Neurocritical Care for Neurosurgeons

Principles and Applications

Eberval Gadelha Figueiredo
Leonardo C. Welling
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Foreword

As every neurosurgeon is aware, our surgical results depend on so much more than just excellent technical competency. Of the many requirements for getting the best outcomes for our patients like appropriate decision-making, great neuroanesthesia, and good staff, none are more pertinent than excellent neurocritical management.

Drs. Eberval Gadelha Figueiredo, Leonardo C. Welling, and Nícollas Nunes Rabelo have collected superb experts and assembled a long-overdue book on the practical aspects of achieving outstanding critical care.

It is divided into four parts — the first presents and details the general basic principles of neurosurgical care, including monitoring and interpretation of exams. In the second part, the authors present and thoroughly discuss general management of neurocritical patients. Specific conditions and diseases care are discussed in Part III. In Part IV, outcomes and strategies of rehabilitation are presented.

This volume is appropriate for all those involved in the care of neurosurgical patients, especially residents, critical care physicians, neurologists, and all neurosurgeons.

I congratulate the authors for the excellent job in presenting this much-needed material and suspect it will be used routinely by physicians taking care of these critical patients.

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Acknowledgments

To think is easy. To act is hard. But the hardest thing in the world is to act in accordance with your thinking. Johann Wolfgang von Goethe

No new project comes about without the tough efforts of a number of colleagues, and this book is certainly no exception. We would like to start by thanking the editorial and production teams at Springer Nature, as always, an extremely talented and most pleasant group to work with. It is clearly through their efforts that the published result is so outstanding. Second, we would like to thank all authors and collaborators that persisted highly committed even in the adversity and uncommon occurrence of the COVID-19 pandemic that changed everyone's life. For a few moments, it seemed impossible to get all the pieces together and their individual contributions, which included skilled editing, production, and design. It shows that even in the face of the impossible dream, it is possible to accomplish great things.

A special thanks to our families, parents, wives, sons, and friends that in hard moments who understood us in difficult times, and always believed and supported the project. For friends and other collaborators who, even in anonymity, were unconditionally supportive.

This book is about *Neurocritical Care for Neurosurgeons: Principles and Applications*, a fundamental part of our routine of patient care. It is well known that the details in the neurocritical care of patients make a total difference in outcome, no matter how beautifully one operates. This book is for medical students, residents, fellows, faculty, neurosurgeons, neurologists, and general physicians who cope with these challenging conditions on a daily basis.

Finally, we would like to acknowledge all our teachers, mentors, and others who inspired us all these years for their guidance, encouragement, and friendship.

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Chapter 1
Neurocritical Care: An Overview

Nícollas Nunes Rabelo, Leonardo C. Welling, and Eberval Gadelha Figueiredo

1.1 History and Evolution of Intensive Care Units

Neurocritical care is described as the intensive care offered to patients with severe neurosurgical and neurological conditions [2–4]. It entails the delivery of comprehensive clinical and specialized support for individuals with severe neurological ailments by incorporating and balancing the management of both the body and the brain [5]. The initial intensive care units (ICU) were established in response to the polio pandemic that led to occurrence of respiratory paralysis and/or bulbar palsy in 316 patients in Copenhagen, with consequent pooling of secretions and respiratory failure in 1952 [6]. The conventional ICUs quickly evolved into general ICUs that concentrated mainly on providing cardiopulmonary support for acutely sick patients. They were operated by a multidisciplinary team of anesthesiologists, cardiologists, pulmonologists, pediatricians, and internists with an individual interest in critical care [1].

Over the last 20–30 years, ICUs intended to primarily deliver care for postoperative cardiac, neurologic, cancer, burn, trauma, and neonatal patients, as well as other specific patient populations, have emerged. The critical care in the ICUs as mentioned above often is offered by clinicians within those fields and practitioner nurses [1]. Nonetheless, an ICU is not a separate entity, but a central part of a dynamic horizontal health care process, since the outcomes depend not only on the proficiency of the multidisciplinary ICU team and the quality of facilities but also on the cares offered in the operating room (OR), emergency department (ED), rehabilitation units, and others where the patients are discharged [7–9]. Thus, the physical paths between the departments, as mentioned above, should be shortened.

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Furthermore, it is not just the physical distance that influences patient care, but also positioning the ICU at the center of the ED, OR, diagnostics, and discharge units allows optimization of the timing of placements to the ICU, as well as facilitate safe and efficient release of patients to a less exhaustive space within the facility for continued observation of resolving organ impairment [10].

1.2 Neurocritical Care Specialty

Recent studies have illustrated that neurological conditions make up between 10 and 15% of placements in ICUs [17]. Besides, a large share of severely sick patients with respiratory failure or sepsis develops neurological complications, like neuromuscular weakness, non-convulsive status epilepticus, or delirium, which may subsequently add to an increased threat for morbidity and mortality [18]. As a result, neurocritical care has progressively evolved into a sphere of nervous system-based treatments entrenched clinical physiology to address challenges similar to the complications above [19]. Layon et al. explain that stroke unit started to emerge in the 70s, which were focused on delivering care of patients with ischemic stroke and are part of the straightforward forerunners to contemporary neuro-ICUs [10]. In the 80s, empirical studies in neurosurgery and neurology commenced taking shape, thereby resulting in enhanced detection and treatment that motivated the instigation of the first specialized neuro-ICUs [10]. The neuro-ICUs merged postoperative neurosurgical patients with a broader array of severe neurological patients, like status epilepticus, neuromuscular respiratory failure, TBI, massive hemispheric infarction, and subarachnoid and intracerebral hemorrhage [5, 20–22]. The latter prompted the necessity for physicians with proficiency in neurosurgical and neurological factors, as well as in the tenets underpinning the management of multifarious organ impairments, mechanical ventilation, and hemodynamic monitoring.

Neurology specialty in the United States involved the conclusion of the twentieth century due to the birth of the field in Europe [19, 23, 24]. Porcayo-Liborio and colleagues indicate that there was a steady and long-term approbation for European training that resulted in the establishment of the neurocritical care specialty in South America [19]. As such, the initial phases in Peru, Chile, Uruguay, Brazil, and Argentina occurred nearly concurrently with the European timeline. Currently, neurocritical care is a maturing subspecialty of critical care medicine that seeks to incorporate content expertise in critical care neurology, experience, and proficiency in general critical care management, as well as reliable delivery of evidence-based care to victims of spinal cord and brain injuries [18]. The objective of neurocritical care subspecialty is to offer prompt diagnosis and therapy of systemic complications, avoidance of secondary neurological harms, offer quality neuroprotection, and, subsequently, the best probable recovery. In summary, as the subspecialty of neurocritical care continuous to bud, a large share of the neuro-ICUs has transformed from “single-system” focus on a single neurological area to a complex

framework, whereby neurointensivist presumes complete answerability for both the neurological and clinical care of the patient.

Similar to general ICUs, specialized neuro-ICUs require the optimal organization of staffing and patient care. The American Heart Association (AHA) recently issued a scientific position that advocates for educational transformation and organizational staffing in cardiac intensive care units (CICUs) in response to the shifting clinical environment [25]. As per the AHA scientific statement, cardiovascular care should be delivered in closed CICU units with unit-based physician staff, committed cardiac intensivist training, and a three-tiered CICU classification [25]. For instance, a survey involving medical research facilities demonstrated that 68% had CICU for addressing the health needs of severely sick cardiac patients [26]. More than 50% of the CICUs were closed units, and only 45% were open ICUs. Irrespective of the above outcome, 87% of the surveyed clinicians concurred that a closed ICU would provide superior quality and reliable care compared to open CICUs. Moreover, even though below 4% of the surveyed CICU managers had past training on critical care management (CCM), 80% considered the presence of cardiologists with the CCM skill sets represented unmet need.

In a similar study, Na et al. conducted a single-center survey to investigate the correlation between cardiac intensivist-steered care and clinical outcomes of n = 2431 CICU adult patients hospitalized in a hospital in Seoul, South Korea between 2012 and 2015 [27]. The CICU was reformed from low- to high-intensity staffing framework in January 2013 that was headed by a dedicated cardiac intensivist. The participants were grouped into low- (n = 616) and high (n = 1815)-intensity staffing models. From the study's findings, 4.1% (n = 74) and 8.9% (n = 55) in the high-intensity and low-intensity cohorts, respectively, died during the research period. Moreover, the CICU fatality rate in the cardiac intensivist-led group was lower than in the low-intensity cohort among patients who underwent extracorporeal membrane oxygenation. Suarez et al. conducted a retrospective analysis of prospectively gathered data to examine the predictors of in-patient and long-term fatality and length of hospital stay among n = 2381 adult patients admitted to Neuro-ICU in Cleveland, Ohio [28]. The launch of a neuro-ICU dedicated team, encompassing a full-time neurointensivist, resulted in a substantial drop in in-patient mortality and shortened length of hospital stay without changes in rehospitalization rates or long-term mortality. In observational cohort studies using historical controls, the introduction of a neurointensivist-steered multidisciplinary team model was linked to an independent positive influence on clinical outcomes, comprising of a reduced length of stay (LOS), ICU mortality, and release to a skilled nursing facility as well as a higher discharge home [29, 30].

The relationship between improved quality clinical outcomes in critically sick patients and the institution of high-intensity staffing in neuro-ICUs is multilayered. It is partly associated with the employment of evidence-based procedures and the readiness of the specific organization, the intensivists' capability to identify and address the severe conditions in time, and the full commitment of the intensivists' focus on ICU patients [27, 31]. Wilcox and colleagues conducted a systematic review and meta-synthesis of n = 52 comparative observational studies to determine

the influence of diverse intensivist recruitment frameworks on clinical upshots for critically ill patients [31]. The comprehensive data synthesis showed that compulsory consultation of an intensivist or transfer of care to an intensivist-steered team was correlated with significantly reduced ICU mortality and hospital fatality compared to lower-intensity staffing. Besides, substantial decreases in ICU and hospital LOS were observed in the high-intensity staffing model than in the open staffing framework [32, 33].

A retrospective, propensity-matched, cohort study conducted in Canada to assess the efficacy and safety of a CICU found that a 24-hour intensive care cardiac/physician anesthesiologist staffing in postsurgical cardiac care is allied to a decreased need for mechanical ventilation, transfusion of blood components, and shorter hospital LOS [34]. Notably, having full-tine intensivists proficient in transfusion management is advantageous to the patients [35]. A study examining the nature of avoidable mortalities in coronary artery surgery patients found that more than 60% of the fatalities were associated with ICU challenges, encompassing 35% of the mortalities due to incorrect detection of severe events [36]. Thus, the presence of dedicated CICU intensivist staff can potentially reduce such flaws by punctually identifying and addressing life-threatening issues that arise after normal working hours [37]. Nonetheless, irrespective of the profits of high-intensity staffing in neuro-ICUs, the presence of a small number of intensivist workforce limits universal enforcement of the model above.

1.3 ICU Organizational Structure and Staffing

Organizational structure has long been identified as a critical issue in intensive care, and findings of empirical studies have recognized it as a core determinant of patient outcomes in ICU [7]. It is recommended that the conventional division of ICU organization frameworks into “open,” where the leading clinician is accountable for decisions regarding the intensive care, with or without consulting the ICU physician, or “closed,” in which the ICU employees make all decisions, should be obscured in the future [7, 11]. Regli and Takala suggest that the prospective ICU model should be viewed as “closed” but communicating and integrative [7]. Multz et al. tested the supposition that unit closure was superior over the open model with regards to curbing the mortality rates and length of both hospital and ICU admission [12]. The upshots of the study showed that the length of hospital and ICU stay was shorter, and days on mechanical ventilation were fewer when the ICU model was “closed” compared to an open organizational model. Similarly, Carson et al. matched the impacts of a shift from open to close ICU model on clinical outcomes, teaching, resource allocation, and views towards the quality of care [13]. The results of the prospective cohort study showed that the ratio of actual mortality to predicted mortality in the open ICU and closed ICU was 22.6%: 25.2% and 31.4%: 40.1%, respectively. Furthermore, the authors noted that the mean length of ICU stay (LOS) for survivors was 3.7 and 3.9 days in closed and open models, respectively. Thus,

grounded on comparison of predicted to actual fatality, a transition from an open to a closed ICU organizational framework enhanced clinical outcomes.

Irrespective of the above studies favoring closed over open ICU models with regard to clinical outcomes of the patients, other analyses have found that the efficacy of the aforementioned models is confounded by significant disparities in care delivery, such as practice heterogeneity, multidisciplinary team dynamics, leadership structure, and provider expertise. For instance, Levy and colleagues performed a retrospective scrutiny of a large, prospectively gathered database of n = 101,832 severely sick adults to assess the relationship between hospital fatality and management by critical care clinicians in 123 ICUs in the United States [14]. Contrary to the findings of Dimick et al.'s study [15], Levy et al. demonstrated no survival profits with management by critical care clinicians. In fact, patients receiving clinical care from critical care physicians had significantly higher probabilities of fatality compared to those addressed by non-critical care physicians [14].

The inconsequential impacts of critical care medical experts in ICU can be ascribed to various factors. First, critical care connoisseurs may depend on their personal evaluations to address patient needs instead of applying evidence-based procedures that are linked to improved clinical consequences. Second, individuals receiving intensive care from critical care physicians might be relocated to disparate, unaccustomed clinicians, while those getting care from noncritical physicians are likely to continue getting care from familiar physicians [14]. In this case, transfers are likely to disrupt continuity of care, medical and management orders, and elevate the odds of miscommunication and mistakes, all of which can negative implications. Third, owing to the critical care physicians' acquaintance and proficiency with procedures, they may apply additional protocols that further complicate patient safety. Often, the physicians mentioned above employ additional procedures, like invasive practices such as placement of catheters that can worsen the prognosis of severely ill patients by increasing their vulnerability to life-threatening nosocomial infections.

Apart from the open and closed ICU formats, a third classification is the semiclosed organizational structure. Layon et al. describe the semiclosed framework as the intensivist may engage in all or several intensive care in consultation with the attending clinician [10]. In the above light, the intensivist's responsibility is restricted to emergency response and triage operations, but more frequently entails nutritional, fluid, respiratory, and hemodynamic management. The semiclosed ICU organizational framework is commonly found in surgical units where the lead surgeon tackles the surgical elements of clinical care, and the intensivist addresses the remaining patient care practices. A systematic review conducted by Provonost et al. to explore the correlation between clinical outcomes and physician staffing patterns [16]. The organizational format in all the 17 appraised papers was categorized as high-intensity (closed ICU or mandatory critical care consultation) or low-intensity (elective consultation or no intensivist). The former was allied to reduced hospital and ICU mortality rates. There was sufficient proof to support the argument that hospital recruitment of physician intensivists resulted in decreased use of radiology, laboratory, and pharmacy services, as well as enhanced patient flow. Provonost and

colleagues concluded that having an intensivist round focusing on postsurgical patients decreases the risk for complications, condenses the length of both hospital and ICU stay, and subsequently lowers the accumulative cost of healthcare.

1.4 Quality Improvement and Neurocritical Care

Neurocritical care entails the commitment of several professionals and multidisciplinary medical providers to deliver high-quality care to patients with neurological needs [10]. On the other hand, quality improvement has described a process by which care provided by clinical practitioners is critically appraised in the context of the health system they are operating, and enforces reforms in procedures that shift the goal of delivering medical care to one that is patient-centered, evidence-based, safe, and reproducible [38]. The practice of QI inspires clinicians to be inventive and generate information in cases where there is a lack of sufficient data on which to ground neurocritical care decisions. According to Layon and colleagues, numerous ICU-specific quality variables influence QI in neurocritical care settings, including the designation of practices to mitigate nosocomial infections [10]. As outlined earlier, one such approach to enhancing patient care is by reducing ICU and hospital LOS through the introduction of full-time intensivists. Nonetheless, appropriate quality indicators emphasized in recently published studies or client-centered outcomes extend beyond neurological recovery and mortality, but also encompass measures as patient/family satisfaction, adoption of realistic and accurate neuroprognostication, and excellent communication.

1.5 Patient/Family Satisfaction

The enrolment of dedicated intensivist has been associated with enhanced patient and family satisfaction with neuro-ICU services. For instance, Sarpong and associates conducted a retrospective analysis of data from a 14-bed neuro-ICU to assess the quality measures and anonymous patient satisfaction scores pre- and post-neurointensivist consultation [39]. Besides, the patient satisfaction with neurocritical care delivered by both nurses and physicians increased by 28.3%, and the confidence and trust of patients in clinicians heightened by >69%. In similar research, Ko and colleagues analyzed records of n = 15,210 neurology patients admitted in neuro-ICU in Seoul, South Korea, to explore the impact of recruiting a full-time neurointensivist to manage a closed-type [40]. The postintervention outcomes showed shortened LOS and increased intrahospital transfers from general ICUs to the neuro-ICUs. The average family satisfaction scores of the patients improved by 11.4%.

Hwang et al. evaluated family satisfaction with care from an academic neuro-ICU and matched the upshots with simultaneous data from the same hospital's ICU

(MICU). The authors distributed the Family Satisfaction-ICU Questionnaire to both MICU and Neuro-ICU patients' caregivers during discharge from the intensive care unit [41]. The results illustrated that 92.7% and 76.3% of the MICU and Neuro-ICU patients, correspondingly, were satisfied with the compassion and respect they received from the respective staff. Participants were less likely to have contended with the consideration of employees if they expressed concerns regarding their non-involvement in family meetings. Furthermore, <60% of the neuro-ICU caregivers were satisfied with support from the ICU staff during decision-making, the regularity of physician communication, and control over the clinical care provided to their loved ones.

1.6 Effective Communication and Handoffs

Effective communication is a fundamental proficiency in the neuro-ICU that connects respiratory therapists, advanced practitioners, physicians, occupational and physical therapists, nurses, dietitians, pharmacists, clerks, and the family/patients [38, 42–45]. Effective communication is also a measure of quality and patient safety without which the provision of safe healthcare is impeded, and attainment of excellent services is made impossible [23, 46, 47]. Furthermore, successful interaction in ICU facilitates efficient handoff of patients between medical professionals by eliminating probable medication errors [48, 49]. Whereas the handoff process is critical in every part of patient care, it is particularly essential in the neuro-ICU owing to the severe nature of the inherent complexity and the patient's severe status [50, 51]. Notably, the condition of a neuro-ICU patient alters quickly, and the rapid-paced setting of the neuro-ICU makes the communication of precise and prompt information extremely challenging [52, 53]. The physical transition of patients from the OR to ICU, or from the emergency room to IC, at times, further complicates the difficulties in communication in neuro-ICU setups [50]. Thus, the outgoing clinical professionals must make accurate evaluations about the details and the volume of information passed during handover, such that the receiving experts can be apprised quickly and build a general clinical portrait of the patient's status without redundant details [54].

Coon and colleagues propose the employment of a structured handoff checklist to enhance clinical outcomes among patients released from the neuro-ICU [55]. The suggested handoff checklist was incorporated into existing workflows, thereby resulting in enhanced reconciliation of intravenous (IV) vasopressors and antihypertensives without elevating demands on other clinical staff. Birk et al. describe the resident-led enforcement of a formal handoff framework that is intended to facilitate the transition of post-neurosurgical patients to neuro-ICU that comprises a brief postsurgical note and an in-person interaction with the receiving medical professional [56]. In Birk et al.'s survey, 33% and 67% of the respondents agreed or strongly agreed that the inclusion of brief notes substantially eased the transition of care and curbed medication errors, respectively. Similarly, Pronovost et al.

recommended the espousal of a structured checklist of daily goals forms during patient care rounds in ICU [57]. The implementation of the daily goals forms in the prospective cohort study facilitated the comprehension of the patients' goals of care among nurses and residents and resulted in a substantial drop in ICU LOS. Notably, a review of daily goals during intensivist-led multidisciplinary rounds ensures that issues are clarified to avoid omission or communication failures. The diurnal interaction objectives encompassed evaluation of X-rays, culture, and laboratory results; review of administered medications; deliberations of clinical processes such as mechanical ventilation glycemic control and sedation management/interruption [57].

In summary, QI in neurocritical care entails the recognition of clinical protocols that require inculcation of a culture of coordination and consultation among the diverse members of multidisciplinary teams, but they should be steered by dedicated intensivists [58]. Precisely, QI ought to be a continuous process in neuro-ICU involving the transformation of the organizational structure, processes, and clinical upshots to enhance patient safety and quality of care [4]. Principally, the organizational structure encompasses shifting it from the conventional physician-led open units to intensivist-operated closed critical care units [59–61]. On the other hand, the process aspects include embracing communication protocols and guidelines to prevent communication breakdowns, which, in turn, elevate the odds of incurring clinical mistakes, delaying decision-making, or performing poor handoffs. Restructuring the organizational formats and improving communication among ICU staff and between ICU experts and patients' families enhance patient/family satisfaction with the care delivery procedures and promote family inclusion in decision-making.

1.7 Neurocritical Care and Emergency Neurology as an Emerging Subspecialty

As outlined earlier, neurocritical care is an expanding multiprofessional subspecialty that incorporates knowledge in neuroradiology, neurosurgery, neurology, and intensive care [62]. During the polio pandemic era, neurologists served an essential role in stabilizing patients suffering from neuromuscular conditions and the resulting respiratory failure and bulbar impairment. However, in subsequent years, the neurologists' responsibility was limited to diagnostic roles instead of active engagement in critical care management [62]. Nonetheless, in the past decades, technological advances, new empirical studies, and the emergence of effective treatments, such as recombinant tissue plasminogen activator (TPA) for severe stroke or hypothermia for neuroprotection after cardiac failure, that widen the comprehension of primary and secondary brain injuries, as well as the interaction of the neurological frameworks and associated conditions, placed neurologists back into active neuro-ICU practices [63–68]. According to Glass et al., the Neurocritical Care Society (NCS) was launched in 2002 with the primary aim of improving outcomes of

patients with severe neurological diseases. Five years later, the Accreditation Council for Graduate Medical Education (ACGME) certified the pioneering examinations [62]. It is estimated that by the end of 2009, beyond 40 neurocritical care programs in the United States had been certified. Presently, numerous national regulations or practice guidelines relevant to adult neurocritical care have been embraced, encompassing the standard procedures for managing spontaneous intracerebral hemorrhage and early ischemic stroke in adults [69, 70].

