP	Actions
Position	• Elevate head of bed 15-30 degrees to promote cerebral venous drainage • Keep head in neutral position. Avoid rotation of head and neck flexion, which otherwise increase ICP and decrease venous drainage • Secure the endotracheal tube in such a way that it does not compress neck veins • Avoid bending over 90°
Movement	• Keep the patient as still as possible but avoid restraints (the struggle to free themselves could inadvertently lead to a Valsalva manoeuvre, which increases ICP) • If you must turn the patient, make a block to keep the head in the neutral position. Tell the patient to exhale while you're turning him/her to avoid the Valsalva manoeuvre
Hypoxia	• Administer oxygen as ordered (The oxygen reduces cerebral blood perfusion by vasoconstriction and thus decreases the PIC, so it is dangerous because it can cause cerebral ischemia) • If you must use an oropharyngeal airway, not immobilized in place. If the patient cannot expel secretions from the throat and mouth by coughing, a Valsalva manoeuvre will be performed. Evaluate the need to maintain the artificial airway frequently
Aspiration	• Do not aspirate the patient unnecessarily • When you need to aspirate, hyperoxygenate (FiO_2 100%) before starting, then quickly aspirate (no more than 10 seconds) and hyperoxygenate again after aspiration
Noise	• Keep the patient's environment as quiet as possible with minimal sensory stimulation • Before repositioning the patient, make sure there is no danger of tripping over monitor cables and equipment • Limit conversations in the patient's room. Whenever possible, talk with nurses, family, doctors, and other people outside the room. • When you need to talk to the patient, do it quietly and calmly. Let the voices of family members be known when communicating with the patient
Pain, discomfort, non therapeutic contact	• Limit painful procedures. For example, insert an intravenous line to obtain blood samples for lab tests rather than perform repeated venipuncture • Avoid any stress on the tubes and fittings • Limit non-therapeutic contacts • Schedule nursing procedures so that the patient can rest without interruption. When you have to touch the patient, do it gently and reassuringly
Fever	• Keep the patient uncovered or use light sheets if necessary • Make all efforts to maintain normothermia

Table 93.4. Actions to prevent an increase in ICP.

could be a serious and dangerous secondary insult. If we lower serum glucose levels, we will restrict the availability of this fuel just when the injured brain needs it most [14]. Although the optimal blood glucose range has not yet been determined, extreme oscillations should be avoided. It's essential to individualize therapy and ongoing monitoring to try to maintain this value stable.

Subcutaneous insulin administration has proved to be unpredictable and less effective than intravenous administration in critically ill patients. One aspect to consider in subcutaneous administration is the low predictability of absorption, even more so in patients with edema, compromised peripheral perfusion or state of shock.

The role of insulin infusion in patients with acute brain injury continues to be investigated. Several protocols have shown satisfactory nurse-led blood glucose control in critical care units.

Since patients with hypoglycemia may have symptoms that mimic an acute stroke, manifesting focal signs, speech disturbances, and cognitive changes, capillary blood glucose monitoring should be a routine practice in patients with impaired awareness.

In addition to the FAST HUG mnemonic, every effort in neurocritical patient care should be focused on the prevention of secondary brain injury due to increased cerebral oxygen consumption and ICP. Some additional considerations and procedures may be performed to prevent increased intracranial pressure (Table 93.4).

93.4 Airway Care

Since hypoxemia worsens the deleterious effects of cerebral ischemia, patients with acute brain injury should be closely monitored to maintain oxygen saturation >95%. According to Traumatic Coma Data Bank (TCDB) results, hypoxemia is associated with increased morbidity and mortality in severe TBI. The most common causes of hypoxia are partial airway obstruction, hypoventilation, aspiration pneumonia, bronchial secretions, and atelectasis. Patients with decreased level of consciousness or signs of brainstem dysfunction are at increased risk of airway compromise because oropharyngeal motility is impaired and there is loss of protective reflexes [15].

Determining a patient's ability to protect the airway is based on the observation of the following clinical parameters: 1) Glasgow Coma Scale score; 2) presence of gag reflex; 3) ability to swallow oral secretions; and 4) presence of signs of airway obstruction.

The **Glasgow Coma Scale** (GCS) has traditionally been used to classify injury severity. Patients with TBI (GCS ≤8) are classified as having severe brain injury, requiring airway instrumentation with placement of an artificial airway to ensure adequate oxygenation and ventilation. Endotracheal intubation should be performed rapidly with manual immobilization of the cervical spine [16]. All patients with TBI should be assumed potential carriers of cervical spine injury and should be immobilized with a rigid collar until proved otherwise.

The **presence of gag reflex** has traditionally been cited as a valid predictor of the patient's ability to protect their airway. However, the **ability to swallow** or remove oral secretions (effective cough mechanism) could be a more reliable parameter. In general, if the patient is able to tolerate placement of an accessory to the airway (e.g., an oropharyngeal cannula), endotracheal intubation is probably required, unless there is a concomitant condition that depresses sensory reflexes but is easily reversible as hypoglycemia or opioid overdose.

The **airway** also needs to be maintained permeable due to the risk of obstruction from the inability to manage copious secretions or anatomic obstruction due to airway ede-

ma or traumatic injury. While it is assumed that the protective reflexes of the airway are nausea and coughing, many authors argue that the gag reflex is also important.
The principal cause of obstruction in patients with sensory impairment is relaxation of the muscles at the base of the tongue which can drop into the hypopharynx. Also, it is important to assess signs of increased breathing effort such as noisy breathing, or snoring, or accessory muscle utilization.
Coma does not represent a loss of response to noxious stimuli; however, loss of this response may precipitate intracranial hypertension and herniation. Therefore, sedoanalgesia should be given properly during airway manipulation whenever possible.
Other important considerations in airway management are:

- **Placement of the tracheal tube**. The tracheal tube should be placed in the middle of the oral cavity, perpendicular to the plane of the face, and properly set to prevent movement. It is recommended to mark the tracheal tube at the time of placement in order to know its depth, taking the dental arch as a landmark reference. This measure adjusts the tube depth in case of displacement. In this regard, it must be remembered that changes in decubitus can displace a tracheal tube up to 2-3 cm.
- **Securing the endotracheal tube**. In the neurocritically ill patient, the standard of care is particularly important since fixing the tube can cause increased ICP due to jugular venous compression, so straps should be fastened gently. It is recommended that tapes are not wound around the entire neck but are applied only to the face or loose enough to pass a finger between the tape and the face. Patients without teeth and with the mouth kept wide open pose a greater challenge in this regard. Migration of the distal end of the tracheal tube into a main bronchus, inadvertent extubation, inadequate ventilation, oxygenation and suctioning, and physical airway injury are some of the consequences of failure to properly stabilize a tracheal tube. The tracheal tube should be anchored whenever necessary to prevent inadvertent extubation and excessive movement.
- **Tracheal tube cuff pressure**. Monitoring the tracheal tube should ensure that the cuff pressure remains <20 mmHg while allowing a safety margin below the tracheal capillary perfusion pressure (25-35 mmHg). It is generally assumed that 25 mmHg is the maximum acceptable value for lateral pressure by the inflated balloon on the tracheal wall. If the patient shows signs of poor perfusion and/or high airway pressures during mechanical ventilation, the pressure value must be reduced. If pressures >25 mmHg are required to provide effective sealing of the airway during positive pressure ventilation, alternative measures should be evaluated: change to a larger tube, a tube with a longer ball, always considering that the tracheal tube may have shifted, in which case it must be repositioned. Less frequently ball puncture may also occur, with leaking of air and pressure or incontinent balloon valve or both. Cuff pressure should be checked at least once a day and after each procedure on the respiratory system (changes in ventilator mode, aspiration of secretions, tracheal tube movements, changes in decubitus). The cuff should be checked immediately after nitrous oxide anesthesia, as the gas diffuses into the cuff, increasing its pressure.
- **Oral cavity hygiene**. All sorts of micro-organisms reside in the mouth and oropharynx and are transmitted to the lungs via microaspiration. This is the main risk factor for pneumonia associated with an artificial airway. The methods currently used for oral hygiene are: gauze moistened with a mouthwash; a toothbrush with soft bristles and toothpaste; diluted hydrogen peroxide and chlorhexidine. It has been shown that dental plaque can be removed with gentle brushing because it removes the bacteria harbouring dental plaque; however, there are reservoirs of bacteria in the mouth that cannot removed by brushing. There is still disagreement about the most effective method to reduce bacterial colonization of the oral cavity. Mouthwashes

containing alcohol can irritate the oral mucosa and should be avoided. In some studies, chlorhexidine reduced the incidence of pneumonia associated with artificial airways but no conclusive recommendations can be made. Therefore, it appears that chemical decontamination with chlorhexidine as a single intervention may be insufficient to significantly reduce the risk of pneumonia, and that the most important method is by mechanical cleaning, eliminating pharyngeal lakes (accumulation of saliva and secretions from the balloon and the tracheal wall) at least every 8 hours. With regard to pharyngeal lakes, which are primarily responsible for microaspiration, numerous studies recommend the use of tracheal tubes with a continuous suction lumen placed at subglottic level. Even simple measures such as the use of abundant water and aspiration of the proximal airway at frequent intervals significantly reduce bacterial load.

- Strongly discouraged is the use of an oropharyngeal cannula in an intubated patient. The cannula is an accessory for maintaining transitory airway permeability and to prevent the patient from biting the tube. If the patient bites on the tube, we must seek the cause. Oropharyngeal cannulas favour the accumulation of secretions and the occurrence of pressure sores in the oral mucosa, lips and gums.
- Oral care is not only part of a standard of care to decrease infection rates but also provides the patient with comfort; oral hygiene and tracheal tube change should done at least once per nursing turn.
- **Tracheobronchial suctioning** (Table 93.5). Bronchial suctioning often results in an increase in ICP, which may be transient or sustained over time and of varying magnitude. Tracheal stimulation during suction catheter insertion induces cough and systemic responses, resulting in an increase in ICP and mean arterial pressure (MAP). By itself, the application of negative pressure during aspiration increases ICP and heart rate. Hyperventilation to decrease $PaCO_2$ can cushion the increase in ICP during aspiration, but since the effect on ischemic brain areas is not known and potentially dangerous it is not advisable. A valid measure to prevent desaturation during suction aspiration is 1-minute preoxygenation with 100% oxygen; each attempt should take no more than 10 seconds. Two entrances into the airway are sufficient to eliminate all secretions in most cases. The use of saline instillation in the airway is absolutely contraindicated. We have seen that saline instillation only increases the fluidity of the proximal secretions. Furthermore, it can drag the biofilm attached to the tracheal tube (with bacteria) into the airway, and can produce profound atelectasis, pneumonia and desaturation with catastrophic effects. It can also trigger the cough reflex, with a concomitant increase in ICP. A carefully designed aspiration protocol can dampen the response of ICP and preserve adequate cerebral oxygenation.

- Oxygenate at 100% one minute before suctioning
- Adequate sedation can help prevent a drop in CPP and increase in ICP by preventing movement and coughing
- Neuromuscular blockers may attenuate an increase in ICP because they prevent elevation of intrapleural pressure caused by coughing; however, due to the harmful effects of prolonged utilization, their use is reserved for specific events rather than routine suction of secretions
- During the manoeuvre, monitor ICP CPP, EKG and SaO_2
- Do not instil the endotracheal tube routinely
- Each pass of the suction catheter should be no more than 10 seconds
- The number of suction passes should be limited to one or two per session
- Although hyperventilation can cushion the increase in ICP in response to aspiration, it can also be harmful. Only use if intracranial hypertension is severe and exhaled CO_2 control ($PaCO_2$) is >28 mmHg

Table 93.5. **Key points of secretion aspiration.**

- **Lidocaine**. Lidocaine is a commonly used drug with local anesthetic and antiarrhythmic properties. In patients with severe TBI it is usually administered intratracheally to prevent increases in ICP during aspiration of secretions. Experimental models of air embolism and focal brain lesions have shown that lidocaine, administered intravenously, can significantly decrease ICP [17,18]. Arbit et al. in experimental models of focal lesion, observed that lidocaine decreased ICP and increased CPP without inducing a significant change in MAP or CBF. However, due to the limited available evidence, lidocaine cannot be recommended as routine practice in neurocritical patient care.

93.5 Respiratory Care

Once the airway is secured and permeable, the next step is to optimize oxygenation and ventilation.

All patients with neurological injuries should have a PaO_2 >80 mmHg, an arterial saturation of O_2 (SaO_2) >95%, and $PaCO_2$ within normal ranges (35-40 mmHg).

Classical definitions of hypoxemia cite values of PO_2 and SaO_2 <60 mmHg and 90%, respectively. The brain has no oxygen reserves, so the values cited below are recommended by experts and utilized in all protocols.

Hyperventilation. Hyperventilation decreases ICP through hypocapnia-induced vasoconstriction, which also decreases CBF. However, since prophylactic hyperventilation has been associated with worse outcomes it is not recommended.

During the first 24 hours after brain injury, CBF may decreased, with the risk of cerebral ischemia with hyperventilation. Nonetheless, there are at least two situations in which hyperventilation may be advisable.

The first is used as a last option in the treatment of refractory intracranial hypertension. Protocols vary as to when therapy should be instituted, but most agree that it should be begun only when all other therapies have failed (sedation, paralysis, pharmacology, CSF drainage, osmolar therapy).

Another indication for hyperventilation is acute neurologic deterioration (pupillary asymmetry, posture, motor), whose cause is known or suspected to be an expanding intracranial mass. In theory, a brief period of hyperventilation can reduce ICP enough to allow the patient to undergo computed tomography (CT) or transfer to the operating theatre for evacuation of hematoma or contusion; however, hyperventilation remains a controversial issue.

Capnography. Continuous quantitative capnography is recommended in mechanical ventilated neurocritical patients. The value of $ETCO_2$ (CO_2 pressure at end expiration) can be derived from the value of $PaCO_2$ and it is a non-invasive and useful tool. The goal is to maintain $ETCO_2$ between 35 and 40 mmHg.

93.6 Hemodynamic Care

Both inhospital and prehospital hypotension have been shown to have deleterious effects on the prognosis of acute brain injury. Even a single episode of hypotension was associated with increased morbidity, and multiple episodes of hypotension in hospital have a strong impact on mortality.

The optimal blood pressure level in such patients depends on the type of neurologic injury. All guidelines define 90 mmHg as the minimum level of systolic arterial pressure (SAP). This issue arises from studies performed in TBI patients in which CPP >60 mmHg was associated with better outcomes. To achieve this goal, SAP must be maintained at ≤90 mmHg. Higher MAP levels remain controversial.

Maintaining an adequate blood volume may require fluid administration (crystalloid or colloid). Avoid administering hypotonic solutions in the early hours of brain injury (e.g., 5% dextrose and Ringer's lactate) because they exacerbate osmotic brain edema and increase ICP.

If the patient has a catheter for ICP monitoring, it is advisable to place an arterial catheter to measure MAP beat by beat, to maintain CPP >60 mmHg, and to prevent cerebral ischemic events.

93.7 Catheter and Tube Care

We recommend the placement of a **nasogastric or orogastric tube** in all patients with acute brain injury, for the evacuation and decompression of gastric contents in order to prevent aspiration, decrease intra-abdominal pressure and relieve pain and discomfort. An orogastric tube is preferred in the traumatized patient who shows signs or suspected basilar skull fracture due to the risk of brain migration. The use of a nasogastric tube is associated with increased nasopharyngeal colonization as it can cause reflux of gastric contents from the stomach, allowing bacterial migration to the upper airway. It's a known risk factor for the development of sinusitis which, in turn, predisposes the patient to develop "intubation-associated pneumonia." For these reasons it is recommended that the probe is placed via the orogastric route. Feeding tubes that are poorly positioned, displaced or coiled in the pharynx, together with enteral nutrition generates a higher risk of aspiration in critically ill patients. A patient with brain injury may decrease gastric emptying due to diminished gastric motility, thus increasing the risk for aspiration. Clinical assessment is ineffective to detect the inadvertent placement of a nasogastric tube in the tracheobronchial tree. The only reliable way to determine with certainty orogastric tube placement is by radiography. The American Association of Critical Care Nurses recommends using a secondary method to confirm the placement of feeding tubes. There is no consensus about what constitutes a high gastric residual volume, what is the frequency and interval of measurement, etc. Although gastric residual volume is not directly correlated with gastric motility, tracking trends in the gastric residual volume may be useful in clinical decision making [19]. The gastric residual should be measured with a 50-60 ml syringe, deposited into sterile collector and reintroduced. This practice is difficult to execute, so it is not recommended as routine measurement of gastric residual, but to carefully evaluate abdominal semiology: abdominal distention, bowel habits, presence of diarrhea or constipation, presence of nausea or vomiting. Some measures have had conflicting results in small series of patients: the use of flexible, small calibre nasogastric tubes in theory reduced the incidence of gastro-oesophageal reflux or microaspiration, and the location of an enteral tube in the jejunum had variable effects on the rate of nutrient intake and the incidence of pneumonia [20].

All intravenous, intra-arterial lines, electrodes, urinary catheter, etc. should be placed so as to avoid unnecessary stress and stimuli. All tubes generate some degree of discomfort, pain and increase cerebral oxygen consumption.

93.8 Positional Care and Environment

During hospitalization in the ICU nursing tasks involve mobilization of patients for bathing, suctioning, changing sheets, etc. It has been reported that ICP increases significantly during routine procedures in the ICU, and although most of these elevations last a few minutes, sometimes they can prolong the duration of intracranial hypertension and secondary injury may ensue [21]. Therefore, one must be alert to monitoring ICP before, during and after the completion of any procedure and evaluate in all circumstances whether to discontinue the activity.

Like all critically ill patients, the neurocritical patient should be mobilized to prevent the complications of immobilization (decubitus lesions, DVT, retention of bronchial secretions, etc.) Rotation causes frequent desaturation, hypotension and a possible increase in ICP, especially in hypovolemic patients. In such cases, the patient should be placed supine, and wait until the parameters stabilize again. We think that while we must protect the brain, we should not forget the cardiac, respiratory, venous, muscular and other organic systems. We should always keep in mind the risks and benefits in each case. Intracranial hypertension refractory to treatment is an absolute contraindication to lateralization of such patients.

Our goal is save the patient's life with adequate neurological recovery, so that the individual can return to normal life with the least possible sequelae. Also to be borne in mind is the concept of **early rehabilitation** that relies on preventing complications that may arise in the natural history of neurological injury. Limb alignment and passive mobilization should be rigorously maintained. Active exercises of the extremities must be performed as soon as the patient is stable.

Every effort should be undertaken to prevent pressure ulcers. Care should be intensified, especially where there is bone contact with the bed and swollen areas. You can use pillows, air mattresses inflated sequentially, hydrocolloid dressings, silicone sprays, but the use of these or other accessories does not replace patient mobilization. Each unit should be have a protocol in place for pressure ulcer prevention and treatment. One of the essentials to meet this target is proper nutritional support (feeding F).

Another no less important issue is observing the patient's attitude in bed. Does it look comfortable or does the patient require sedoanalgesia due to anxiety, pain, or delirium? There are many measures that can be implemented to avoid patient discomfort. We will ask the family about the position in which the patient usually lies, if there any taste or preference, for example, about the type of pillow the patient uses, or headphones for listening music, etc. Do not forget that patients who wear glasses or hearing aids will need them during hospitalization. Skin contact is very important. Encourage the family to touch and cuddle even if the patient is unconscious. Human contact given by nurses without gloves is desirable. These are all measures that can be very well received and have no influence on infection control.

Give the patient a notion of time, dim the lights and noise at night or allow the use of a clock to help prevent disorientation.

Whenever possible, avoid physical constraints in the agitated patient. These can increase agitation and injury and increase ICP when performing the Valsalva manoeuvre.

Noise in the ICU creates a hostile environment for the patient, with the consequent disturbance of sleep and development of anxiety. Noise in the ICU is produced by alarms, mechanical ventilators, phones and staff conversations. Levels above 80 decibels should be avoided and levels below 35 decibels promote sleep. A complementary measure may be to provide the patient with earplugs to reduce the amount of noise perceived.

The sleep-wake rhythm must be respected as far as possible, trying to get through the night with the least amount of sleep disturbances by procedures, and provide an envi-

ronment with as little light as possible. This should be implemented using a guide to promote the control of noise and a night light in the ICU.
Massage can be an alternative or adjunctive to drug therapy. Back massage for an average of 5-10 minutes or foot massage for 5 minutes can promote relaxation and improve sleep. The combination of acupressure massage has shown the same benefits.
Music therapy can contribute to relaxation and decrease pain. Music can mask the noise. In mechanically ventilated patients, music therapy is associated with a decrease in anxiety, systolic and diastolic blood pressure and heart rate. Because music therapy is an intervention devoid of adverse effects, and has a low cost, it should be considered as a control measure of anxiety and noise in the ICU [22].
Another important and often forgotten item is to inform the patient about their illness and procedures that we will perform. The lack of information or an improper handling of information to the patient augments anxiety. A better understanding of their disease and interventions can improve collaboration and reduce anxiety. It also seems reasonable to avoid inadequate medical or nursing conversations that the patient may overhear.

93.9 Delirium

Patients admitted to the ICU often have an altered state of consciousness, cognition, perception, and time and space disorientation [23]. These conditions are variously described under more than 25 terms: coma, delirium, acute confused state, cognitive dysfunction, acute brain failure, ICU psychosis, encephalopathy, etc. All of them are clinical expressions of a single entity called acute brain dysfunction, a pathophysiological spectrum, which covers three clinical forms: delirium, stupor and coma.
The definition of delirium was set down in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM) of the American Psychiatric Association published in 2000: **altered level of consciousness or cognitive and/or perceptual impairment (disorganized thinking) of acute onset and fluctuating course, accompanied by attention deficit**.
The delirium may precede or follow the onset of stupor and coma. It occurs within hours or days, and is usually reversible. The patient usually shows memory impairment, disorientation, agitation, slurred speech and irrelevant, hallucinations or delusions. The ability to receive, process, store or recall information is compromised.
Delirium has also been associated with an increased risk of complications (decubitus ulcers, pneumonia) and duration of mechanical ventilation. In 2001 published results showed that delirium is an independent risk factor for prolonged ICU stay. In addition, it predisposes survivors to neuropsychological deficits that impair the quality of life and has been shown to generate an increase of 31% or more in hospital costs [20,24,25].
Despite these data, it is recognized as an underdiagnosis in 66-84% of cases. In a survey of 912 doctors between 2001 and 2002 only 5% monitored delirium [20].

93.9.1 Clinical Forms

There may be prodromal symptoms such as anxiety, irritability, and sleep disorders which progress to a frank picture of delirium in 1 to 3 days.
This syndrome is classified according to alertness and psychomotor activity in three ways:

- Hyperactive delirium: the patient is restless, garrulous with disordered and incoherent speech, irritable, agitated, combative, and aggressive and may be a risk to him-

self (tendency to withdraw probes, catheters, and struggle or fall injuries) or other. The literature describes this form as "ICU psychosis" [26].
- Hypoactive delirium: the patient withdraws and has minimal interaction with ICU staff and family, with lethargy, affective flattening, apathy and decreased response to external stimuli. There is often also, as in hyperactive delirium, an altered sleep-wake cycle, temporo-spatial disorientation, difficulty in concentration and memory.
- Mixed delirium with a combination of the two previous types.

93.9.2 Etiology and Pathophysiology

Delirium usually develops in a susceptible patient exposed to one or more triggers.
The predisposing factors are present on admission to hospital and indicate baseline vulnerability to delirium. These include: age >70 years, male gender, referral from an institution, prior cognitive impairment or dementia, history of depression, malnutrition, hearing loss, reduced visual acuity, cerebrovascular events, epilepsy, habitual use of psychoactive medications, history of alcohol abuse or other drug consumption, and coexisting medical conditions such as hypo- or hyperthyroidism, AIDS, neurologic, hepatic, renal and or congestive heart failure (Table 93.6).
Precipitating factors are noxious stimuli or injury related to hospitalization that trigger the onset of delirium, including primary neurological disorders, infection, shock, hypo- or hyperthermia, hypoxia, dehydration, electrolyte abnormalities, surgery, moderate to severe pain, hypoglycemia, exposure to pharmacological agents (opioids, benzodiazepines, anticholinergics, corticosteroids at a dose of 40 mg/day or more of prednisone or equivalent), removal of substances, mechanical ventilation, central venous or bladder catheterization, constipation, urinary bladder overdistension and sleep deprivation.
A recent study [27] reported that the most important risk factors in the ICU were older age, severity of disease, and administered doses of benzodiazepines.
The exact pathophysiological mechanisms involved in the development and progression of delirium are unknown, although a number of avenues of study are being pursued.

CNS disorders	• Head injury • Seizures • Postictal state • Vascular pathology
Metabolic disorders	• Kidney failure • Liver failure • Anemia • Hypoxia • Hypoglycemia • Thiamine deficiency • Endocrinopathies • Water and electrolyte imbalance • Acid-base disorders
Cardiopulmonary disorders	• Myocardial infarction • Congestive heart failure • Arrhythmias • Shock • Respiratory failure
Systemic diseases	• Substance intoxication or withdrawal • Infection • Neoplasms • Severe trauma • Sleep deprivation • Deregulation of temperature • Post-operative

Table 93.6. **Clinical conditions associated with delirium.**

93.9.3 Diagnostic and Monitoring Methods

Delirium is often not recognized or confused with other disorders in over 84% of cases. Failure in the diagnosis may be explained by inadequate assessment of cognitive functions in an uncooperative or mechanically ventilated patient. In addi-

tion, signs that suggest the presence of this syndrome can be subtle or attributed to other causes.

The DSM recommends the Confusion Assessment Method (CAM) in the diagnosis of delirium, although other scales can be used: Intensive Care Delirium Screening Checklist, Delirium Cognitive and Cognitive Test for Delirium Abbreviated scale. The CAM was validated in 2001 for use in ICUs, including patients receiving mechanical ventilation (CAM-ICU). It's effective and can be implemented by minimally trained doctors or nurses.

CAM-ICU assesses four criteria, three of which must be met for a diagnosis of delirium: (A or D) + B + C

where:

- A: Altered level of consciousness.
- B: Acute change or fluctuation in mental status.
- C: Attention deficit.
- D: Disorganized thinking.

When possible, it will be important to identify the baseline cognitive functional status and differentiate chronic cognitive disorders, mainly dementia and oligophrenia. Dementia is established slowly, over weeks or months; it refers to a lack of intellectual skills and is diagnosed when there is an alteration in memory and at least one of the following: aphasia, apraxia, agnosia or disturbance of executive functions. Its evolution can be progressive, stable or reversible, depending on the disease and availability of effective treatments. It is important to note that patients with dementia may also suffer hallucinations. The CAM-ICU has been shown to be valid and reliable even in these patients.

First, use the Richmond Agitation-Sedation Scale (RASS) to assess the level of consciousness. Patients with a score of -4 (stupor) and -5 (coma) cannot be evaluated, and the diagnosis should be reconsidered when it detects a change in this score.

- The first criterion (A) is to confirm the presence of an altered level of consciousness, as evidenced by any nonzero score (0 = alert and calm) on the RASS.
- The second criterion (B) is to confirm that the change in the level of awareness is new (within 24 hours) and/or fluctuating. For example, a patient drowsy until an hour ago (score -1) is now very agitated (score +3). The new level of consciousness is "alert and calm" and therefore meets criterion A, and since has appeared in acute form it also meets criterion B.
- The third criterion (C), attention, is assessed using the Attention Screening Examination (ASE), and can it be visual or auditory, ensuring that the patient understands the task and can hear or see properly.
- The auditory method entails reading a series of ten letters, such as S, A, H, E, V, A, A, R, A, T and asking the patient to pronounce the letter "A". The visual method involves showing an initial series of five figures, and then a new series of ten figures, five new and five interleaved originally filed, and asking the patient to indicate when a figure is repeated. With either method, the test is positive (attention deficit) when the score is <8 (three or more errors). If the patient cannot speak, he or she may respond by raising their hand or nodding their head, making it possible to evaluate also patients under mechanical ventilation.

Group A	Group B
• Can a stone float on water? • Are there fishes in the sea? • Does one kilo weigh more than two kilos? • Can you use a hammer to hit a nail?	• Can a leaf float on water? • Are there elephants in the sea? • Do two kilos weigh more than one kilo? • Can you use a hammer to cut wood?

Table 93.7. Questions (alternating group A and group B).

- The fourth criterion (D) investigates the presence of disorganized or incoherent thinking which may be evidenced by two or more incorrect answers to four questions like the following:

Questions (alternating group A and group B): see Table 93.7.

93.9.4 Treatment

Proper management of delirium involves prevention, early diagnosis and pharmacological treatment. This requires frequent monitoring of all patients admitted to the ICU, mainly those with predisposing factors: age >70 years, prior cognitive impairment, hearing loss, history of alcohol or drug use, neurological disorders, etc.

A major strategy for delirium prevention is to avoid oversedation, stop and re-evaluate daily requirement, and consider the use of short-acting drugs in case of frequent or continuous administration. Clinical guidelines recommend the use of protocols and scales to improve the dosage of sedatives and analgesics by keeping the patient calm and alert with lowest doses of sedative drugs.

These manoeuvres can help us to reorient the patient: promote the sleep-wake cycle, avoid excessive noise and artificial light at night time, minimize pain, encourage physical therapy and early mobilization, early removal of catheters, optimize contact with the family, and promote visual and auditory stimulation, facilitate temporal-spatial orientation through the provision of eyeglasses, clock, calendar, music headset, radio, photographs of close relatives, favourite food or objects. These interventions reduce by up to 40% the incidence of delirium, and should be part of prevention and treatment strategies.

Once delirium has been diagnosed, we will try to minimize or eliminate all potential precipitating factors. It is imperative to reverse shock, hypoxia, dehydration, abnormalities of sodium and glucose, thiamine replacement, identify a distended bladder or other causes of pain, and remove drugs (anticholinergics, corticosteroids) before selecting a specific drug.

Health personnel and family members should maintain a non-confrontational dialogue with the patient, who displays altered opinion and perception, and not to exacerbate or trigger agitation. The most effective way is to listen and respond with attitudes directed to contain general discomfort, showing that he or she is in a safe environment.

Physical restraint may be necessary in cases of severe agitation to prevent the patient from removing catheters, tubes or probes, and to prevent injury to self or to the attending staff. It will always be a temporary measure which will be reassessed frequently while awaiting the action of drug treatment.

93.10 Eye Care

Some 20-42% of patients develop keratopathies during hospitalization in the ICU. If not treated quickly, it can progress to microbial keratitis, corneal ulcers and subsequent loss of vision, all of which can have devastating effects on the subsequent quality of life.

The ocular surface in healthy individuals is protected by natural defence mechanisms such as the bactericidal effect of the tear film, blinking and proper closure of the eyelids. Depression of consciousness, the use of muscle relaxants and sedation in mechanically ventilated patients contributes to a lack of lid closure caused by the decrease in the tonic contraction of the eye muscles (lagophthalmos). Therefore, the lack of protection

mechanisms and the constant exposure of the ocular surface to environmental pathogens put the ICU patient at a high risk for developing keratopathies.
The most widely studied methods for the prevention of keratitis are the application of lubricating drops and ointments, closing the eyes with duct tape, and humidity chambers. The use of swimming goggles and regular moistening of eyelids with gauze soaked in sterile water provides a more effective humidity chamber than the combination of ocular lubricants and placing tape over the lid [28,29], possibly due to the simplicity of implementation and ease of maintenance, because the humidity chambers should not be applied every 2 hours but placed and allowed to stay put, removed for only short periods of time to clean the eyes and evaluate them. With the application of simple protocols, keratopathies can be prevented and the care of coma patients improved.

93.11 Fever

Fever is an independent predictor of poor outcome in TBI. Hyperthermia or fever is commonly encountered in neurocritical patients. According to published reports the incidence varies between 25 and 50%. It is known that the brain is enclosed in a rigid case and has a high metabolic demand and irrigation, at a temperature approximately 1-2°C higher than the rest of the body. So in a patient with fever and neurological injury, the cerebral temperature is higher, with increased brain metabolism. This increased metabolism leads to an increase in CBF, with the subsequent increase in cerebral blood volume, causing ICP to rise.
The use of lower thresholds for treating hyperthermia is recommended in patients with intracranial hypertension, and every effort should be made to maintain body temperature <37.5°C [30].
Temperature control should be a primary mechanism for controlling ICP [31].
Drug treatment should be combined with physical measures to control hyperthermia. The application of ice or cold water directly to the patient's body causes peripheral vasoconstriction, inhibiting the dissipation of body heat and reduction of fever. It also can cause chills and muscle contractions which produce more heat and shock, in turn, generating a catecholaminergic storm and elevated ICP This situation can be resolved with profound sedoanalgesia.
The most effective cooling method is by combining convection and evaporation. This is achieved by spraying the patient with warm water or placing a sheet saturated with warm water over the patient and using a fan to promote evaporation.
After 60 minutes, at which time the body temperature should have decreased; the patient should be dried and the sheets changed so as not to cause other injuries. This manoeuvre should be performed as often as necessary until the temperature is reduced [32,33].

93.12 Intracranial Pressure Monitoring

The most common types of monitoring are with an intraventricular catheter or an intraparenchymal optic fibre sensor. The intraparenchymal sensor does not pose major challenges for measurement, whereas the intraventricular catheter requires highly trained personnel. That is why we refer to this method in detail.

93.12.1 Calibration of the Intraventricular System

The transducer must be set to zero of atmospheric environment and the ICP device re-calibrated according to the specifications of each team once per shift and each time the patient is mobilized.
According to U.S. National Institute of Health (NIH) guidelines, the pressure transducer of an intraventricular catheter should be located at the height of the patient's face (i.e., the foramen of Monro) at the level of the external auditory meatus or lateral canthus. Other sources say that it should be placed at the midpoint between the lateral canthus and the tragus of the ear. The important thing is that the transducer should always be in the same point. It is therefore good practice to mark the anatomic place of localization.

Intraventricular System Maintenance and General Care

- It is essential to adopt strict aseptic technique during manoeuvres of CSF drainage and sampling. We recommend closed drainage systems, always keeping the set open to the pressure transducer for continuous monitoring, only opening it when we wish to perform therapeutic drainage. Maintain the cleanliness of the system.
- The insertion site must be clean, dry and occlusive. The frequency and type of healing can vary. In general, minimum care should be performed once a day and any time the site is wet or dirty. If the gauze is moist with leaking CSF, this must be reported as it can be a sign of a leak in the system.
- Secure the catheter to the site. It is preferable to place a bandage with a brimmed hat for maximum safety of catheter fixation. A catheter that moves or is dislodged will lead to greater morbidity, increased risk of infection and higher costs.
- The U.S. Centers for Disease Control and Prevention (CDC) advises against the application of antibiotic ointment on the site of insertion of the ventriculostomy.
- It is advisable to carry out cytochemical and bacteriological examination of the CSF in all cases after the third day of monitoring. Order tests for determining lactic acid levels in CSF (levels >4 mmol/l are highly suspicious of meningitis in neurosurgical patients).
- Perform therapeutic drainage if the displayed value does not represent the true ICP after opening the system.
- In case of decompressive craniotomy or CSF loss, monitored ICP values will not reflect the severity of cerebral edema.
- Movements or changes in patient position must be taken into account and the system re-calibrated by adjusting the height again.
- Do not perform excessive drainage, as this manoeuvre can provoke ventricular collapse and, eventually, intraventricular hemorrhage ex vacuo) or reflux (to the patient's ventricular system, with the risk of infection of the CNS).
- The collection bag should be emptied when three-quarters full or more than 24 hours has elapsed without any casting. The stopcock should be disinfected and sterile gloves used to maintain cleanliness of site drainage.
- The volume of CSF drainage should be recorded. Alert the physician when the rate exceeds 20 ml/h.
- Record characteristics of the CSF (appearance and colour). Opacification heralds the possibility of infection.
- Do not secure the catheter to the bed to measure ICP as this will interfere with patient mobilization.
- Do not instil any fluid through the catheter or try to permeate the occlusion by applying pressure.
- Do not re-insert a catheter that has become dislodged.

93.13 CSF Sampling

CSF samples should be obtained from the port of the stopcock closest to the patient. First, you must disinfect the top of the stopcock with alcohol iodine for one minute. For this manoeuvre you should use an aseptic technique, sterile gloves and mask. After donning the sterile gloves, open the system and place the top of the stopcock on sterile gauze. The time to take the sample should not be more than 3 minutes. Sending the CSF collection bag directly to the laboratory for culture may be an alternative to sampling. Physicochemical analysis is then ordered for Gram staining and culture, glucose and lactic acid (>4 mg% suspected postoperative bacterial infection) determinations. Clinical suspicion is warranted. Note the presence of fever and/or neurological deterioration not attributable to other causes.

93.14 Measurement of ICP

With a ventriculostomy, ICP can be measured by connecting a transducer to the drainage system or to the same catheter used to drain CSF. To measure through the catheter, once the system has been calibrated (at the level of the Monro aqueduct), the catheter must be raised until there is a "short" column of liquid in the drainage system. The point where the liquid column is short is the level of ICP, it and can be estimated with a ruler in cmH_2O. Divide this value by 1.36 to obtain the value in mmHg.
Each time the bed is raised or lowered the system has to be re-set to zero to prevent emptying of the ventricles or reflux of CSF into the ventricles.
Measurement of ICP with a transducer is preferable since it avoids handling of the liquid column and enables constant assessment of the ICP value and shape of the curve.

93.15 CSF Drainage

The Monro-Kellie hypothesis states that if one of the components of intracranial content increases, the others must decrease to maintain ICP stable. Therefore, a decrease in one of the three components will reduce ICP. In 1960, Lundberg showed that ICP decreases if we remove CSF through ventriculostomy. The withdrawal of only 3 ml of CSF decreased ICP by 10.1% relative to baseline. CSF drainage protocols include "time-dependent" (leave the drain open for 5 minutes, then close), "volume-dependent" (drain 5 ml and then close) and continuous drainage (leave the system open all the time but close it at intervals to read the ICP).
With a ventriculostomy we need to know the height at which we should place the drain. The height of the chamber determines whether the CSF will drain to the outside or not. A chamber with high CSF pressure that exceeds the pressure of the height of the liquid column allows the fluid to exit freely. A chamber with low pressure (lower than the height of the liquid column) will not permit CSF drainage. In conclusion, CSF drains only if the pressure in the ventricles exceeds the pressure in the liquid column. Therefore, the cmH_2O (ICP) must be specifically recorded as the threshold for drainage.
Two situations should be distinguished:

- **Control of intracranial hypertension (ICH)**. The catheters used for controlling ICH should be kept closed and opened only to control ICH (a first level measure),

monitoring the amount drained by hours: 20 ml/h is the limit, beyond which there is the risk of ventricular collapse. On the other hand, opening of drainage should be provided against a positive pressure that will be achieved by raising the drip chamber above the zero level, as many inches as specified by the neurosurgeon.

- **Control of hydrocephalus**. If the control catheters for hydrocephalus of various origin are left permanently open, draining against a preset pressure will be adjusted according to ventricular size given by computed tomography (CT) and the patient's clinical condition. The measure of ICP in these cases is less important and is recorded every hour [34].

93.16 Intraventricular System Dysfunction

- **System blockage or malfunction**. Contact the attending neurosurgeon; do not instil any solution through the catheter without prior consultation with him. A cranial CT scan should be obtained to check the current position of the catheter (this serves to mark the position of any catheter movement during transfer for imaging studies). In the context of subarachnoid hemorrhage (SAH), the dysfunction may be due to obstruction by clots (sometimes true plugs at the intraventricular blood level). There is recent experience with the infusion of fibrinolytics through the catheter to improve outcomes, allowing better control of ICP.
- **Section or rupture of the catheter**. The catheter should be clamped proximally and evaluated together with the attending neurosurgeon and according to the patient's clinical condition.
- **Opening the sterile system**. Consider the system useless if a leak or disconnection occurs. Close the stopcock closest to the patient to occlude CSF drainage and report immediately. Replace the system using an aseptic technique.
- **Damped wave**. Note the presence of bubbles or leaking connections. If you see bubbles, close the port that communicates with the patient in the three-way stopcock closest to the head and flush the system with sterile saline solution from the same key to the collection bag. Always use aseptic technique: antisepsis 3 minutes for the stopcock, sterile gloves and mask.

93.17 Transfers of Patients With ICP Monitoring

Intra- or interhospital transfers are a risky practice because they may adversely affect the results, generating secondary injury. They should only be performed when the patient is adequately resuscitated and hemodynamically stable. It involves trained personnel and adequate monitoring, at least EKG monitoring and pulse oximetry. The ICP measurement equipment must be open and closed only when the patient is transferred to another table or bed. You should always calibrate the system at the level of the foramen of Monro, regardless of the position of the bed or couch.

Avoid manual hyperventilation and **always** carry supplemental oxygen. It is desirable that during transfer the patient receives the same drug infusion as in the referring service in order to maintain intracranial hemodynamics. All patients must travel accompanied by a doctor, nurse and orderly.

93.18 Continuing Neurological Assessment

Although neurological assessment is part of the physical exam, a complete neurological assessment is beyond the scope of this chapter. We will only refer to continuous neurological monitoring by the nurses in the ICU.

The primary objective of neurological assessment is to detect any changes early during hospitalization and to avoid overlooking a new brain injury or deterioration. It is important to remember that neurological deterioration often occurs unnoticed, and time to treatment will determine its subsequent evolution. So the more frequently you perform neurological evaluation, the faster the diagnosis and treatment and the better the evolution of these patients.

The causes of neurological impairment are not only neurological injury but also response to metabolic disorders, intoxication, and hemodynamic deterioration. It is important to remember that poisoning can occur in parallel with brain injury and that it is dangerous to attribute to alcohol or drugs changes in mental status without imaging. Focal deficits should never be attributed to intoxication.

Initial assessment of the level of consciousness is critical for evaluating pupillary response and motor function. A more complete neurological examination should be performed as part of tertiary assessment.

93.18.1 Level of Consciousness. Glasgow Coma Scale (GCS)

The GCS is the universally accepted scale for assessing consciousness. It is simple and can be performed quickly and repeatedly, it is widely understood and is recommended by many guidelines and protocols. The GCS is not a neurological examination in itself (motor evaluation only reflects the best response) and should not be substituted for such.

Originally developed to monitor the progress of the patient with acute TBI, it is now considered a useful tool to assess all patients at potential risk of neurological impairment, regardless of their primary pathology.

The motor component of the GCS (more than the sum of the total score) has been shown to be an equal or better predictor of outcome in patients with brain injury.

Despite the scale's apparent simplicity, misunderstandings can occur in its application. "Quick and easy to use" does not denote insignificance. In practice, although staff is trained to mark the correct box on the assessment sheet, few nurses appreciate the mechanism underlying the valuation, which can prompt appropriate action when the patient's condition changes. It is not uncommon that a change in the patient's neurological status is not detected early, which could save lives or prevent future brain insults [35].

You should record what you see, avoiding the temptation to adjust the information to the clinical history data. Another potential error is to not encourage patients sufficiently to obtain a true reflection of their neurological response.

Conditions for assessing the GCS. Always obtain and record the best response and apply the scale once the patient is stabilized, without evidence of cardiorespiratory instability (hypotension, hypoxemia, hypercapnia). Once the patient is adequately ventilated and oxygenated, only then can the GCS be applied. We must rule out toxic (alcohol, drugs), CNS depressants and metabolic disorders (hypoglycemia, hyponatremia, etc.) before and after performing evaluation with the scale.

How to assess the best eye response. Evaluation with the GCS begins by observing the patient. You should speak in a normal tone and, if necessary, gradually increase the vol-

ume of your voice. If no response is obtained, you can touch or gently shake the patient's shoulder. If there is no response to this manoeuvre, a deeper stimulus is required. Evaluation of the ocular peripheral stimulus is preferred because a central stimulus will cause the patient to close his eyes and wince, which is not the answer we are trying to elicit. Before applying any stimulus, it is essential to explain to the patient and family exactly what will be done and why, apologizing in advance for the pain you are going to cause (even if the patient is unconscious). Peripheral stimulus is delivered by applying pressure with a pen on the lateral aspect of the second or third finger near the nail, rotating the point of stimulation at each assessment. Pain should be applied gradually for a maximum of 10 seconds. A second opinion should be obtained if the expected response is not elicited. In some cases a nociceptive stimulus is applied to the finger nail bed or pressure on the sternum (rubbing it injures the tissues), but these stimuli can generate residual pain.