In the past, empirical evidence showed that specialized neuro-ICUs significantly enhanced clinical consequences of patients with subarachnoid hemorrhage, trauma, and stroke [71–73]. Thus, owing to the progress in therapy and surveillance, alongside the wealth of empirical proof of improved medical outcomes, there is mounting support of adult neurocritical care as a discrete subspecialty [5, 74, 75]. Likewise, another myriad of dedicated neurocritical care subspecialties has been delineated from adult neurocritical care discipline. For instance, the first-ever pediatric neuro-ICU department was established at the Neurology Department of Children's Hospital Boston [62]. Currently, the well-established neonatal neurocritical care units commonly diagnose acquired brain injuries, brain malformations, seizures, and hypoxic-ischemic encephalopathy (HIE) [62, 76–78].

According to Peloquin et al., pediatric neurocritical care is an evolving subspecialty that amalgamates the knowledge of neurology and ICU with that of nursing and other medical experts in a multidisciplinary team advance to healthcare [79]. The neonatal neuro-ICUs have focused principally on the diverse direct and indirect conditions that complex the delivery of quality critical care, as well as the factors influencing LOS, morbidity, and mortality [80, 81]. Nonetheless, irrespective of building on knowledge about adult neurocritical care, the efficacy of pediatric neuro-ICUs in improving neonatal outcomes remains scanty owing to the availability of few studies [62, 82–85]. Furthermore, unlike other evidence-based-driven delivery of care and specialized care units, pediatric neurological care is confronted by distinctive difficulties [83].

Notably, infants with neurological impairments frequently have extended stays in a neonatal ICU (NICU). Their metabolism alters over the first 12 months, and the physical assessment shifts with maturation, thereby requiring the persistent engagement of neurologists even post the resolution of the severe critical ailments [83]. In the above light, neurocritical care in NICU is also emerging as a subdiscipline that aims to tackle both preventive and supportive care, as well as optimized neurologic consequences for vulnerable infants. Thus, nurses are necessitated to be ready to enforce procedures that particularly address neurologic illnesses appropriately, recognized severe alterations in neurologic conditions, and meticulously monitor neurologic status to avert secondary harm [79, 86]. Additional neurocritical care subspecialties include neuropalliative care [87]. The clinical priorities of the neuropalliative subdomain encompass the necessity to design and enforce efficient frameworks to incorporate palliative care into neurology and to create and implement educational quality initiatives to assess and match palliative techniques [88]. Likewise, the neonatal neuro-ICUs, studies evaluating the effectiveness of neuropalliative care models in improving patient safety, are unavailable owing to the

evolving nature of the subspecialty. Thus, there is a need for additional research to appraise the efficacy of newer neurocritical subspecialties, like neuropalliative and pediatric neurocritical care models, in promoting QI in neuro-ICUs.

1.8 Conclusion

The objective of the book chapter, Neurocritical Care for Patients in Intensive Care Unit, was to provide a comprehensive analysis of neurocritical care organizations, quality improvement and neurocritical care, and neurointensive care medicine as an emerging ICU subspecialty. From the reviewed pieces of literature, neurocritical care is defined as the intensive care offered to patients with severe neurosurgical and neurological conditions. It is an evolving subspecialty in neuromedicine that has led to a significant reduction of LOS, mortality, and morbidity among patients with severe neurological diseases. The success of neurocritical care models, however, is influenced by a diversity of factors, including the recruitment of dedicated intensivists, promotion of effective communication skills, adoption of evidence-based practices, and ensuring family satisfaction.

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Part I
The Basics and Monitoring

Chapter 2
Metabolism and Cerebral Blood Flow

Markus Dengl and Gabriele Schackert

The human brain is believed to be unique in the animal kingdom; it is the only organ which distinguishes humans from all other animals due to its relative size and elaborated architecture – at least in our actual scientific view. The organ is secured by a thick bone – a prime requisite for survival in an environment where mechanical, thermal, or chemical forces might easily disrupt the fine embellished architecture, but this confinement on the other hand is one of the main reasons for the existence of neurocritical care at all, as we experience today and has led in evolution to other physiological peculiarities which shall be briefly discussed in this chapter. Furthermore, our brain is embedded in a liquid cushion which also dampens mechanical forces exerted on it by virtually lowering the relative weight and as a "side effect" is also a room for metabolite transportation.

Our brain is an organ, which needs a high amount of energy. One fifth of our blood is pumped directly into this organ which weighs approximately 1/50 of our total body.

A meticulous regulation for blood flow in this central organ is needed to maintain a continuous delivery of the needed substrates. Two major mechanisms have been identified for upholding this regulation:

1. The *cerebral autoregulation* on different levels of the vasculature and with a plethora of triggers.
2. The *blood-brain barrier*, a microscopic barrier for both prevention of organ swelling and effective extraction of required metabolites.

Blood is pumped into the skull bone via four main vessels: the paired internal carotid arteries and the paired vertebral arteries. Connecting these arteries before they split up in different regions of the brain has proven advantageous and that might be the reason for the existence of the circle of Willis. Most of the blood is

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brought to the brain cortex. More difficult to understand (and up to day not nearly as good understood as the arterial influx) is the drainage of blood and other perfusion by-products. A thorough presentation of the hypotheses for the drainage alone is far beyond the scope of this chapter. Most of the venous blood is leaving the cranium through the venous sinus collecting the blood from two drainage systems:

(a) The superficial system on the cortical surface drains often to the nearest venous sinus (i.e., the superior sagittal sinus or the transverse sinus). This system is interlinked via superficial eponymic veins (Troland and Labbé). The drainage runs from central to the periphery (centrifugal) [21].
(b) The deep drainage route (which starts only 10–20 mm below the cortical surface in the white matter and in the basal ganglia) goes centripetal to the basal and internal veins to the vein of Galen and the straight sinus [18].

Suffice to say that there is still ongoing debate on how the cerebrospinal fluid (*CSF*) exits the central nervous system: initial reports of the importance for the Pacchionian granulations have been challenged [6], other locations for CSF drainage have been brought forth: the olfactoric-frontobasal system, anatomically called the cribriform plate, and on the other hand the arachnoid villi located at the origin of the spinal nerves [8] and also the pial capillaries and brain surface [6] to name only a few major players.

The interaction of CSF flow and the intracranial pressure will be discussed in another chapter.

2.1 Cerebral Autoregulation

One evolutionary main problem is that the inability to uphold a constant supply of energy substrates for the brain might lead to sudden death of the individual in a hostile environment where vigilance is the key to survival. But the complexity of our overgrown brain is inexorable: a lack of oxygen leads to unconsciousness in only a few seconds – an easy prey for any hungry predator around. While every other organ in the human body has a far greater tolerance for hypoxia and many have their own reserves for substrates (oxygen-saturated myoglobin and glycogen), the central organ is lacking this backstop. So (pre)cerebral arteries have to respond very fast to any demands the brain is making. But on the other hand a luxury perfusion of the brain as a remedy has also not evolved because the skull is a tight place and hyperperfusion does also lead to brain dysfunction and might result in the same outcome in nature.

The latter fact is also one consequence of the so-called and often cited *Monro-Kellie doctrine* (or even called *dogma*), implying that the space in the cranial vault is fixed to a constant volume and can only be filled by the three compartments: brain matter, cerebrospinal fluid, and blood (in blood vessels!) – any increase of one of those leads to elevated pressure in the skull (*intracranial pressure, ICP*) and has to be compensated by reduction of either of the other two. Nearly every neurocritical

condition and many neurological disorders can be explained by this simple fact, and the purpose of neurosurgical intervention has often the common goal of bypassing the doctrine (e.g., decompressive craniectomy) or compensate via reduction of the accessible compartments (i.e., the CSF space or even the blood volume).

For about 60 years cerebral autoregulation is known for the human brain. Autoregulation is the response to various signals (neuronal, myogenic, and chemical) to establish a constant cerebral blood flow. The main actor is the myogenic tonus of the cerebral vessels. The definition of "cerebral autoregulation" is not uniform as the measurement of it depends also on the experimental setting. The best known experiment is the relatively constant cerebral blood flow in the wide range of different perfusion pressure applied to the subject's brain. A constant blood flow can be established via myogenic regulation of the cerebrovascular resistance. But simple blood pressure is not the only regulator. Carbon dioxide (and of course along with it the pH or more simply the proton concentration) in the blood has also a big influence on brain perfusion. The easily memorizable fact is that relative *CBF* (*cerebral blood flow per 100 g of brain weight, ml/min* 100 g*; a normal value would be around 50–55 ml/(min * 100 g)) is nearly constant in a range of *cerebral perfusion pressure* (*CPP*, the theoretical perfusion pressure in the skull vault perfusing the brain in *mmHg*) (Fig. 2.1) [2].

The correlation of CBF and CPP is a basic equation, an analogy to the well-known Ohm's law:

$$\mathrm{CBF} = \frac{\mathrm{CPP}}{\mathrm{CVR}}.$$

CVR is the *cerebrovascular resistance* (*mmHg * min * 100 g/ml*), another actor in the regulation of brain blood flow. To keep CBF constant over increasing or decreasing CPP, the CVR has to change in the same direction. But this autoregulation has its limits and is only effective in a range of a *CPP from 50 mmHg to 150 mmHg*. Beyond those limits autoregulation mechanisms are not capable of

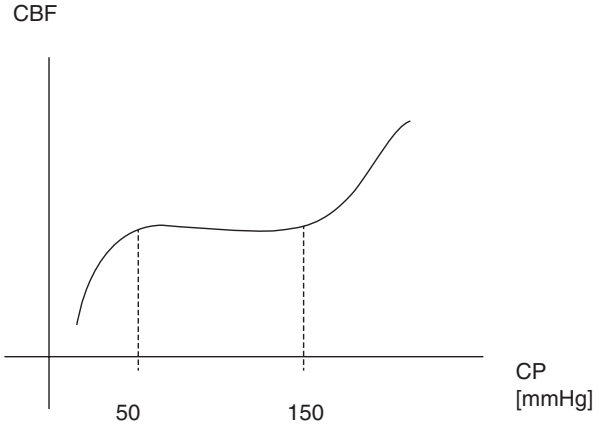

Fig. 2.1 Cerebral autoregulation as the ability to maintain a constant cerebral blood flow (CBF) over a wide range of cerebral perfusion pressure (CPP)

complete compensation. Anatomically, the small arteries and arterioles (where autoregulation is thought to take place) are at the maximum relaxation at the lower point of 50 mmHg and have the lowest cerebrovascular resistance (CVR) and are maximally constricted at 150 mmHg of perfusion pressure [13]. A perfusion pressure beyond this threshold leads to the abovementioned hyperperfusion, increases the intracranial pressure, and finally causes cerebral dysfunction as seen in the clinical setting of a hypertensive crisis.

But this is just one aspect of the whole autoregulation concept. The autoregulation "measured" in the abovementioned setting was done in steady-state situations, meaning that after any change of blood pressure to a stable niveau, an undescribed amount of time has passed until no changes of CBF were seen anymore (steady state). Therefore, this kind of autoregulation is called "*static autoregulation*." In contrast, sudden changes in blood pressure lead to similar responses of countermeasures but are named differently (i.e., "*dynamic autoregulation*"). So one has to keep in mind how "autoregulation" was measured.

Why is autoregulation so important in neurocritical care? The main reason is that autoregulation capability might be changed in clinical situations like traumatic brain injury or brain swelling after subarachnoid hemorrhage – to name the two most important conditions for neurosurgeons. There are other conditions under which autoregulation might be impaired even conditions remote from the brain at all, like a septic shock or cardiac surgery. Many studies have been performed investigating impairment of autoregulation in many different neurocritical diseases [13]. The degree of impairment correlates with outcome and the severity of the brain damage. That is one of the major conclusions of many trials concerning autoregulation and neurocritical situations.

Also physiologic conditions can diminish the capacity of autoregulation: high carbon dioxide leads to vasodilatation and narrows the range of stable CBF to a smaller band until no regulation can be found at all (for instance, in [11]). And finally, the physician himself can unwillingly impair autoregulation, which might lead to neurological complications. For example, volatile anesthetics are potent vasodilators, impair the natural cerebral autoregulation, and are suspected to be liable for at least some unexplained neurologic deterioration in an non-neurosurgical perioperative setting [7].

For measuring CBF and CPP, which both are not easy to perform, surrogates have been found. CPP is obviously only measureable, when putting a catheter in all four main vessels perfusing the brain and measuring the blood pressure in the basal intracranial segment. That is not an option for routine clinical use. So the best estimation is calculating the difference between the mean arterial pressure (*MAP*) and the intracranial pressure (*ICP*), leading to the famous formula:

$$\mathrm{CPP} = \mathrm{MAP} - \mathrm{ICP}.$$

In clinical practice the same reference point should be used for ICP and MAP, but in non-neurocritical care units, MAP is referenced to heart level and ICP should always be referenced to the level of the third ventricle or as surrogate to the outer

acoustic meatus (which is easier to identify!). About this there is still an uncertainty in practitioners and astonishingly also in quite a few clinical trials [20].

To measure CBF in a high temporal and spatial resolution is the holy grail of neurocritical care; any device or method which would achieve the feat would certainly lead to a big step forward in treating patients and understanding neurocritical conditions. But, unfortunately, there is no such device available today. Depending on the setting, CBF can be measured either at one time point for the whole brain with a reasonable spatial resolution (then called "regional CBF" *rCBF*) with imaging devices (e.g., with BOLD-MRI, Xe^{133}-CAT-scan, or even O^{15}-PET) or continuously at the bedside with no real spatial resolution. There is a great deal of research going on to measure CBF and CVR with imaging methods. Many diseases show different values for these parameters compared to "normal" population, and new hypotheses for the development of these diseases have been made, most prominent for Alzheimer's dementia [22]. Also many physiologic properties can be studied with these methods, and a lot of knowledge goes back to PET or MRI studies. We know that the blood flow is much higher in the gray matter than in the white matter. We know that activation of brain areas leads to an overproportional increase in blood flow, so that the *oxygen extraction fraction* (*OEF*, another important term used in MRI and PET studies) is lower than under resting conditions [16]. Still those methods could not be translated into clinical routine or into widely established research methods for neurocritical disorders – which would deem to be very promising!

All the bedside methods use surrogates for CBF, so certain prerequisites have to be made (and many of them are still under discussion) [4]. The bedside methods can be divided into invasive methods measuring the surrogate at one point using intracerebral probes (could be coined as "probe technology") or more or less non-invasive methods measuring surrogates of the whole hemispheres or undefined regions of the brain. Because of the nature of these methods (measuring only a surrogate of CBF and ruling out an unknown amount of uncertainty by defining prerequisites), it might not be surprising that all those methods, which exist for some 20–40 years, haven't made the breakthrough in neurocritical care, are still under discussion, abandoned by many practitioners, or only used in trial settings for selected patients.

Surrogates of CBF for the probe technology are, for instance, the partial pressure of oxygen in the brain tissue in one point of the brain (most often the frontal white matter of the non-dominant hemisphere). The prerequisites which are made (implicitly!) are:

1. The oxygen levels in the whole body are constant, which is sometimes difficult to maintain in a living dynamic body, who is ventilated by a respirator.
2. The probe measures only a small amount of brain volume (only a few mm^3); the physician has to define whether this region represents the whole brain and gives an insight of the mean disruption of the whole brain when using in neurocritical conditions *or* the region is a sentinel for early detection of secondary damage (of which some neurocritical conditions are notorious, like delayed cerebral ischemia

after subarachnoid hemorrhage) *or* the region is in the center of disruption, from where no useful data has been extracted for clinical decision-making up to now [15].

These problems of representability and probe placement arise with all other probe technologies.

Up to date none of these methods have found its way in (inter)national guidelines, and it has taken more than 20 years to formulate at least some thresholds for these technologies as a trigger for clinical intervention (which are also not well defined!). But considering the lack of alternatives, one is inclined at least to clutch at this straw in the hope of improving the individual outcome of patients.

The non-invasive bedside methods like transcranial duplex or Doppler (TCD) or near-infrared spectroscopy (NIRS) have also excellent temporal resolution, but spatial resolution is also very low or even not definable. TCD suffers from a high user variability and has limitations of its own (for instance, in [19]). NIRS has been reinstalled in neurocritical care, but has still to prove its versatility in clinical routine [17].

Apart from the global cerebral autoregulation, which is thought to take place in the whole brain and incited mainly from extracerebral signals (i.e., the systemic blood pressure), a similar regulation of local cerebrovascular resistance for small regions of the brain can be seen incited by intrinsic signals. This regulation is called *neurovascular coupling*. Within local brain areas, neurotransmitters are able to change the local CVR and respond to metabolic demand. This mechanism is very helpful in maintaining cerebral function: an extensive use of neuronal signaling via synapses and along neurons is energy-costly (most of the energy is used to keep up the transmembrane gradient of ions and by that generating the membrane potential!), for every action potential inverts the polarity of the membrane potential and it has to be turned back with use of ion channel pumps. An effective call for local hyperemia (called *functional hyperemia*) might just provide enough energy substrates (glucose and oxygen) to prevent a long-term neuronal shutdown [1]. This discovery has led to a better understanding of pathophysiology of neurocritical situations and seems to be closely related to the phenomenon of cortical spreading depolarization [10].

2.2 Blood-Brain Barrier

The other key player situated in the brain that regulates the metabolism and maintains the equilibrium is certainly the blood-brain barrier (*BBB*). The brain, as mentioned above, has no own reserves for oxygen and energy substrates and is therefore totally dependent on the body supply in an adequate and continuous manner. The BBB is easier to understand (at first) because there is an anatomical correlate. In contrast to all other regions of the human body, the microvasculature has a “watertight” coating around the blood, consisting of endothelium without any fenestration

and *tight junctions* between the endothelium cells and a complete basement membrane. Around those vessels, there is another almost complete sheath of astrocyte end-feet. Other cells participating in this region are pericytes, microglia, and of course neurons. All these cell types have important functions: pericytes take part in the regulation of CBF [9], and microglia (albeit being mentioned often at the end of the list of cerebral cells, they make up to 15% of all cells in the brain) are immune cells and the first line of defense against infectious particles and tumors (for instance, in [23]).

This formation has been coined *neurovascular unit*. Apart from a few exotic regions of the brain, where the BBB does not exist, it is the BBB, who decides what is going inside and what stays outside.

What goes in? The barrier is nearly impermeable for water and hydrophilic substances. Oxygen, carbon dioxide, and other volatile substances pass the barrier; they don't need special attention – as long as there is oxygen-enriched flowing along in the brain capillaries, there won't be cellular hypoxia, and CO_2 will be washed out by the same flow. The same is true for volatile anesthetics, and that might also be the reason why they have anesthetic properties at all (the high cerebral blood flow ensures a timely rise in concentration, and the lipophilic property might easily disrupt the neuronal membrane function leading to narcosis). So every water-soluble particle has to find his own transporter, and those are, of course, of a special type. For instance, glucose – one of the main cerebral energy nutrients – is mainly transported into the brain via a transporter named GLUT-1, which is enriched in the endothelial cells in the brain, and facilitates the transport of glucose along the concentration gradient from the vascular lumen into the endothelial cell (and from there further on, also via dedicated transporters). Although the receptor can be found in a variety of other organ types, the sheer number of transporters of the brain capillaries gives the brain the edge over the other organs [14]. Deficiency of this transporter leads to a distinct syndrome associated with epilepsia, cognitive dysfunction, and delayed neuronal development, underlining the importance of this single protein.

All other nutrients have also their respective transporters. Of special interest as alternative energy nutrients are *glutamate* (with the double function of a neurotransmitter), *ketone bodies*, and *medium chain triglycerides*, which have been shown to be able to replace and supplement in part the primarily glucose-dependent brain under certain conditions, e.g., in hunger [3].

Small lipophilic molecules have it easier to enter the brain by simple diffusing through the cell membranes, which is a main reason why most of the neurotropic drugs are lipophilic. But our brain has also evolved strategies to remove these compounds. The protein mdr-1 is a potent efflux transporter specialized on small lipophilic substances, removing many substances back into the systemic blood flow, so that no harm can be done to the brain. This protein is also known from drug-resistant epilepsies and also from cancer biology [5].

The process of *transcytosis* through the BBB involves only a small part compared to other regions in the body. But still up to 25% of the amyloid β is excreted through the BBB via transcytosis; failure to perform it at this level is thought a risk factor for Alzheimer's dementia [9].

This blood-brain barrier also has correlates to other "surfaces" of the brain, like to the CSF, then called blood-cerebrospinal barrier (localized in the choroid-plexus epithelium), and an outer coating called outer brain barrier (in the arachnoid barrier holding the CSF in place). The latter is well known by neurosurgeons [12]. There is always the same pattern of sealing off, and tight junctions between the barrier cells can be found in all these barriers. Tight junctions are comprised of transmembrane proteins named imaginatively *claudins* (over 25 subtypes have been described) or *occludins* or *JAMs* (junction-adhesion molecules). JAMs belong to the immunoglobulin superfamily and are supposed to mediate leukocyte extravasation [5].

There is a vast body of research for neurocritical disorders that disrupt the BBB and for the hypotheses of their pathophysiology. For instance, in traumatic brain injury (in animal models), the BBB becomes permeable after the initial insult, but in a biphasic manner 24 and 72 hours after insult and leads to local brain swelling, but this course of events might also be a process for neuroprotection, which is not quite understood today. Even the BBB itself is changing in its integrity on a daily basis (wake/sleep) or with aging of the individual, and even the bacteria in our guts are accused of sending signals to the BBB for the better of both [9].

2.3 Summary

Our brain is a tightly secured organ to excel the animal kingdom. Various measures have evolved to maintain the best performance under various conditions, e.g., variable blood pressure or hunger or infections. Our knowledge of these systems stems from totally different approaches to brain physiology, and that might be the main reason why a uniform depiction is not easily achievable. And a lot of the cellular physiology is still unknown or not understood. The two main installments for regulation of cerebral metabolism and its blood flow can be summarized as the cerebral autoregulation of the cerebral vessels and the blood-brain barrier. Both happen to be localized in the extremely interesting area of the blood-brain interface, what is a nice prospect for the hope of reaching a more satisfying theory of cerebral metabolism and blood flow.