Important points to consider:

- If the patient's eyes are closed as a result of edema or facial fractures, 1 point is assigned to the general sum and this should be recorded as "NV" (no value), "E" (edema) or the letter that the team agrees on and knows. In such cases an accurate assessment of the patient's arousal level is impossible to make.
- One point must be subtracted if the patient's eyes are closed because he is sleeping. A common mistake is "eye opening to the call" when the patient is physiologically asleep instead of being depressed.

How to assess the best verbal response. Ask the patient about who he is where and why, the present year and month. If these questions are answered satisfactorily, the patient is oriented.

If any of these questions are answered incorrectly, the situation is unclear. If the patient was recently transferred from another hospital, he or she will have an understandable degree of disorientation; nonetheless, a subtle disorientation may be an early indicator of neurological impairment. Typically, patients who do, deteriorate with time, place and people, in that order.

Important points to consider:

- If the patient is unable to respond due to the presence of a tracheostomy or tracheal tube, 1 point is assigned in the overall sum and should be recorded on the form with a letter "T" (tracheal tube) or the letter that the group should agree on and learn.
- If the patient has dysphasia, this must be recorded with the letter "D" (dysphasia).
- A reliable baseline observational record is the most important element of the GCS and allows early identification of signs of deterioration. For this reason, each operator must apply the same stimulus in the same way and examine each patient in the same way.
- A criticism of GCS is that patients cannot be adequately assessed if they have difficulty in communicating related to age (cannot be used in children under age 5 years), language (do not understand the same language), or any pre-existing condition that may affect speech and learning difficulties or stroke. It is important not to try to adapt, change the form or write to try to "fit it" to the patient. Information obtained from the family, such as the patient's preferred name or details of any previous deficits, may be important for a reliable assessment.

How to assess the best motor response. To be sure that the patient obeys orders, ask him to perform various movements, for example, sticking out the tongue, raising the eyebrows, showing the teeth or raising the thumb. If you are prompted to "squeeze the hand", this also entails releasing it to discontinue a primitive grasp reflex. It is good practice for the patient to obey two different commands, so that one is sure that at least he can obey the same command twice.

Supraorbital pressure	Supraorbital pressure was identified as the "gold standard" but should only be used when you have trained staff to implement it properly. Just below the arc of the eyebrow, there is a small notch through which a branch of the facial nerve runs. The operator's hands rest on the patient's head and the surface of the thumb or knuckle is placed on the supraorbital rim below the eyebrow. The pressure should be gradually increased for up to 30 seconds. This is contraindicated if there is damage or orbital fracture of the skull base (in which case the pressure on the trapezius is an alternative)
Pressure on the margin of the jaw	Pressure is applied to the angle of the jaw. The surface of the thumb rests on the curve of the junction of the maxilla and mandible and the pressure is gradually increased for a maximum of 30 seconds
Pressure on the trapezius	The trapezius muscle extends across the back of the shoulders from the middle of the neck. Keep the muscle between the thumb and index finger and apply gradually increased pressure for a maximum of 30 seconds. The trapezius muscle has motor and sensory components and no risk of causing a spinal reflex to stimulation

Table 93.8. **Implementing central nociceptive stimuli**.

Apply a central nociceptive stimulus to assess the response to pain. It should only be applied if the patient does not respond to verbal commands and it need not be applied if the patient is oriented, for example, when trying to withdraw an oxygen mask or a nasogastric tube.

To classify as a "location", the patient must move his hand toward the point of the stimulus, putting his hand to his chin, crossing the midline, coordinated in an obvious attempt to remove the cause of pain. It is useful to start with the arms in a flexed position of 30° to minimize any abnormality when assessing abnormal flexion or extension.

The National Neuroscience Benchmarking Group recognizes three methods for applying a central painful stimulus: supraorbital pressure; the pressure in the angle of the jaw; and the pressure on the trapezius muscle (Table 93.8). Other methods of applying central stimulus are not recommended because they can only generate a peripheral reflex response.

The answer "taken the pain" is obtained from a central painful stimulus, when the patient bends his arm above the elbow flexion as a reflection of normal, but fails to locate the source of pain.

Abnormal bending, also known as decorticate posture, can be recognized because it is a slower response to painful stimuli. The patient flexes the upper arm and wrist separately. Sometimes the thumbs are placed between the toes.

Abnormal extension or decerebrate posture is characterized by extension of the upper limbs and internal rotation of the shoulder and wrist. Sometimes the legs are also in extension, with the feet pointing downwards.

If there is no motor response, we must ensure that an appropriate stimulus is applied. A patient cannot respond due to illness or injury local (e.g., spinal trauma).

Important points to consider:

- Always record the best answer of the upper limbs by using a central painful stimulus: when assessing motor response the brain is being measured and not the answer cord. A spinal reflex can cause a sudden bending of the limbs and can occur even when brain death has been certified.
- Operators should be aware of their own nonverbal behaviour, since the patient may simply imitate what they see, leading to misinterpretation.

The level of consciousness is the most sensitive indicator of neurological impairment. Unless the patient receives sedatives or anesthetics, with the GCS it may be possible to identify deterioration before changes occur in the pupils or in vital signs.

When communicating the GCS score, it should be done in terms of its individual components, e.g., O3, V2, M4, indicating that the patient opens his eyes to speech, a verbal response is incomprehensible, and flexes to painful stimulation.
A decline of 1 point in motor response or 2 points in the total GCS score is clinically significant and should be reported immediately. To ensure consistency, the same member of the staff should conduct the assessment in a work shift. On delivery, the incoming shift nurse should compare the recorded with new GCS scores. Without such continuity, subtle changes may be overlooked.
Patients often give subtle clues of deterioration, such as being less communicative, with slow responses, and these are particularly related to changes in behaviour. Be aware of these changes and note them on the medical chart.
Lack of confidence in completing the registration can be influenced by previous assessments. Always ask a colleague to revaluate if you are unsure of the procedure. GCS should not be used in isolation. Instead, it should be used in conjunction with other aspects of neurological assessment and pupillary reactivity, the response of members, etc.

93.18.2 Pupils

This procedure should assess the size, symmetry and reactivity to light of both pupils. Any change in these parameters is a late sign of increased ICP. It must be remembered that pupillary reactivity is the only way to monitor the neurological status of a sedated patient. A unilaterally dilated pupil, either slow or fast, is an indicator that the swelling or bruising is getting worse and is compressing the oculomotor cranial nerve through the foramen magnum.
Pupillary asymmetry, loss of reactivity to light or unilateral or bilateral dilatation should raise the suspicion of brain herniation until proven otherwise. It must be remembered that some patients may have a pre-existing eye condition that causes a unilateral dilated pupil, like a waterfall or localized injury; however, although a traumatic optic neuropathy can cause a unilateral pupil to be dilated and not reactive, the presence of local orbital trauma should not be overlooked as an intracranial lesion.

Procedure	Basis
Inform the patient, whether conscious or not, about who will look into his eyes with a light and explain the procedure	Helps reduce anxiety. Ensure, as far as possible, that the patient consents and understands the procedure
Reduce the light overhead or ceiling to observe pupillary reactivity	Provides a better view of the eyes and reaction to light stimulation
Wash your hands thoroughly	Prevents contamination of the eyes and reduces the risk of infection
Keep the patient's eyes open and observe the size, shape and symmetry of the pupils	Normal pupils are round, usually centralized and have a diameter of 1.5-6.0 mm
Keep one eye open and move the light from the outside to the pupil. This should cause rapid pupillary constriction (direct response to light)	To assess pupil reactivity to light. A normal response indicates no injury or pressure on the third cranial or trunk regulating pupillary reactivity
Record any unusual movements such as nystagmus gaze deviation	To assess cranial nerve damage
Repeat the test in the opposite eye	To assess the equality of the reaction and ensure that all areas are working properly

Table 93.9. **Guidelines for the assessment of pupillary reactivity to light.**

Before pupillary signs of cerebral herniation, immediate efforts should be made to reduce ICP while performing diagnostic studies. Urgent intervention at this time can make a significant difference in patient outcome.

Table 93.9 provides a guide for the assessment of pupillary reactivity to light and the basics of the procedure.

Important points to consider:

- If both eyes are closed due to high orbital edema, record this with the letter "E" (edema)
- Rapid pupillary reactivity is recorded as "+" or "R" (reactive). Nonreactive pupils as "-" or "NR" (not reactive) and slow pupils as "L". Each service must formally record the acronym.
- Use a small pen-type flashlight not an ophthalmoscope.
- Slight differences in pupil size may be normal.
- It is not uncommon for healthy people to have different sized pupils.
- Very small pupils (1-2 mm) may suggest the use of opiates, benzodiazepines or barbiturates.
- The use of eye drops such as atropine can dilate the pupils.

93.19 Motor System

Although the GCS only assesses the response of the best extremity, it is necessary to conduct a comprehensive assessment. Hemiparesis, monoparesis, quadriparesis or paraparesis may reflect intracranial or spinal injury and these are not mutually exclusive. Evaluation of the response of extremities provides details on the geographical distribution of the injury and it is an important consideration when performing full neurologic assessment. Each extremity should be valued separately. Ask the patient to hold his arms out in front of him, then look signs of weakness or deviation of the limb. Rate the legs by asking the patient to push his feet toward the evaluator or lift his legs off the bed and keep them bent. In patients unresponsive to a verbal call, a nociceptive stimulus should be applied to a distal region of both legs and arms. If you notice "withdrawal" of the limb, nociceptive stimulation should be performed in a central location to differentiate "withdrawal" from "localization". The response of "localization" (motor response of 5 points) is reached when a limb crosses the midline to the contralateral stimulus or when the arm is raised above the jaw to a stimulus such as supraorbital pressure.

93.20 Vital Signs

The final warning is the triad or Cushing reflex, a classic set of signs and symptoms that indicate that IC is dangerously high and the patient is at risk of life-threatening cerebral herniation. This reflex is a very late sign and is characterized by hypertension, bradycardia and irregular breathing.

Hypertension. The patient typically has high systolic pressure combined with a pulse pressure (wide difference between systolic and diastolic). This causes systemic vasoconstriction and hypertension.

Bradycardia. The heart rate can drop to 35-50 beats per minute. This allows each systole to pump more blood at higher pressure, forcing the entrance of blood to the brain during the peak systolic blood pressure.

Irregular breathing. The pressure on the respiratory centre on the lower and upper spine causes deterioration of the respiratory pattern. The following patterns can be seen:

- Cheyne-Stokes.
- Hyperventilation which removes carbon dioxide, and cerebral vessels constrict in an attempt to reduce ICP.
- Breathing in clusters: periods of rapid, irregular and noisy breathing alternating with periods of apnea.

93.21 Frequency of Evaluation

The 2003 NICE Guidelines recommend that patients with TBI admitted to an emergency department with a GCS score <15 must be observed hourly to determine whether the score improve. Patients admitted with GCS of 15 points must be evaluated every half hour for 2 hours, every hour for 4 hours and every 2 hours thereafter.

Although this is a useful guide in clinical areas, the neurological condition usually dictates the frequency of observations, and any adverse change in the patient's condition is an indicator to increase the frequency of observations.

The quality of observation is as important as quantity. Discontinuation of neurologic assessment depends on the individual clinical trial, but it is reasonable to suspend it when the patient has been stable for a couple of days and the initial condition has been resolved.

93.22 Conclusions

Neurocritically ill patients account for a growing fraction of ICU admissions due to the changing sociocultural characteristics of the population and new technologies that allow more interventions in high-risk patients.

The treatment of these patients is based primarily on preventing secondary injury and treating the complications that may arise during the course of the illness. A multidisciplinary team must be able to work together, with clear objectives and protocols to provide the best care for our patients.

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94 Outcome Rating Scales in Neuroinsensivism

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94.1 Introduction

An important aspect as the classification and initial assessment of brain injury is the accurate evaluation of the results. The effectiveness of many interventions during the acute care will depend on the evaluation of the results.
When evaluating results we must consider not only physical but also cognitive, mental, and social disabilities. Many of the survivors have deficits (neurological and/or cognitive) that interfere with quality of life.
Rating scales are useful tools to attempt to quantify outcomes in a reliable and accurate way in patients who have suffered neurological injury.
Then we'll describe the most used.

94.2 Outcome Rating Scales

94.2.1 GOS (Glasgow Outcome Scale)

It is still the most used outcome rating scale to evaluate neurological injuries (traumatic and non-traumatic). It assesses general social skills (or dependence) of the patients, taking into account the combined effect of mental and neurological deficit [1]. It determines the independency of a person in the society and the return to the previous life style. Different studies have shown that it is a reliable scale and easily used by different observers.
The GOS includes five categories:

1. Death.
2. Vegetative state(VS): patients can not interact with the environment, they do not respond.
3. Severe disability: patients are able to follow orders, they can not live independently.
4. Moderate disability: patients can live independently, they can not return to work or school.
5. Good recovery: patients are able to return to work or school.

For statistical purposes, the GOS can be dichotomized in Poor outcomes (Dead, VS, severe disability) and Good outcomes (mild disability and good recovery). The GOS allows comparing results of patients treated with different treatments protocols or in different sites. One of the main criticisms is that its simplicity makes it relatively insensitive to changes in recovery that are not enough to make a change in the category.

94.2.2 GOS-E (Glasgow Outcome Scale Extended)

The GOS-E was developed to address the limitations of the original GOS due to the lack of a structured interview.

1. Dead.
2. Vegetative state.
3. Lower severe disability.
4. Upper severe disability
5. Lower moderate disability.
6. Upper moderate disability.
7. Lower good recovery.
8. Upper good recovery.

The structured interview has improved the classification reliability. It has demonstrated to be more sensitive than GOS to changes in patients with mild and moderate Traumatic Brain Injury (TBI).

The interview can be administered to the patient, to a family member, or to any other person who can provide information. The GOS-E is not considered an instrument of self perception, evaluators must give a score to each item based on the most accurate information available, regardless the source.

94.2.3 DRS (Disability Rating Scale)

It is a scale that allows to measure with precision general functional changes (disabilities and impairments) in the recovery process. It was developed and proved in patients with severe and moderate TBI in the rehabilitation environment.

Scores range from 0 (without disability) to maximum score of 29 (vegetative state).

The DRS assesses 8 items: The first three items ("eye opening", "communication" and "motor response") are a modification of the Glasgow Coma Scale and reflects the worsening degree.

The cognitive capacity for self-care activities like "feeding", " hygiene" and "cleanliness" shows the level of disability.

The " functioning level" and " employability" reflect impairment degree and are based on the capacity and not in performance (dependency and social adaptation).

It is one of the best scales to evaluate outcomes in patients with moderate TBI.

Advantages: proved reliability and validity, useful in a great variety of patients, data can be obtained from patients or family, can be done by phone or either by medical records revision, and not requires a great experience of the evaluator.

The ease of administration and the brevity of the scale are the most important reasons for its popularity (15 minutes).

Disadvantages*:* One of its limitations is its relative insensitivity to minor injuries (mild TBI) and its inability to reflect subtle but often significant changes, within a specified window of recovery. It does not measure changes in a short period of time.

94.2.4 FIM (Functional Independence Measure)

It was developed to solve the generalized lack of data of outcome in rehabilitation [2].

It's a basic indicator of the severity of the disability, it evaluates what the person does with the impairment whatever its diagnosis or disability is.

It is an ordinal scale of 18 items including: self care independence, sphincter control, transfers, locomotion, communication, and social-cognitive state.

Scores range from one to seven: a score of seven in a FIM item is categorized as "complete independence", while a score of one means "total assistance" (performs less than 25% of the task). Scores under six require another person for supervision or assistance.

By summing the scores for each item, the possible total scoring ranges go from 18 (lowest) to 126 (highest).
It is very useful for the evaluation of progress during rehabilitation. It is the most widely used functional evaluation measure in rehabilitation. Limitations are that their reliability depends on training and certification of assessors.

94.2.5 Rancho Los Amigos Scale (Level of Cognitive Functioning Scale)

It assesses cognitive function in patients after coma [3]. Allows planning the treatment and following up of recovery. Classifies patients into eight levels:

- I: No response.
- II: Generalized response.
- III: Localized response.
- IV: Confused, exited.
- V: Confused, not exited.
- VI: Confused, appropriate.
- VII: Automatic, appropriate.
- VIII: Deliberate, appropriate.

The level assigned provides a clear description of patient behavior and may be used to develop specific treatment interventions.
Does not require the collaboration of the patient, can be classified based on the observation and response to the environment.
Not attempts to predict long-term improvements. Rapid progresses are usually the first weeks and then they stabilize at levels VI or VII.

94.2.6 Barthel Index

Despite great personal and social impact of stroke, the best method to evaluate results, it is not clear.
One of the most used scales is the Barthel Index; it measures the ability of the person for the accomplishment of ten basic activities of daily living, obtaining a quantitative estimation of the dependence degree of the subject. Includes: eating, transferring from chair to bed, self-cleanliness, toileting, bathing/showering, moving (walking on smooth or wheelchair), going up/down stairs, dressing/undressing, bowels and bladder control. The activities are valued differently, assigning a value of 0, 5, 10 or 15 points. The global range can vary between 0 (completely dependent) and 100 (completely independent) It's an easy measure to apply, with a high degree of reliability and validity, can detect changes, easy to interpret, and its use does not cause discomfort.
Disadvantage: it does not evaluate language, so patients can be evaluated with good recovery despite having aphasia.

94.2.7 Neuropsycological Tests

Even though diagnostic imaging such as MRI, CT, PET or SPECT may show damage to the structural integrity of the brain, blood flow or metabolism, it cannot measure the loss of memory or the ability to maintain attention. Neuropsychological tests assess these deficiencies of cognitive functioning. The tests consist of pencil and paper tasks, verbal tasks, structured and unstructured interviews, and construction tasks.

Area	Tests
Verbal fluency	Verbal Fluency Test (letters, animals, actions)
Higher cognitive functions	Color Trail Test 2
Speed of information processing	Color Trail Test 1/Digits and Symbols/Symbol searching
Working memory	WMS-III Spatial Span/PASAT 50
Learning and Memory	Verbal learning test/Brief visuspatial memory test
Fine motor coordination	Grooved Pegboard Test

Table 94.1 **Some of the most widely used neuropsychological test and the areas involved.**

They are used to analyze and interpret patients' responses to cognitive tasks by comparison with a normal sample. These samples are usually composed of large groups of people with similar characteristics to the patient examined (age, education and cultural training) and the results are expressed in percentiles. It allows to infer what the patient is able to do in his environment on the basis of how he does a set of tasks in relation to how others do these tasks in the population.

Although many patients may not be capable of performing all neuropsychological tests at 6 months, it is recommended that the examiner attempts to perform each test, discontinue them according to the criteria and document why the test was not completed (e.g. aphasia, motor problems, etc.).

Table 64.1 details some of the most widely used neuropsychological test and the areas involved.

94.3 Conclusions

The selection of the functional outcome scale used is based on clinical relevance, reliability and sensitivity to changes.

The reliability indicates the extent to which the scales are reproducible, so that the results obtained allow us to conclude that the assessments made by observers were reliable and therefore the measures to apply. There are some factors associated with patients, observers or with the own scales that can influence the variation of the measurements.

Trained examiners should carry out assessments and periodic re-trainings should be performed to minimize inter-observer variability.

The global results assessment (functional and neuropsychological) provides a better understanding of the behavior of the individual so that the Interdisciplinary Treatment Team may use individual advantages and compensate for limitations in cognitive function associated with brain injury.

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95 Concepts and Management of Brain Death and Management of Potential Organ Donation

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95.1 Part I. Concepts and Management of Brain Death

95.1.1 Introduction

Even though before the Modern Era the death of a person was considered unequivocal when related to corporal signs (rigidity, lividity and the beginning of putrefaction), the development of medical concepts have changed this. In the context of the creation of intensive care units (ICUs) and with the development of cardiopulmonary reanimation techniques, concepts about the death of a person have been modified, and now can be related to organs like the heart or lungs. All this leads to the concept of death related to the only essential organ to life: the brain.
Another problem is how to determine the moment of death in patients with severe brain lesions who have previously experienced variable periods of unconsciousness.

95.1.2 Brain Death Concept

Until the 20th century, the concept of death was related to cardiorespiratory arrest. However, in 19th century, with Virchow's tissue theory, death was considered a process in which different organs and tissues (with a different vital potential) progressively ceased to function. This concept is still strongly accepted and is the origin of the requirement for waiting 24 hours before the burial of the cadaver.
It was in 1968, during the 22nd World Medical Association Meeting, that a declaration about death was elaborated, actualized in later meetings, establishing the responsibility and competence of physicians in the diagnosis and determination of the moment of death.
There are currently three main concepts of brain death: global death, brainstem death, and neocortical death. However, the first two are the most prevalent.
Brainstem death was developed following the criteria established in 1976 in the Conference of Medical Council and their Faculties of the United Kingdom, developing the definition in the document entitled the United Kingdom Code. It is based on the fact that brain death is established when there are lesions in the brainstem with a loss of function. In this case, it is sufficient to perform a clinical examination to make the diagnosis.
Global brain death, a more widespread concept, considers brain death as the summation of brainstem death and neocortical or telencephalon death, i.e., the complete absence of all encephalon and brainstem functions.

Arousal (capacity of consciousness) with loss of awareness (content of consciousness) is considered neocortical death and so the diagnosis should be based on the clinical demonstration of absence of content of consciousness (awareness).

Brain Death Diagnosis

Brain death diagnosis is based on the principle that a patient suffers an irreversible lesion. Therefore, it is essential to know the mechanism of cerebral damage, without which it would be impossible to establish the irreversibility of the process. Determining the irreversibility of the process before performing a clinical diagnosis is mandatory to eliminate the existence of possible factors which could simulate brain death or have an impact on a clinical examination.

Before a diagnosis of brain death can be established, it is mandatory that a patient presents with:

- Absence of systemic arterial hypotension. Systemic arterial hypotension can decrease cerebral blood flow, so blood pressure must be normalized prior to the clinical examination, being coherent with age and medical history.
- Absence of hypothermia. Accidental or induced hypothermia leads to a general decrease in brain activity and can even alter brainstem reflexes if the body temperature is <28°C. The situation must be reversed and the patient must be explored with a body temperature >32°C.
- Absence of effects of neuro-depressant drugs, muscle relaxants and anticholinergics which can mask brain death signs. Among the most frequently used drugs in the ICU is midazolam (benzodiazepine), with a half-life of 1.8-6.4 hours (average, 3 hours). In patients with renal dysfunction this could be more prolonged and may remain for 24 hours. In patients who received benzodiazepines it could be useful to employ antagonist drugs such as flumazenil (dosage of 0.2 mg per minute, with a maximum dosage of 2 mg). Thiopental is another widely used drug, very soluble in fat tissues and low grade of ionization, which allows it to pass easily through the blood-brain barrier. It has a half-life of 3-8 hours after a single injection, but it can be prolonged for 27 hours when administered by continuous intravenous perfusion. As a general rule, authors propose that clinical examination for brain death diagnosis must be postponed until the half-life has elapsed by four times.

Clinical Diagnosis

This diagnosis shows the absence of brainstem function through the absence of reflexes of a given anatomical region. There must be bilateral findings, following a detailed protocol with the next steps.

Absence of direct and consensual pupillary reflex. This is performed with stimulation of a powerful light source, observing in normal conditions pupillary contraction. The pupils can appear round, oval or disc-shaped, medium size or mydriatic, from 4 to 9 mm, and unresponsive to light. There must always be an absence of a consensual reflex. The afferent pathway starts at the retina, continues via the optical nerve until the geniculate ganglion, connecting bilaterally with the Edinger-Westphal nucleus (mesencephalon). The efferent pathway is the parasympathetic portion of the III cranial nerve until the iris muscle constricts. Some drugs (anticholinergics: tricyclics, atropine and adrenergic drugs) produce paralytic mydriasis. So an atropine test must not be done before exploring the pupillary reflex.

Absence of oculocephalic reflex. Exploration is done keeping the eyelids open with the index fingers and thumbs, holding the head with both hands, and moving the head horizontally from left to right (or vice versa) in rapid succession. If a reflex is present, it is

observed by conjugated ocular deviation opposite to the head movement, returning to the initial position with a temporal lag. In brain death, with the reflex absent, the eyes do not move and follow the head movement. Always exclude unstable cervical spine lesions before exploring this reflex because it could produce spinal lesions which could lead to cardiac or hemodynamic instability due to the suddenness of the motion. The afferent pathway starts at the semicircular channels in the middle ear, continuing via the VIII cranial nerve (statoacoustic) until the vestibular nucleus (bulb-pontine level), continuing by the medial longitudinal fasciculus and reticular parapontine formation, interconnecting with the efferent pathway, that is the III and IV cranial nerves.

Absence of corneal reflex. Corneal stimulation is performed using sterile gauze (having previously gently opened the upper eyelids with the fingers), observing a palpable contraction and tearing in a live patient, and an absence of response in brain death. The afferent pathway is the ophthalmic branch (first branch of the trigeminal nerve) which leads to its sensory nucleus and determines a bulb-pontine level of prosecution. The efferent pathway is through the III and VII cranial nerves.

Absence of oculovestibular reflex. This is explored with the head elevated to 30°. A volume of 50 ml saline is injected at 4°C into the ear canal, while maintaining the patient's eyes open for 1 minute. In normal conditions, nystagmus is observed with slow components towards the irrigated ear and a fast corrector cortical component in the opposite direction. It is advisable to wait at least 5 minutes before exploring the contralateral reflex. Nystagmus is regular and rhythmic, and lasts <2-3 minutes. In brain death there is no ocular movement. The afferent pathway is the semicircular lymph channels, continuing via the VIII cranial nerve until the medial longitudinal fasciculum and reticular pontine formation. The efferent pathways are the III, IV and VI cranial nerves.

Absence of nauseous reflex. The soft palate, uvula and oropharynx are stimulated using a wooden tongue depressor. A nauseous reflex is observed in normal conditions and no response in brain death. The afferent pathway is through the IX cranial nerve, connected to the ambiguous nucleus and determining the afferent by the X cranial nerve.

Absence of cough reflex. This is explored by introducing a probe through a nasotracheal tube or tracheostomy to produce tracheal stimulation; in normal conditions cough production is observed and no response in the case of brain death.

Absence of response to atropine. The atropine test explores the activity of the X cranial nerve and its brainstem reflexes. Physiological response consists of increasing the cardiac rate by 10% of the basal cardiac rate after injection of 0.04 mg/kg of atropine sulphate intravenously. In brain death there is no response. It must be administered through a vein not shared by any amine which could have a positive chronotropic effect.

Absence of oculocardiac reflex. Normal response (Ascher's sign) consists of decreasing cardiac rate by 10% and decreasing blood pressure by 35% after applying pressure on the eyeballs. There is no response in brain death. The afferent pathway is the V cranial nerve; the prosecution centre is the nucleus of the V cranial nerve at the bulb level. The efferent pathway is through the X cranial nerve.

Absence of spontaneous breathing demonstrated by the apnea test. Generally, this is the last test because it can generate deleterious systemic and intracranial effects. To perform this test it is recommended that the patient be previously hemodynamically stabilized, with adequate preload, with serum ions and an acid-base balance within the normal range. The respiratory centre is stimulated when the arterial pressure of CO_2 is >60 mmHg or 20 mmHg higher than the usual value (normal arterial pressure, 35-45 mmHg); patients with chronic obstructive pulmonary disease (COPD) often present compensated respiratory acidosis with CO_2 >45 mmHg. Arterial pressure of CO_2 increases 2.5-3 minutes per minute in apnea, so the apnea test must be prolonged until the $PaCO_2$ is >60 mmHg or >20 mmHg higher than the usual value.

Steps to perform this test:

- An initial sample to know the basal CO_2 arterial pressure.
- Period of apnea:
  - The classical way is to disconnect the patient from the ventilator, introducing a probe with an oxygen flow of 6 l/min through an endotracheal tube. The time is calculated to allow the increase in CO_2 >60 mmHg or 20 mmHg higher than the usual value (2.5-3 mmHg for each minute in apnea). A second sample must be drawn to check if the CO_2 values are previously indicated.
  - In respiratorally unstable patients in which it would be impossible to maintain disconnection from the ventilator for a prolonged period, and/or with risk of pulmonary collapse, another technique can be performed: using the ventilator with spontaneous ventilation mode with positive end-expiratory pressure (PEEP) but without support pressure and triggering by pressure (not by flow to avoid auto-cycling) in ventilators where it is possible to disconnect the safety ventilation mode. In older ventilators, the inspiratory branch can be disconnected and connected to a T-tube with oxygen 6 l/min, with a PEEP safety valve in the expiratory branch.
- In all cases CO_2 arterial pressure after 5-8 minutes (approximately) must be achieved and after maintaining an upper level of 60 mmHg or 20 mmHg higher than the basal value. Furthermore, the patient cannot have any respiratory movements.

Absence of spontaneous or provoked facial or muscle movements. No spontaneous facial movement (neither spontaneous nor induced) can be observed in a brain dead patient. No spontaneous or painful facial movement or anywhere in the rest of the body. However, the presence of spinal motor activity does not preclude the diagnosis of death. The presence of plantar cutaneous reflexes, priapism and some complex movements (for example, the Lazarus sign) and no spontaneous facial movement (spontaneous or induced) can be observed in a brain dead patient.

Brain death in children has specific connotations in children under 2 years of age. It is noteworthy that the presence of spinal reflexes is more frequent than in adults. Observation periods are different and more prolonged than in older patients:

- Less than 2 months. The observation time before certifying death is 48 hours. Clinical signs must be explored, such as suction reflex and search reflex. It is recommended to have two flat electroencephalograms (EEGs).
- From 2 months to 1 year. The observation time is 24 hours, the absence of reflexes mentioned above, and two flat EEGs.
- From 1 to 2 years. The observation period is 12 hours. When the mechanism of brain damage is ischemic-anoxia, it is recommended to maintain a period of observation for at least for 24 hours.
- It is important to note that the apnea test takes less time than in older patients because the CO_2 arterial pressure increases faster than in adults (4.2-5.3 mmHg per minute).

Instrumental Diagnosis

Prior to commencing, it is necessary to perform a clinical diagnosis. In clinical diagnosis, certain requirements must be met (hemodynamic stability, etc.). It is important to highlight that instrumental diagnosis is not enough to make a diagnosis but complements the clinical diagnosis. There are tests to explore bioelectric functions (EEG) and to explore cerebral blood flow (cerebral angiography, gammagraphy, transcranial Doppler sonography).

Electroencephalogram is one of the oldest techniques in the diagnosis of brain death. It is based on the demonstration of the absence of bioelectrical brain activity. It was pro-

moted by Harvard Medical School. The American Society of Clinical Neurophysiology set the following requirements for diagnosis:

- A minimum of 8 electrodes must be employed (a complete set in frontal, temporal, occipital and parietal regions).
- Impedance between electrodes from 100 to 10000 Ù.
- Distance between electrodes at least 10 cm.
- Increase in sensitivity must be 7 at <2 mV and the recording must be at least of 30 minutes duration.
- The filtering system has to be adequate to diagnose EEG silence.
- Extensive monitoring of EEG, electrocardiogram (ECG), respiratory, etc.
- There must be no electrical response after somatosensory, visual or auditory stimuli.
- The recording must be performed by skilled personnel.

One of the limitations of this technique is interference from neuro-depressant drugs, barbiturates. Levels of 40 ug/ml are correlated to burst-suppression, and an upper limit of 70 ug/ml is correlated with a flat EEG. So it necessary to determine serum levels as diagnosis capacity can be influenced.

Multimodal evoked potentials. Combined somatosensory and auditory potentials are very useful. Report the integrity of conduction pathways or place of lesion at the peripheral level. Evoked responses which show the bulb as upper prosecution levels are compatible with brain death. This diagnosis is compatible with the following patterns:

- Auditory evoked potentials of bilateral flat brainstem, bilateral or unilateral isolated wave I and unilateral or bilateral isolated waves I and II.
- Somatosensory evoked potentials of short latency for stimulation of the median nerve: P15, N20 and P25 absence, and cortical potentials more overdue in the cephalic-cephalic derivation. Presence of the components P9, P13, Nm (Nm is the derivation cephalic-no cephalic) and presence of the potential of Erb.
- Evoked potentials and electroretinography with persistence of retinal activity and absence of visual cortical evoked potentials.

Transcranial Doppler sonography (TDS). The usefulness of TDS in the diagnosis of brain death is based on the demonstration of an absence of cerebral blood flow in the arteries of the cranial base. The test must include exploration of anterior cranial base circulation (middle cerebral artery and anterior cerebral artery) and posterior cranial base circulation (basilar artery and vertebral arteries). TDS has the advantage that it can be performed at the bedside and can be repeated as often as necessary. Furthermore, records can describe the progressive process of cessation of cerebral circulation through the decrease in diastolic velocity of blood flow, determining four patterns: diastole-systole separation; diastolic reversion or reverberant flow; systolic spikes; and complete disappearance of the sonographic signal. In late patterns in which obtaining signals is impossible, it must be sure that the flow records of the extracranial arteries are adequate, and comparing it with the flow at the intracranial level. Alternative windows can be used such as the orbital to observe whether there is residual flow in the carotids at the carotid siphon. A document by the Task Force Group on Cerebral Death of Neurology determined that in cases in which intracranial flow cannot be recorded, it must be done on the extracranial arteries. This can create the problem of having to perform sonographic diagnosis of cerebral circulatory arrest in patients with decompressive craniectomy, in those with ventricular drainage, or in infants with open fontanels. In such cases it is necessary to perform an EEG or multimodal evoked potentials.

Cerebral angiography. Another option in the exploration of cerebral circulation to establish the diagnosis of cerebral circulatory arrest is cerebral angiography which includes anterior and posterior intracranial circulation. Here are some described patterns of circulatory arrest seen in brain death:

- Total arrest of arterial contrast without vein filling and retrograde disappearance.
- Detention of arterial circulation at the level of the Circle of Willis.
- Extreme slowing down of arteriovenous circulation: more than 15 seconds is considered incompatible with cerebral function.

Like other cerebral perfusion studies, their main limitations are low blood pressure, open fontanels in newborns, large fractures of the vault or skull base, internal or external drainage of cerebrospinal fluid or emissary veins.

Cerebral perfusion studies with isotopes. The study of cerebral perfusion can be done with I 123 IMP and Tc 99 HMPAO, the latter of which has more benefit. There are two phases: the first is angiogammagraphic to appreciate the cerebral flow and the second phase with static images at 5-10 minutes with anterior, right and left lateral protections which disclose parenchymal retention. In cases of brain death, isotopes are not observed in either the perfusion phase or the retention phase.

95.1.3 Communication of Brain Death to the Family

It is very important to develop communication skills for giving information on brain death and its premonitory processes. Communication with the family in the final stages of life is related to the temporal development of the disease, the family's educational level, empathy between the medical staff and the patient's family, family and physician adaptation to situations of crisis and cause of death. Health professionals must help these families understand and accept brain death as they do for families of dying patients in asystole. This may occasionally be complicated for some because it can be complex to understand if the process and information about death are not well explained. This is especially difficult when the family observes that the heart is still beating and the chest is moving because of the mechanical ventilator. This visual aspect may be unsettling for the family, preventing them from grieving in a normal manner. It does not have the same impact when death occurs in situations where the duration of the illness is prolonged and a relationship of trust has been established between the care team and the family. In instances of sudden illness, accidental or fatal, fulminant progression to death, the time needed for adaption to and acceptance of imminent death and a trusting relationship between family members and the doctor is lacking. The medical and nursing staff need to show empathy to the families and provide them with information appropriate to their cultural level. It is important to avoid the use of technical language incomprehensible to the family which may generate mistrust in this relationship. In many cases, family members will inevitably experience a state of crisis. This is defined as traumatic life crisis in a temporary state of greater or lesser duration that leads to disorder and disorganization, characterized mainly by the individual's inability to cope with unforeseen, uncontrolled or unexpected situations. The person is temporarily unable to adequately resolve current problems or address situations or process information. This may be delineated in a series of stages:

- Initially, a reaction to the external event and an increase in tension due to the inability of the person to deal with the specific circumstances.
- Mobilization of other personal resources that reduce the external threat.
- Successfully deal with the adverse situation.
- Redefine the problem as well as others.

The inability to activate some of these strategies can lead to personal disorganization and a state of confusion and disorientation, resulting in psychological mechanisms of denial or intrusion (intrusion means to have feelings of pain, impact images, nightmares,

etc.) that require accompaniment and support to address, integrate and overcome the incident.

Intrusion leads to penetration processes which express, identify and disseminate thoughts, feelings and images of the crisis experienced. It involves defining the problem, making decisions or learning new solutions to mobilize personal resources, reduce unpleasant effects, etc.

This leads to the final stage of complete integration of the crisis in the life of the individual. The crisis may result in an improvement in rationalizing the pain or a worsening in which misconduct can be set from depressive states of the subject.

After communicating death to family members, the first support must be quick and short. Grief reactions may be varied, and psychological responses may include numbness or intense emotional release, sometimes unaware of what happened or showing semi-automatic conduct. For those showing inhibition, lethargy or denial of feelings, the individual may try to separate emotionally from the reality of death. In other people, the reaction is flight or liberation of movement; these are less structured and may be admitted as long as it does not endanger other people or are of a destructive nature. It is important to control the number of people who initially receive this information, because a range of reactions can appear contemporaneously and may be uncontrollable. Hence, there is a need to select as much as possible those who should receive the initial information. The domain of verbal communication skills, active listening, clarification of any issues that may be confusing for understanding the process which has led to this final outcome, summary of information, reflections of feelings and the appropriate management of silences are a priority.

Nonverbal communication must be maintained appropriately, so that spatial positioning is utilised with an attitude of interest, leaning towards the family and not losing eye contact with them. It is important to use a caring tone of voice that should be serene, firm and sufficiently clear, without doubt in clarifying the situation. Occasionally, subtle physical contact may be needed to comfort the family to help them overcome the situation and it can be the first support received by the family. Sometimes these contacts are rejected by the family, in which case we have to change our approach immediately.

When imparting information about brain death, the situation must be handled with care because it may influence personal reactions. In this time of a crisis for the family, future memories will be influenced by the environment in which the news was reported. It must be ensured that the number of family members is limited and they must be the closest relatives. Sometimes the circle can be extended according to the patient's personal circumstances (many children), while anticipating the risk of having less control over possible adverse reactions.

The family has to be notified, if possible, by a physician knowledgeable about the critical situation, opening the possibility of a future unfavourable evolution and placing it in position to progressively accept the death process. After giving the information, the physician should guide the conversation while the body is in the hospital. If the deceased is an organ donor, there is the responsibility to inform the family in an appropriate place and give the necessary support during the waiting time until surgery. If the deceased is not an organ donor, the physician must offer adequate information about where and whom they have to enquire regarding the removal of the body until they leave the hospital.

Communication about the time of death and the organ request must be clearly differentiated. The latter phase must be made by transplant coordinators, as they have adequate prior preparation, with counselling courses and specific training in such situations. Also, depending on particular reactions, the family will need a period of reflection which should not be prolonged, sometimes being a supportive response prior to donation.

95.1.4 Ethical and Management Problems of ICU Admission of Patients With Brain Death

New management and ethical issues are described about managing ICU beds. Basic principles of modern bioethics in order of importance regard: autonomy, non-malfeasance, justice and beneficence. These principles are basic, mandatory and distinct.

Autonomy refers to the evaluation of the opinions and choices of individuals, whether competent or not causing clear harm to others. An action is considered independent when it is taken through the process of informed consent. In cases of unconscious or deceased patients, if there is a written will, it must be consulted, and if the deceased made no living will, the physicians have to attend to the wishes expressed in this life by those who lived with him.

Non-malfeasance must be applied by all physicians because contraindicated procedures cannot be performed without a patient's consent. It is based on the principle of *primum non nocere*.

Justice is to give every man according to his own rights or impartiality in the distribution of risks and benefits. It is imposed by the central government.

Beneficence is the act of maximizing potential benefits and minimizing risks.

A patient is guided by the principle of autonomy. The figure of the doctor has two sides, i.e., those who perform their professional practice in public medicine as being responsible for the patient and administrative management representative, who must apply the principles of non-malfeasance, justice and beneficence. In countries where the media is private, the principles will be non-malfeasance, followed by beneficence (because patients pay for their own treatment) and ultimately justice. In the public sphere, where waiting lists have a specific weight, the principle of justice by the central administration is mandatory. These three principles (non-malfeasance, beneficence and autonomy) are related to an individual's good, whereas justice is related to common good. Common good is always more important than individual good, and this is the reason why there is a certain hierarchy between these principles. These principles were put in place by the Belmont Report, based on the terminology devised by David Ross, becoming a fundamental outline of bioethics from the bioethics book by Beauchamp and Childress entitled *Principles of Biomedical Ethics*, published in 1979.

ICU admission criteria were broadened in 1983 in the First Consensus Conference on Critical Care Medicine. The U.S. National Institutes of Health stated they had to extend the indications. In 1999 the ACCCM and SCCM published admission and discharge criteria based on a list of specific diseases or conditions which, by their nature, determine appropriate admissions to ICUs, resolution criteria and ICU discharge. Everything is conveniently issued in the journal Critical Care Medicine-ICU care of patients in brain death, admission of patients who will progress inevitably to brain death, or those which have already been diagnosed for care and maintenance in order to be donors is now a fact, and needs a rationale analysis.

In recent years, a set of criteria has been established for ICU admission. These criteria are organized by order of importance, but more and more organ donors are candidates for ICU admission. One of the main reasons for ICU admission is to manage changes in the internal medium and the preservation of organs, in order to ensure the future of multiple recipients who may benefit from functioning organs.

This raises the ethical question of whether admission of a brain-dead patient to an ICU is an appropriate action. On the one hand, it could be considered a positive aspect for patients who could benefit from organ donation. On the other, it could be considered a futile and unjustifiable form of therapy.

95.1.5 Key Concepts

- The more widely extended criterion is global brain death, which considers brain death as an addition of brainstem death and neocortical death. Global brain death implies not only permanent cessation of all consciousness functions but also cessation of integrated brain functions, as well as cessation of all brainstem functions.
- For the diagnosis of brain death, the patient must meet certain pre-requirements: absence of systemic arterial hypotension, absence of hypothermia, and absence of neuro-depressant drug effects, muscular blockers and anticholinergics, these being circumstances and drugs which can mask signs of brain death.
- Diagnosis must include the demonstration of cessation of all reflex activity of the brainstem: direct and consensual pupillary, oculocephalic, corneal, oculovestibular reflexes, absence of spontaneous or provoked facial or muscle movements, nauseous reflex, cough reflex, response to atropine, and the apnea test. Complementary instrumental tests are also useful: EEG, multimodal evoked potentials, TDS, cerebral angiography, and perfusion studies with isotopes.
- Communication of the end of life to the family requires training and an accurate technique for special care: presentation of the medical staff; progressive giving of information; clear management of information with low emotional content and special attention to non-verbal communication, favouring empathy, expression and identifying the family's immediate needs and to offer help if needed.
- A patient is guided by the autonomy principle, a physician by non-malfeasance and beneficence, and the family and others by the justice principle. Non-malfeasance, beneficence and autonomy are related to the individual good, whereas justice is related to the common good. More and more organ donors are candidates for ICU admission to improve care and organ optimization for transplant to multiple recipients who can benefit from optimised organs. Saving costs is established by the preservation of quality of the donated organs and the long-term benefit to minimize health problems in the post-transplant period.

95.2 Part II. Management of Potential Organ Donation

95.2.1 Introduction

Although there is a growing need for transplantable organs due to longer waiting lists, we found a disparity between the number of potential organ donors and those who actually donate organs. For designed strategies to be effective and successful there must be awareness, acceptance and opportunity to convey the message to the population. Today, we are reaching the limits of donation: donor type profiles are changing as is the profile of the patients admitted to our units, with a shift of the prototype of young healthy trauma patients to elderly patients affected predominantly by vascular disease. Whatever the trend, it is mandatory to recover viable organs and provide the recipients with the highest quality and probability of optimal outcomes. Therefore, after a brain death diagnosis, donation is requested from the patient's family members, the surgical teams are coordinated, and the receiver hospital is alerted. This strategy may take from 4 to 24 hours. Currently, this time period can be shortened with proper management.
Considering the setting, the time element is highly important, given that it is increasingly common to find donors meeting extended criteria as donors. The latter concept is understood as the number of donors whose organs were thought to be associated with an

increased risk of poor graft function or primary failure or transmission of diseases from the donor. Traditionally, these were older donors, fatty livers, positive serology for hepatitis C or B, central nervous system tumours, and postcardiac arrest donors. However, this concept has changed with the increasing experience of transplant groups, leading to improved outcomes even with organs from donors with the characteristics mentioned above.