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Chapter 3
Brain Edema: Pathophysiology, Diagnosis, and Treatment

Jesse A. Stokum, Phelan Shea, Gary Schwartzbauer, and J. Marc Simard

3.1 History

Brain edema and swelling are among the most common and pressing problems faced by neurosurgeons. It is surprising that, as recently as the 1940s, the mere existence of brain edema was doubted by certain pathologists, who argued that brain swelling was driven only by vascular distention [1]. This lack of understanding contrasts starkly with maladies such as intracranial hemorrhage and skull fracture, which were described as early as the *Edwin Smith Surgical Papyrus*, ca. ~1600 BCE [2]. However, to many neurosurgeons, the existence and importance of brain swelling was never in doubt. In 1942, G.F. Rowbotham wrote "That generalized edema can occur there is no doubt. …I have occasionally found the brain, in the acute phases of a head injury, under such great tension that it bulged into the wound as soon as the dura was opened, and later at autopsy have been able to show that the increased tension was not due to hydrocephalus and could not have been due to the amount of blood extravasated" [3]. In this section, we discuss the evolution of our understanding of cerebral edema.

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3.1.1 1700s: Formation of the Monro-Kellie Doctrine

Prior to the 1700s, hydrocephalus was believed to underlie all cases of increased intracranial water content. In the late 1700s, Robert Whytt (1714–1766) and George Cheyne (1671–1743) noted that excess intracranial fluid can occur without enlarged ventricles. They described brain tissue that grossly appeared to be soft and water-logged [4]. During an autopsy, Cheyne eloquently remarked that "On cutting [the brain tissue], fluid exuded so as to bedew the new surface."

In 1783, Alexander Monro hypothesized that the volume of blood within the skull must be constant [5]. This theory, combined with writings by George Kellie (1720–1779) and John Abercrombie (1780–1844), led to the formation of the Monro-Kellie doctrine. Interestingly, the original conceptualization of the Monro-Kellie doctrine referred only to the vascular compartment, since it was assumed that the other intracranial compartments were fixed in volume [6].

3.1.2 1800s: Discovery of CSF Dynamics and the Blood-Brain Barrier

In the 1820s, Magendie, a French neurosurgeon with a penchant for live public vivisections, described CSF and documented its drainage from his eponymous foramen into the subarachnoid space [7]. Interestingly, he postulated that the pineal gland served as a flapper valve [7]. Later, Paul Ehrlich's (1854–1915) discovery of the blood-brain barrier (BBB) with aniline dyes in 1886 led to the recognition of the unique physiology of the cerebral vasculature.

3.1.3 1900s: Basic Pathophysiology and Treatments Are Discovered

Connections between interstitial osmolality, brain swelling, and increased intracranial pressure (ICP) were formally stated in the early 1900s. Cannon postulated in 1901 that increased ICP can impair CBF and that injured brain exhibits increased osmotic pressure, causing influx of circulating water. Later in 1905, Reichardt defined cerebral swelling as increased brain volume not due to hyperemia or increased cerebral spinal fluid (CSF) [8]. Finally, in 1942, ICP elevation was directly linked to brain edema by Perret and Kernohan.

In 1919, Weed and McKibben reported that hypertonic saline causes shrinkage of brain tissue, whereas intravenous injection of free water resulted in brain expansion [6]. This seminal study demonstrated that the brain parenchyma itself can change in volume. Interestingly, these experiments also represented the first use of

hyperosmotic therapy. In 1920, Harvey Cushing was the first to use hypertonic saline for the reduction of brain bulk during surgery [9]. Later, in 1962, Wise and Charter similarly used mannitol to decrease brain mass [10].

In the first half of the 1900s, brain edema pathophysiology remained poorly understood. As late as the 1940s, the mere existence of brain edema was hotly debated, with some researchers arguing that brain swelling was mostly driven by ventricular and vascular distention [1]. This confusion was rectified with the development of electron microscopy in the 1960s. In 1965, Bakay and Lee first used electron microscopy to examine edematous brain [11]. Later in 1967, Igor Klatzo (1916–2007) published his seminal work describing "cytotoxic" and "vasogenic" edema [12]. He defined vasogenic edema as an exudate containing plasma proteins, and cytotoxic edema as cell swelling. His nomenclature remains widely used today.

3.1.4 2000s: Molecular Mechanisms Are Investigated

Up to the 1980s, the pathogenesis of edema remained largely unknown, as all current models remained purely phenomenological. Molecular biology techniques developed in the 1980s allowed for the investigation of molecular mediators of cerebral edema. It is now recognized that brain edema formation represents a maladaptive transcriptional program that is activated after an insult.

3.2 Clinical Condition

Cerebral edema, which is defined as a net increase in brain water content, occurs after all CNS injuries, and is invariably linked with worsened outcome. After ischemic stroke, severe brain edema can worsen mortality to nearly 80% [13]. Even when not life threatening, post-ischemic edema formation is a predictor of poor outcome [14]. In traumatic brain injury, brain swelling, which may due to edema and hemorrhage, accounts for ~50% of deaths [15]. In glioblastoma, brain edema is an independent predictor for reduced survival [16–18]. In intracerebral hemorrhage, perihematomal edema is associated with worsened morbidity and mortality [19].

3.2.1 Basic Principles

The pathophysiology of cerebral edema varies depending on the nature of the insult or injury. The following stages can be viewed as an archetypal framework. Of note, these stages do not necessarily occur in stepwise fashion but rather may co-exist in injured tissue.

Within minutes of injury, the neuroparenchyma exhibits cytotoxic edema, comprised mostly of astrocyte swelling [20, 21]. Various astrocytic ion transporters and channels mediate cytotoxic edema by mediating cellular uptake of interstitial ions, which promotes influx of interstitial water. Example transporters include the sulfonylurea receptor 1–transient receptor potential melastatin 4 (SUR1-TRPM4) channel [22, 23], the Na+/K+/2Cl– transporter subtype 1 transporter (NKCC1) [24, 25], the Na+/H+ exchanger (NHE) [26], and the excitatory amino acid transporters (EAAT) [27]. Notably, cytotoxic edema, in isolation, does not include addition of new water to brain tissue, and therefore does not result in brain swelling [28].

During cytotoxic edema, interstitial Na^+ is depleted, resulting in a new Na^+ gradient across the blood-brain barrier that favors influx of vascular Na^+ [29] through various endothelial ion transporters [30–32]. Influx of vascular Na^+ promotes influx of water, resulting in the formation of ionic edema, which generates brain swelling.

Of note, during ionic edema, the BBB remains impermeable to circulating plasma proteins. As brain injury progresses, the BBB becomes permeable to these proteins, and the edema fluid becomes a proteinaceous suspension, which is termed vasogenic edema. Mechanistically, VEGF upregulation [33], matrix metalloproteinase expression [34], and changes in endothelial morphology [35] underlie vasogenic edema formation. Vasogenic edema differs from hemorrhage in that the BBB still excludes circulating erythrocytes.

3.2.2 Peritumoral Edema

Peritumoral edema is formed by several unique mechanisms. Brain tumors are hypervascular yet are poorly perfused and hypoxic since as many as 50% of tumor vessels cannot convey erythrocytes [36, 37]. Tumor hypoxia encourages angiogenesis, which results in immature vessels that lack a complete BBB and can permit passage of molecules as large as ~550 nm [38, 39]. The hyperpermeable tumor vessels permit extravasation of circulating plasma proteins and water, which leads to the formation of vasogenic edema.

3.2.3 Perihematomal Edema

In intracerebral hemorrhage, edema forms in the surrounding neuroparenchyma via several unique mechanisms. Perihematomal edema occurs in three stages: ionic edema, vasogenic edema, and delayed vasogenic edema [40]. In perihematomal ionic edema, transendothelial osmotic forces mediate influx of circulating water. In addition to cytotoxic edema, perihematomal osmotic pressure is also generated by a phenomenon called clot retraction. In clot retraction, the coagulation cascade results in extravasation of serum proteins, which increase the local osmotic pressure [41, 42].

Perihematomal vasogenic edema, the second stage of perihematomal edema, is also produced by several unique mechanisms. Thrombin, through PAR-1 mediated microglial activity and leukocyte transmigration, can cause endothelial activation and BBB opening [42, 43]. The compliment cascade also contributes to vasogenic edema through production of anaphylatoxins and activation of the membrane attack complex [43].

In delayed perihematomal vasogenic edema, hemoglobin degradation products such as methemoglobin accumulate in tissues at ~3 days after hemorrhage [44]. These products promote generation of reactive oxygen species (ROS), activation of matrix metalloproteinases (MMP), microglial activation, and BBB breakdown, resulting in delayed vasogenic edema [42].

3.2.4 Cerebral Edema and Swelling

Cerebral edema is a pathological increase in the water content of the brain parenchyma. Cerebral edema is detrimental because it manifests as brain tissue swelling, which refers to a volumetric expansion of tissue. Swelling can be generated by tumor, edema, or blood. Brain swelling exerts a mass effect on the surrounding tissue. The rigid skull places an upper limit on the volume the brain may expand into. Beyond this volume, ICP increases. When ICP exceeds capillary pressure, tissue ischemia occurs. With increased local pressure, herniation of brain tissue across rigid structures also may occur.

3.3 Physical Examination/Imaging

3.3.1 Ocular Findings

Various ocular signs have been proposed for noninvasive assessments of ongoing brain herniation secondary to edema formation. Due to the uniform symmetry of pupil responses among healthy individuals [45], pupillometry can be used as a reliable tool for patients affected by cerebral edema and swelling. Taylor et al. reported a pronounced association with reduced pupillary constriction velocities (less than 0.6 mm/second) and patients with active or impending increases in brain volume [46]. Optic nerve sheath ultrasound has also been used to assess ICP and cerebral edema, with optic nerve sheath diameters greater than 5.0–5.8 mm correlating with elevated ICPs [47, 48]. Ultrasound exhibits high negative predictive values, and sensitivities are reported to be as high as 100% [47, 48]. Although commonly associated with cerebral edema, papilledema should not be relied upon to rule out an acute ICP elevation — in one study, only a single occurrence of papilledema occurred in 37 patients with acutely elevated ICP [49].

3.3.2 Herniation Syndromes

When local pressures increase substantially, brain tissue can herniate through rigid cranial structures in certain conserved patterns. Notably, these herniation syndromes may occur concurrently, and therefore an amalgamation of physical examination findings can be present. Symptoms of increased ICP, such as headache, nausea, vomiting, altered mental status, somnolence, papilledema, blurred vision, and Cushing's triad, can accompany most herniation syndromes.

Transtentorial or central herniation occurs when the diencephalon is compressed through the tentorium cerebelli. In the early diencephalic stage [50], pupils are typically small and reactive. Breathing progresses from intermittent pauses to Cheyne-Stokes respirations. Motor responses become limited to decorticate posturing. During the midbrain-upper pons stage [50], third nerve compromise causes pupillary dilation to 3–5 mm, breathing becomes tachypneic, and posturing can become decerebrate. During this stage, the oculocephalic reflex may become impaired, requiring more radical head-turning to elicit. The lower pons-upper medullary stage is characterized by absent reflex responses (with the exception of bilateral Babinski signs), flaccidity, absent oculocephalic reflex and cold water calorics, and a persistent shallow tachypnea. Terminal stages of transtentorial herniation manifest with bradypnea leading to apnea. Wide pupillary dilation from hypoxia secondary to apnea may occur during this stage as well. In addition, "automatic stepping" or spontaneous alternating flexion of the hip, knee, and ankle that deceptively appear purposeful may occur [51]. Transtentorial herniation can also cause compression of the posterior cerebral artery (PCA), with corresponding deficits and the development of occipital lobe infarction.

Upward cerebellar herniation is caused by compression of the cerebellar vermis through the tentorium cerebelli, usually in the setting of a posterior fossa mass lesion or over-drainage from a ventriculostomy [52]. Upward herniation of the cerebellum can cause compression of the superior cerebellar artery and cerebellar infarct, presenting with characteristic miotic fixed pupils and absent vertical doll's eye movements, as well nonspecific features such as coma, hyperventilation, and posturing. Additionally, upward cerebellar herniation can present with Parinaud syndrome or hydrocephalus from aqueduct compression.

Uncal herniation can initially present with pupillary dilation (up to 6–9 mm) from CN III compression, a contralateral Babinski reflex, normal respirations, and intact oculocephalic reflex. As pupillary dilation progresses, respirations become rapid and deep, and contralateral paralysis progresses to bilateral decerebrate posturing – typically skipping decortication. Kernohan's phenomenon presents as ipsilateral weakness from compression of the contralateral cerebral peduncle against the tentorial edge. Compression of the PCA by the temporal lobe can lead to ipsilateral or bilateral occipital lobe infarction and the corresponding presentation (blurry vision, blindness) [53]. In the terminal stage, oculomotor ophthalmoplegia occurs while pupils shrink to become fixed at mid position; late stages of uncal herniation generally resemble the advanced stages of central herniation.

Subfalcine herniation occurs when the cingulate gyrus herniates under the falx cerebri, which can cause occlusion of the ipsilateral anterior cerebral artery with subsequent frontal lobe infarction. Key presenting features of this syndrome are contralateral leg or bilateral weakness, urinary incontinence, and aphasia [54]. Herniation of the dominant hemisphere can result in disruption of the arcuate fasciculus and present with a conductive, receptive, or expressive aphasia [55]. Subfalcine herniation can progress to central or uncal herniation.

Tonsillar herniation occurs when the cerebellar tonsils are wedged through the foramen magnum, resulting in compression of the medulla, bradycardia, bradypnea, and rapid cardiopulmonary arrest. A notable finding is the presence of a loud vascular bruit due to herniation of the vertebral arteries below the foramen magnum [56].

Transcalvarial herniation occurs when edematous brain is compressed through a defect in the calvarium. The presentation is highly variable depending on the location of the defect and corresponding cortical vessels and parenchyma.

3.3.3 ICP Monitoring

Indications for ICP monitoring have been best studied in patients with traumatic brain injury. Per the Brain Trauma Foundation guidelines [57, 58], monitoring is appropriate in severe head injury patients (GCS 3-8 after cardiopulmonary resuscitation) with an abnormal admission CT scan, which includes the presence of contusion, edema, compressed basal cisterns, or hematoma. Severe head injury patients with normal CT scans are monitored if at least two of the following features are present on admission: unilateral or bilateral motor posturing, age over 40 years, or systolic BP <90 mm Hg. Relative contraindications to ICP monitoring vary by institution, but generally, patients that are GCS >8, awake, and following commands or with refractory coagulopathy should not receive monitors. In these instances, or where resources are sparse, with severe head injury, clinical vigilance to exam change and appropriate CT scan monitoring are paramount [59]. ICP monitoring may be practiced in other pathologies such as subarachnoid hemorrhage, but the indications are less well studied.

3.3.4 Imaging

Cytotoxic edema typically exhibits diffusion restriction on diffusion weighted imaging (DWI) and low signal on apparent diffusion coefficient (ADC) [60]. Since cytotoxic edema is strictly a water rearrangement, without any net gain in tissue water, a pure cytotoxic edema should technically exhibit no changes in T2, FLAIR, or CT attenuation. However, since cytotoxic edema co-occurs with ionic and vasogenic edema, T2 hyperintensity and decreased CT attenuation are often observed

[61]. Extracellular ionic and vasogenic edema exhibit increased diffusion and ADC signal, T2/FLAIR hyperintensity, and decreased CT attenuation [60]. Extracellular edema signal generally predominates in the white matter [60].

3.4 Differential Diagnosis

The differential diagnosis of cerebral edema is broad, as the early signs of cerebral edema are relatively nonspecific and can represent a variety of CNS pathologies. Symptoms such as headache, nausea, vomiting, tachypnea or bradypnea, altered mental status, and blurred vision can also occur with meningitis, encephalitis, stroke, seizures, acute hydrocephalus, intracranial hemorrhage, subdural/epidural hematoma, toxidrome, or metabolic abnormalities. Papilledema, which is typically associated with increased ICP due to edema, can also be present with meningitis, encephalitis, malignant hypertension, and certain medications, including isotretinoin, corticosteroids, and tetracyclines.

Pupillary dilation is commonly used as a marker of increased cerebral edema and herniation; however, this can be inaccurate with a superimposed mydriatic agent, toxidrome, or CNS disease. Common illicit drugs with pronounced mydriatic effects include cocaine, amphetamine/methamphetamine, LSD, MDMA, and cathinones. Toxidromes with associated mydriasis are benzene, chloroform, belladonna, and botulism (which may have the additional confounder of descending paralysis). Syndromes unrelated to cerebral edema with associated pupillary dilation include glaucoma, Guillain-Barre syndrome, multiple sclerosis, seizure, and Adie tonic pupil.

Hemiparesis, flaccidity, decorticate/decerebrate posturing, and other motor manifestations of the herniation syndromes can also be mimicked by other pathologies. Cortical and capsular stroke can cause hemiparesis, while brainstem stroke may cause hemiparesis, posturing, or total flaccidity. Syndromes such as Guillain-Barre, botulism, myasthenia gravis, central pontine myelinolysis, and acute disc herniation can present with a rapid onset paresis or paralysis that resembles late stages of herniation. Of note, spongiform encephalopathies such as Creutzfeldt-Jakob disease have demonstrated decorticate posturing, albeit in the late stages of the disease [62]. An obvious yet occasionally overlooked confounding factor in a patient with motor flaccidity is the usage of paralytics and sedation; it is imperative that both be paused prior to an accurate clinical assessment.

3.5 Treatment Options

There currently exist no specific therapies for cerebral edema. Rather, all approved treatments aim to mitigate negative downstream consequences on ICP. ICP treatment is typically initiated with ICP >20–25 mmHg. In this section, current treatments are discussed, followed by a section that introduces possible future therapies.

3.5.1 Medical Optimization and Patient Positioning

A critical component in the management of patients suffering from brain edema is the optimization of any additional metabolic or respiratory derangements. In addition, sedation and adequately analgesia should be adequate. It is often appropriate to apply short acting sedatives such as propofol or midazolam and analgesics such as fentanyl.

As many as 20–25% of patients with severe traumatic brain injury suffer from acute lung injury [53], with many of these patients exhibiting hypercapnia and hypoxemia. Since CO_2 and oxygen are potent cerebral vasoregulators [51], respiratory derangements can worsen ICP crises. Unsurprisingly, lung injury is associated with worsened outcomes in patients with brain injury [63]. Therefore, in obtunded patients with GCS <8, or in patients with respiratory failure, intubation and mechanical ventilation may be necessary, in part for ICP management. Notably, while mechanical ventilation may theoretically increase ICP secondary to raised thoracic pressure [64], empirically, lung protective ventilation does not substantially impact ICP in patients with brain injury [65].

Hyperglycemia occurs in ~12% of patients with severe brain injury [66] and in over 50% of patients with ischemic stroke [67], and is an independent predictor of worsened outcome. Hyperglycemia worsens cerebral edema and brain swelling [68], though the mechanism remains unknown. Therefore, blood glucose should be normalized to <80 mg/dL within the first 24 hours of stroke or TBI.

ICP can often be successfully managed by optimizing patient positioning. It is common practice to position the head midline, which can reduce ICP by up to ~7 cmH_2O by optimizing venous drainage [69]. In addition, the head of bed (HOB) is often elevated to 30 degrees, which reduces ICP by as much as 10 cmH_2O without compromising tissue oxygenation [70–72]. For every 10 degrees of HOB elevation, ICP is decreased by ~1.3 cmH_2O [73]. Beyond 30 degrees elevation raises concerns for appropriate cerebral perfusion pressure to be between 60 and 70 mmHg, but each patient may have an ideal position to maximize these parameters.

3.5.2 Hyperventilation and Hyperosmolar Therapy

CO_2 is a potent vasoregulator. Temporary therapeutic hyperventilation, which reduces CBF and ICP, remains a powerful tool for managing acute ICP crises. In therapeutic hyperventilation, end tidal PCO_2 is lowered to ~30–32 mmHg [74]. Hyperventilation can lower ICP up to ~47%, with an average time to onset of 8 minutes [75]. After a return to normoventilation, ICP will return almost immediately to baseline levels [75]. Hyperventilation must be used sparingly and with caution, however, since it can promote cerebral ischemia.

In patients that continue to exhibit elevated ICP, hyperosmolar agents may be used. Hyperosmolar agents increase plasma osmotic pressure, favoring movement

of water out of the brain parenchyma. An ideal hyperosmolar agent is biologically inert and is completely excluded by the BBB. While numerous compounds have been used historically, currently approved agents include mannitol and hypertonic saline.

Mannitol is given intravenously in doses of 0.5–1.5 g/kg. Dosing can be repeated every 4–6 hours. Serum osmolarity should be monitored during mannitol therapy, and should not exceed 320 mOsm/kg, for risk of causing kidney injury [76]. In a study that examined the clinical efficacy of mannitol in intracranial hypertension due to a variety of etiologies, mannitol was found to lower ICP by 52% [75]. Hemodynamics should be monitored, as mannitol can cause osmotic diuresis [77].

Hypertonic saline is supplied in a variety of concentrations but is typically given either as a 30 mL bolus of 23.4% saline over 5 minutes or as a continuous infusion of 3% saline. Sometimes continuous infusion is applied as a preventative measure against swelling in hyponatremic patients, whereas more often boluses are administered in response to acute deterioration or acute symptomatic hyponatremia. Since sodium chloride is more avidly excluded by the BBB than mannitol, theoretically, it is a more ideal hyperosmotic agent [78]. However, numerous studies have failed to show differences in mortality in patients treated with hypertonic saline versus mannitol [79, 80]. There are various advantages favoring hypertonic saline, most notably its tendency to maintain euvolemia [72].

3.5.3 Decompressive Craniectomy

In patients with elevated ICP refractory to medical management, decompressive craniotomy (DC) can be employed to increase intracranial compliance and decrease ICP. The craniotomy size should be at least 15 cm × 12 cm [81] and should include duraplasty. DC became widely practiced only within the past ~30 years [82]. Its use has been mostly studied in large vessel ischemic stroke and in traumatic brain injury.