Similarly, cold ischemia time should be as tight as possible to ensure good graft function after transplantation. It has been shown that preservation at a temperature between 0 and 4°C results in less cell damage and that the use of special solutions, according to the organ preserved (Euro-Collins, Belzer and the University of Wisconsin), can prolong preservation time, for example: 2 days for the liver, 3 days for the kidneys and pancreas, and 12 hours for the heart. As far as possible, we seek to limit the maximum time for these procedures as the success of graft viability is inversely proportional to the time of preservation.

Also very important is knowing the pathophysiology of the events that occur gradually, as well as the management of hemodynamics, renal function, arrhythmias, protective ventilation, and maintenance of temperature, electrolyte and endocrine balance. Also essential is having a written protocol for managing these patients for the successful preservation of transplantable organs.

95.2.2 Pathophysiology of Brain Death

Death is an irreversible process that can be slowed down by the administration of substances that the body fails to produce. In brain death, after the loss of brain function, including the brainstem and medulla oblongata, there is a massive release of catecholamines which produces extreme tachycardia and hypertension; the duration is variable although limited. This period is critical because it can generate deleterious arrhythmias, destabilizing a previously stable heart disease; at the same time it can precipitate left ventricular failure and acute pulmonary edema or myocardial ischemia by increasing blood pressure.

Once the above phenomena have been mitigated or passed, we can see sudden hypotension that can manifest itself in a multifactorial form. Shock is a consequence of the loss of neurogenic activity, inducing the release of the adrenergic reserve. The loss of fluid by diuresis secondary to the release by the hypothalamic-pituitary axis, hypovolemia due to the traumatic process itself or the use of diuretics, can influence the intensity of the hypotensive response. Another factor that can contribute to arterial hypotension is heart failure (cardiogenic shock) from the action of the adrenergic wave generated at this time.

Tachyarrhythmias and bradyarrhythmias arise in the context of ventricular dysfunction in up to 30% of cases of brain death. Approximately 18% of the patients are young and without previous cardiac abnormalities. These abnormalities are secondary to hemodynamic and neurohormonal disorders that occur during brain lock, i.e., neurogenic myocardial stunning or ischemia. Other causes include hypothermia or electrolyte disturbances (hypocalcemia, hypokalemia, acidosis). Not all clinical pictures are reversible (myocardial stunning), but a great majority are, so this is the basis for waiting several hours until the organs can be extracted, otherwise testing the myocardial reserve with dopamine and troponin I determination are recommended.

Central or pulmonary hypoxemia is frequent after brain death. We must actively protect the lungs, adopting strategies similar to those proposed by the American and European Thoracic and Intensive Care Societies, as defined in the Consensus Statement of 1994.

The proposal is to initiate lung-protective ventilation without generating excessive volumes or pressures harmful for the body. On the other hand, decreased metabolism after brain death produces a drop in CO_2 generation and levels. This facilitates ventilation with lower tidal volumes than in subjects of equal body weight. We must avoid generating atelectasis and prevent infections developing from the accumulation of secretions. Also, we will avoid excessive fluid intake or maintaining high blood pressure with exogenous amines because they can potentially trigger acute pulmonary edema and loss of organs.
The lack of neuroendocrine control is expressed especially in water and electrolyte balance; for example, diabetes insipidus secondary to hypothalamic or neurohypophyseal dysfunction (supraoptic and paraventricular nuclei). Diuretic losses can reach 3-4 cc/kg/h, exceptionally 6 cc/kg/h, so we have to constantly monitor volemia status in addition to replacing lost fluids in order to avoid hypovolemia. Another aspect that we will consider is the loss of hypothalamic regulation of the thyroid and adrenal axis and its direct impact on carbohydrate metabolism. This tends to be altered mainly for two reasons: 1) indiscriminate administration of hypotonic fluids (dextrose 5%) to reduce hyperosmolality due to the lack of ADH and 2) utilization of strict blood glucose control regimens that, as recently published, put some organs at risk. Hormones such as triiodothyronine produced in the anterior hypothalamic area also help to maintain hemodynamic stability.
The destruction of the nuclei in the preoptic area of the anterior hypothalamus alters temperature regulation, increasing hypothermia in most cases. Temperatures <35°C are correctable and temperatures <34°C generate ECG abnormalities such as QRS widening, QT lengthening and Osborn J waves, all of which are frequent events. Although brain death does not produce hypothermia or hyperthermia, some authors postulate that if hyperthermia is present, one explanation might be an underlying infection, but the body temperature can increase when pituitary hormone levels do not decrease, even when the absence of cerebral blood flow by arteriography is established.
Problems in homeostasis and coagulopathy secondary to the release of fibrinolytic agents can originate in the last phase. This may be accompanied by anemia due to hemorrhage or hemodilution. We must not allow hematocrit levels to fall <30%.

95.2.3 Monitoring the Organ Donor Patient

We previously mentioned the serious pathophysiological changes that occur in the process of brain death. In order to monitor its progression, we will monitor the donor. There are minimum requirements that must be met to ensure the success of the process.
Hemodynamic monitoring should include: continuous ECG (arrhythmia monitoring) with a central venous catheter will allow us to determine central venous pressure (blood volume control); the catheter also should allow fluid infusion. Blood pressure can be determined invasively with an arterial catheter, especially when the patient requires vasoactive drugs. Another recommendation is to determine hourly diuresis (Figure 95.1).
Complex monitoring with Swan-Ganz catheters (currently not used) or pulse-induced contour cardiac output (PiCCO) (widely used) affords advantages if they have been inserted beforehand or if you want to optimize the management of these donors in cases of severe or mixed hemodynamic instability (Figure 95.2).
Continuous temperature measurement with external systems is sufficient, although internal probes can be used to measure core temperature.
Another control is to closely monitor lung function: pulse oximetry ensures continuous oxygenation in these circumstances. PET CO_2 is no longer necessary as brain protective ventilation has been stopped.

It is also important to monitor laboratory parameters such as glucose, lactate, and blood count values that not only detect blood loss but also hemodilution and coagulopathy. Also important is the determination of blood group, isogroups and Rh factor because blood may occasionally be needed. Determining electrolytes in blood and urine and blood gases is essential for monitoring the internal environment and preventing acid-base deficiencies or excesses that may impair graft viability. Specific parameters in re-

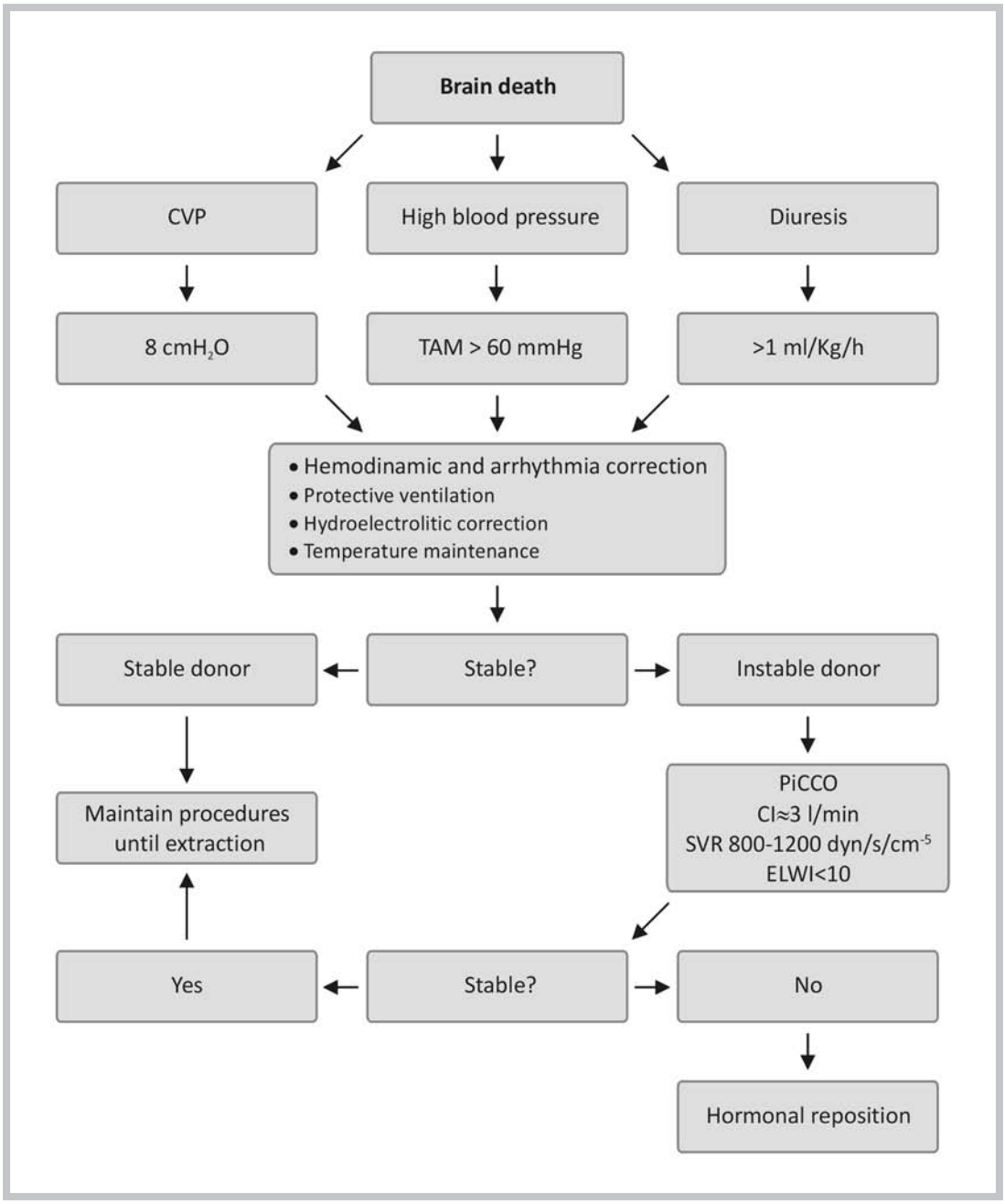

Figure 95.1. **General approach for the management of organ donor.**

CI = cardiac index
CVP = central venous pressure
ELWI = extravascular Leng water index
SVR = sistemic vacular resistance

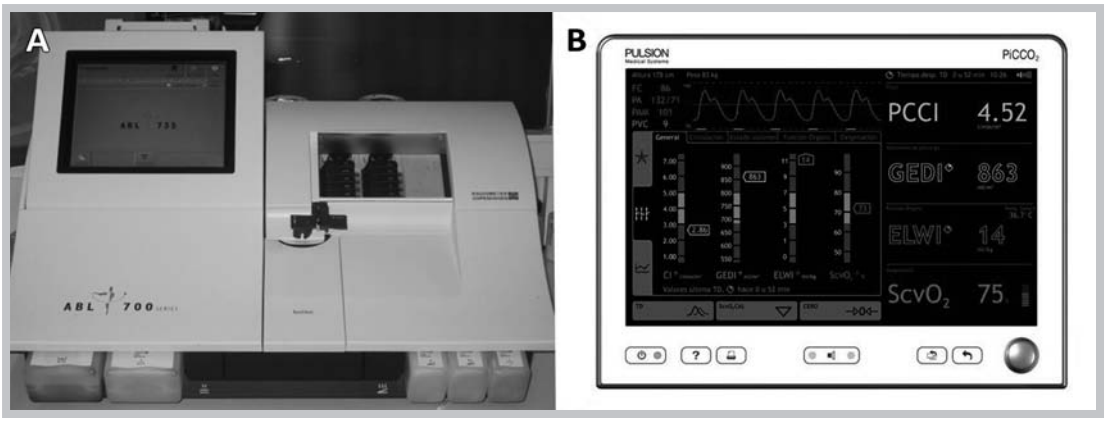

Figure 95.2. **Apparatus necessary for the control of the donor. (A) Control electrolyte, blood gases and tissue ischemia by laboratory determinations at the bedside. (B) Control the hemodynamic state using the PiCCO technique.**

lation to different organs are expressed in profiles: liver, kidney, with the calculation of creatinine clearance, the pancreatic profile and the cardiac profile.
When changes are happening quickly, serial determinations by decentralized basic acute care services are key to achieve donor stabilization before transfer to the operating room.

95.2.4 Management of Organ Systems

Hemodynamic Control

This is certainly the most important element to ensure good viability of organs for transplantation. Hemodynamic disorders subsequent to brain death are related to neurogenic shock that determines the loss of vascular resistance and causes relative hypovolemia, but also it can also be the result of polyuria due to diabetes insipidus.
Finally, the administration of hypertonic solutions (mannitol or hypertonic saline) for the treatment of intracranial hypertension can induce excessive diuresis. This situation triggers hypernatremic dehydration in most cases, unless the physician is aware of the changes occurring in the donor.

	Drug/substance	Half-life	Bolus	Perfusion
Hemodinamics	Esmolol	8 minutes	250 µg/kg in 1 min.	25-50 µg/kg/min
	Labetalol	4 hours	50 mg in 2 min	1-2 mg/min
	Urapidil	4.7 hours	25-50 mg in 20 sec	2 mg/min
	Vasopresin	19-20 minutes	1U	0.01-0.03 U/min
Antiarrhythmics	Dopamine	2 minutes	-	5-10 µg/kg/min
	Adrenaline	2 minutes	-	0.1-1 µg/kg/min
	Isoproterenol	5 minutes	-	2-10 µg/kg/min
Hormones	Desmopressin		-	0.03-0.15 µg/kg
	Triiodothyronine (T3)		4 µg	3 µg/h
	Tyrosine (T4)		20 µg	10 µg/h
	Methylprednisolone		15 mg/kg/day	

Table 95.1. **Dosage and half-life of drugs and hormones in the management of donor organs.**

Not recommended is the treatment of the Cushing effect that precedes the final hypotensive phase since it is difficult to handle and because there is little or no pharmacological response. The ultrashort agent beta-blocker esmolol decreases the hypertensive and arrhythmogenic response. It is preferred when associated with tachyarrhythmias. Labetalol (alpha and beta-blocker) has a longer half-life and poor implementation. Another option s is hypotensive agents in patients with brain pathology, for example, alpha-blockers with controlled duration (e.g., urapidil) since they don't affect cardiac rhythm or mask the bradycardia secondary to uncal herniation (Table 95.1). Despite the usually very transient crisis, drug administration may compromise hemodynamic stability, so further hypotension is the rule.

For the hypotensive phase, fluid administration is the first choice, guided by patient monitoring. Provide all necessary actions to maintain central venous pressure between 10 and 12 cmH_2O. In most cases vasoactive amines will be needed. The type of fluids to infuse should be related to the patient's osmolar state.

In cases of hypernatremia, we must administer hypotonic solutions such as dextrose (dextrose 5%) or hyposaline (0.45%) to adjust serum sodium. In the remaining cases, we use isotonic saline (0.9%) or Ringer's lactate, adding as a regular basis colloids in a proportion of 1:3.

It is not uncommon in blood pressure management to administer amines, including norepinephrine (preferable) or dopamine up to 10-12 μg/kg/min. We adhere to these dose schedules to avoid causing tissue damage especially in the heart. In chest trauma with proven cardiac contusion, inotropes such as dobutamine up to 15 μg/kg/min as the maximum dose may be necessary, while taking care not to cause excessive vasodilation, which reduces diuresis. It may be necessary at times to use a combination of vasoactive drugs to prevent the deleterious effects of hypotension especially in the elderly, where the kidney is perfused at high pressure, to ensure that urine flow is maintained >100 ml/h. Adrenaline 0.1 μg/kg/min may be a viable alternative to excessive norepinephrine requirements in addition to improving hepatic blood flow. The administration of corticosteroids, thyroid hormones or vasopressin, which now is increasingly in disuse, can achieve hemodynamic stabilization in some cases (Table 95.1).

Vasopressin at a vasopressor dose (1-2 IU/h) in conjunction with other amines increases resistance in a similar way as used in acute spinal cord injury.

Before transferring the patient to the operating room for organ removal, the surgical team should be informed of amine requirements.

Control of Arrhythmias

The brain-dead organ donor is very susceptible to develop brady- or tachyarrhythmias, atrial or ventricular in origin, as well as different degrees of heart conduction blocks.

Bradyarrhythmias are generally self-limiting, reversible, and do not require treatment; however, if you do need a pharmacological agent, the choice is dopamine at beta-dose; and if no response is obtained, epinephrine or isoproterenol may be tried. Rarely, the need for temporary pacemaker implant may be considered (Table 95.1).

For **tachyarrhythmias** and other conduction abnormalities, after ruling out etiological causes of cardiac or extracardiac origin, amiodarone should be considered the treatment of choice. Up to 10% of donors may have cardiac arrest in which cardiopulmonary resuscitation (CPR) can be performed according to international standards, except for the use of atropine due to central denervation of the heart muscle since brain death prevents the heart from responding to this drug. If CPR is unsuccessful and the donor remains in cardiac arrest, he or she can be transferred immediately to the operating room under breathing bag-assisted breathing and chest compressions for the removal of or-

gans suitable for donation; in hospitals with implemented protocols heart-beating donation should be applied immediately.

Respiratory Control

In the brain-dead patient, hypoxemia of any origin should be avoided and the lungs must be protected by so-called "protective ventilation", especially if the patient is younger than 50 years of age, with no history of smoking or bronchopulmonary diseases that exclude the likelihood of organ donation. The hyperoxia test to check gas exchange values will be made by ventilation with oxygen at 100% and PEEP of 5 cmH_2O for 5 minutes reaching a PaO_2 >300 mmHg. If this test confirms good gas exchange, mechanical ventilation will be <3 days, and we can confirm the possibility by measuring chest circumference and chest radiology without infiltrates: all such parameters can help to predict a successful lung transplant and exitus care in preserving the lungs.

PEEP (cmH_2O)	FiO_2 (%)
5-10	60
10-15	80
15-20	100

Table 95.2. PEEP and FiO_2 values.

Protective ventilation entails limiting tidal volumes, so that the machine is set to 6 ml/kg with FiO_2 necessary to maintain pulse oximetry ≥95%, generally 50% or lower to decrease the possibility of oxygen toxicity. This objective will be sufficient to maintain optimal function. The PEEP is set at 5 cmH_2O and peak inspiratory pressures are kept ≤30 cmH_2O.

Since metabolic needs decrease in the donor brain-dead patient, CO_2 should be not a problem. It is not uncommon that donors are hyperventilated, so serial blood samples should be taken every 4 hours during the time of preservation.

In atelectasis, the recommendations of the Acute Respiratory Distress Syndrome (ARDS) Network Working Group should be followed, handling PEEP according to the inspiratory fraction of oxygen (Table 95.2).

These values should not be exceeded; if peak pressures are >45 cmH_2O during recruitment, controlled pressure ventilation will be necessary.

The excessive positive fluid balance will be controlled with diuretics; this is not usually frequent unless treated with donors with suboptimal pathology control or without organic reserve. In young people there is often a loss of water due to endocrine disruption. Such patients should be managed with PiCCO for volume management.

Decreased tidal volume can also produce atelectasis. This occurs due to a loss of volume of the alveoli and subsequent collapse. Re-expansion with the standard apnea test can provoke atelectrauma. This forces us to introduce PEEP regularly. If the lungs prove sensitive, we can apply the variant T-tube and PEEP valve or, if the patient is on an adapted ventilator, spontaneous breathing modes such as continuous positive airway pressure (CPAP) to the lung can be induced. Aspirations of secretions should be done carefully with an aseptic technique without depressurizing the system in closed suction systems.

In patients who had suffered significant bronchoreactivity, high doses of steroids or beta adrenergic drugs can be given to solve the problems of mast cell degranulation and precipitation of the crisis. However, the use of steroids and adenine-vasopressin agents implies restricting the volume of fluid to infuse.

The administration of prophylactic antibiotics is mandatory, especially in donors eligible for lung transplant or who remain >48 hours in the ICU. Cultures at an early stage should be obtained, and broad-spectrum antibiotics administered such as amoxicillin-clavulanate, cephalosporins, quinolones, or those that have been formalized in the ICU in relation to the prevalent flora.

Endocrine Control

A wide range of changes in hormonal pathways occur after brain death. The brain is a great central controller, principally localized in the hypothalamus.

Diabetes Insipidus

Vascular ischemia secondary to circulatory arrest in the context of cerebral herniation and intracranial hypertension results in the destruction of the hypothalamus and the axis that regulates the secretion of ADH released from the neurohypophysis. Biphasic and triphasic patterns that may occur in surgical patients or in patients with Sheehan syndromes are not often encountered, where within about 6 hours all hormone traces disappear, although the presence of the symptoms can be manifest with ADH levels of 10-90% of the normal range. The result is hypotonic polyuria with a urine output of 4 ml/kg/h, urine density <1005, hyponatremia, plasma hyperosmolality, usually >300 mOsm/kg and urinary osmolality <300 mOsm/kg. This water loss not only carries away sodium but also provokes the loss of potassium, magnesium, phosphorus and calcium. All these alterations must be corrected.

If urine output is >5-7 ml/kg/h and electrolyte control is difficult to achieve, treatment with vasopressin analogues is necessary. This can be given as vasopressin or desmopressin, the latter is now the treatment of choice because of its excellent action and almost no pressor action. Desmopressin has an antidiuretic action 2000 times more potent than vasopressin and its action is 3 to 5 times longer. The administration can be intranasal, intramuscular or intravenous. Vasopressin is only indicated in the presence of severe hypotension resistant to treatment with fluids or amines. The desmopressin dose varies between 0.03 to 0.15 µg/kg titrated to maintain urine output between 2 and 3 ml/kg. Usually, the pharmaceutical presentation is 1-ml vials containing 4 µg of desmopressin. Nasal instillation drops are used in the treatment of chronic deficits.