In traumatic brain injury, two major trials have examined the application of DC. In the DECRA trial [83], bifrontal decompression was compared with non-operative management in patients with ICP >20 mmHg for 15 minutes in 1 hour, despite tier 1 medical management. DECRA showed no differences in mortality with DC, although DC was associated with worsened morbidity at 6 months. In the RESCUE-icp trial [84], lateral or bifrontal DC was compared to medical management in patients with ICP >25 mmHg for more than 1 hour, despite tier 1 and 2 medical management. RESCUE-icp showed reduced mortality with DC (48.9% versus 26.9%). However, ~40% of the patients rescued by DC were highly dependent at 12 months [85]. From these studies, DC may be employed reduce mortality in patients with ICP crises secondary to TBI, but at the cost of substantial downstream morbidity.

In malignant MCA syndrome after ischemic stroke, three trials have examined the role of DC. In the 2001–2005 DECIMAL trial [86], 18–55-year-old patients within 24 hours of ischemic stroke encompassing >50% of the MCA territory on CT

or DWI volume of >145 were randomized to DC within 6 hours versus DC after 30 hours of medical management. Patients submitted to early DC exhibited ~53% reduction in mortality. In the 2004–2005 DESTINY trial [87], 18–60-year-old patients with >2/3 of the MCA territory on CT were randomized to medical management versus DC within 36 hours. DESTINY results were roughly consistent with DECIMAL. Finally, in the 2002–2007 HAMLET trial [88], 18–60-year-old patients with >2/3 of the MCA territory on CT were randomized to medical management versus DC within 96 hours. DC was associated with an absolute risk reduction of death of 38%. Meta-analysis of these three studies showed ~50% reduction in mortality, and ~50% reduction in moderate-to-severe disability/death. To reduce mortality and to reduce moderate-to-severe disability/death, the number needed to treat was 2 [89].

3.5.4 Experimental Therapies

Several new anti-edema drugs have recently been subjected to clinical investigation. These drugs are distinguished from the above treatments in that they directly inhibit the molecular mechanisms that generate edema, rather than simply mitigating its downstream consequences. These agents include vaptans, inhibitors of arginine vasopressin [90, 91]; fingolimod, a functional inhibitor of spingosine-1-phosphate signaling [92–94]; celecoxib, a cyclooxygenase-2 inhibitor [95]; and glyburide, an SUR1-TRPM4 channel inhibitor [96–98]. For a comprehensive review of all anti-edema drugs that have been clinically evaluated, please refer to [99].

3.6 Complications

Many of the various herniation syndromes can result in permanent neurological deficits. Subfalcine herniation can cause occlusion of the ipsilateral anterior cerebral artery with subsequent frontal lobe infarction. Key presenting features of this syndrome are contralateral leg or bilateral weakness, urinary incontinence, and aphasia [54]. Transtentorial herniation can cause compression of the PCA by the temporal lobe, which can lead to ipsilateral or bilateral occipital lobe infarction [53]. Transtentorial herniation can also cause diabetes insipidus, and a parkinsonian syndrome, with the former occurring due to anterior force vectors shearing the pituitary stalk and the latter from midbrain compression and thinning of the pars compacta [100].

Descending transtentorial herniation can also lead to Duret pontine hemorrhages. Mechanistically, herniation stretches the perforating arterioles supplying the pons, resulting in hemorrhagic infarction, which characteristically occurs in the midline. Duret hemorrhages are radiographically observed in 5–10% and pathologically observed in 30–60% of cases of brainstem herniation [101].

The various therapeutics used to treat swelling may also induce significant morbidity and mortality. The side effect profile of both mannitol and hypertonic saline are well characterized and should be considered prior to their use. Mannitol can induce osmotic diuresis and result in hypotension [76]. Additionally, since mannitol can cross the BBB, if mannitol is repeatedly given over long (>60 minutes) periods of time, mannitol can accumulate in the parenchyma and worsen edema [76]. Mannitol is also associated with azotemia, hyperkalemia, pulmonary edema, and heart failure [76]. Compared to mannitol, hypertonic saline has a more benign side effect profile. Nevertheless, hypertonic saline can cause volume overload, thrombocytopenia, and metabolic acidosis [76].

While therapeutic hyperventilation is a potent therapy for increased ICP, hyperventilation should be employed with caution. Since CO_2 is a potent vasoregulator – a 1 mmHg drop in $PaCO_2$ translates to a 4% reduction in CBF [102] – there is risk for cerebral ischemia with inappropriate hyperventilation. Any reduction in CO_2 beyond P_aCO_2 of 30 mmHg should be avoided, since (i) reductions in ICP rarely occur with $PaCO_2$ below 30 mmHg [74] and (ii) a $PaCO_2$ lower than 30 mmHg risks incurring ischemic damage [103]. Furthermore, therapeutic hyperventilation should not be sustained longer than 4–6 hours, as sustained hyperventilation is associated with worsened outcome in patients with severe head injury [104] and can result in rebound edema upon reversal.

While DC is often regarded as a definitive treatment for brain swelling, it should also be cautiously applied. DC is a major surgery, typically undertaken in critically ill patients. Unsurprisingly, DC is associated with substantial morbidity. In a meta-analysis of complications secondary to decompressive craniectomies, the investigators reported a complication rate of 13.4% after the initial decompression, a rate of 6.4% after cranioplasty, and a total complication rate of 19.8% [105]. Thus, approximately every 1 in 5 patients undergoing DC will experience a complication.

Pearls/Tips

- The existence of brain edema was debated as recently as the 1940s, with detractors arguing that ventricular and venous distension drove brain swelling.
- In ischemic stroke, brain swelling is usually due mostly to edema; in TBI, brain swelling is often due to both edema and hemorrhage.
- Brain herniation syndromes may occur concurrently, and therefore an amalgamation of abnormal neurological findings can be present.
- ICP monitoring is appropriate in severe head injury patients (GCS 3-8 after cardiopulmonary resuscitation) with an abnormal admission CT scan, or in patients with normal CT scans and at least two of the following on admission: unilateral or bilateral motor posturing, age over 40 years, or systolic BP <90 mm Hg.
- The presence of papilledema in acute ICP elevation is very uncommon and should not be used to rule out an ICP crisis.
- Respiratory and metabolic derangements are common in patients with CNS injury and can worsen edema. Of severe TBI patients, 20–25% have acute lung injury and 12% have hyperglycemia. Of patients with stroke, over 50% have hyperglycemia.

- Patient positioning is a powerful component of ICP management.
- Therapeutic hyperventilation, where end tidal PCO_2 is lowered to ~30–32 mmHg, can lower ICP by nearly 50%. However, it should not be sustained longer than 4 hours.
- If mannitol is repeatedly given over long (>60 minutes) periods of time, it can accumulate in the parenchyma and worsen edema.
- In TBI, DC should be employed only as a last resort intervention. It reduces mortality, but at the cost of substantial downstream morbidity.
- In stroke, DC reduces mortality by ~50% and moderate-to-severe disability/death by ~50%, each with a number needed to treat of 2.
- Approximately every 1 in 5 patients undergoing DC will experience a complication.

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Chapter 4
Intracranial Pressure: Invasive Methods of Monitoring

Ruy Castro Monteiro da Silva Filho and Paulo Eduardo de Mello Santa Maria

4.1 Historical Overview and Basic Concepts

Since the discovery of a small foramen in the floor of the fourth ventricle and its connection to the subarachnoid spaces of the brain and spinal cord by François Magendie in the late eighteenth century, neurologists and neurosurgeons have studied the physiological relationships between the cerebrospinal fluid flow and the problems caused by the raising of its pressure [1], although initially the concept of cannulation of the ventricles was frowned upon, as commented by Robert Whytt in his *Observations on Dropsy in the Brain*, published in 1768: 'any such attempt to draw off the water, could have no other effect than to hasten death' [2].

The first to standardize the technique for lumbar puncture and measurement of the cerebrospinal fluid (CSF) pressure by connecting the lumbar puncture needle to a fine glass pipette open to atmospheric pressure was Quinke, who in 1891 published his studies on the diagnostic and therapeutic applications of diverting the fluid from the subarachnoid space of the spinal cord [1].

Later on, researchers started moving from the lumbar puncture to the direct catheterization of the ventricular system, the first report of an organized method of measuring intracranial pressure took place in France, 1951 by Guillaume and Janny, which consisted in the use of *continuous intracranial manometry*—an electromagnetic transducer to measure ventricular CSF pulses in patients with various types of intracranial lesions [3].

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4.1.1 Lundberg's Waves

It was not until the publications of Nils Lundberg in 1960, though, that foundation for modern intracranial pressure (ICP) monitoring was laid: involving conscious volunteers with a multiplicity of intracranial pathologies, his work aimed to develop a cannulation and measurement method that was minimally traumatic, easy to manipulate and with a low infection and leakage risks [1, 2].

After initial studies with 48 patients, Lundberg classified rhythmic fluctuations in the ICP in 3 graphically measured waves: A, B and C. It is important to point out that Lundberg's method provided a quantitative analysis of the ICP wave, not a qualitative one as the monitors available nowadays.

'A' waves (Fig. 4.1)—or *plateau waves*, as they were baptized by Lundberg—are always associated with intracranial pathology, during which is common to observe clinical signs of herniation such as bradycardia and hypertension. Yet without a certain aetiology, it is hypothesized to be related to the loss of cerebral autoregulation, as cerebral perfusion pressure (CPP) becomes inadequately low to meet brain tissue's metabolic demand, causing micro cerebral vasodilation and raise of intracranial blood volume, which then causes further decrease of the CPP in a vicious cycle [1, 4] (Fig. 4.2). They have amplitudes of 50–100 mmHg and last between 5 and 20 minutes, as described my Lundberg:

> The tracing may reveal a number of different spontaneous pressure variations. Among these, one type is of particular interest, because it is closely related to acute cerebral symptoms in patients with intracranial hypertension. This type of pressure variation is characterized by a sudden rapid rise, continuation on a high level for some time, and finally a rapid fall. Because of the typical shape which these pressure variations give to the VFP curve, I call them "plateau waves." [4]

'B' waves (Fig. 4.3) are the most frequently observed pattern and less correlated with adverse clinical outcomes as they can be observed in patients with normal mean ICP, being interpreted as non-specific indicators of diminished compliance. They consist of clustered acute peak-shaped upstrokes without plateau waves

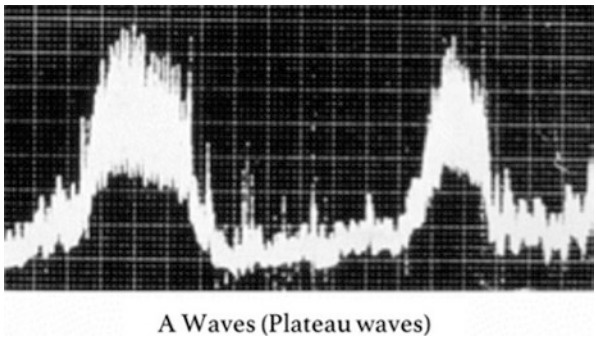


Fig. 4.1 Lundberg's 'A' waves [5]

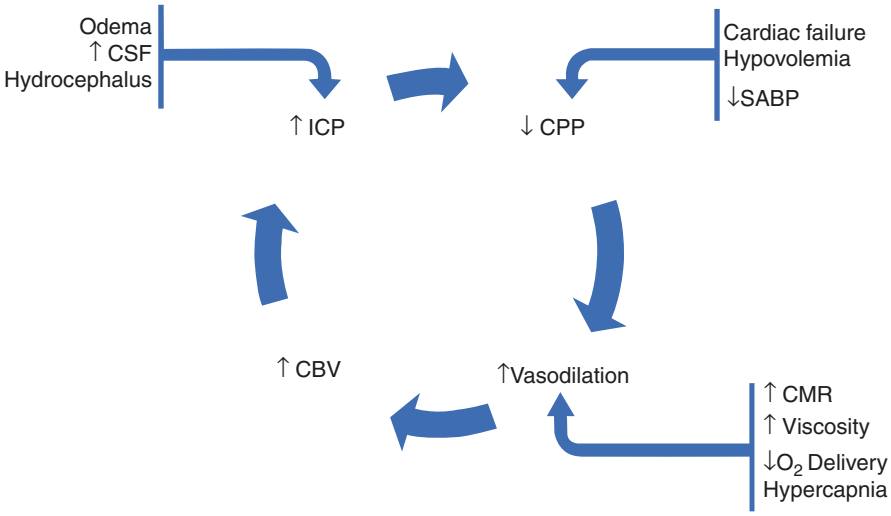
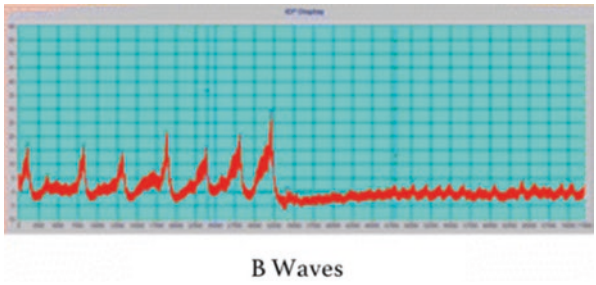


Fig. 4.2 Cerebral vasodilatory cascade. ICP Intracranial Pressure, CPP Cerebral Perfusion Pressure; CBV Cerebral Blood Volume CSF Cerebrospinal Fluid, SABP Systolic Arterial Blood Pressure, CMR Cerebral Metabolic Rate

Fig. 4.3 Lundberg's 'B' waves [5]



occurring in a frequency of 1–2 per minute and ranging between 20 and 30 mmHg above the baseline level, up to 50 mmHg. B waves cluster interval duration varies between 5 and 30 minutes [5].

'C' waves have been documented in healthy individuals and have little clinical or pathological significance, probably related to the respiratory and cardiac cycles. They are rapid oscillations, in average 4–8 per minute and up to 20 mmHg, thus unrelated to intracranial hypertension [1].

A and B waves require attention and medical intervention in order to maintain CPP and reduce ICP, and even though Lundberg's patterns nowadays are more of historical than clinical value, continuous intracranial pressure monitoring is a useful tool in evaluating the treatment results and feedback.

4.1.2 The Monro-Kellie Doctrine

The principles and rationale of the dynamics between the intracranial elements and pressure are condensed in the doctrine first postulated by professor Alexander Monro Secundus and his pupil George Kellie, which determines that in an intact cranium with closed sutures the volume of the brain plus the CSF plus the intracranial blood volume is a constant; therefore, an increase in one should be compensated by a reduction in the volume of one or both of the remaining two [6].

A similar phenomenon can be observed when a new intracranial volume is added, displacing CSF and/or venous blood volumes, which can be physiological—as in the inflow of arterial blood in systole—or pathological—as the development of a brain tumour or haematoma [1, 6]. Therefore, ICP is a product of the relationship of the alteration in craniospinal volume and the craniospinal axis' ability to accommodate the added volume.

If a new volume is installed, initially there is little change in ICP. Although when cerebral compliance is reduced due to progressive exhaustion of the volumetric compensatory reserve—initially CSF, followed by venous and then arterial blood volume—the continuous inflow of the cerebral component of the cardiac cycle leads to an exponential increase in the mean ICP (and in the amplitude of the ICP wave), which results in the decrease of the CPP until it becomes too great to be overcome by the mean arterial pressure (MAP), resulting in brain death [1].

The aforementioned dynamics, when put in graphical language, take the form of the Langfitt curve (Fig. 4.4), which can be divided in four phases [7]:

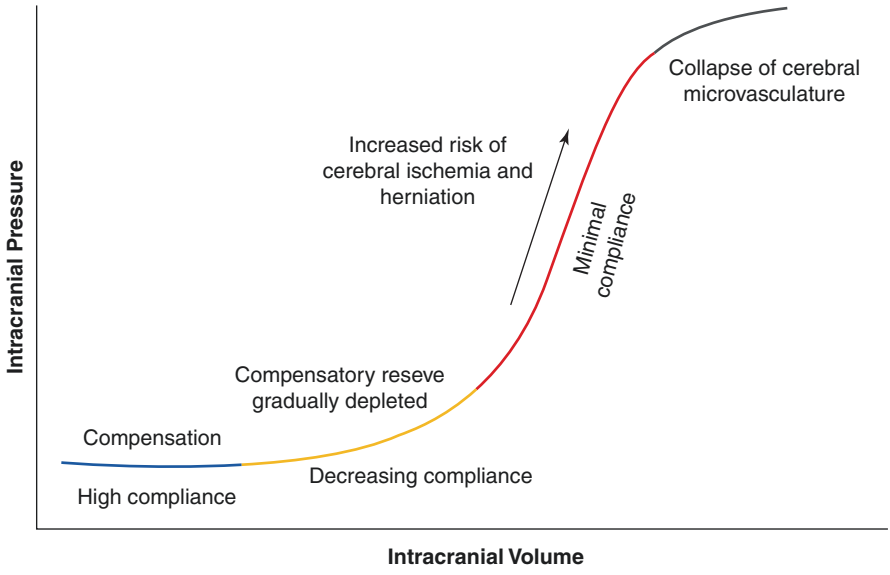


Fig. 4.4 Langfitt's curve, phases 1–4 [5]

- Phase 1, when, initially, expansive lesions cause proportional dislocation in CSF—from the ventricular system to the spinal subarachnoid space—without increase in ICP.
- Phase 2, when there is virtually no CSF left in the intracranial compartment. There is alteration in the local perfusion, causing lactic acidosis and activation of the vasodilator cascade, increasing blood volume in the cranium.
- Phase 3, when there is an exponential increase in the cerebral blood volume, related to the loss of cerebral autoregulation, with the ICP raising until it equals the MAP and the CPP tends to zero.
- Phase 4, vasoplegia.

4.2 Eligibility Criteria for Invasive Monitoring

Intracranial pressure monitoring allows early detection, and therefore early assessment and intervention, in case of expanding focal or diffuse lesion and the calculation of CPP, which are key information in the management of intracranial hypertension.

It is useful in a variety of pathologies such as traumatic brain injury (TBI), hydrocephalus, stroke and encephalopathy. It can be measured using devices inserted into the ventricles, parenchyma, subdural and subarachnoid spaces, being the intraventricular catheter the gold standard [8] (Fig. 4.5).

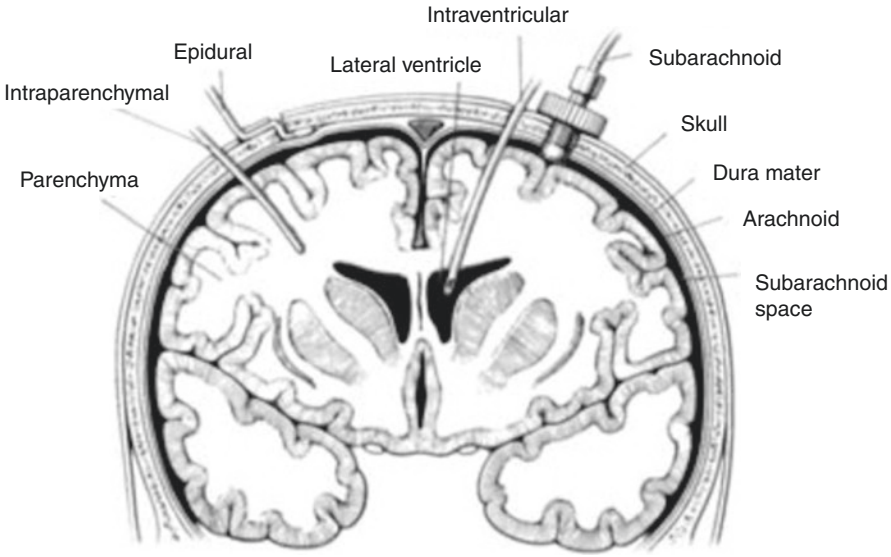


Fig. 4.5 Different positioning for ICP catheters [5]

In the context of TBI management, invasive intracranial monitoring has become standard of care, as the Brain Trauma Foundation (BTF) recommends invasive ICP monitoring in all salvageable patients with severe TBI—that is, Glasgow Coma Scale (GCS) 3–8 after neurological resuscitation—and an abnormal computed tomography (CT) scan in order to reduce in-hospital mortality and in the initial 2 weeks (Recommendation level II B). In patients with severe TBI but normal CT, ICP monitoring is indicated if two or more of the following criteria are met at admission: age over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure < 90 mmHg [9]. The authors of this chapter do not recommend the installation of invasive ICP in patients with admission GCS 3 associated with severe brainstem disfunction after neurological resuscitation, due to limited prognostic and therapeutic possibilities.

Recently, a multicentre randomized trial has been published comparing invasive ICP monitoring to serial CT imaging in patients with severe TBI. It found no advantage in the former when compared to the latter [10]. This study had great international repercussion and has been widely questioned, mainly about its external validity—once it was conducted exclusively in lower-income countries with less routine access to ICP monitoring—and methods [11].

In patients with ischemic stroke, it is not recommended routine use of ICP monitoring, either in malignant cerebral or cerebellar infarction [12]. In case of cerebellar stroke with oedema and compression of more than 50% of the fourth ventricle, due to the high risk of hydrocephalus and direct brainstem compression, a suboccipital decompressive craniectomy immediately preceded by an external ventricular drainage (EVD) associated with intraventricular ICP monitoring is indicated (class I, level of evidence C) [13].

There are two main scenarios in which ICP monitoring is used for malignant cerebral infarction: (a) patients in intensive care for whom medical (non-operative) management is the primary line of care and (b) patients awaiting secondary decompressive craniectomy (DC). ICP values may be used to guide medical treatment intended to reduce ICP or to indicate DC, but solid ICP thresholds for neither of those interventions have been settled, rendering invasive monitoring uncommon in practice. In these patients, transtentorial herniation and clinical deterioration can be observed without any ICP rise [9, 12].

The authors, with this last information in mind, in case of clinical and radiological evidence of malignant thrombosis of the middle cerebral artery (MCA), prefer a primary decompressive craniectomy instead of exclusive ICP monitoring. In the primary DC scenario, ICP monitoring can be used to observe post-operative complications or secondary injuries—for example, epidural haematoma, haemorrhagic transformation.

Patients presenting with mass lesions or ischemia on the temporal lobe should be submitted to routine neuroimaging once they are also prone, due to anatomic reasons, to uncal herniation without great variations in the intracranial pressure.

4.3 Definitions in Intracranial Dynamics and Monitoring Methods

4.3.1 Definitions

4.3.1.1 Intracranial Pressure (ICP)

ICP is the pressure exerted by the intracranial components on the inside of the cranium and on each other. It can be measured by a variety of devices and its normal value varies with age: 1.5–6 mmHg in term infants, 3–7 mmHg in young children and up to 15 mmHg in older children and adults. In newborns, it can be subatmospheric [14].