The undesirable effect is mainly water intoxication. Hours after desmopressin administration there is a dramatic reduction in diuresis which can result in severe dilutional hyponatremia with hemodynamic overload, leading to heart failure. If vasopressin is used, vasoconstriction is a potentially dangerous side effect because it can trigger severe bronchospasm and ischemia of various territories including the myocardium, splanchnic and renal peripheral areas among others.

Glucose Metabolism

The adrenergic and metabolic crisis that ensues after brain death leads to moderate hyperglycemia which can sometimes become severe due to other reasons such as: administration of catecholamines to maintain blood pressure, administration of glucose to maintain normal osmolarity or decrease serum sodium, hypothermia; the use of steroids is another factor involved. Some studies have failed to demonstrate a lack of insulin production in potential donors: the levels may be low, normal or increased.

The major pathophysiological consequences of hyperglycemia are metabolic acidosis, ketosis, hyperosmolarity (of the extracellular environment that leads to intracellular dehydration) and electrolyte changes. Furthermore, hyperglycemia causes osmotic diuresis with polyuria and urinary loss of water and electrolytes contributing to hypovolemia and therefore hemodynamic instability. We must initiate rapid intravenous insulin treatment by continuous infusion to maintain blood glucose between 150 and 200 mg/dl. Some studies have reported a negative action on pancreatic beta cells, so they should be closely monitored in pancreas donors.

The treatment with short-action insulin is indicated and, if necessary, will be maintained with continuous infusion for better control. The control in cases of instability must be done frequently, and if pumps are used to maintain dosing schedules the recommended target is between 80 and 150 mg/dl. Infusion will be administered according to the

protocols in place in the ICU; glucose levels >200 mg/dl should be maintained with 2 to 7 units of insulin per hour.

Alterations of the Hypothalamic-Pituitary-Adrenal and Thyroid Systems

It has been observed in studies by Novitzky, Schrader and Jeevanandam that levels of triiodothyronine (T3), tyrosine (T4) and cortisol are reduced after brain death. Although the levels of thyroid stimulating hormone (TSH), prolactin, growth hormone and luteotrophic (LSH) do not vary over baseline, the decrease in peripheral hormonal levels at 6 hours after brain death triggers a chain of events: high-energy phosphate depletion, increased lactate and free fatty acids that signal the change from aerobic to anaerobic metabolism, and mitochondrial failure. However, some studies showed that after the administration of TRH, TSH increases slightly, suggesting a preserved partial flow after the cessation of cerebral blood flow. All these phenomena result in organ deterioration (e.g., heart and kidneys).

Some authors have reported that the decrease in thyroid hormones detected after brain death is accompanied by a fall in cortisol and insulin levels which can occur in other pathological conditions such as head trauma, severe sepsis, burns, and the so-called sick euthyroid syndrome. This syndrome is characterized by lower T3, accompanied by high levels of rT3; tyrosine (T4) may be normal, high or low, showing a defect in the conversion of T4 to T3 in the periphery, while maintaining normal levels of TSH, so the hormonal profile is configured as a criterion to establish euthyroidism.

It is important to note that alterations in heart rate, bradyarrhythmias resistant to medication or hypotension refractory to inotropes can be treated with thyroid hormone or corticosteroid replacement. Replacement therapy can be initiated as follows: intravenous bolus of 4 μg of T3, continued with an infusion of 3 μg/h. The alternative is T4 which requires a bolus 5 times larger and then continuous infusion of 10 μg/h in conjunction with steroids: bolus of 15 mg/kg methylprednisolone which can be repeated daily while maintaining hydrocortisone, which has a very short duration: 2 hours of efficient action after a dose of 100 mg of the drug, so the administration must be repeated (Table 95.1).

Electrolyte Control

One of the changes immediately after brain death is secondary endocrine failure. Alterations derived from the loss of regulation of the hypothalamic-pituitary axis must be monitored closely. Such alterations usually occur almost immediately. The loss of free water in the urine carries an increased loss of potassium which, unless properly replaced, can generate severe and life-threatening disturbances with critical implications principally for the heart and the potential loss of the donor. To avoid this complication, serial determinations are performed. If the potassium concentrations fall below critical values, replace immediately with the necessary amount of milliequivalents.

It is not unusual at times and in relation to hormonal correction to find hyperkalemia which also may occur secondary to cytolysis due to long-term maintenance or renal failure and metabolic acidosis. In such cases, the levels may rise quickly and unexpectedly. Hemolytic states, occasionally subsequent to blood transfusion, can increase potassium levels and require urgent treatment. Other causes of hypokalemia include: administration of glucose and insulin to facilitate potassium entry into the cell, 1 mol sodium bicarbonate infusion, beta-stimulants, calcium gluconate and loop diuretics such as furosemide.

Serum sodium disorders are very common: hypernatremia is especially frequent usually multifactorial in origin.

It's very common to find hypernatremia prior to brain-death diagnosis, principally due to the treatment of intracranial hypertension with sodiumHypertonic solutions. In cas-

es it is a result of diabetes insipidus with concomitant contraction of blood volume. This alteration is especially harmful for liver function and may compromise subsequent graft take. The treatment is with hypotonic infusions such as dextrose or hyposaline solutions. Hyponatremia is less frequent but can ensue from inadequate intake, inappropriate correction of hormonal disorders, gastrointestinal losses or kidney failure. Treatment is based on fluid restriction and isotonic saline administration with serial laboratory monitoring.
Less frequent are alterations in magnesium, which often occur with refractory hypokalemia, both preventable with the administration of magnesium in conjunction with phosphate to preserve cell membrane integrity.

Temperature Control

The progressive destruction of the hypothalamus leads to a loss of body temperature in relationship to the external environment, with the patient becoming a poikilotherm donor. We must therefore prevent the dispersion of heat by mean of heating systems and fluid replacement. Hypothermia can generate hemodynamic instability, cardiac arrhythmias, renal and coagulation alterations and deviation of the dissociation curve of hemoglobin to the left.
Infused solutions, as well as ventilation gases, should be heated with humidifiers and inspired gas heaters, thermal electric blankets, all directed to maintain a core temperature of 35°C.
Hyperpyrexia should be avoided; in patients who had infections we must ensure negative cultures, negative screening for emboligenic foci from the heart and other locations, and adequate antibiotic treatment before authorizing organ donation.

Hematological Control

The origin of hematological disturbances is multifactorial: it may be due to severe blood loss in multiple trauma, previous transfusions with citrated blood, hypothermia and the continued release of large amounts of tissue fibrinolytic factors, as well as severe skull base trauma, multiple fractures internal organ (liver) injuries, major pelvic fractures or severe leg damage. Furthermore, ischemic-necrotic tissues can release great amounts of thromboplastin. There may also be non-specific abnormalities due to disseminated intravascular coagulopathy. Treatment is based on the administration of plasma and platelets and packed red cells if the hematocrit is <30% for kidney donors or 35% for multiorgan donors.

Renal Function

It is necessary to maintain an hourly urine output of 1 ml/kg in adult patients and 2 ml/kg in children. Polyuria, (urine output >3-4 ml/kg) can perpetuate a situation of hypovolemia due to diabetes insipidus or hyperglycemia.
If the donor is oliguric, with urine output <0.5 ml/kg/h despite maintaining adequate blood pressure and appropriate central venous pressure, administration of diuretics will be necessary. The most frequently used include furosemide at doses of 20-60 mg and intravenous mannitol at doses of 0.25-0.50 g/kg.

Specific Corneal Care

Exclusion criteria for cornea donation are the same as general criteria. We should specifically take care of the donor's eyes, trying to keep them moist and properly occluded. Periodically, lubricants, artificial tear solutions, antibiotic drops of tobramycin or gentamicin should be administrated. Occasionally, corneal epithelial alterations should be minimized with the administration of local cold.

95.2.5 Tests and Special Care for Organ Donation. Diagnostic Determinations in Intensive Care

General diagnostic tests are performed to monitor potential donors; however, to evaluate different viscera we must follow a series of requirements as described below. A general test is the determination of blood count and blood group with Rh factor and investigation of isogroups, which have been obtained by previous requirements. In addition, immunological compatibility between donor and recipient is necessary for heart, liver and lung transplants, as is determining serology. Determination of the type (typing) by extracting lymph nodes is not usually done in the ICU, but is now performed in the operating room.

Monitoring and Special Tests for Lung Donation

Previous care is essential to avoiding volutrauma and barotrauma in mechanically ventilated patients. Indispensable is serial monitoring of blood gases. Assessment will include previous infections, history of smoking, drugs, chemotherapy or radiotherapy, and evaluation of previous occupational risks.

Determination of specific laboratory profiles and arterial blood gases, pH, partial pressure of O_2, CO_2, and serum bicarbonate must be monitored every 4 hours. Before a patient can be considered as a potential lung donor, it is imperative to measure PaO_2 >300 mmHg after the administration of 100% oxygen for 15 minutes with a PEEP of 5 cmH_2O.

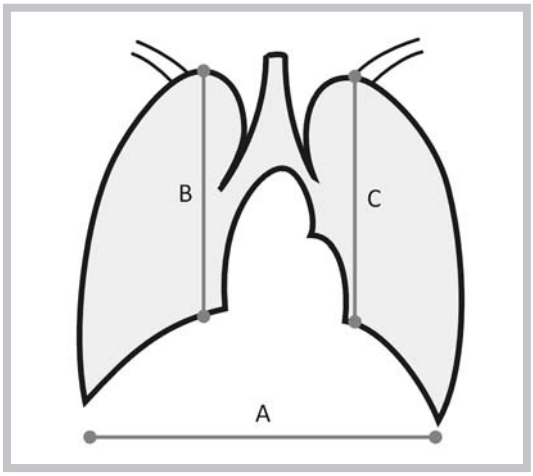

Figure 95.3. **Measures to determine the suitability between donor and recipient: dome-lung apex axis (B and C) and the largest thoracic diameter measured between both costophrenic sinuses (A).**

Chest radiography is important for lung assessment. Check for the presence of pneumonia, neurogenic or cardiogenic pulmonary edema, pneumothorax or hemothorax, which are highly prevalent in patients with severe head injuries under mechanical ventilation. Anthropometric assessment will include measurement of body weight, height, waist circumference and chest circumference. Lung transplantation also requires measurement of the diaphragmatic dome-lung apex axis (B and C) and the largest thoracic diameter measured between both costophrenic sinuses (A) (Figure 95.3).

Monitoring and Special Tests for Heart Donation

It is essential to anticipate an adrenergic storm, which is not dangerous for the heart and will not provoke heart failure. Just as in the lung donor, we must search for salient events in the medical history and risk factors. An ECG is essential.

Determination of specific cardiac laboratory profiles: levels of CPK, CK-MB, troponin to assess possible heart damage, especially in cases of chest trauma, cardiac arrest and cardiac massage.

ECG is mandatory and as is coronary angiography in patients over 45 years of age, so we can assist the donor as quickly as possible.

Monitoring and Special Tests for Liver Donation

Complete and detailed medical history and determination of risk factors for liver disease.

Determination of the hepatic profile: levels of GOT, GPT, GGT, total and direct bilirubin, glucose, electrolytes and clotting times, prothrombin time, partial thromboplastin time and INR. Alterations in these enzymes may indicate chronic liver disease, hepatic necrosis secondary to tissue hypoperfusion due to complications arising from maintenance of hemodynamic status. Also important is the search for tumour markers such as alpha-fetoprotein associated with hepatocellular carcinomas and germ cell tumours.

Abdominal ultrasound.

Monitoring and Special Tests for Kidney Donation

Detailed clinical history and risk behaviours.

Renal profile by laboratory determinations should include: complete urinalysis, proteinuria, blood urea and creatinine.

Also indispensable is determination of chorionic gonadotropin (HCG) to search for choriocarcinoma, germ cell tumours (ovary and testicles), and tumours with ectopic secretion of HGH such as urinary bladder. Prostate specific antigen (PSA) as a marker of prostate cancer, has significance when the values are >10 mg/l.

Ultrasound assessment of the kidneys and excretory pathways.

Monitoring and Special Tests for Pancreatic Activity

Clinical history and risk behaviours are a common step to other organs, focusing on smoking habits, history of gallstones, and alcohol consumption.

The specific pancreatic profile for the laboratory includes: blood glucose and serum amylase and lipase, especially for assessing the viability of the pancreas for transplantation. Lipase levels are not usually affected by brain death, but blood glucose and amylase >10 mg/l are.

Ultrasonography of the pancreatic area; computed tomography (CT) is mandatory if there are any abnormalities in the parenchyma or their excretory pathways.

Key Concepts

- It is important to know the pathophysiological changes that occur in the body once the brain has lost control. Taking these changes into account helps us to determine its specific value and facilitate the treatment of deviations in homeostasis. However, there are many aspects that are yet to be determined and clarified in observational studies.
- We perform a minimum of diagnostic tests and monitoring of variables; the complexity to reach stabilization can be as intense as the maintenance of a living patient.
- The management of control systems of the donor requires not only hemodynamic management with fluids or amines, but also cardiac control after adrenergic discharge. Beta blocking drugs are generally not necessary.
- Implement lung protective ventilation with low lung volumes and PEEP.
- Endocrine and electrolyte disturbances are one of the fundamental problems: hypernatremia, hyperosmolarity and potassium imbalances. Thyroid hormone levels often behave as in sick euthyroid patients. Diabetes insipidus and hypocortisolism can be effectively treated with hormone replacement: vasopressin, desmopressin, T3 or T4, hydrocortisone or methylprednisolone.
- Hypothermia is common, although occasional hyperthermia is present, which is difficult to explain but almost always associated with infection prior to brain death.

- It's very important to preserve hourly diuresis in adults at 2 ml/kg/h and 1 ml/kg/h in children.
- The brain-dead patient may develop blood disorders of varying severity.
- It is always possible to donate corneas.
- We will know the tests to be performed to assess different organs because they sometimes require specific examination when unstable donors are transferred out of the ICU.

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96 Reporting Neurocritical Patient's Status to the Family

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96.1 Introduction

Neurocritical illness, a group of life-threatening diseases of the brain and spinal cord, is associated with poor prognosis or slow recovery, disability or chronic medical complications. The most common include: cerebral hemorrhage, ischemic stroke, head injury, seizures, and infections such as meningitis. Mortality from these diseases has declined in parallel with the intensity of care received, whereas morbidity has risen with the growing number of patients surviving with sequelae, deterioration in quality of life, and mounting social and health costs in the treatment of neurocritical injury and its aftermath.

Communicating information about diagnosis, treatment or prognosis carries a significant emotional burden for both the team attending the patient and their families. Often this communication is imparted in public places (hall information) or at inappropriate times (request for informed consent), augmenting anxiety, uncertainty, and sometimes distrust toward the treating team. Clearly conveying information about the patient's progress and demonstrating a willingness to answer questions can help to reassure the families and establish confidence.

The intensive care unit (ICU) team must be trained to inform family members about the patient's condition and to allow time them time to accept this "news."

In the doctor-patient relationship, "giving bad news" refers to situations where a feeling of hopelessness predominates, along with a sense of threat to the person's physical and mental well being, a risk to their lifestyle or where the message involves making important personal decisions. Bad news can sometimes be associated with a less "severe" diagnosis such as a temporary disability, the administration of traumatic or painful treatment, or even something that for the attending staff seems banal but comes at an inopportune time, for example, surgery a week before a daughter's wedding or informing a professional athlete fully recovered from a head injury that he or she may perhaps never be able to compete again, and so on.

In such situations, the family plays a central role as the majority of neurocritically ill patients are at different stages of neurological impairment or coma and are unable to understand any information. Subsequently, family members will be called to intervene in the decision-making process because they are usually the ones who best know the patient's preferences and desires. However, these are the same families who are anguished by the threat of imminent death of their loved one. So what we must keep in mind is that, because the family is at an emotional loss, they will barely understand the unpredictability of the course of the illness or treatment outcome.

One of the main ways to reduce the risk of medical litigation is through constant communication among the treating team members, openness to dialogue, and providing accurate information across the entire therapeutic process.
About half of the families of patients in intensive care experience difficulties in communicating with their doctors. This shortcoming can be resolved by answering three questions:

- Which are the common mistakes?
- What do you expect from the family behind the door?
- How should bad news be communicated in the ICU?

96.2 Which Are the Common Mistakes?

The family is relegated to a minor role that is usually overlooked in medical reasoning. After we define the diagnosis, after planning a strategy, often (only much later) someone on the team asks: "And how much does the family know...?" Meanwhile, the family has been suffering from the uncertainty of having their loved one in an ICU. This uncertainty always generates worry and fear, especially when the patient is young and unexpectedly ill. Added to this is the changing and unforeseeable course of intensive care patients. This gives rise to legitimate concerns, "But if he/she walked into the hospital... How can he/she be so serious now?" or "The doctor told me that yesterday he/she was better... How can it worsen so suddenly?"
The ICU is bewilderingly complex: differences in care protocols, routines, attitudes and conduct, diverse visiting hours and staff change from shift to shift. These changes are often seen by the family out in the waiting room as an inconsistency that arouses the suspicion that such inconsistencies can reoccur in other even more important areas of care, for example, the use of analgesics or antibiotics.
In this context it is important to ensure that communication is smooth, consistent and honest with the closest family members. This is achieved by speaking clearly, without jargon. For example, instead of saying "oliguric", you can say "urinating little"; instead of saying "has a pump failure", you can say "his heart is weak". It takes training to handle this basic language with ease in front of family members.
Also, another group of people (friends, doctors, etc.) may also request information.
Many families have one or two spontaneous leaders who are important to identify because their status (age, educational level, profession) can exert a decisive influence on the family. Part of the success of the interview relies on how we communicate with such heads of the family. To keep the information consistent and uniform, the same doctor who writes the report should speak with the family. This information should be imparted calmly, ensuring there is privacy to talk and listen in comfort. There should be no excuses or exceptions for delaying information. Waiting rooms are filled with tension and anxiety grows the longer the delay in receiving news. On the caregiver's side, being punctual expresses respect and consideration for the family. The report will necessarily include the family's needs and the complexity of the patient's situation.
When we refer to the diagnosis, we should express ourselves with honesty and common sense, supported by our knowledge to predict the outcome in critically ill patients. It is appropriate to set short-term goals ("We want to improve your ability to breathe... And then find the cause of respiratory distress."). Once we have defined the plan, it is good practice to make it known and also report alternative plans: this alleviates anxiety and builds confidence within the team. The diagnosis should be adequately detailed and supported by additional studies, which can often be useful to illustrate the structural damage the patient has sustained and present it in a way the family can understand.

All team members must be trained to report consistently, even after hours if necessary, on all changes that occur, including interventions such as intubation, chest tube placement, tracheostomy, and they should be reported to the family prior to the procedure. Omissions in this respect are a source of conflict or loss of confidence.
Nursing staff should be involved in the reports since nurses can help to answer specific questions and collect complaints or opinions from family members. The report must include daily nursing notes to complement the medical report. This allows for documenting information on certain topics such as sleep quality, care of pressure sores, food and mood in a more thorough and timely manner. Nursing notes will support the reports with personal information and impressions gathered in the waiting room.

96.3 What Does the Family Outside the ICU Door Expect?

- Expect respect for personal values, beliefs, preferences and needs. Most family members feel anonymous; making the effort to call them by name has a high value.
- Expect integrated and qualified care which we must ensure is happening. One way is to answer all questions clearly and without hesitation.
- Expect accurate information; if the news is not good it should at least be truthful.
- Expect emotional support given by a health professional who treats them as such; this means that the professional will provide status reports of the patient but also listen to their fears, respect their beliefs, and use words as a therapeutic gesture in the full context of care.

96.4 How Can I Give Bad News?

At the initial interview with the family, the members are anxious and tense. As mentioned above, "bad news" has at least one target component (depending on the severity of the bad news) and a subjective component that depends upon several other factors such as the time when information is given, the psychosocial context, the age of the patient, family and personal obligations, previous experience of illness, values and beliefs, and so on.
The current literature supports the idea that families prefer care professionals who speak with a normal voice – not aggressive or dismissive or superior – and allow the family to ask questions and express their feelings through sincere dialogue.
Studies have shown that learning communication skills can have a positive impact on both the giver and the receiver of bad news. To facilitate this task, a six-step protocol described by Baile and Buckman is given below. Although intended for patients and families of cancer patients, it is highly useful and can be adapted to the management of information from relatives of intensive care patients.

96.5 Steps of Management

96.5.1 Step 1: Preparing the Report

Assemble a detailed review of medical records and confirm the diagnosis, either presumptive or definitive. Establish a mindset of what you want to report, and that it will

be done in a private place without interruptions. Start the interview with a greeting and introductions of the family group, and then invite them to sit down.

96.5.2 Step 2: Discovering What the Family Members Know

Most often the patient will be absent from the report due to illness or coma or under sedation-analgesia and mechanical ventilation. It may be helpful to ask family members: "What do you know already about what is going on?" This question will tell us how much the family group knows about the processes involving the patient; however, the stress of the situation or degree of disruption often does not allow family members to express themselves properly. Seize this stage to assess the cultural level of the family and the emotional weight bearing on the illness event. Depending on their educational level, families may have distorted ideas or confusing opinions. Knowing this in advance will help us to reinforce points in the report that are inaccurate or misleading.

96.5.3 Step 3: Recognizing How Much You Want to Know

The objective at this stage is to match the information you give to what you want to know. Questions like "Do you want me to tell you how the operation will be", "Is there someone you would like me to tell related to what's going on?" This can only be done if the patient is awake and able to process the information that we provide.
In reporting to the family we must take into account that:

- Many families mount a defence mechanism to minimize painful truth or request that you repeat certain topics in the hope that the adverse news may be amended. It is essential that the information supplied to them is clear, firm and true, without creating false expectations.
- Wider access to medical information through magazines, television or the Internet ideally provides for a better understanding of the situation their family member is in; however, this information can be confusing: experimental therapies under investigation or quasi-miraculous cures touting treatments known from the evidence to be ineffective. Such misinformation must be counteracted with the conviction that the treatment the patient is receiving is appropriate, averting useless discussions that lead nowhere.

By the same token, we must be open to the possibility that the family expresses the wish for a second opinion or consultation. Often this is the result of pressure from the family or the fear of losing a loved one. Providing access to a second opinion will help the family to lessen the emotional burden and increase confidence in the treatment team. If we act by applying scientific medical criteria and principles of bioethics, a second opinion can bring more satisfaction than ingratitude.