Almir Ferreira de Andrade, Brazilian neurosurgeon and researcher, in his works regarding traumatic brain injury and intracranial pressure, defines values between 15 and 20 mmHg as *altered ICP* without intracranial hypertension [15]. ICP values between 20 and 40 mmHg represent mild intracranial hypertension, which already requires medical attention and intervention. Sustained ICP values greater than 40 mmHg represent severe, life-threatening intracranial hypertension [13–15].

The most recent BTF guidelines indicate intervention in patients with ICP greater than 22 mmHg [9]. The authors recommend stricter attention to patients showing altered intracranial pressure (15–20 mmHg) in addition to (a) reversal of the P1/P2 amplitude ratio (P2 > P1) or (b) difficulty in keeping CPP > 60 mmHg.

Some studies demonstrate lesser mortality in patients who underwent intervention with ICP > 15 mmHg than in those with ICP > 20 mmHg. The authors strongly recommend, whenever available, multimodality monitoring of the ICP (absolute values and waveform) and $PtiO_2$, once severe brain tissue hypoxia can be found in patients with normal ICP (Fig. 4.6) [16].

Fig. 4.6 Intracranial multimodality monitoring—ICP, temperature and $PtiO_2$

4.3.1.2 Cerebral Perfusion Pressure (CPP)

CPP is the net pressure gradient that drives oxygen and glucose delivery to brain tissue, is measured in millimetres of mercury (mmHg) and is calculated by subtracting the ICP from the mean arterial pressure (MAP), *ergo*, **CPP = MAP – ICP**.

Normal CPP varies between 60 and 80 mmHg, but these values can change depending on the patient's pathology [17].

4.3.1.3 Cerebral Blood Flow (CBF)

The brain receives 15–25% of the cardiac output and the cerebral blood flow ranges from 40 to 50 mL/min for each 100 mg of brain. As there is no invasive method of directly measuring the CBF, it is estimated by the cerebral metabolic rate of oxygen consumption ($CMRO_2$), which in turn varies according to the cerebral vascular resistance [18].

4.3.2 ICP Monitoring Methods

The gold standard method for invasive intracranial pressure monitoring is the insertion of an intraventricular catheter, which enables not only the measurement of the ICP but also the drainage of the CSF in order to treat intracranial hypertension. With that in perspective, there are possibilities of fluid-filled systems and transducer-tipped catheters [18, 19]. The intraventricular catheter is the most cost-efficient method. After Kocher's point trepanation, the device is placed on the hemisphere with most lesions in the imaging studies in order to avoid complications due to a possible interhemispheric pressure gradient. In patients without focal lesions, the surgeon should prefer placing the device in the right hemisphere, due to the greater prevalence of left hemisphere dominance.

After trichotomy, proper asepsis and draping of the patient, a 3-cm straight skin incision is made centred over Kocher's point—11 cm posterior to the glabella, 2–3 cm lateral to the midline, in order to avoid posterior lesions to the superior sagittal sinus or the primary motor cortex (Fig. 4.7a, b). Upon exposition of the frontal bone (Fig. 4.7c) and after identification of the coronal suture, a burr-hole is placed at Kocher's point with a twist drill (Fig. 4.7d), which varies in diameter depending on the type of catheter. Then, cauterization and incision of the now exposed dura with a no. 11 blade are followed by bipolar coagulation of the frontal underlying cortex and opening of the pia mater (Fig. 4.7e). After that, the ventricular catheter is inserted no more than 7 cm into the frontal horn of the ipsilateral ventricle aimed in the coronal plane to the nasion and in the sagittal plane to the tragus' line, toward the foramen of Monro (Fig. 4.7f)—in case of an intraparenchymal catheter, catheter introduction should not exceed 3 cm. After visualization of the CSF through the

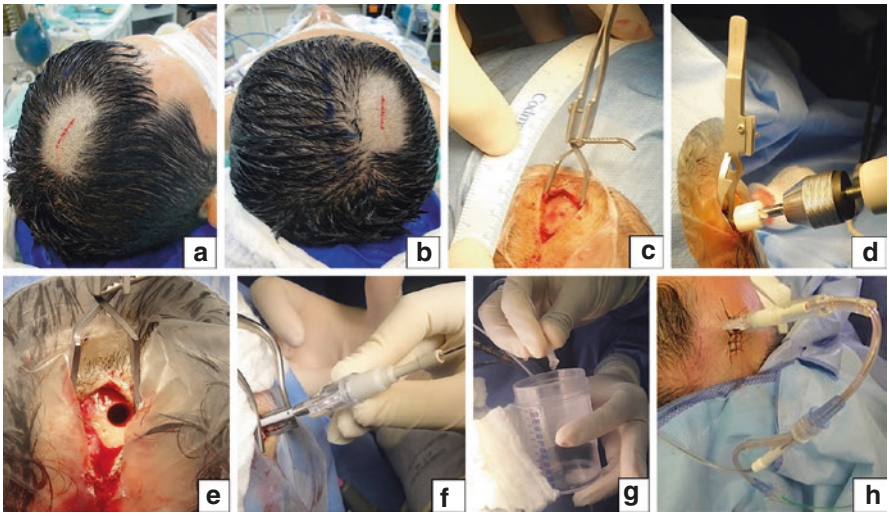


Fig. 4.7 ICP catheter insertion. (**a**–**b**) Skin incition. (**c**–**e**) Burr role drill in Skull. (**f**) Catheter insertion. (**g**) Catheter CSF check. (**h**) ICP system conected

catheter lumen, some can be collected to laboratorial analysis if necessary (Fig. 4.7g), with posterior fixation and connection of the catheter to the ICP monitoring system and suture of the skin (Fig. 4.7h) and dressing.

Complications secondary to intraventricular catheterization include infection, especially if the catheter stays in place for more than 5 days. Tunnelling the catheter as far as possible from the incision site and strict aseptic conditions in the moment of catheter placement—as well as in any manipulation of the EVD system—are known to reduce the infection rates. Intravenous antibiotic prophylaxis is not recommended [18]. Other possible device placement sites include intraparenchymal, subdural, epidural and lumbar; although the only one frequently used in practice nowadays is the intraparenchymal.

Fluid-filled systems are composed of a catheterized fluid line that connects with an externally placed transducer fixed at the level of the tragus—same level of the foramen of Monro and, ideally, the tip of the catheter. As there is a patent communication between the intraventricular space and an outer system, these systems have the advantages of enabling CSF drainage and, eventually, administration of therapeutic agents such as antibiotics and fibrinolytics [20].

Transducers for measuring pressure are based on strain gauges, originally designed to measure effects of tension and compression in beams, adapted to transmitting the pressure into a pen recorder or an oscilloscope. The preferred device for ICP recording is the *catheter-tip transducer*, which consists of a flexible diaphragm at the tip of a fibreoptic catheter. The diaphragm reflects light and alterations in its intensity are translated into pressure variation.

Another possible device is the *implanted microchip transducer*, which is a very small titanium or ceramic case containing a pressure sensor-microchip system

connected by wires into a nylon tube to complete a Wheatstone bridge type circuit. It can be inserted directly into the parenchyma, but can also be associated with an intraventricular catheter [19, 21].

4.4 Interpretation of ICP Monitoring

Besides analysing the absolute ICP value, monitoring gives relevant information regarding the cerebral compliance (curve morphology) and, consequently, autoregulatory disorders. This allows us to plan early treatment for ICP raise before irreversible lesions to the brain parenchyma take place [15].

Various upsweeps can be distinguished in the ICP curve morphology, mainly *cardiac waves* and *respiratory waves* [18], aside from the aforementioned Lundberg's waves:

Cardiac waves (Fig. 4.8) are the intracranial repercussion of elements in the cardiac cycle and its reflex in the cerebral blood vessels, and are composed of three upstrokes:

- P1 (Percussion wave): the first upstroke and the one of greater amplitude in the average patient. Reflects the arterial input during systole and its echo in the vessels on the choroid plexi [18].
- P2 (Tidal wave): the second upstroke and of lesser amplitude than P1. In the average patient, P2 corresponds to 80% of P1 in amplitude. Reflects the fluid (venous blood/ CSF) output in response to the brain's volume intake after systole. It is pertinent to note that a reversal of the P1/P2 amplitude ratio reflects a state of low cerebral compliance, once intracranial inflow and outflow seems to be out of synchrony [18, 22].

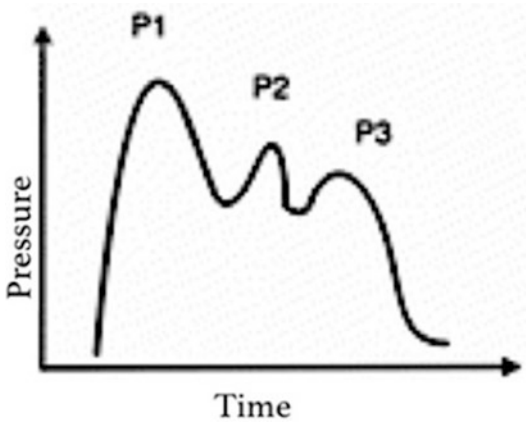


Fig. 4.8 ICP cardiac wave: percussion (P1), tidal (P2) and dicrotic (P3) waves [5]

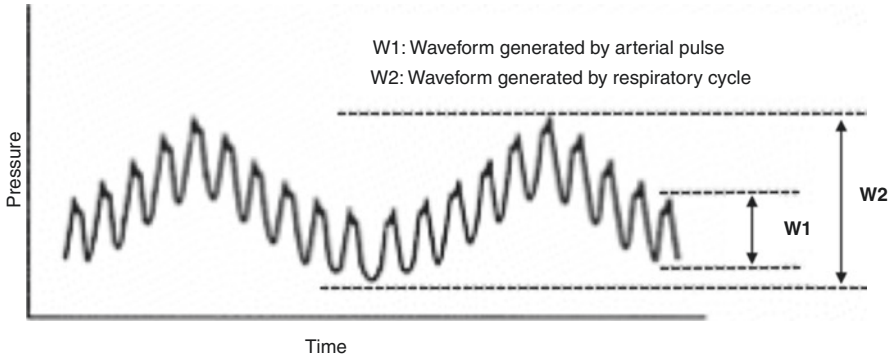


Fig. 4.9 ICP respiratory waves [5]

- P3 (Dicrotic wave): the third and last upstroke is also the one with less amplitude. Immediately follows the dicrotic notch on the arterial waveform, reflecting the closure of the aortic valve. It has no clinical or pathological value.

Respiratory waves (Fig. 4.9) are synchronous with variations in central venous pressure due to changes in intrathoracic pressure along the respiratory cycle.

4.5 Complications

As any other invasive procedure, installation and maintenance of an intracranial catheter are not free of complication, although most of the times the management of these is not of surgical nature. The most common is infection, with an incidence of 5–14%—colonization of the catheter is more incident than clinical infection. There is no association between infection reduction and prophylactic substitution of the system.

Some factors not associated with infection are insertion in neurologic ICU, previous catheter insertion, CSF drainage and use of steroids. The use of antibiotic-coated intraventricular catheter reduced the risk of infection from 9.4 to 1.3% [14].

Other complications are haemorrhage (with an overall incidence of 1.4%), which rarely has indication for surgical evacuation, malfunction, obstruction and malposition. The authors recommend that in suspicion of ventricular catheter obstruction, the physician does not proceed to blindly irrigate the system before a brain CT may eliminate the possibility of ventricular collapse—in which case irrigation will be fruitless and may elevate the infection risk.

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Chapter 5
Noninvasive Intracranial Pressure Monitoring

Leonardo C. Welling, Gustavo Frigieri, Nícollas Nunes Rabelo, and Eberval Gadelha Figueiredo

5.1 Introduction

Intracranial hypertension (IH) is a significant cause of secondary brain injury and its association with poor outcomes has been extensively demonstrated [1]. It is defined as pathological when intracranial pressure persistently rises above 20–25 mmHg. Conditions associated with IH can be classified into extracranial (fever, increased abdominal pressure, increased intrathoracic pressure, venous obstruction, hypercarbia, hypoxia) and intracranial causes (hematoma, contusion, cerebrospinal fluid changes, cerebrovascular factors, or edema) [1, 2].

The monitoring of intracranial pressure (ICP) is essential in neurocritical patients since the clinical signs of IH may appear late in the clinical evolution and sometimes are not reliable [3]. Most of the studies that evaluate methods of monitoring intracranial pressure are done in head trauma populations [1, 3]. Despite this, the methods that will be discussed also apply to other nontraumatic pathologies. Ideally, monitoring of noninvasive intracranial pressure should be inexpensive, reproducible, portable, and should not emit radiation in order to allow continuous monitoring.

Benefits of this technology are not limited only to the neurosurgical applications but include other clinical emergencies, ophthalmology, and aerospace medicine as well [4, 5].

Traumatic brain injury (TBI) is responsible for up to 45% of hospital trauma mortality [6]. Computed tomography (CT) is necessary for the initial diagnosis of

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structural damage to the brain, and millions of brain CT scans are performed annually worldwide [7]. In traumatic and nontraumatic situations, measuring ICP aims to optimize treatment in addition to maintaining the appropriate perfusion pressure [4–7]. However, the classic indications for insertion of intracranial catheters are still subject of controversy and constantly questioned by the literature. In addition, there are still situations in which it was believed to have intracranial hypertension, but the risks involved make surgical catheter implantation impossible [8].

The Brain Trauma Foundation guidelines recommend the surgical implantation of ICP catheters in patients suffering from skull trauma and Glasgow coma scale (GCS) of 8 or less with abnormal CT scans (hematoma, contusion, edema, or compressed basal cistern). In those with normal computed tomography with two or more risk factors (such as age over 40, motor posture, or systolic blood pressure less than 90 mmHg), the placement of ICP catheters is also indicated. There are other situations where the evidence is less robust, but there are indications such as hemorrhagic stroke, extensive ischemia, and subarachnoid hemorrhage [8].

Despite the classical indications, the neurocritical patient is under a very dynamic process. According to Kishore et al., 17% of patients with "normal" computed tomography at admission will develop intracranial hypertension [9].

On the other hand, many patients with abnormal computed tomography do not develop intracranial hypertension. Intracranial hypertension requires rapid recognition to allow adequate treatment. As tomographic findings do not always correspond directly with intracranial hypertension, there is a need to develop noninvasive methods. In this context, the indication of invasive ICP monitoring will be accurate, and financial resources will be better allocated. In parallel, the use of these methods is essential in situations where clinical conditions do not allow invasive procedures [4].

5.2 Imaging Methods for Estimating Intracranial Hypertension

5.2.1 Computed Tomography

The ability of computed tomography to define the presence of intracranial hypertension is a controversial subject in the literature. Attempts to predict ICP in patients who have an abnormal head CT scan have not been as successful [4].

Sadhu et al. evaluated 21 patients and did not demonstrate increase in ICP in patients with "normal" brain tomography. In patients with cleft ventricles, the correlation was weak. In patients with dilation of the temporal horn contralateral to the mass effect, it showed a high correlation with the increase in ICP [10]. Kishore et al., when evaluating 150 patients with severe head trauma, observed that in those with hemorrhagic injuries, intracranial hypertension was observed in 55% of cases. Also, about 15% of patients with normal tomography at admission evolved with intracranial hypertension in the first 48 h [9]. Tabaddor et al. demonstrated that

ventricular compression as well as the presence of a hemoventricle were predictors of intracranial hypertension. However, lesions with deviation from the midline did not present a good correlation with intracranial hypertension [11]. Lobato et al. demonstrated that patients with normal CT scans in the first post-trauma week would hardly develop intracranial hypertension [12]. However, Eisenberg et al. demonstrated that 10–15% of patients with normal initial CT developed intracranial hypertension [13].

In 1992, Marshall et al. introduced a classification system based on computed tomography findings. This system grouped patients with TBI into six groups based on multiple characteristics of CT. The patients were differentiated based on the presence or absence of focal mass lesion. Diffuse lesions were subdivided into four groups based on CT signs suggestive of increased intracranial pressure (compression of the basal cisterns and deviation from the midline) (Fig. 5.1). Subsequently, numerous studies have been published in an attempt to correlate tomographic findings with the presence of intracranial hypertension [14].

In an attempt to estimate the initial ICP in patients with severe head trauma, many authors have incorporated several findings from the initial CT, including the appearance of the cisterns, size of the subdural or intracerebral hematoma, ventricular size, degree of subarachnoid hemorrhage, perilesional edema, and the magnitude of the deviation the midline [4]. Miller et al. presented a model with five tomographic characteristics, which included ventricular size, basal cisterns, presence of grooves, transfalcine herniation, and differentiation between white and gray matter.

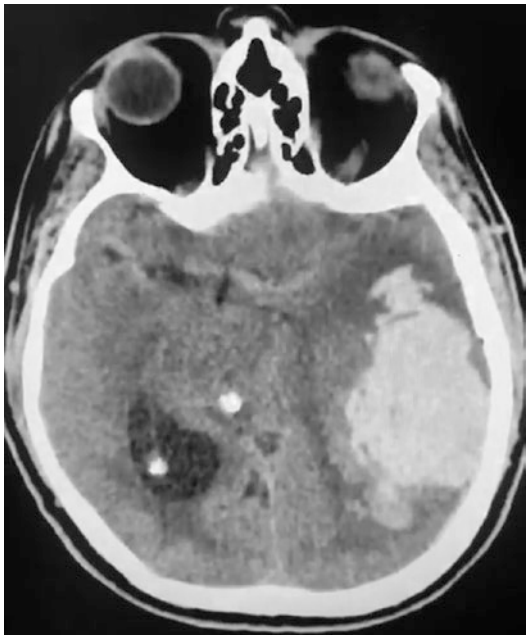

Fig. 5.1 CT scan (Marshall VI classification: high or mixed lesion >25 cm^3, not surgically evacuated)

Despite not having a predictive value, the observed linear relationship allows defining which patients will benefit from ICP catheter implants [15].

A general limitation of radiological interpretation is that TBI is a dynamic process, and computed tomography gives us a momentary image. Therefore, serial computed tomography is indicated in different clinical scenarios. Patients with severe head trauma should be reexamined frequently, as 25% of patients with "normal" CT scans on admission had tomographic changes in the first 24 h. Two-thirds of patients who deteriorate after 48 h have new hemorrhagic lesions. These late injuries are associated with worse outcomes. However, early recognition can improve prognosis [14–16].

Therefore, tomographic changes predict the presence of intracranial hypertension, but do not define values for it and cannot be used as the only standard of assessment in neurocritical patients.

5.2.2 Magnetic Resonance Images

The assessment of ICP by magnetic resonance began to be studied about 20 years ago [17]. In the initial model, the elastance index, which served as the basis for subsequent studies, was initially validated in two baboons, eight healthy adult volunteers, and nine adult patients with intraventricular catheters to measure ICP. The ICP predicted by the dynamic magnetic resonance method showed an excellent correlation for five patients in whom invasive monitoring was performed [17].

More straightforwardly, the techniques for measuring ICP through MRI (MRI-ICP) use a relationship between intracranial compliance and pressure. It is observed, as already demonstrated by Marmarou et al., that when the initial ICP is low, small increases in volume will cause small increases in pressure due to cerebral compliance [18]. By measuring the intracranial volume and pressure fluctuations that occur with each cardiac cycle, we can calculate the elastance. So, it is defined as DP/DV, the inverse of complacency. The volume variation is calculated through a contrasted MRI phase of the arteries, veins, and CSF flow that occur with each cardiac cycle. The flow is calculated by multiplying the speed of the blood through transverse areas of the intracranial vessels. The speed is proportional to the difference between the incident and resonant resonance signals, and the cross-sectional areas are obtained from static magnetic resonance exams. DP is derived from velocities in the CSF that are calculated from velocity-encoded MRI images [19].

Concerning hydrocephalus in children, considering its prevalence and doubts as to whether the system is functioning correctly, noninvasive methods of measuring ICP are essential. Conventional imaging patterns, such as ventricular width or hyperintensities in periventricular topography in T2- and FLAIR-weighted sequences, do not correlate well with ICP in patients with shunt systems, probably at least partially due to the stiffness of the ventricular walls. Other flow measurements, such as the pulsatility index, or by imaging, such as the diameter of the optic nerve sheath (whether by ultrasound, tomography, or resonance), are of limited

agreement and reproducibility in the pediatric population with bypass systems [20]. In the cohort of Muehlmann et al., the MRI-ICP correlated positively with the opening pressure of the bypass valve, thus supporting the previously described linear relationship between the elastance index and the ICP. In a properly functioning bypass, the intraventricular pressure is assumed to be close to the bypass valve opening pressure. If the MRI-ICP measurement is higher than the opening pressure of the valve, it is assumed that there is system dysfunction, even if the patient is asymptomatic [20].

Despite the promising results demonstrated, Marshall et al. assessed the variability of the applied parameters and considered them to be poorly reproducible. It is well known that it is essential to select an appropriate image, and the variability in the observed vascular anatomy can cause measurement errors and secondarily impair the interpretation of results [21]. Also, MRI is very sensitive to differences in heart rate in individual cases. In this context, Dhoondia et al. described a technique to overcome difficulties with variations in heart rate, but this function is not available in magnetic resonance systems outside research centers [22].

In general, magnetic resonance imaging could structurally detect the cause of the increase in intracranial pressure. In pediatric patients, with dysfunction of the ventricular bypass system, it may have some applicability. However, the method is expensive and impractical for continuous monitoring of the ICP.

5.2.3 Optic Nerve Sheath Diameter (with US)

The optic nerves are phylogenetically an evagination of the brain. The course of the optic nerve can be subdivided into an intraocular, intraorbital, canalicular, and intracranial segment [23]. About 4-mm medial to the central posterior pole of the globe, the nerve fibers of the inner ocular superficial layer converge and perforate the external retina, the choroid, and the sieve blade, where the optic nerve head and the intraocular segment of the optic nerve form. The optic nerve, in its intraorbital segment, describes a slightly tortuous path about 4–4.5 cm in length. In a posteromedial direction, it reaches the orbital apex and enters the optical channel. The optical channel is about 5 mm long and 3–4 mm wide [23, 24]. Some authors describe that the optical channel can be from 4 to 12 mm, which has implications that will be exposed later [25]. The optic nerve, in its intraorbital and canalicular segment, is surrounded by arachnoid sheaths, which include a tube-shaped subarachnoid space. These wraps are extensions of the corresponding intracranial structures [23–25].

With the technological development of ultrasound devices, it has been possible to measure the sheath of the optic nerve in the intraorbital segment. The patients are placed in the supine position, and a thick layer of gel is applied to the closed upper eyelid and the neutral look of the patients. Two measurements are made for optic nerve: one in the transverse plane, with the probe in horizontal, and one in the sagittal plane, with the probe in the vertical. The final optic nerve sheat diameter (ONSD) is the average of these measurements. ONSD is measured 3 mm behind the optical

disc [26, 27]. The optic nerve appears as a sagittal hypoechoic structure, 4.5–5 mm thick, with 25 mm in length that runs from the outer part of the eyeball to the apex of the orbit. The optical disc is seen as a hyperechoic line at the posterior pole of the globe, with the high interobserver agreement and a median difference of 0.2–0.3 mm [26].

It should be noted that the diameter of the optic nerve sheath does not change with the patient's position. The Trendelenburg position is often used in hypotensive patients, and the reverse Trendelenburg position (30° upside) is often used in patients with a head injury to help lower intracranial pressure. According to Tayal et al., the diameter of the optic nerve sheath measured by ultrasound in healthy individuals does not change significantly with the Trendelenburg or reverse Trendelenburg position compared to the supine baseline [27].

Ultrasonography of the optic nerve sheath is easy to perform. Despite this, in-depth knowledge of the anatomy of ultrasound and the scanning technique is mandatory for the proper use of the technique in the appropriate clinical setting [26, 27].

When the ICP is normal, the diameter of the optic nerve sheath remains the same as the baseline. When elevated, the CSF flows into the perineural subarachnoid space and increases the pressure around the optic nerve. This increase results in the expansion of the dural sheath and the increase in the diameter of the optic nerve sheat (ONS). The asymmetric distribution of the trabecular fibers and the subarachnoid space, and the retrobulbar (intraorbital) portion of the optic nerve sheath is where the thinnest envelope along the nerve path. The anatomical explanation of why the expansion mainly affects the anterior segment of the dural sheath 3 mm behind the globe. On the other hand, the posterior regions exhibit markedly less or nonexistent dilation [23–26]. Hansen and Helmke showed that a segment of the diameter of the optic nerve sheath, approximately 3 mm behind the papilla, showed maximum variations in diameter induced by gelatinous injections in post-death. This diameter landmark has been used in several clinical trials correlating intracranial pressure derived from elevated CSF pressure with intracranial pressure derived from the diameter of the optic nerve sheath [28].

Most authors have suggested that the reasonable upper value of ONSD is 5 mm. However, further studies suggest that the cutoff value of the ONSD that provides the best precision for the prediction of intracranial hypertension (ICP = 20 mmHg) is 5.7–6.0 mm and that the ONSD values above this limit should alert the doctor for the presence of raised ICP [24, 27, 28] (Fig. 5.2).

According to Geeraerts et al., a strong relationship was found between the ONSD average and the ICP. When using 5.8 mm values as a cutoff point, a very low probability of having a high ICP was observed when the ONSD had smaller dilations [29].

The thickness of the optic nerve and the presence of intracranial hypertension were also analyzed. Little correlation was found between OND and ICP, and other authors corroborated these findings. The variation in ONSD during elevated ICP cannot be related to the dilation of the optic nerve (as during edema of the optic nerve). However, it is secondary to the distention of the sheath due to the increase in CSF pressure around the optic nerve [29].

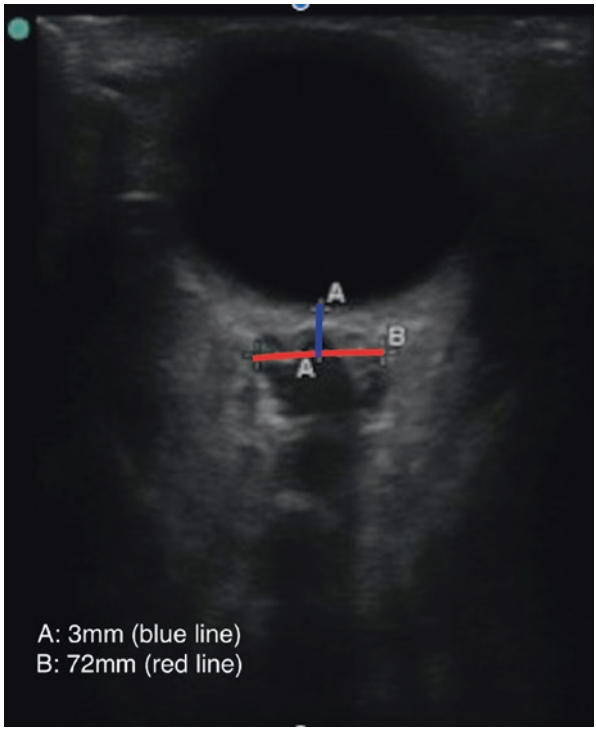

Fig. 5.2 Optic nerve sheath diameter in a patient with raised ICP

Cases of unilateral papilledema and asymmetric dilations of the perineural sheath have been reported. Although, for confirmation purposes, the ONSD ultrasound measurement should be performed bilaterally. The increase in ONDS is a dynamic process. Also, it varies according to changes in the ICP. It should be observed with caution as the reduction in ICP values does not follow the same kinematics for reducing the diameter of the optic nerve sheath [27].

Despite the advantages, ultrasound of the optic nerve sheath has some limitations. In patients with ocular trauma and other diseases of the optic nerve complex, the assessment of ONSD can be challenging. Traumatic optic neuropathy is seen in a significant number of patients with severe head trauma, and the effects of eye trauma on ONSD are unclear [27]. Besides, the increase in the optic nerve may occur due to the secondary involvement of a variety of orbital and systemic abnormalities, such as tumor, inflammation, Grave's disease, sarcoidosis, pseudotumor, metastasis, and hemorrhage in and around the optic nerve complex.

The standardization of the examination is of great importance since the ONSD measurements are minimal, and any changes approach the precision limits inherent to the ultrasound equipment. The poor technique can lead to significant errors and reduce the benefit of the method. Common pitfalls include an inadequate representation of the optic nerve in the axial plane, an inaccurate designation of the sheath contours, and incorrect positioning of the cursors [26–29]. Therefore, only trained medical staff must perform the examinations.

5.2.4 Optic Nerve Sheath Diameter (with CT Scan)

Measurement of the optic nerve sheath by tomography is also a valid method. In a study with 41 patients, with a cut-off point of 6.35 mm, a sensitivity of 0.93 (95% CI 0.84–1.00), specificity of 0.80 (95% CI 0.50–1.00), and AUC of 0.87 (95% CI 0.69–1.00) were obtained. The values are different between several studies. Sekhon et al. reported that ONSD measured 3 mm posterior to the retina by a portable CT to predict elevated ICP with a cutoff point of 6.0 mm, the sensitivity of 97%, and specificity of 42% [30]. Vaiman et al. describe that ONSD could also predict elevated ICP when measured 10 mm posterior to the retina with a cutoff point of 5.5 mm, the sensitivity of 83%, and specificity of 94% [31].

Recently, Liu et al. described that 4.99 mm was the ideal cutoff point to predict ICP > 20 mmHg, with a sensitivity and specificity of 68.75% and 94.74%, respectively. Also, these authors developed a prognostic model associating the admission of GCS and Rotterdam tomographic scores. They observed that when the measurement of the optic nerve sheath was included, there was a higher discriminative power, sensitivity, and specificity for surgical indication. There are standard indications for surgical intervention described in the various guidelines (hematoma, compression of the cisterns at the base, deviation from the midline, and GCS). Complementary, the width of the sheath of the optic nerve, especially if higher than 5.09 mm (in this, Liu et al. model) can be a predictor of surgical indication [32].

Majeed et al. in a retrospective study with 242 patients using linear regression analysis demonstrated a statistically significant correlation between ONSD and opening ICP ($r = 0.40$, $P < 0.001$) and peak ICP ($r = 0.31$, $P < 0.0001$). When including a prognostic model when an ONSD ≥6.0 mm + Marshall score ≥ 3 in the first head of the CT demonstrated a sensitivity of 92.5%, a specificity of 92.6%, and positive predictive value of 96.1% for development of ICP ≥ 20 mmHg during hospitalization [33].

Some observations should be made regarding the location of the measurement of the diameter of the optic nerve sheath. Some studies recommend measuring 3 mm posterior to the retina, where the sheath is broader and easily measurable. Other authors use 8–12 mm (on average 10 mm) because it is where the ophthalmic artery crosses. At this point, the nerve is more fixed than behind the retina, and there is no eye movement influence, especially in cases where the patient is not collaborative. Besides, it is important to use the multiplanar reformation system to adjust tomography images and ensure proper alignment of the lens, eyeball/retina, and optic nerve that are in the same horizontal plane [32].

Several divergences are involved (regarding ONSD) in the ideal cutoff point to predict intracranial hypertension.

Despite this, we note that this analysis will positively help in decision making. New studies with a more significant number of patients will be able to assess whether the sheath of the optic nerve will be included in flowcharts for surgical indication [32, 33].

5.2.5 *Optic Nerve Sheath Diameter (with MRI)*

The measurement of the optic nerve sheath by magnetic resonance imaging is very accurate and potentially useful in detecting elevated ICP. High-resolution MRI is accurate when measuring OSND and has been proposed to detect idiopathic intracranial hypertension and dysfunction of the peritoneal ventricle shunt system [4, 5, 20, 29].

ONSD (but not OND) is strongly related to ICP, a finding that reflects the distention of the nerve sheath during increased pressure in the CSF. In T2-weighted sequences, water (and the CSF) exhibits a high signal (white). The fat and gray matter appears as light gray and the white substance as dark gray. Perioptic CSF is surrounded by orbital fat. The contrast between CSF and orbital fat can be improved with techniques that include fat suppression, increasing image resolution for ONSD measurement [29].

When evaluating the agreement between radiologists, it is observed that the differences in the ONSD measurements are less than 0.2 mm, which does not compromise the interpretation of the results [29].

Even outside the most acute situations, the ONSD measured by MRI can help to define patients with subdural collections in which there is doubt as to whether the collection is passive or generates intracranial hypertension. In the study by Watanabe et al., 12 patients with subdural collection underwent ONSD measurement before and after surgery. Intracranial pressure was measured at the opening of the dura mater (correlating with the preoperative ONSD) and in the postoperative period, a new control RM was performed, which showed a reduction in the ONSD from (6.1 ± 0.7 mm) to (4.8 ± 0.9 mm) $p = 0.003$ [34].

The most useful clinical message derived from current data may be the following limits: an ONSD less than 5.30 mm is unlikely to be associated with a high ICP and an ONSD above 5.82 mm indicates that the probability of a raised ICP is 90%. When comparing these results with the data obtained in several studies that used ultrasound as a diagnostic method, we observed that the cutoffs are similar (between 5.7 and 6.0 mm) [29, 34].

The most significant limitation of its use in the acute phase of trauma is related to the examination duration and the need for care related to the magnetic field.

5.3 Indirect Pressure Transmission

5.3.1 *Fundoscopy*

Fundoscopic evidence of papilledema may provide useful evidence of intracranial hypertension in cases of chronic elevated ICP. When the ICP increases, the pressure in the ONS increases linearly, which stretches the nerve sheath. The increase in pressure results in stasis of axoplasmic transport, which is believed to cause

papilledema [35]. Due to the close relationship between ICP and papilledema, an examination of the optic nerve with an ophthalmoscope can estimate ICP.

The Frisen scale classifies the severity of papilledema on the exam, with grade 0 being normal and grade 5 being the most severe. According to Frisen et al., who published the initial study, it shows a sensitivity of 93–100% and a specificity of 88–96% for detecting papilledema from photographs of the optic nerve [36].

On the other hand, experimental studies clearly show that optic disc edema requires a few days to develop and resolve. Another limitation is that doctors are not confident in their ability to perform a fundus examination. According to Steffen et al., even when the nerves can be safely examined, the absence of papilledema does not exclude increased ICP [35].

Another aspect of the examination of the optic nerve used to approximate the ICP is spontaneous venous pulsations (SVPs). Levin et al. showed that, when pulsations are present, the ICP should be less than 190 mmH_2O. However, SVPs are absent in 10% of healthy people, so the lack of heartbeat pulsations does not always indicate an increase in ICP [37].

Ophthalmoscopy remains of great clinical value; however, we cannot rely exclusively on its findings. Alternative methods to predict the presence of intracranial hypertension are essential in the care of neurocritical patients.

5.3.2 Tympanometry

Tympanometry is an exam used to evaluate the middle ear in which, after a sound stimulus, the stapedial or acoustic reflex causes changes in the pressure–volume of the external ear, occluded by the device. If the cochlear aqueduct is patent, the ICP is transmitted to the cochlea perilymph and, in this way, displaces the stapedium and alters the acoustic reflex. High pressures in the CSF compartment would move the stapedium laterally, allowing for a greater range of motion medially and consequently more significant tympanic movement medially, which can be measured with tympanometry [4].

In other words, the central concept is that the pressure of the cochlear fluid in direct relation to the ICP would affect the stapedial excursions. Consequently, the tympanic membrane displacement (TMD) can be measured in response to auditory stimulation in order to gain insight into the dynamics of intracranial pressure. Marchbanks et al. demonstrated the effects of TMD on variations in ICP and observed that the technique was sensitive in identifying variations in ICP [38]. However, this method is associated with a low success rate (up to 40%), due to several methodological limitations related to the technique itself (difficulty in obtaining an adequate acoustic reflex or obstruction of the cochlear aqueduct). It becomes less patent with age, and this can compromise the correct estimation of endolymphatic pressure [39].

Furthermore, TMD amplitude can also depend on several anatomical factors (the integrity of the ossicles, presence of masses in the middle ear, or obstruction of the Eustachian tube).

The available evidence shows that tympanometry is a helpful screening tool that can be useful in the evaluation and monitoring of patients with increased ICP. However, they do not allow the establishment of specific ICP values, and there are limitations regarding the method itself [4, 38, 39].

5.3.3 Skull Deformity

In the mid-1980s, the first studies that attempted to evaluate the expansion of the skull in situations of increased intracranial pressure appeared. However, these studies have not evolved [40].

Recently, Mascarenhas et al. developed a new noninvasive method for monitoring the ICP curves that has promising preliminary results but has not yet been tested in large clinical trials. This new technique is composed of an electrical strain gauge (sensor) attached to a mechanical apparatus that touches the scalp surface. When it is placed on the head, it is capable of capturing bone deformations resulting from the variation of intracranial pressure (Fig. 5.3) [41, 42].

At the current stage of development of the method, it is known that the shape of the ICP curves obtained by this noninvasive method is statistically more similar to the shape of the curves obtained with invasive intracranial monitoring than to the shape of the invasive blood pressure curves, despite being derived from it [43]. However, the noninvasive ICP values obtained in milliVolts (mV) cannot yet be appropriately transposed to the traditional measurement in millimeters of mercury (mmHg), mainly due to aspects of calibration and validation in more extensive clinical studies [44].

The analysis of the shape of the ICP curves (Fig. 5.4) has been the object of study for many years, and its interpretation brings relevant information regarding cerebral compliance, physiological reserve, and cerebral self-regulation mechanism. The intracranial pressure wave is mainly related to the cardiac cycle, but it is not the same as the mean arterial pressure wave. In typical situations, P1 is higher than P2, which in turn is higher than P3. In situations of loss of cerebral compliance, P2 begins to rise, often higher than P1. In situations of severe intracranial hypertension, the wave loses its peaks and takes on the appearance of a venous wave [43–45].

Several studies in the literature have attempted to identify pathological changes in the layout of these curves to try to predict disproportionate increases in ICP (DIICP, disproportionate increases in ICP) with conflicting results. In these studies, the amplitudes of P1 and P2 were measured and the P2:P1 ratio was calculated. The pathological elevation of P2 was defined as a P2:P1 ratio greater than or equal to 0.8. However, there was never any concern in estimating the ICP through the shape of the curve. This new monitoring method is able to obtain the P2:P1 ratio in a

Fig. 5.3 *Brain4care*™ sensor positioning for monitoring of cranial deformity

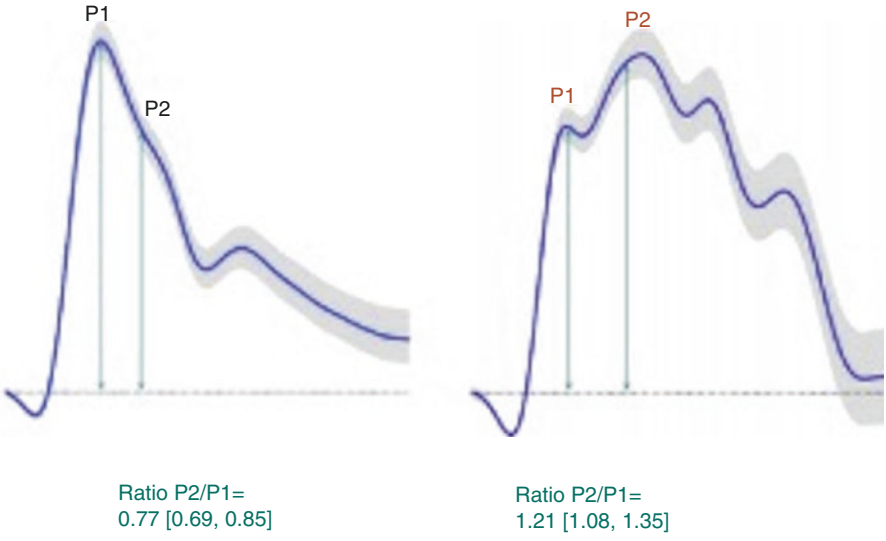

Fig. 5.4 Noninvasive ICP pulse waveforms result of the skull deformity method. Ratio P2/P1 greater than 1 indicates that P2 peak is higher, indicating abnormal morphology

noninvasive way, without knowing the ICP value in mmHg, making this estimate relevant. New studies are underway, and promising results are expected [45].

The mechanism for analyzing cranial deformity was developed by *Brain4care*™, a Brazilian medical innovation company focused on noninvasive solutions for monitoring brain compliance through the analysis of intracranial pressure pulse morphology. *Brain4care*™ sensor mechanically captures the volumetric variations of the skull and sends them to an automated algorithm hosted on its own cloud. This process is responsible for carrying out the analysis of the signals creating automated reports to health professionals.

The Brazilian health surveillance agency has already granted certification for marketing the system in Brazil, where it is already in use in several hospitals for diagnostic assistance, in addition to the FDA clearing house in the United States, where several centers already use the method for scientific research.

Screening of patients with neurological symptoms in emergencies, outpatient clinics, and intensive care units has been the initial focus of using the sensor, in addition to monitoring patients under suspicion, risk, or changes in brain compliance. The sensor allows rapid and serial monitoring to check clinical condition and therapeutic efficacy.

5.4 Cerebral Blood Flow Methods for Estimating Intracranial Hypertension

5.4.1 Transcranial Doppler

The possibility of studying cerebral hemodynamics with Doppler ultrasonography was first reported in 1982 [46]. A new era for clinical assessment of cerebral blood flow self-regulation (FSC) was initiated.

The use of transcranial Doppler (TCD) as an ICP marker was initially described by Klingelhöfer et al. in a pilot study. Changes in ICP were compared with the findings of TCD in the middle cerebral artery. Data from five brain-dead patients showed that changes in ICP significantly influenced local blood flow patterns. These changes were recorded quantitatively using the pulsatility index (PI) and the average VF. Increases in ICP were accompanied by an increase in PI (due to a decrease in diastolic and mean velocities). The authors subsequently demonstrated an association between ICP and flow patterns in a subset of neurosurgical patients with intracranial hypertension [46].

The best bone window for using TCD involves the middle cerebral artery. Different indices such as the Pourcelot resistance index and Gosling's pulsatility index have been explored to correlate with ICP. Gosling's index is more used because it does not change due to external factors with angle and insonation [47].

According to Behrens et al., the evaluation of the PI correlated well with the ICP (r = 0.94), indicating its applicability as a noninvasive method of measuring

ICP. However, other authors do not support the measurement of the speed of intracranial blood flow as a determinant of ICP. Computer simulations demonstrate that this deficiency can be attributed to the individual variation of physiological parameters that can be associated with the disease, but it can also be related to the normal variation [48].

Some authors state that in situations of raised ICP (higher than 20 mmHg), they present a good correlation with the findings of the transcranial Doppler. There are even formulas, such as PI –ICP = 10.93 X PI − 1.28, that were developed in an attempt to predict ICP. We note that further studies are needed to validate such estimates [49].

Recently, Fernando et al., in a meta-analysis (in which 792 patients were evaluated), calculated the ROC curves and the AUROC values for the TCD-PI to detect ICP higher than 20 mmHg. AUROC values ranged from 0.550 to 0.718. In this context, the samples included were not appropriate [50].

The variability of the ICP-PI ratio in vivo in previous studies does not support TCD as a tool to provide reliable information about ICP. Despite these data, TCD can play a role in situations where the indication for invasive monitoring is not established: stroke, pediatric cases, liver failure, mild head trauma evaluated in accident and emergency wards, and preeclampsia [47, 51].

5.5 Metabolic Alterations

5.5.1 Near-Infrared Spectroscopy—NIRS

Near-infrared spectroscopy is a recent technology that works with the principle of differential absorption of light in the vicinity of the infrared spectrum to detect changes in the concentration of oxygen and deoxyhemoglobin. Thus, this method estimates intracerebral oxygen saturation and subsequently reflects cerebral metabolism, cerebral blood flow, and regional oxygenation (rSO2). The ratio of oxygenated to total hemoglobin is expressed as the tissue oxygenation index, which can be considered as a substitute measure for local changes in cerebral blood flow if the metabolism remains constant [52].

As the elevated ICP compromises cerebral flow and oxygenation, the NIRS variables could theoretically predict intracranial hypertension and, thus, a noninvasive method of monitoring ICP. Animal models of hydrocephalus demonstrated that raised ICP directly influenced NIRS values [53].