96.5.4 Step 4: Communicating Information to Families

During critical care it is useful to know the gap between the patient's or family's expectations raised by the actions of the treatment team and the effective enforcement of those expectations. The greater the gap between expectations and reality, the greater the emotional stress on the family, the greater the feeling of dissatisfaction and the lower the degree of communication.
Use simple language appropriate to the family's intellectual and cultural level.

Information can be imparted all at once or divided into smaller topics, making it more effective to improve understanding on the part of the family. We should start with general issues before focusing on more complicated topics or problems that are difficult to communicate, and then lead into a possible prognosis. Before talking about an adverse prognosis, we should begin with an introductory sentence, "We fear that the course is not what we expected". This will relieve the emotional impact of the bad news to come. Avoid using technical terminology; instead, be clear and understandable, leaving space between sentences to allow emotions to flow, be honest and always maintain good eye contact with family members. When imparting vital information it will be important to repeat it several times throughout the report, so that it is better perceived by the family. Throughout the report we will also need to check how much the family has understood of what we have said.

96.5.5 Step 5: Responding to the Family's Reactions

The impact on the family of bad news can be chaotic if given haphazardly. Humour is inappropriate during the report since it can be mistaken by the family. Avoid discussing long-term scenarios and predictions when short-term goals could be more realistic. Assure the family that you will keep them informed continuously of the situation as it changes and that their questions will be answered in future reports.
Patients and their families react to receiving a diagnosis in different ways. An effective way to counter overreaction is to provide an empathetic response. A typical empathetic response comprises 4 stages:

- Try to identify the main emotion that overwhelms the patient and their family.
- If the diagnosis is met with silence, ask how they feel.
- If it is the patient who receives the "bad news" and move physically closer if you can touch their arm or hand. Tell them that their reactions are understandable.
- Allow enough time for the patient to freely express their feelings and emotions.

96.5.6 Step 6: Designing a Treatment Plan

One of the main factors that causes distress in the relatives of ICU patients is uncertainty. It must be handled in a clear, sensible, subtle and delicate manner, explaining that the therapeutic goals are modest, short-term, not miraculous or immediate cures, and that the outcome will ultimately depend on the dynamics of myriad factors that will influence every forecast (avoid creating unfounded expectations of clinical improvement). The objectives at this stage are to show the family that the treatment team is concerned about their ill family member, that a treatment plan is being followed, that if the results are not those expected, there are alternative plans that will be initiated started without delay, and that many decisions will be shared (request to conduct early tracheotomy).
All therapeutic interventions should be mentioned, including urgent intubation, placement of catheters or drainage tubes, mechanical ventilation, surgery and other procedures. They should be communicated and explained clearly and in as much detail as necessary; not doing so invites conflict and no end of ethical, moral and medicolegal contention.
This takes into account the following aspects:

- If the patient asks about his prognosis, provide him or her with a realistic hope.
- Always consider the views of patients and their families.
- Explain and justify the tests and treatments planned.
- Develop alternative plans.

Often, the gravity of the situation or the management of urgency does not allow enough time to follow through with all these initial steps; nonetheless, "emergency" does not justify "misinformation." Once the urgent actions have been taken and the patient's condition and family so permit, the report must provide adequate, detailed and updated information. Do not terminate a family interview leaving the main topics to be covered by the report to the family.

Providing a flow of information on the relationship between the health team, patient and family is one of the most complex and important challenges we face daily. Often communication skills are not taught in academic undergraduate or graduate courses, so it becomes a matter of individual training.

Proper notification of relatives is a therapeutic moment that can lay the basis for a smooth flow of communication, permitting the family to work with the treatment team toward a common goal for the patient's benefit. We must remember that the family and the patient go through different emotional states and that families will express their own needs, fears and worries about their loved one's condition and care. If we can capture these fears and alleviate them, if we can explain the most likely prognosis, treatment options, in brief, if we support the family, we are supporting the patient.

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97 Ethical Considerations in the Neuro-Intensive Care Unit

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97.1 Introduction

Decisions to withhold or withdraw life-sustaining care are some of the most difficult and ethically challenging decisions made by physicians and family members in the intensive care unit (ICU), primarily because the patient will likely die within hours after making the decision so there will be little or no opportunity to change your mind. Such decisions typically are made for comatose patients, or those with rapidly progressive and incurable medical disorders such as metastatic cancer, or end-stage cardiac or pulmonary disease. Less frequently they involve withdrawal of life-support therapies for alert patients with steadily progressive diseases for which there currently is no effective treatment, such as Parkinson's disease or amyotrophic lateral sclerosis. Ethical questions revolve around issues of autonomy, confidentiality, futility of treatment, surrogate decision-making, the best-interest principle, and the withholding and withdrawal of treatment (Table 97.1). Respect for patient autonomy and dignity are fundamental ethical components of end-of-life decision making. The overarching ethical principle is that treatment of the patient should not simply prolong the process of dying, and should meaningfully incorporate patient and family concerns about the quality and dignity of life. For example, cardiopulmonary resuscitation of the terminal cancer patient is considered by most as a violation of the dignity of the irremediably ill.

Treatment of the patient with terminal illness should change from "critical care" to "palliative care", or from a reductionist approach to a more humanistic approach. Most patients, families, and health care providers believe that such palliative care should be home-based and focused on ameliorating patient symptoms through minimally invasive means, rather than hospital-based acute care which has as its primary focus to extend life through invasive approaches. But in the U.S. critically ill patients for whom no effective therapy exists are routinely transferred to the ICU without end-of-life discussions. Rady et al. examined the end-of-life care of 156 such patients, none of whom had discussions of palliation or end-of-life care as an alternative treatment prior to transfer to the ICU [1]. The authors concluded that the quality of end-of-life care was substantially disrupted as a result of their admission to the ICU and the intensity of invasive care associated with that transfer. Lack of clinical experience, knowledge, and competency with end-of-life care influenced admission of patients to the ICU regardless of poor prognosis. The rate of progression of the disease also influences recommendations for acuity of care. In one large study, those with end-stage COPD were 3 times more likely than those with lung cancer to be institutionalized in a long term care setting or receive long-term home care dur-

- Autonomy
- Confidentiality
- Futility of treatment
- Surrogate decision-making
- The best-interest principle
- Withholding of treatment
- Withdrawal of treatment

Table 97.1. Ethical concepts encountered in the ICU.

ing the last 12 months of life, whereas those with lung cancer, a much more rapidly progressive disease, were more likely to be hospitalized in an acute care hospital during that time [2].

The medical certainty of the physician's prediction of futility of further treatment, and ability to clearly communicate that certainty to the patient and/or family members, are critical components of the end-of-life decision making process. For many diseases, such as severe traumatic brain injury, massive stroke, or metastatic cancer, the terminal nature of the disease is clear. But for other diseases, such as gradually progressive dementias and chronic pulmonary or cardiac diseases, it may not be, and instead the disease may result in a slowly deteriorating quality of life and gradual loss of independence. In one Swiss study, disagreement between nurses and doctors was frequent with respect to the doctor's judgment of futility of medical interventions [3]. In general, nurses were more pessimistic but were also more often correct than doctors in predicting which patients would die. In that study of 521 ICU patients, it was apparent that the future quality of life could not be reliably predicted either by doctors or nurses. With advancing technology, there now is a computerized decision-support tool, the Acute Physiological and Chronic Health Evaluation III (APACHE III), which predicts the probability that a patient will die. APACHE III already is being used in several California hospitals to "prove to payers that healthcare resources are being used effectively and efficiently", but the APACHE data is not routinely shared with patients or surrogate decision makers [4].

97.2 End-of-life Decision-making

In the U.S., the concept of end-of-life decision making arose more than 50 years ago out of the acceptance of "brain death" as a criterion for permitting comatose patients who meet specific objective medical criteria to be considered "dead" for the purposes of ventilator withdrawal and organ transplantation. In parallel with the transplantation issue, a firm consensus has emerged in U.S. law and ethics that patients have a virtually unlimited right to refuse any unwanted medical treatment, even if necessary for life itself. Indeed, one of the two most important factors for perceived quality of death experiences is not having cardiopulmonary resuscitation during the last 8 hours of life, the other being having someone present at the moment of death [5]. And because they are trained to aggressively treat and attempt to cure disease, physicians generally tend to be less inclined toward hospice care or quality-of-life considerations. Because of advances in technology that have influenced a more aggressive approach of medical professionals to end-of-life care, physicians often offer medical interventions when such interventions may not be necessary, or may not significantly alter the quality of life. However, some recent studies suggest a change in this tradition. In one survey of 118 community-dwelling persons 65 or older with advanced disease, 58% of those with a desire to receive highly intensive intervention to treat their underlying disease received only symptomatic treatment [6]. This study, at least, suggested that many "terminal" patients were receiving less aggressive care than they were willing to undergo.

The hospice and palliative care movements have been instrumental in increasing the understanding of end-of-life care, and in providing patients alternatives to dying in the hospital. The most significant barrier in coordinating and providing end-of-life care is inadequate communication, and at present only 25% of patients who would be eligible for hospice actually enter hospice programs. Early discussion of prognosis and end-of-life care options can help facilitate earlier entry into hospice and palliative care programs. But the reality is often very different, and a survey of 29 cancer nurse specialists found

that interventions in the acute setting are typically driven by a preoccupation with treatment, routine practice, and negative perceptions of palliative care [7]. All of these factors can shape clinical decision-making and prevent patients and their families from fully participating in clinical decision-making at the end-of-life. But it is clear that the implementation of a formal palliative care protocol can improve the quality of care provided to patients dying in an acute care setting. In one prospective study, the implementation of such a program resulted in a significant increase in the number of symptoms documented, and the number of care plans recorded [8]. Opioid medication availability increased from 57% to 83%, and do-not-resuscitate orders increased from 62% to 85%. And these improvements in the delivery of palliative care did not result in an increase in the mortality rate in the ICU, suggesting that they were not simply medical interventions intended to hasten death.

The effect of race and cultural background on end-of-life decision-making has been examined, and at least one U.S.study of 9,076 patients hospitalized with illnesses associated with an average 6-month mortality of 50% did not find that race was associated with decisions to withhold or withdraw ventilator support or dialysis, or to withhold major surgery. However, another U.S.study found that patients with access to a private attending physician were significantly less likely to undergo the active withdrawal of life-sustaining therapies than were patients who did not have a private attending, despite having similar predicted mortality rates by Acute Physiology and Chronic Health Evaluation II scores [9]. That study also found that the patients who did not have a private physician had significantly shorter hospital and ICU lengths of stay, a shorter duration of mechanical ventilation, and fewer total hospital costs and charges. Since access to private physicians is directly related to the patient's economic status, these findings suggest that, in the U.S. at least, socio-economic status can be an important factor in determining the quality of end-of-life care a patient will receive. In addition, the quality of care at the end of life is strongly correlated with where patients die. Both patient and health care system variables effect access to the most common venues of death, such as hospice facilities, acute care hospitals, nursing homes, or the patient's own home. And studies of patients' care and treatment preferences at the end of life suggest that they prefer comfort more than life-extension, wish to participate in decision-making, and wish to die at home.

To be sure, the effectiveness of palliative care programs in promoting end-of-life decision-making is closely associated with the certainty of the prognosis. For example, with patients who have advanced dementia it can be difficult for a palliative care team to influence the care the patients receive in the acute hospital setting because there often is prognostic uncertainty, difficulty assessing the patient's comfort level, and biases among the decision makers. In addition, the likelihood that the terminally ill patient may have access to, or take advantage of, palliative care may be related to their age. Studies suggest that elderly patients with terminal illnesses are much more likely to receive palliative care prior to death, while patients younger than 50 years are more likely to be admitted to acute care hospitals and receive invasive life-support measures.

97.3 Advanced Directives

Advanced directives were devised as a means of expressing the individual's refusal to live in deep unconsciousness with no chance for recovery. Most believe that advanced directives should be respected because they comprise the patient's autonomous decision concerning life-sustaining treatment and death with dignity. The vast majority of patients who die in acute care hospitals, nursing homes, or hospice facilities have "do-

not-resuscitate" orders in place, indicating that the health care providers and family members have been anticipating their death. In a study of 64 patients aged 55 and older who were admitted to an ICU after injury and subsequently died, 23.4% had written advanced directives available [10]. Those with advanced directives were much more likely to have withdrawal of life-sustaining therapies prior to death than were those without such directives.

However, the implementation of Advanced Directives is often complicated by uncertainties of prognosis. It is not always clear, especially in the case of trauma or stroke, if a brain injury will cause a permanent vegetative state or if that patient can in fact regain consciousness. Moreover, preferences for life-sustaining treatment are dependent on the context in which they are made, and individuals may express different treatment preferences when they are healthy than when they are ill. For example, in one study of 88 individuals 65 or older, who were hospitalized for 48 hours or more, the subjects reported less of a desire to receive life-sustaining treatment, and particularly cardiopulmonary resuscitation or artificial nutrition and hydration, when surveyed 14 days after discharge from the hospital than they did prior to their hospitalization [11].

The decision of a patient or patient's family for a "do-not-resuscitate" (DNR) order clearly has important implications for the care the patient subsequently receives. In one retrospective cohort study of 174 moribund patients, those who did not have DNR orders received significantly more inotropic agents, dialysis, and mechanical ventilation at the time of death compared with those who did [12]. Conversely, DNR patients received a 5-fold larger cumulative dose of morphine during their final 12 hours of life. In one study of 270 patients with spontaneous intracerebral hemorrhage, outcomes for those with early (<24 hours from presentation) DNR orders were compared to outcomes for those without such orders [13]. After adjustment for age, gender, ethnicity, Glasgow Coma Scale score, hemorrhage volume, and presence of intraventricular hemorrhage, there still was a 2-fold increase in the likelihood of death for the 34% of patients with an early DNR order. And in a study of nearly 5,000 patients admitted to 11 different hospitals with acute heart failure from 1995-2000, it was found that patients with DNR orders were less likely to have had their left ventricular function assessed, or to receive renin-angiotensin system blockade, anticoagulation, or nonpharmacologic interventions compared with those without DNR orders [14]. Thus, the designation of a patient as "DNR" led to a markedly lower use of quality assurance measures in patients with heart failure.

Patients with dementia also are more likely to have DNR orders and receive less aggressive medical care toward the end of their lives. In a retrospective study of 94,100 patients aged 67 or older, the likelihood of being admitted to the ICU, or receiving ventilatory assistance, cardiac catheterization, pulmonary artery monitor, or dialysis during the last 30 days of their life was compared for patients with and without dementia. Compared to those without dementia, the 31,654 patients with dementia were significantly less likely to receive any of these five aggressive medical therapies at the end of life [15].

In addition, there can be significant differences in the interpretation of hospital resuscitation policies, and of what DNR decisions mean in relation to the practical care of patients. One report from Ireland cited confusion in translating policy into practice as contributing to communication difficulties in initiating, documenting, and implementing cardiopulmonary resuscitation decisions [16]. In this regard, one interesting and potentially challenging problem is the temporary suspension of DNR orders during the perioperative period for surgery that is recommended to resolve a treatable problem or improve quality of life. The alert patient, or family members of comatose patients, are especially disturbed when they realize that the procedure involves the temporary placement of an endotracheal tube and mechanical ventilation because this intervention is so emblematic of the prolongation of life that they are trying to avoid. Such cases often re-

quire detailed discussions with the patient or family member in order to convince them of the need for the procedure, or that the procedure will be beneficial to the patient and is not just meant to prolong life. A trusting relationship between the treating physician and patient or patient's family is essential under these circumstances.

97.4 Withholding or Withdrawal of Treatment

Withholding or withdrawing of life-support practices vary between countries, ICUs, and individuals depending on cultural and religious backgrounds, family and peer pressures, and local practices. But such decisions must always respect four key ethical principles: beneficence, nonmaleficence, autonomy, and distributive justice [17] (Table 97.2). It is incumbent on healthcare providers to be sure that families and the dying patient never feel abandoned, and nurses and doctors should make it very clear that *care* is not being withheld or withdrawn, only unnecessary medical interventions. Unfortunately, decisions to withhold or withdraw treatment are often not given sufficient attention by healthcare providers, and studies suggest that physicians need to do a better job communicating with family members about the various ramifications of these decisions. In one study of 102 elderly patients with terminal diseases admitted to two acute care hospitals in Spain for terminal care, relatives or other primary care givers were questioned about various aspects of the care being provided [18]. The relatives felt that the medical information they were given was accurate in only 67.6% of cases. Control of medical symptoms was considered good in 55%, but there was a perception that pain persisted in 14%, and 45% of patients had uncontrolled dyspnea. Predicting outcomes for critically ill patients is an important aspect of discussions with families in the ICU, but such predictions also can bias the care that ICU physicians may provide, or at least recommend. In one study, mechanical ventilation, inotropes or vasopressors, and dialysis, were significantly more likely to be withdrawn if the physician predicted a less than 10% probability of survival for the patient [19]. Indeed, such predictions were found to more powerfully predict ICU mortality than illness severity, evolving or resolving organ dysfunction, and use of inotropes or vasopressors.

Discontinuation of the mechanical ventilator, and removal of the endotracheal tube, are the most common ways in which life support systems are removed from a patient for whom no further treatment would be of benefit. Patients may be judged to be "symptomatic" during the process of extubation, and require sedation with either a benzodiazepine or opioid medication. In one study of 22 ICU patients, sedative or analgesic medications were given to 75% of the patients during withholding or withdrawal of life support [20]. The recorded reason for administering the medications was to decrease pain in 88%, decrease anxiety in 85%, decrease air hunger in 76%, to comfort families in 82%, and to hasten death in 39%. But in no instance was hastening death the only reason cited for administering the sedative or analgesic. During the 24 hours prior to withholding or withdrawing of life-support, average doses of diazepam were 2.2 mg/h, and of morphine were 3.3 mg/h. After withholding or withdrawal of life-support significantly higher doses of the medications were administered, with average doses of diazepam of 9.8 mg/h, and morphine sulfate 11.2 mg/h. In one Canadian study, the family members of 206 ICU patients who had mechanical ventilation discontinued prior to death were interviewed regarding

- Beneficence
- Non maleficence
- Autonomy
- Distributive justice

Table 97.2. **Key considerations for withholding or withdrawal of care [17].**

their perceptions of the comfort of their loved-one prior to death [21]. All patients were sedated following withdrawal of mechanical ventilation, with the most common medication being morphine (119 pts), followed by midazolam and lorazepam. In 91% of the cases, family members reported that their loved-one was totally, very, or mostly comfortable at the time of death.

Family members should be prepared for a possible delay in the patient's death following extubation, and it should not be suggested that death will necessarily occur immediately. In one study of 32 non-brain-dead patients who were terminally extubated, 25% died within an hour of extubation but one third of the patients survived for 24 hours or more, and the median survival following extubation was 7.5 hours [22]. Moreover, removal of the endotracheal tube often is associated with excessive respiratory secretions that can cause a distressing stridor which may lead relatives to believe the patient is choking and suffering. This "death rattle" is most commonly reported in patients dying from pulmonary malignancies, primary brain tumors, and brain metastases, and predicts death within 48 hours in 75% of patients. A group in the Netherlands has developed a medical protocol that they claim is effective in eliminating the death rattle [23]. Six hours before extubation, enteral feeding is stopped and parenteral fluids are reduced. Overhydrated patients are dehydrated with furosemide. Sedatives, opiods, and methylprednisolone are administered, and butylscopolamine is given 30 minutes before extubation. As a result of this treatment, the authors claim that the terminal extubation process is calm, and not associated with respiratory stridor or undo distress of the patient's family. However, terminal restlessness, or the unsettled behaviors and delirium that occurs in a substantial proportion of patients during the last few days of life, may sometimes be due to some of these same medications. Treatment induced delirium or restlessness has been associated with opioids, antisecretory agents, anxiolytics, antidepressants, antipsychotics, antiepileptics, steroids, and nonsteroidal anti-inflammatory drugs.

Withholding or withdrawal of the feeding tube is considered by most to be the single most controversial and ethically challenging decision for both family members and treating physicians. For example, a survey of Japanese physicians revealed that while most were comfortable withholding mechanical ventilatory assistance, the majority felt that tube feeding should actually be initiated in patients with terminal illness [24]. In fact, half of those surveyed did not even view tube feeding as "life-sustaining treatment". However, when it is clear that death is imminent, and particularly when the patient is obtunded, the provision of nutrition and hydration is usually considered futile. And while the primary concern has been that withholding of these fluids is cruel and causes the patient to suffer, experienced palliative care doctors and nurses have actually found that terminal dehydration appears to lessen suffering for dying patients [25]. These experts have found that medically assisted nutrition and hydration at the end of life rarely benefits patients, and as long as adequate mouth care is given, patients do not suffer.

97.5 Surrogate Decision Makers

Family members or other next of kin are often called upon to help make decisions about withholding or withdrawing life-support for patients with terminal, untreatable diseases who are cognitively impaired or unconscious. Their decision-making ability or confidence is largely related to the level of trust they have in the information being provided by the treating physician, but often times very little trust exists. This may be because many of these patients present following sudden, catastrophic events such as stroke or trauma, and there is little time for family members to establish a trusting relationship

with the healthcare providers. Zier et al. interviewed 50 surrogate decision-makers of critically ill patients in the intensive care units of a public hospital, a tertiary care hospital, and a veteran's hospital in San Francisco [26]. All but 6 of the 50 surrogates had doubts about the treating physician's ability to prognosticate the outcome of the patient. The primary reasons for this doubt were a belief that God could alter the course of the illness or that predicting the future is inherently uncertain, prior experiences where physician's prognostications were inaccurate, and other experiences with prognostication during the patient's intensive care unit stay (Table 97.3).

Some of the most important factors leading to a belief in the physician's prognosis were receiving similar prognostic information from multiple physicians, and prior experiences where they received accurate prognostic information. In another survey of 81 surrogate decision makers at a large county hospital, nearly half of the family members indicated that they had a poor understanding of the nature of their family member's illness [27]. The primary reasons for this were that the surrogate decision makers were not given enough time to speak with the healthcare providers, or that the explanations they were given were too complicated. In their observations of 51 physician-family conferences in which there were deliberations about major end-of-life treatment decisions, White and colleagues found that physicians tend to focus on discussions about the anticipated functional status or quality of life of the patient [28]. The educational level of the family, as well as the degree of physician-family conflict about withdrawing life support, were independently associated with the extent of prognostic information offered by the physician.

The critical aspects of physician communications with family members was examined in a Seattle study of four different hospitals [29]. Fifty-one ICU family conferences in which withholding or withdrawing life support was discussed were audio taped and evaluated. From these analyses, three types of clinician statements were found to be associated with increased family satisfaction: 1) assurances that the patient will not be abandoned before death, 2) assurances that the patient will be comfortable and will not suffer, and 3) support for family's decisions about end-of-life care, including support for the family's decision to withdraw, or not to withdraw, life-support (Table 97.4). Another survey of 48 family members was done to identify critical psychosocial supports and areas of conflict for family members one year after decisions to withdraw or withhold life-sustaining therapy [30]. That study found that many families perceived conflict during end-of-life treatment discussion in the ICU that centered on the communication and behavior of staff. Pastoral care and prior discussions of treatment preferences were sources of psychosocial support. Private family con-

- A belief that God can alter the course of the illness
- A belief that predicting the future is inherently uncertain
- Prior experiences where physician's prognostications were inaccurate
- Other negative experiences with prognostication during the patient's ICU stay
- Not provided enough time to speak with the physicians
- The information provided was too complicated, not understandable

Table 97.3. **Typical causes for mistrust between family members and ICU physicians [26,27].**

- Assurances that the patient will not be abandoned before death
- Assurances that the patient will be comfortable and will not suffer
- Support for the family's decisions about end-of-life care, including support for the family's decision to withdraw, or not to withdraw, life-support
- Availability of pastoral care
- Prior discussions of treatment preferences
- Availability of private family conference rooms
- Lenient ICU visitation policies

Table 97.4. **Strategies most likely to engender trust and satisfaction with end-of-life decision making among family members [29,30].**

ference rooms and lenient visitation policies in the ICU were considered especially important.

Limerick interviewed 17 surrogate decision makers in a large Texas hospital system and developed a model for how typical surrogates make decisions for withholding and withdrawing of life-sustaining measures [31]. He described: a **personal domain**, in which the surrogate rallies family support, evaluates the patient's past and present condition, and views past and future quality of life; the **ICU environment domain**, characterized as chasing doctors, developing relationships with the healthcare team, and confirming probable medical outcomes, and the **decision domain**, characterized by the surrogate arriving at a new belief, getting alone to make the decision, and communicating the decision.

Decisions to withdrawal life support treatment are sometimes made without surrogate input, particularly if family members are not present or are difficult to contact. In other cases, physicians or the healthcare system itself may unilaterally require withholding or withdrawing futile medical interventions because of limited resources (financial and physical). The state of Texas passed the Texas Advance Directives Act in 1999, one provision of which allows a health care facility to discontinue life-sustaining treatment against the wishes of the patient or the guardian ten days after giving written notice if the continuation of life-sustaining treatment is considered medically inappropriate by the treating medical team. If they follow all the provisions of the Act, physicians and the hospital are provided legal immunity from prosecution. When there are disagreements between health care providers and surrogate decision makers, such disputes occasionally are settled in court. A review of such cases in Australia reveals three legal criteria for withholding or withdrawing treatment that have been incorporated in that country's common law: 1) present and future quality of life, 2) futility of present treatment, and 3) burdens versus benefits of present and future treatment and its discontinuance [32]. In a review of critically ill adults from 7 different hospitals in the U.S., 30 of 451 deaths in ICUs occurred after a withdrawal of life-support systems that was ordered by treating physicians without the input of a surrogate decision maker [33]. Most of these withdrawal of life-support decisions were also made without institutional or judicial review, and in a manner inconsistent with the American College of Physicians guidelines for judicial review. Other studies have shown that there are dramatic geographic variations in the prevalence of these unilateral decisions for withdrawal of life-sustaining therapies, and there is evidence that this variation may be driven more by physician attitudes and biases than by factors such as patient preferences or cultural differences. In one large public hospital, decisions to limit life support for 16% of patients who were admitted to the medical ICU, and lacked both decision-making capacity and a surrogate decision-maker, were made independently by the treating physicians and without judicial or institutional review [34]. The majority of these patients were white males older than 64 years.

97.6 Physician's Responsibilities

Improved communication between physicians and family members of critically ill patients can decrease the prolongation of dying in the ICU, but physicians frequently miss opportunities to listen and respond to family members, acknowledge and address emotions, and pursue key principles of medical ethics and palliative care. This includes the exploration of patient preferences, explanation of surrogate decision-making, and affirmation of non-abandonment. It is not always apparent how well physicians do with regard to communication and education of patients and family members. Comprehensive documentation of end-of-life care is lacking in many U.S.medical records, and one study

found that only 10% of the medical records of patients who died after withdrawal of care had documentation of physician participation in the decision making process [35].
In communicating with patients or their surrogates about withholding or withdrawing care, doctors typically withhold information about interventions that are judged too futile to offer. Thus, they retain greater decision-making burden and power, and face weaker obligations to secure consent from patients and proxies. Physician bias clearly has an overarching impact on decisions for withholding or withdrawing care for critically ill patients. In a Canadian study of 851 ICU patients receiving mechanical ventilation, the strongest determinants of the withdrawal of ventilation were the physician's perception that the patient preferred not to use life support, and the physician's prediction of a low likelihood of survival in the intensive care unit, but not the severity of illness and organ dysfunction as assessed on objective scales [36]. A large survey of 1000 generalist and subspecialist internists from Delaware found that respondents were least likely to withhold or withdraw treatment in those who were nonterminally ill, and in alert patients [37]. They were more likely to withhold or withdraw treatment from those with terminal illnesses, dementia or coma. In addition, respondents were most comfortable withholding or withdrawing dialysis and ventilators, and least comfortable withholding or withdrawing feeding tubes and antibiotics. This study clearly found that a large proportion of physicians may be unwilling to adhere to some patients' wishes to withhold or withdraw life-sustaining treatment, especially when they included withdrawing enteral nutrition, and that the clinical scenario and type of treatment are likely to affect the physician's decisions.
In one U.S.hospital, "Q Methodology" was used to locate and describe subjective influences on physicians for end-of-life medical decision making [38]. Second-order factor analysis on seventeen viewpoints used by physicians in four hypothetical urgent decision cases revealed that physicians were guided by patient-focused beneficence, a patient- and surrogate-focused perspective that included risk avoidance, and the best interest of the patient guided by ethical values. Economic impact on the physician, expediency in resolution of the situation, and the expense of medical treatment, were not found to be influential determinants in that particular study. From an ethical and medico-legal perspective, others have specifically emphasized three key issues: the distinction between allowing patients to die in accordance with their wishes versus causing them to die; the fine line between respecting a patient's wish to die with dignity and control versus the risk of subsequent allegations of euthanasia or physician-assisted suicide; and the adjunctive use of medications that simultaneously provide comfort but also may hasten death, such as high doses of morphine.
There is considerable debate about the use of "terminal sedation", with some arguing that this represents physician-assisted suicide or euthanasia, while others believe such treatment is good medical care aimed at reducing the consciousness of a terminal patient in order to relieve distress. In some cases it is used as a measure of last resort, when all other measures to reduce pain and suffering have failed. But in other cases, such as the patient who is brain dead, high doses of opioids may be used to calm the patient and hasten death, and in those cases some have labeled the practice as "slow" or "backdoor" euthanasia. However, in one survey of family members of patients who died after withdrawal of life support, the perception of over 90% of 196 respondents was that their loved-one was either totally, very, or mostly comfortable during the hours prior to death, and this undoubtedly was due to the administration of sedatives such as morphine, midazolam, or lorazepam during and after withdrawal of life support measures [21].
The principle, or doctrine, of "Double Effect" is a set of ethical criteria for evaluating the permissibility of acting when one's otherwise legitimate act, such as relieving pain with

• The nature of the act is itself good, or at least morally neutral • The agent intends the good effect and not the bad, either as a means to the good or as an end in itself • The good effect outweighs the bad effect in circumstances sufficiently grave to justify causing the bad effect, and the agent exercises due diligence to minimize harm

Table 97.5. **Criteria that justify the doctrine of Double Effect.**

opioid analgesics, will also cause an effect that one would normally be obliged to avoid, such as death. Criteria that some suggest make Double Effect treatment justifiable include: 1) the nature of the act is itself good, or at least morally neutral; 2) the agent intends the good effect and not the bad, either as a means to the good or as an end itself; and 3) the good effect outweighs the bad effect in circumstances sufficiently grave to justify causing the bad effect, and the agent exercises due diligence to minimize the harm (Table 97.5).

During the 1990s, physician-assisted suicide received massive media coverage when Dr. Jack Kevorkian wrote about his interventions with at least 130 patients, and especially when he allowed the U.S. television news magazine "60 Minutes" to film an ALS patient administering lethal doses of medication to himself. In 1991 the State of Michigan revoked Dr. Kevorkian's medical license, and he was convicted of second-degree murder and imprisoned from 1999 to 2007. However, U.S. sentiment about physician-assisted suicide is gradually evolving. In 1997, after an extended Court battle, the state of Oregon's "Death with Dignity Act" went into effect and essentially legalized physician-assisted suicide in that state. Similar legislation exists in The Netherlands. Justice requires that we should allow assisted death for patients with terminal illness where no curative therapy exists, and when the steady progression of the disease is physically and emotionally devastating. The compassionate argument is that the patient has a right not to suffer or have constant pain. From a legal perspective, the argument revolves around individual liberty versus state interests. Though society has a strong interest in preserving life, that interest lessens when a person is terminally ill and has a strong desire to end their life. A complete prohibition on assisted death can be viewed as excessively limiting personal liberty. The opposing argument is that physician-assisted suicide is immoral, and disregards the sanctity of life and our religious and secular traditions against taking human life. There also is a clear potential for abuse. For example, certain groups of people, lacking access to care and support, may be persuaded to undergo assisted suicide, or the procedure may become a cost-containment strategy. It is clear that for physician-assisted suicide to be both legal and ethical, there must be a great deal of trust between the patient and the physician. The system as a whole must be constantly vigilant that voluntary, active assistance in dying never becomes involuntary.

Germane to this issue is an ethical analysis of the removal of implanted cardiac pacemakers or cardio-defibrillator devices at the patients' or surrogate's request. Ethicists at the Mayo Clinic reviewed 6 such cases treated at their hospital, and determined that granting terminally ill patients' requests to withdraw unwanted medical support is legal and ethical [39]. Death after removal of the implanted cardiac pacemaker or cardio-defibrillator device was considered due to the patient's underlying pathology, and not the same as physician-assisted suicide or euthanasia.

97.7 The Role of Religion

Organized religions, and various religious beliefs, play an important role in shaping the way most patients and family members think about end-of-life decision-making. While

there are too many different religions to chronicle the relevant teachings of each, the recommendations of some of the most common religions are of interest and provide insight into the common themes. Specific directives of the Roman Catholic Church were articulated by Pope John Paul II in his address to the participants at the International Congress on Life-Sustaining Treatments and Vegetative State: Scientific Advances and Ethical Dilemmas, presented on March 20, 2004. In that address he clearly stated that the removal of feeding tubes from people in vegetative states is immoral, and that no judgment on their quality of life could justify such "euthanasia by omission." The Pope said even the medical terminology being used, such as persistent vegetative state, was degrading, and that no matter how sick a person was, "he is and will always be a man, never becoming a 'vegetable' or 'animal.'" "Providing food and water to such patients should be considered natural, ordinary and proportional care – not artificial medical intervention." As such, it is morally obligatory to continue such care. Since no one knows when a patient in a vegetative state might awaken, […] we cannot ethically justify the abandonment or the interruption of minimal care for the patient, including food and water. "If this is knowingly and deliberately carried out, this would result in a true euthanasia by omission," he said.

To be sure, this papal allocution has not been universally embraced by all Catholic groups, some of whom see the statement as inferring that the average Catholic patient is incapable of making proper judgments about their own care [40]. In most protestant communities, the decrees of the Pope as described above are considered somewhat out of step, and inconsistent with the concepts of the right of self determination and death with dignity. As a result, and as will be seen in the next section regarding international differences in end-of-life decision making, there are significant differences in the way some northern Europeans view withholding and withdrawal of care as compared to those in the south, and particularly the Italians.

The worldwide emergence of religious fundamentalism, and the associated vitalistic view about the sanctity of life, may result in a significant reversion to older, more conservative rules about withdrawal of life support decisions, particularly in the Middle East and Asia [41]. But while this may be a trend for the future, it is not currently observed in all of these countries. For example, in the predominantly Muslim country of Pakistan, one survey of 137 physicians and nurses from 3 separate hospitals did find that while 28% considered it their responsibility to sustain life at all costs, even for a DNR patient, only 8% gave religious beliefs as their reason [42]. Moreover, 85% of respondents recognized "brain death" as a legitimate medical diagnosis.

97.8 International Differences in End-of-life Decision Making

There are significant differences between countries regarding end-of-life medical practices. In some cases this is related to the predominant religion of the country, but in others there also are important non-religious influences. The findings of a large prospective investigation of end-of-life decisions in 37 European intensive care units located in 17 European countries (the EURELD Project) were recently published. The study found that physicians from Switzerland and Sweden were most likely to withhold or withdraw treatment with the intention of hastening the end of life, while those from Denmark and Belgium were least likely [43]. In addition, 73% of all participants frequently admitted patients with no hope of survival [44]. While 80% felt that DNR orders should be applied for such patients, only 58% did so, and there was a wide varia-

tion between countries – DNR orders were recorded in only 8% of cases in Italy, but in 91% of cases in the Netherlands. Moreover, physicians in the countries of southern Europe were less likely than those in the north to apply DNR orders, withhold treatment, and to discuss such issues with the patients and their families. According to the survey, withholding of life-sustaining therapy was much more common than withdrawal of therapy, the reverse of what has been reported for U.S. ICUs. Forty percent of respondents reported that they would deliberately administer large doses of drugs until death ensued. The survey also revealed that ICU admissions were frequently limited by the availability of beds, and this was most pronounced in southern European countries and in the United Kingdom.

In some European countries there also is an increased focus on emergency department end-of-life decision making. One French study reported a series of cases where the decision to withhold or withdraw treatment was actually made in the prehospital setting by emergency physicians [45]. Perceived imminent death due to multiple trauma, chronic disease with severe heart failure, or post anoxic coma, were the most common reasons for withholding or withdrawing life-sustaining treatment in that study, and 79% of these patients died before reaching the hospital. In another French study of 14,875 patients, 119 had decisions to withhold or withdraw life-support made in the emergency department [46]. The mean age of the patients was 75 years, and most had underlying chronic cardiopulmonary disease or metastatic cancer. Life sustaining measures were withdrawn in 37% and withheld in 63%. The median time interval from the decision to death was 16 hours, though at least one patient survived for 140 days. The family was involved in the decision-making process in 72% of patients. In the French ICU, decisions to forgo life-sustaining therapy rarely involve the patient's perception of his or her quality of life, and in a study of 105 patients, the decision to withhold life-sustaining therapy considered the patient's wishes or religious values in only 15% of cases [47]. The advice of the medical team was the most important factor considered in 95.3% of cases. However, a study of end-of-life decision making in a French pediatric ICU suggests much more involvement of family members of dying children, and in that study parents' opinions regarding life-sustaining treatment were obtained in 72.1% of cases [48].

In Spain, the treating ICU physician plays a very active role in decisions to withdraw or withhold care. In one study of 6 adult ICUs, the proposal to withhold or withdraw life support was initiated by physicians in 92.9% of cases [49]. The patient's family was not involved in the decision to withhold or withdraw life support therapy in 28.3%, and patient's advanced directives, where patient's had expressed their wish to decline life-prolonging therapy prior to ICU admission, were present in only 9%. Germany has specific legislation that requires a physician to seek permission for end-of-life decisions from a formally legitimized guardian, and that individual is then legally required to seek permission from a Court of Guardianship before end-of-life medical decisions are made in those cases where the patient is not competent to make their own decisions. But the vast majority of surrogate decisions on incompetent patients are actually not covered by legally valid consent because neither the legal nor the medical systems in Germany are capable of coping with the volume of cases if consent for end-of-life withholding or withdrawal of care were always requested according to legal regulations. In the Netherlands, a large national survey revealed that a nontreatment decision was made in 30% of all deaths in 1995 [50]. Artificial nutrition, hydration, and antibiotics were the treatments most frequently foregone. Thus, in most cases the treatment withheld did not involve high-technology treatment. In 17% of cases, the nontreatment decision was made without being discussed with the patient or the patient's relatives, and without knowledge of the patient's wishes.

Compared with the European countries, withdrawal of care is much less common than withholding of care in Israel. In one study of end-of-life care, 91% of discussions with family members revolved around withholding of care but only 9% were about withdrawal of existing life-support measures [51]. No patient underwent active shortening of the dying process, 69% of patients actually had treatment withheld, and only 5% underwent withdrawal of treatment. In most Israeli clinics, withdrawal of treatment is limited to those diagnosed with brain death, and in one study, no patient had antibiotics, nutrition, or fluids withheld or withdrawn [52]. The reluctance to withdraw treatment also was seen in Lebanon, where a survey of one ICU revealed that among those who died, the decision had been made to withhold life-sustaining therapies in 38%, but to withdraw therapies in only 7% [53].

End-of-life procedures in Argentina are very conservative, perhaps due to a strong Roman Catholic religious influence. In one study of 16 pediatric intensive care units, most children underwent cardio-pulmonary resuscitation before death, and active withdrawal of life-support treatment was rare [54]. DNR orders were present in 16%, and life-sustaining care was withheld in 20%, of those who died. In a major teaching hospital in Hong Kong, of 490 patients who died in the intensive care unit, limitation of life support occurred in 58.8% [55]. Relatives or patients requested limitation of life support in 11%, though the family and/or patient concurred with limitation of life support in 95% of the cases. Therapy was withheld in 31%, and withdrawn in 28%, of the deaths.

In the U.S., withdrawal or withholding of care decisions were associated with approximately 50% of ICU deaths [56]. Withdrawal of life-support was 4 times more common than withholding of life-sustaining therapies in those with a poor prognosis. In patients admitted to one large U.S. ICU with severe neurologic illness, the role of the severity of the illness, healthcare system issues, and social factors were assessed to determine their impact on the decision to withhold or withdraw care [57]. In that study of more than 2000 patients, decisions to withdraw mechanical ventilation were based primarily on the severity of the acute neurologic condition and age. Marital status, premorbid functional status, attending status (private vs. academic), and type of health insurance were not associated with decisions to withdraw ventilation. African-American patients, and those who had had surgery, were less likely to have mechanical ventilatory support withdrawn.

97.9 Unique Pediatric Issues

There is no more ethically and emotionally laden challenge than that of end-of-life decision making for terminally ill infants and young children. Many parents are devastated to the point of being dysfunctional, while others are just emotionally numbed, by the thought of losing their child. Thus, it often is extremely difficult for physicians to discuss withholding and withdrawal of care with these parents. Factors that influence parents in their decisions to withhold or withdraw life-sustaining therapy for their terminally ill child include previous experience with death and end-of-life decision making for others, their personal observations of their child's suffering, their perceptions of their child's will to survive, their need to protect and advocate for their child, and their family's financial resources and concerns regarding life-long care (Table 97.6) There also are racial differences in the likelihood that withdrawal or withholding of care recommendations will be accepted, and they appear to involve such factors as mistrust, religiosity, and perceived discrimination. A study comparing acceptance of withdrawal/withholding of care recommendations between African-American and white parents of

- Previous experience with death and end-of-life decision making for others
- Personal observations of their child's suffering
- Perceptions of their child's will to survive
- The need to protect and advocate for their child
- The family's financial resources, especially with regard to life-long care

Table 97.6. **Issues that are most important to parents in their decisions to withhold or withdraw life-sustaining therapy for their terminally ill child.**

moribund infants found that approached families of white infants agreed to limit life-sustaining medical treatment 80% of the time compared to 62% of families of African-American infants [58]. During the past 2 decades there does appear to be improved communication between parents and healthcare providers leading to a greater acceptance of end-of-life decision making, and at least one study has found that withholding of care, and particularly CPR, has became more common in the pediatric and neonatal ICU [59].

Infants and children with gradually progressive terminal diseases, such as certain inborn errors of metabolism or aggressive malignancies, present particularly difficult ethical challenges. Acute caregivers frequently struggle with feelings that they are saving children that should not be saved, or, conversely, that they are giving up on children too soon. Because most of these children have complex medical problems, they are usually cared for at major University hospitals by multiple caregivers, and studies suggest that there can be significant interdisciplinary differences in biases, knowledge, and beliefs, especially between nurses and doctors, with regard to withholding or withdrawing of life-sustaining therapies. For example, in one study of 781 clinicians working in a pediatric ICU, twice as many nurses as attending physicians felt that they were saving children who should not be saved [60].

When life-sustaining treatment is withdrawn from infants or young children, the decision to do so usually occurs after a prolonged ICU stay of 20-30 days [61]. Most life-sustaining treatments are withdrawn simultaneously rather than stepwise. Perhaps more so than with adults, the neurologic status of the sick child has become a focal point for end-of-life decision-making, and a consulting neurologist, working with the critically ill children and their families, is often a key figure in determining diagnoses and prognoses.

97.10 Conclusions and Key Concepts

The most important aspect of end-of-life decision making in the ICU and elsewhere is communication between the physician and patient, or family members if the patient is cognitively impaired or comatose. Physicians must be sensitive to the emotional needs of these individuals, and to their level of understanding of the complex medical issues related to withdrawal or withholding of care. It is important to clearly relate the degree of certainty with which the physician is able to make the prognosis of death, and the futility of treatment, in terms that the patient and/or family can understand. It should be clearly explained that while death may be postponed by the addition or continuation of certain life-sustaining medical interventions, withholding or withdrawal of those interventions should not be viewed as the cause of the patient's death. Rather, the underlying disease is the cause of their death. In addition, it must always be emphasized that a high quality care will continue to be provided to the patient even after the withholding or withdrawing of specific and futile life-sustaining therapies. The administration of sedatives or narcotics after extubation of the patient can help relieve the patient's distress or pain, but also demonstrates to family members the continued involvement of their healthcare team.

97.11 Disclaimer

The views expressed in this chapter are solely those of the the Author, and do not represent official policy or views of the US Government, US Military, US Department of Defense, of US Department of Veterans Affairs.

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