However, studies with other types of brain injuries (trauma, intracranial hemorrhage) have found controversial results. Some did not describe a relationship between rSO2 and PCI and discouraged the use of rSO2 as a predictor of intracranial hypertension. Also, no study reported any rSO2 value that could indicate a critically high ICP, and that would have the potential to assist in early diagnosis [54].

According to Weerakkody et al., patients with raised ICP have alterations in the NIRS, mainly during the Lundberg B waves. Based on their observations in patients with TBI, spontaneous fluctuations in Hb and HbO2 changed their pattern with an increase in ICP [55].

Therefore, the current recommendation is that the NIRS standards observed in the monitoring of neurocritical patients be analyzed instead of evaluating the absolute values [53–55]. Considering the pending technical challenges, the limited number of patients studied, and the conflicting results and opinions on this subject, we believe that this noninvasive method of predicting ICP should be restricted to research centers.

5.6 Conclusion

The authors of this chapter strongly support the need for continuous invasive ICP measurement in Neuro-ICU patients with suspected raised ICP. The insertion of an intracranial probe remains the gold standard for ICP monitoring in selected cases. Our objective is to expose some noninvasive methods to predict the risk of intracranial hypertension. It is essential in situations where clinical conditions do not allow invasive procedures or the benefits of the standard ICP monitoring are not well established.

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Chapter 6
Brain Tissue Oxygen Monitoring

Fábio Santana Machado, Leonardo C. Welling, Nícollas Nunes Rabelo, and Eberval Gadelha Figueiredo

6.1 Introduction

The primary brain injury (PBI) is defined as any or all injuries resulting from the first neurological event. The PBI (Figs. 6.1, 6.2,and 6.3) may be due to traumatic brain injury (TBI), stroke, tumors, subarachnoid hemorrhage (SAH), among others. The pathophysiology, diagnosis, and treatment of the various causes of PBI will be addressed in specific chapters.

Secondary brain injury (SBI) is conceptualized as any brain lesion that follows PBI. This type of injury occurs in more than 90% of acute neurological patients. In general, they are ischemic and are directly associated with hypoxia, hypoperfusion, reperfusion, and inflammation. The acutely injured brain is more vulnerable to systemic aggressions such as hyperthermia, seizures, hypoxia, and hypotension. Hypoxia and hypotension are early phenomena that can occur right after PBI, when the brain is more susceptible to ischemic phenomena [1, 2].

Most acute neurological patients have their prognosis (mortality and morbidity) determined by the presence and duration of SBI. Understanding this concept is essential to improve functional results since SBI can be prevented as well as treated. This knowledge opens up a vast field for prevention and treatment strategies for all acute neurological patients.

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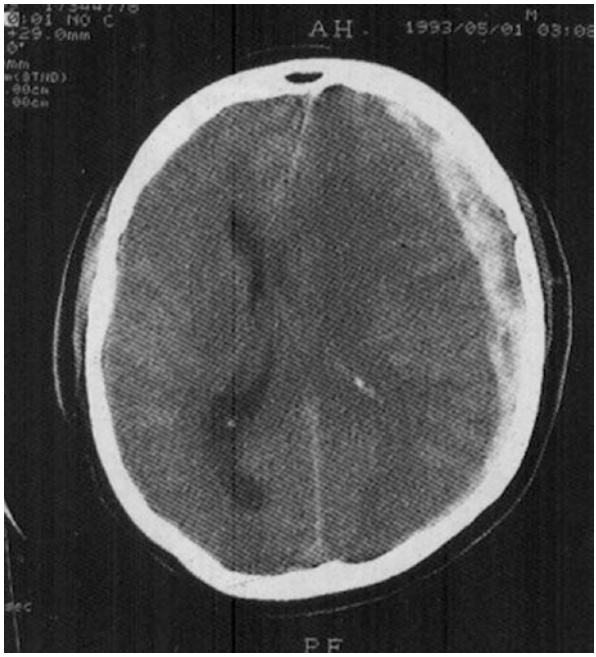

Fig. 6.1 Primary brain injury example: acute subdural hematoma, midline deviation, cerebral edema

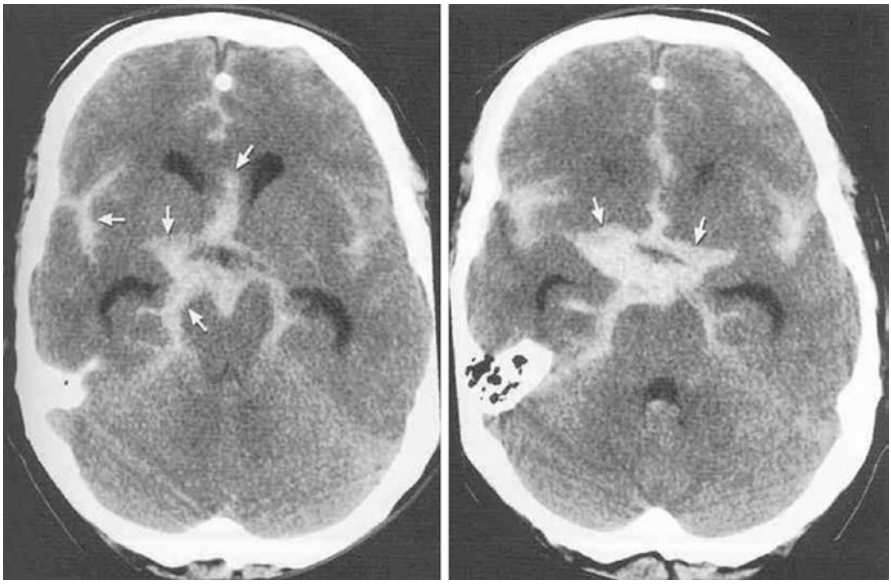

Fig. 6.2 Primary brain injury example: subarachnoid hemorrhage

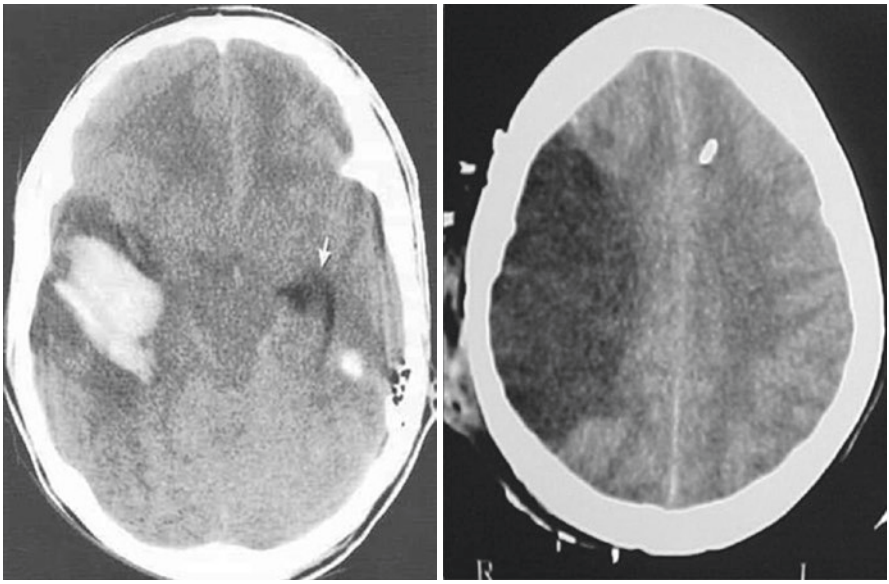

Fig. 6.3 Example of primary brain injury. Left: intraparenchymal hemorrhage. Right: ischemic stroke

6.2 Secondary Brain Injury Classification

The SBI can be classified according to its pathophysiology into the intracranial or extracranial origin. The most frequent and severe SBI of extracranial origin are hypotension, hypertension, hypoxia, hyperoxia, hypercapnia, hypocapnia, hyperthermia, hypothermia, anemia, hypoglycemia, hyperglycemia, abnormalities in water and sodium metabolism (see specific chapter), sepsis, and systemic inflammatory response syndrome (Fig. 6.4).

The most frequent SBI of intracranial origin are intracranial hypertension, swelling, cerebral edema, vasospasm, herniations, deviations, seizures, hydrocephalus, meningitis, ventriculitis, abscesses, vascular lesions, and inflammation [3].

One of the main pathways of SBI is the reduction of brain blood flow and tissue oxygenation. It is not yet possible to measure the flow routinely, but tissue oxygenation can be performed using tissue oximetry, which will be discussed below.

6.3 Neurological Monitoring

Neurological monitoring is essential in the early and prompt identification of secondary lesions. Monitoring improves the rates of morbidity and mortality. The different monitoring modalities are intracranial pressure (ICP), transcranial Doppler,

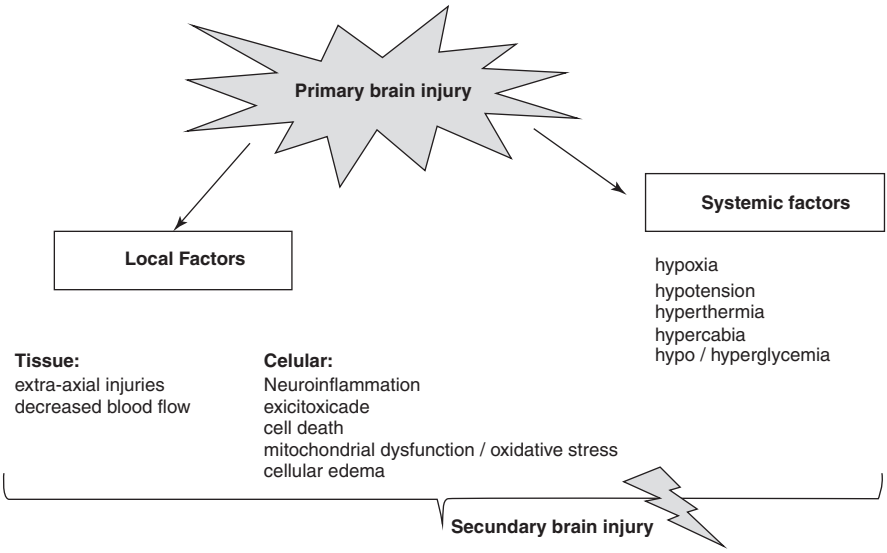

Fig. 6.4 Systemic mechanisms and secondary neurological injury

jugular bulb oximetry, transcranial oximetry, electroencephalography, cerebral microdialysis, and cerebral tissue oximetry.

Jugular bulb oximetry had its clinical application idealized by Cruz et al. Its principle is based on the relationship between the supply and consumption of brain oxygen. Under normal conditions, cerebral oxygen consumption (CMRO2) corresponds to 3.5 mL/100 g/min or 1.56 mmol/g/min. This value corresponds to 20% of the total body energy expenditure at rest. The oxidation of glucose gives 99% of the ATP produced. In uncomplicated traumatic brain injury (TBI), brain metabolism is globally decreased by 30–50% (in TBI, the average CMRO2 is 1.74 mL/100 g/min). CMRO2 can be calculated using the formula: CMRO2 = CBF × AVjDO2. CBF = cerebral blood flow, AVjDO2 = artery–venous jugular difference O2 [4].

Under normal conditions, CMRO2 and CBF are "coupled," that is, CMRO2 mainly regulates CBF. In this situation, AVjDO2 remains constant with CMRO2 variations. However, only 45% of TBI patients in a comatose state present the coupling of these variables. In most of these patients, CBF increases or decreases regardless of CMRO2. In these situations, CBF starts to depend directly on blood pressure and paCO2. Although SvjO2 (value obtained from venous oximetry of the jugular bulb) does not provide quantitative information about CBF or CMRO2, it can reflect the relationship between these two variables. Thus, a jugular arteriovenous difference in normal oxygen suggests that CBF is adequate for CMRO2. However, altered AVjDO2 indicates with all certainty that the CBF is inappropriate for CMRO2, either due to decreased flow (e.g., hypotension) or increased consumption (e.g., fever) [4]. Despite the elegant pathophysiological reasoning, jugular bulb

oximetry is practically in disuse as a way of monitoring cerebral oximetry and therefore, will not be treated in this chapter.

Transcranial oximetry is a promising technique for monitoring cerebral oximetry, with some degree of correlation with jugular bulb oximetry. However, this technology is not yet available in clinical environment for routine use, and therefore we will not deal with it in this chapter.

Current guidelines for the treatment of severe TBI, described by the *American Association of Neurological Surgeons and the European Consortium of Brain Trauma*, emphasize the monitoring of ICP and cerebral perfusion pressure (CPP) [5, 6]. The association between increased ICP or reduced CPP and worse outcome is well established [7–9]. However, a large part of the increase in ischemic brain events after SAH and TBI can occur with normal ICP and CPP values [10–12].

The monitoring of brain tissue oxygen was approved by the FDA for use in the United States in 2001 and mentioned in the guidelines for the treatment of severe traumatic brain injury in 2007 [6].

6.4 Regional Brain Oximetry—PtiO2

6.4.1 General Methodological Aspects

The direct measurement of cerebral oxygenation using PtiO2 catheters is a novel method (last 20 years) of monitoring and treating acute brain injury in patients suffering from severe TBI and SAH in advanced degrees. PtiO2 is measured directly using a small flexible catheter that is placed in the brain region of interest [13].

There are three types of catheters available commercially (Fig. 6.5). The Licox® system (*Integra NeuroSciences®*) uses the polarographic technique (Clark electrode) to measure PtiO2 and is capable of measuring brain temperature. The polarographic technique consists of polarizing the oxygen molecules of the tissue. These polarized molecules are further quantified. The Neurovent®-PTiO2 device—oximetry catheter (*Raumedic®*) uses a technique similar to pulse oximetry to quantify the amount of tissue oxygen. The Neurotrend® system (*Codman®*) uses optical luminescence and is capable of measuring oxygen (PtiO2), carbon dioxide (PtiCO2), and pH (ptiH) in brain tissue. All of these systems have something in common: the equilibrium time so that the oximetry measurement is reliable between 60 and 120 min [14–16].

The best location for catheter placement remains controversial. In diffuse lesions, it was agreed to insert the catheter in the right frontal region. In patients with severe TBI and heterogeneous lesions, the best option is in or near the penumbra area. In cases of SAH, in the presence of severe vasospasm, the catheter must be placed in the area at risk of developing infarction. Before inserting the catheter, the surgeon must perform the test in the air or in water (the companies already standardize the values) to evaluate the oxygen measurement that the catheter is doing. This

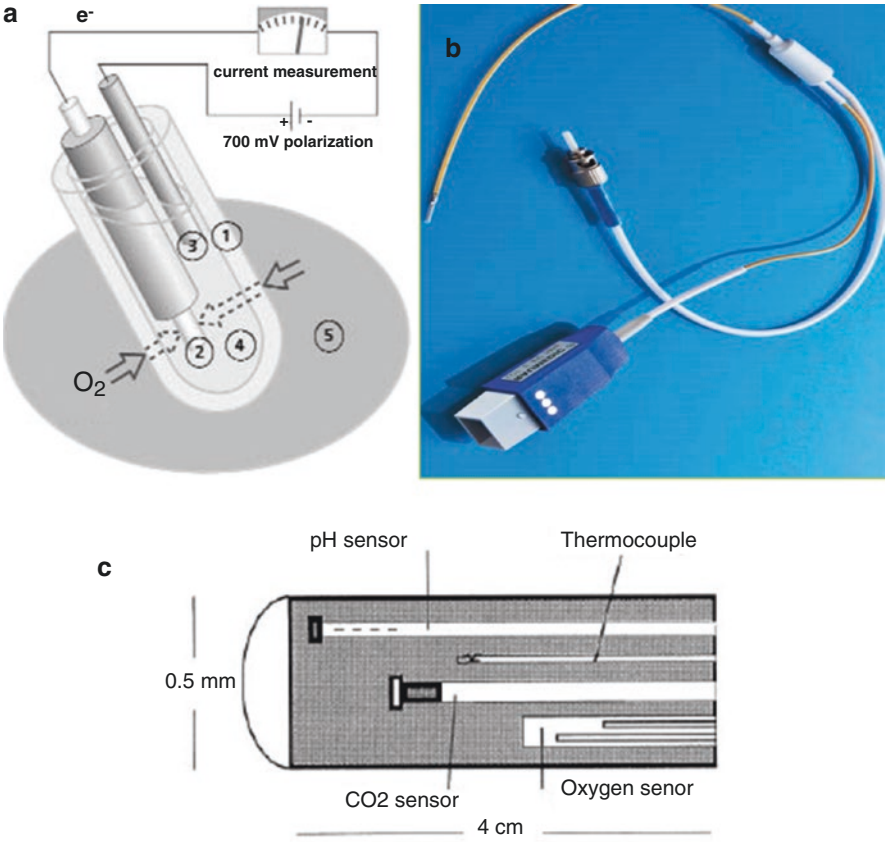

Fig. 6.5 Tissue oximetry measurement systems. (**a**) Licox® system; (**b**) Neurovent-PTiO2 – Oximetry catheter; (**c**) Neurotrend®

procedure reduces the risk of installing a malfunctioning catheter. A specific introducer guides its positioning. It is fixed in the cranial bone, 2–3 cm below dura mater. The measured tissue surface is approximately 15–17 mm^2. After installation and waiting for the equilibrium time, no conduct should be based on the values obtained. After the equilibrium phase has passed, three possible measures can be obtained [17–22]. First, the values are within the expected. Second, values are above expected, which may mean that the patient is being submitted to a hyperoxia regimen. Third, the values are low.

In the latter, some possibilities should be considered, namely, the low value of PTiO2 represents poor cerebral blood flow or tissue hypoxia or catheter malfunction. In this situation, the intensivist must increase the inspired oxygen fraction to 100% to try to diagnose the problem. If the catheter is functioning correctly, PTiO2 will increase significantly. If PTiO2 does not increase, a brain computed tomography scan should be performed to verify the proper location of the catheter. The catheter may be inside a hematoma, or a hematoma was formed around the catheter

(a complication of the method) or within an area of cerebral infarction, and this makes PTiO2 unreliable. In case the catheter is positioned correctly, it must be considered that the patient has a low CBF and tissue hypoxia in that measured region.

6.4.2 Catheter Safety

A literature review [23] showed that in 292 patients monitored with the Licox® system, only two adverse events were reported. Both were hematomas described by Dings et al. in a study of 101 patients [21]. In both cases, the hematoma was small and did not require surgical treatment. No catheter-related infectious complications have been reported [21, 23]. In a study that evaluated 34 patients with traumatic brain injury, catheter malfunction was detected in 11.8% of patients at an average of 2.0 ± 2.2 days after insertion. The displacement of the catheter was found in 5.9% of cases, with an average of 4.0 ± 2.8 days after insertion [24]. The available data suggest that monitoring PTiO2 is a safe technique for monitoring cerebral oxygenation.

6.4.3 $PTiO_2$ Monitoring: Indications, Reference Values, and Prognosis

The initial works of cerebral oximetry were in severe TBI patients. Therefore, the PtiO2 monitoring indications are confused with the ICP monitoring indications. In the case of SAH, the principal suggested indications are based on the highest risk of ischemia, whether global or regional, due to vasospasm [25, 26]. In this population, loss of consciousness to ictus and the presence of higher Hunt–Hess score (≥3) was more associated with early cerebral edema. While the presence of aneurysm ≥10 mm, loss of consciousness to ictus, Hunt and Hess ≥3, and use of vasopressors were related to the appearance of late cerebral edema [27]. Thus, patients with a higher risk of vasospasm assessed by the Fisher's tomographic scale and those with a higher risk of early or late global cerebral edema should be candidates for monitoring with PtiO2.

Except for the indications mentioned above, PtiO2 monitoring is an integral part of multimodal neuromonitoring in diverse neurosurgical conditions and neurological intensive care units but with a discrete level of evidence for its application. Other situations such as cerebral aneurysm surgery and arteriovenous malformation are also described [24, 25].

Initial studies pointed to average PtiO2 values around 42 ± 9 mmHg, with values less than 20 mmHg being considered critical [14, 15, 24, 25]. Direct PtiO2 measurements in patients with SAH or TBI in the intensive care unit (ICU) show that reductions below 10 mmHg are associated with worse neurological outcome [26].

Subsequent studies have found typical tissue oximetry values ranging from 25 to 30 mmHg [28]. Experimental and clinical data suggest that the critical threshold for neuronal injury and the worst clinical outcome would be for PtiO2 values below 10 mmHg [27, 29, 30]. Recently, a study assessed tissue oximetry in patients undergoing Parkinson's surgery and demonstrated an average value slightly lower than the previous data: PtiO2 = 23.1 ± 6.6 mmHg. The presence of PtiO2 > 30 mmHg, in the absence of hyperoxia, suggests metabolic decoupling/cerebral perfusion. It is associated with vasodilation, hyperemia, and global luxury perfusion and, consequently, increased ICP [30].

6.4.4 What Is Measured with Cerebral Oximetry?

The monitoring of cerebral oximetry is based on the measurement of the amount of oxygen in the tissue. The amount of oxygen that reaches the tissue depends on the diffusion capacity of the dissolved plasma oxygen (Fig. 6.6). Other factors, such as the integrity of the neurovascular unit and the edema that may involve the blood–brain barrier and its endothelium, are essential determinants in the diffusion of plasma oxygen toward brain tissue. The isolated analysis of variables such as cerebral blood flow, cerebral arterial, and venous oxygen content, cerebral oxygen arteriovenous difference, and oxygen supply or consumption is unable to correlate with PtiO2 values (Table 6.1).

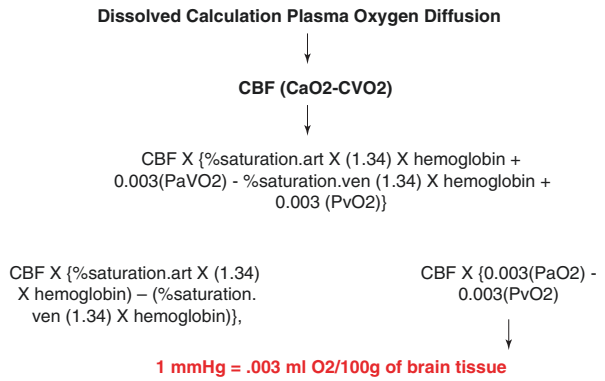

Fig. 6.6 Calculation of the diffusion of dissolved plasma oxygen to the brain tissue: Based on the variables that make up the supply and consumption of oxygen to the tissues, we can arrive at the formula for diffusing oxygen to the tissues that follows CBF × {0.003 (PaO2) – 0.003 (PvO2)}. CBF cerebral blood flow, % Saturation art. = % of arterial oxygen saturation, % Saturation ven. = % of venous oxygen saturation, CaO2 arterial oxygen content, CvO2 venous oxygen content, PaO2 partial pressure of oxygen in arterial territory, PvO2 partial pressure of oxygen in venous territory

Table 6.1 The isolated analysis of variables such as cerebral blood flow, cerebral arterial, and venous oxygen content, cerebral oxygen arteriovenous difference, and oxygen supply or consumption are unable to correlate with PtiO2 values

		Univariate			Multivariate	
Physiological parameter	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
FSC	0.59	(0.01–1.19)	0.05	0.92	(−1.83–3.67)	0.51
CaO_2	8.60	(2.50–14.70)	0.006			
CvO_2	2.95	(−0.41–6.31)	0.08	3.62	(−1.25–8.49)	0.14
$DAVO_2$	4.64	(−0.31–9.59)	0.07	3.65	(−2.08–9.39)	0.21
DO_2 local	1.89	(1.91–9.32)	0.003	−12.65	(−32.41–7.11)	0.21
$CMRO_2$ local	28.27	(17.87–38.66)	<0.001	−0.45	(−21.49–20.59)	0.97
FSCx(PaO_2–PvO_2)	0.0064	(0.0053–0.0075)	<0.001	0.0077	(0.0063–0.0090)	<0.001

Therefore, the analysis of the variables obtained in the equation of Fig. 6.6 is essential, where the product of cerebral blood flow by the difference between partial pressure of oxygen in the arterial and venous territory is the best correlation index with the values of PtiO2 [25].

6.4.5 Cerebral Oximetry: Implications of Clinical Interventions

Several factors can interfere with PtiO2 values. Hyperoxia for interfering with PaO2 and PvO2 can increase oximetry values artificially. Increases in FiO2 to 80–100% can double or even triple the initial baseline value [30]. Although hyperoxia increases PtiO2, this is not necessarily associated with an improvement in oxygen transport or an increase in brain O2 consumption. However, the increase in the oxygen stress gradient could facilitate the diffusion of O2 through swollen tissues and reach the mitochondria more easily. On the other hand, hyperoxia is associated with damage to the eyes, lungs, heart, and digestive tract, as well as increasing the formation of free radicals. Hyperbaric oxygen therapy can induce epileptic seizures. Concerning brain blood flow, hyperoxia (100% inspired oxygen fraction) can cause vasoconstriction and reduce cerebral perfusion pressure regardless of previous vasoconstriction degree. For all these questions, we should not use hyperoxia to correct low values of cerebral oximetry [31, 32].

Hyperventilation triggers respiratory alkalosis (PCO2 drop). This fact may in turn trigger both local (e.g., PtiO2 installation site) or global vasoconstriction leading to reduced oxygen supply (hypoperfusion), anaerobic metabolism, and even ischemia with or without cerebral infarction. It should be noted that metabolic

alkalosis increases the hemoglobin affinity for oxygen, making it difficult to transport it to the tissues. The duration of hyperventilation (the longer) increases the chances of secondary cerebral ischemia [33]. However, hyperventilation remains essential in the treatment of brain herniation and in the treatment of refractory intracranial hypertension (optimized hyperventilation). While PaCO2 values less than 25 mmHg to treat intracranial hypertension are associated with worse functional results and higher mortality, the hyperventilation values that can reduce PtiO2 are not established.

The cerebral perfusion pressure (CPP) is directly proportional to the brain blood flow, and this, in turn, is fundamental for the transport of oxygen to the brain tissue and the PtiO2 values. So, it is logical to think that reductions or increases in CPP trigger a decrease or increase in PtiO2, respectively. This phenomenon occurs due to the reduction (increase of PtiO2) or increase (reduction of PtiO2) of the arteriovenous oxygen difference [34]. Generally, the CPP values ranging from 60 to 70 mmHg do not significantly influence the ICP values [35]. However, CPP values greater than 75 mmHg are associated with greater cerebral and pulmonary edema in TBI patients. PtiO2 is in an adequate range, in general, when PPC is greater than or equal to 70 mmHg [36].

Hypothermia in the context of treatment of intracranial hypertension secondary to severe TBI can reduce brain metabolism, oxygen supply (vasoconstriction), brain inflammation, the release of free radicals, cytokines, and excitatory amino acids. All of these effects triggered intracranial pressure reduction and, therefore, a decrease in the deleterious effects of the secondary lesion. However, it was observed during mild hypothermia (34–36 °C) that there was a reduction in PtiO2 associated with a decrease in ICP and maintenance of CPP at the recommended levels. This drop-in PtiO2 value is explained by vasoconstriction (effect of hypothermia) and by the increased affinity of hemoglobin for oxygen that occurs during hypothermia [37]. Therefore, great care must be taken when interpreting cerebral oximetry values in the presence of mild hypothermia, and possibly their values are not amenable to interpretation below 34 °C.

6.4.6 Brain Oximetry and Autoregulation After Primary Brain Injury

The assessment of autoregulation in neurological and neurosurgical critical care patients is a bedside challenge, and a standardized way to evaluate has not yet been achieved. Meixensberger et al. [20] studied severe TBI and SAH patients who were monitored with serial perfusion pressure (CPP) and cerebral oximetry (PtiO2) and developed the concept of PtiO2 autoregulation (PtiO2AR). PtiO2AR was defined as the ability of regional brain hemodynamics to maintain PtiO2 levels despite variations in CPP. PtiO2AR was calculated based on the area under linear regression obtained from CPP and PtiO2 values. Depending on the results obtained by PtiO2AR, autoregulation was classified as present, reduced, absent, or inverse.

Table 6.2 Obtained ORx in 67 patients after SAH in order to detect changes in cerebral autoregulation and its relationship with late cerebral ischemia

	Group Nonstroke	Group Stroke	
Variable	($n = 47$)	($n = 20$)	P
PPC (mmHg)	81.1 ± 12.1	82.8 ± 11.4	0.43
PIC (mmHg)	12.2 ± 3.9	14.4 ± 5.2	0.10
$PtiO_2$ (mmHg)	23.9 ± 5.8	20.8 ± 5.0	0.06
ORx	0.23 ± 0.14	0.43 ± 0.09	0.0000002

The present autoregulation was considered when PtiO2 was maintained regardless of variations (increases or decreases) in CPP. Reduced or absent autoregulation was defined when the increase in PtiO2 occurred associated with the increase in CPP. In cases of severe dysfunction in autoregulation, slight increases in CPP triggered increases in PtiO2. Inverse autoregulation was described when increases in CPP resulted in a decrease in PtiO2. Using the previous study as a reference, Jaeger et al. [30] developed an index to assess whether autoregulation was adequate or not. This new index was called ORx. ORx is obtained through a linear correlation coefficient (Pearson's coefficient) between the CPP and PtiO2 values collected at the same time. The closer to the unit value, the worse the autoregulation would be, while negative values or close to zero would reflect autoregulation with less dysfunction. In another study, Jaeger et al. [19] obtained ORx in 67 patients after SAH in order to detect changes in cerebral autoregulation and its relationship with late cerebral ischemia (Table 6.2). The group that presented infarction had significantly higher ORx indexes (closer to the unit value), suggesting more significant impairment of cerebral autoregulation. In this study (data obtained in the 5th and 6th days after SAH ictus), the group of patients who presented ORx < 0.25 had 9% of infarction, while those who demonstrated ORx between 0.25 and 0.40 had rates of 30% of infarction. The group with the highest ORx (>0.40) had cerebral infarction rates of 61%.

Considering that late infarction was detected after the 7th day of SAH, the higher ORx values on days 5 and 6 may suggest a higher risk of severe vasospasm and, consequently, of late infarction. These data could assist doctors in making decisions regarding therapeutic interventions in the treatment of vasospasm.

6.4.7 Prognostic and Interventional Studies

Ramakrishna et al., prospectively studied 46 patients with SAH and correlated the number and duration of episodes of cerebral tissue hypoxia and hospital mortality. Reductions in PtiO2 defined episodes of cerebral tissue hypoxia. In this study, nonsurvivors had a mean PtiO2 (26.25 ± 2.72 mmHg) on the very first day compared to survivors (mean PtiO2 = 34.69 ± 3.87 mmHg, $P = 0.04$) [17].

In a series of 53 patients with severe TBI, therapy based on tissue oximetry showed lower mortality when compared to therapy based exclusively on ICP/CPP. 11 In another series of 123 patients, a better result (GOS = 4 or 5) was also observed when the therapy was based on PtiO2 monitoring [38]. A systematic review showed that a PtiO2 less than 10 mmHg had a significant positive predictive value associated with a worse functional outcome in severe TBI (OR 4.0; 95% CI 1.9–8.2) and increased mortality (OR 4.6; 95% CI 2.2–9.6) [23]. In another series, 101 patients with severe TBI were analyzed. In this study, PtiO2 less than 10 mmHg for more than 30 min was associated with a worse result (functional result and mortality) when compared to patients who did not present this condition. PtiO2 less than 10 mmHg for more than 30 min was an independent variable for an unfavorable outcome even when analyzed together with age, Glasgow coma scale, pupils, polytrauma, intracranial pressure, and tomographic findings [39].

6.4.8 *Brain Oximetry Dysfunction Treatment*

This treatment guide (Fig. 6.7) aims to assist the reader in reasoning and interpreting the values obtained by cerebral oximetry and at no time should the reasoning of multimodal monitoring or clinical data be abandoned.

Despite the literature, presenting a critical level of PTiO2 10 mmHg, the authors prefer to consider values below 20 mmHg as a reference to start the reasoning of cerebral oximetry. If a low oximetry value is found, the physician must increase the

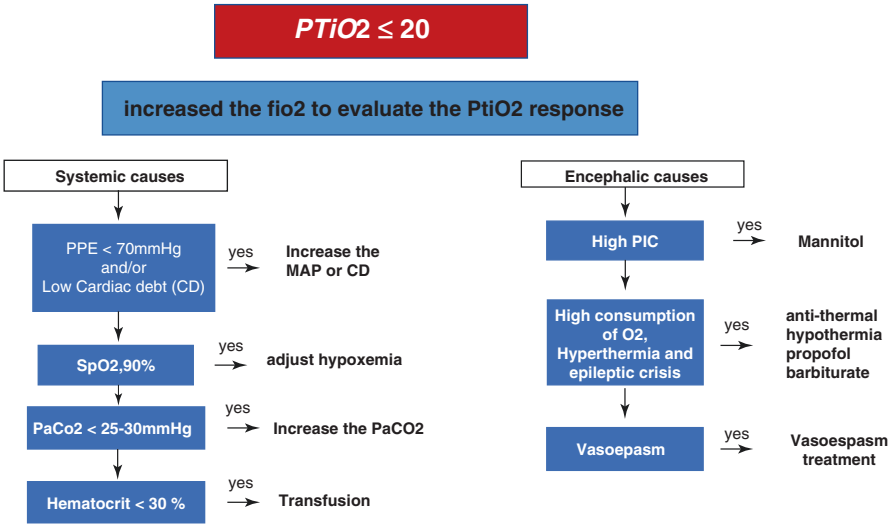

Fig. 6.7 Treatment guide based on cerebral oximetry. PTiO2 partial pressure of oxygen in brain tissue, FIO2 fraction of inspired oxygen, PEP brain perfusion pressure, SpO2 peripheral oxygen saturation, PaCO2 partial pressure of carbon dioxide in arterial blood, MAP mean arterial pressure, CD cardiac output, ICP intracranial pressure

fraction of inspired oxygen to 100% in order to check if the catheter is appropriately functioning. If the catheter integrity is adequate, the oximetry will increase. However, this is not the treatment of PTiO2 unless there is systemic hypoxemia.

After the catheter's proper functioning is confirmed, the inspired oxygen fraction should return to the previous values, and thought must be formulated regarding the possible causes that will lead to a critical PTiO2. The causes can be divided into systemic and brain etiologies. Intervention should begin with systemic causes that are easier to diagnose and treat. Assess first the systemic hemodynamics, maintain the brain perfusion pressure greater than or equal to 70 mmHg. If this value has already been obtained, assess blood volume (hypovolemia) and, if possible, cardiac output (pump failure) because these factors can cause a drop in brain blood flow and PTiO2 even with mean arterial pressure values considered normal. Next, assess if there is no hypoxemia and correct it immediately. Often, these neurocritical patients are left without respiratory physical therapy for fear of increased intracranial pressure (ICP); however, worsening of the pulmonary condition will lead to an increase in ICP and a decrease in PTiO2. Do not forget to check if the patient is hyperventilating. PaCO2 should not be below 30 mmHg because it can trigger vasoconstriction and reduce cerebral blood flow and consequently decrease PTiO2. Finally, evaluate the hematocrit, if it is below 30% and all other systemic and brain variables are adequate, red blood cell transfusion can be considered.

After the evaluation of the systemic variables that could be influencing the low values of oximetry, the evaluation of the brain variables begins, starting with the intracranial pressure. It is suggested maintaining an ICP less than 20 mmHg and CPP greater than or equal to 70 mmHg. Care must be taken not to increase CPP indiscriminately. After it is verified that the ICP is controlled, the PtiO2 may be increased by higher cerebral consumption of oxygen, hyperthermia, epileptic seizure, or cerebral vasospasm. The use of the electroencephalogram may help in the assessment of cerebral oxygen consumption and the diagnosis of epileptic seizures. In both diagnoses, treatment will be based on the use of hypnotic drugs (midazolam, propofol, or barbiturates). Hyperthermia can lead to increased consumption and the deviation of brain flows and therefore deserves to be controlled. The target is normothermia (central nervous system temperature between 36 and 37 °C). It should not be forgotten that hypothermia may lead to a reduction in PtiO2 without signifying tissue hypoxia. Finally, check that there is no brain vasospasm. The method of choice for this bedside diagnosis is transcranial Doppler. Its treatment will depend on each case and the technological availability of the service.

6.5 Conclusions

Cerebral oximetry is a consistent method of assessing regional cerebral tissue hypoxia. It is a reliable and safe technique (low complication rates) with predictive prognostic value. However, thus far, the data are insufficient to state that a therapy guided by this methodology is capable of reducing morbidity and mortality in patients with TBI and SAH.

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Chapter 7
Brain Microdialysis Monitoring

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7.1 Introduction and the Concept of Cerebral Microdialysis

One of the fundamental objectives of the treatment of patients with a severe traumatic brain injury (TBI) is the prevention of secondary brain lesions, hence the importance of being able to make early detection of cerebral tissue ischemia. This concept can be extended to the context of other neurocritical patients. Microdialysis (MD) is a technique based on the principle of solute exchange through a

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semipermeable membrane, which emulates the functioning of a blood capillary [1–3]. MD is an extremely sensitive technique that can provide early metabolic information about the establishment of a tissue lesion. Although complex, this technique provides much better information than any other monitoring system, since it allows one to monitor: (1) the tissue availability of different metabolites, such as glucose; (2) the elements released by the cells; and (3) the cellular consequences of tissue hypoxia-ischemia.

Cerebral MD (CMD) was introduced in 1966 by Bito et al. for in vivo dialysis of the canine brain [4] and is now used for an extensive array of applications that explore the regional chemistry of the human brain. The first known application of CMD in humans was reported in 1990 by Meyerson et al., who implanted MD probes during thalamotomy procedures in patients with Parkinson's disease [1]. In the same year, the first report of changes in energy-related metabolites during frontal lobe resection in five human patients was published [5]. Since that time, CMD has been increasingly used as a neuromonitoring technique in neurocritical patients with TBI, middle cerebral artery infarction (MCAI), and spontaneous subarachnoid hemorrhage (SAH) to monitor cerebral energy metabolism during the acute phase after injury or stroke [6]. Despite the great potential of this monitoring technique, in 2012, Kitagawa et al. showed that only 42 centers worldwide used MD for clinical decision making in the management of neurocritical patients [7]. In addition to its clinical utility; however, it is important to note that CMD is a unique research tool that allows in-depth analysis of the complex physiological derangements that occur in acute brain injuries.

The semipermeable membrane is located at the distal end of the MD catheter implanted in the brain (Fig 7.1) and through it the solutes are exchanged between a solution of known composition and the extracellular space fluid. In the brain, the placement of an MD catheter allows the analysis and quantification of the changes that occur in various "energetic" metabolites, such as lactate, pyruvate, adenosine, inosine, or hypoxanthine. It also allows studying the release of neurotransmitters and neuromodulators (e.g., glutamate, aspartate, GABA, and taurine) or the release of products of inflammatory origin (cytokines) or resulting from tissue degradation (glycerol, potassium). Although CMD catheters allow a large number of molecules and ions to be obtained, in clinical practice, neurochemical monitoring is limited to sequential quantification of four or six metabolites, the maximum number allowed by the analyzer equipment used at the patient's bedside (CMA-600 or ISCUSflex, CMA Microdialysis, Stockholm, Sweden).

CMD involves the insertion of a catheter, of fine caliber (0.62-mm external diameter) and double lumen, into the extracellular space of the brain parenchyma. One of the "lumens" of the catheter is connected to a small precision pump that infuses saline or ringer serum without lactate at extremely low speeds (0.1–5 μL/min). Because there is a concentration gradient between the two spaces, there is a passage of molecules contained in the extracellular space into the catheter, which depends on the diameter of the pores of the semipermeable membrane. Through the second lumen of the MD catheter, the solution loaded with tissue metabolites is collected in a microvial that is replaced every 10–60 min. The microvials obtained are analyzed

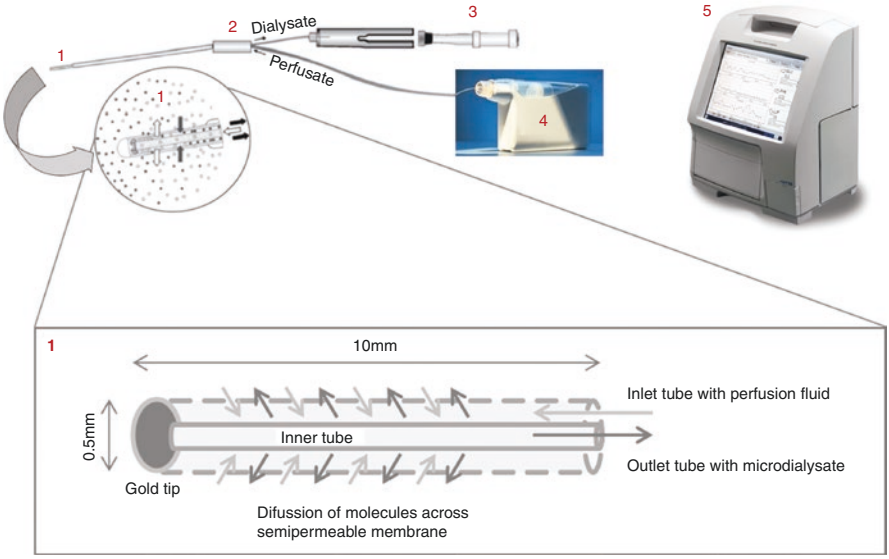

Fig. 7.1 Cerebral microdialysis catheter and the basic elements for performing this technique: (1) dialysis membrane, (2) double-lumen catheter, (3) microvial, (4) infusion micropump, and (5) the portable analyzer ISCUSflex placed at the bedside

at the patient's bedside, which allows four to six analytes to be sequentially quantified by enzymatic techniques. However, for this brain information to be valid and useful, it must be contrasted with the information provided by an additional catheter placed in the subcutaneous tissue. The latter provides information on systemic (extracerebral) metabolism.

7.2 Basic Methodological Aspects of the Cerebral Microdialysis

The application of the CMD includes the use of five key elements: the MD catheters, a semipermeable membrane, infusion micropumps, special microvials, and a portable analyzer placed within the same ICU (bedside). Microdialysis *catheters* (CMA-70 or CMA-71, CMA Microdialysis, Stockholm, Sweden) are flexible, with a small diameter (<1 mm), and contain a double lumen with a *semipermeable membrane* at the distal end (Fig. 7.1). Small solutes can pass freely across this membrane due to an osmotic gradient. The internal lumen of the catheter contains a metabolite-free solution (Ringer solution without lactate or an isotonic saline serum). The catheter is attached to a continuous *infusion micropump* (CMA-106, CMA Microdialysis) that infuses the solution at a constant and predetermined velocity. At the distal extreme of the catheter, and through the semipermeable membrane, there is an

exchange of solutes of a particular molecular weight (<20 kDa in standard catheters [CMA-70] and up to 100 kDa in high-resolution catheters [CMA-71]). The microdialysate obtained contains molecules from the extracellular space and flows through the external lumen of the catheter. This microdialysate is recovered through special microvials, which are replaced periodically. A portable analyzer (CMA-600 or ISCUSflex) analyzes the microdialized by enzymatic and fluorometric techniques (urea) and quantifies changes in the composition of the initial solution (Fig. 7.1).

The metabolites dissolved in the fluid of the extracellular brain space come from the tissue capillaries, neurons, and adjacent glial cells [2]. The passage of substances to the MD catheter depends on its molecular weight (the semipermeable membrane of the usual catheter only allows the passage of ions and molecules of molecular weight less than 20,000 Da), the infusion rate of the perfusion fluid, the length of the membrane, and the diffusion coefficient of each substance in the tissue to be studied [8]. The recovery of the different metabolites is always a percentage of the actual content that exists in the study tissue, which introduces the concept of "relative recovery," which is explained in detail in the following section.

7.3 The Recovery Principle

The dialyzing properties of the MD membrane are routinely expressed as its recovery for a particular solute [9]. The *recovery* of a certain metabolite is defined as the concentration of this element that contains the microvial divided by the actual concentration in the interstitial space, a fraction expressed as a relative recovery *(RR)* [2], which is calculated as a simplification of the following equation: RR = (Cout—Cin) / (Cex–Cin)**,** where Cout is the concentration of a given substance in the dialysate, Cex is the concentration of the same substance in the *extracellular fluid*, and Cin is the concentration of the solute in the perfusion fluid. RR is expressed as a percentage. The concentration of the solute in dialysate will always be lower than that in the *extracellular fluid*. Therefore, RR will always be below 100%, except when the flow rate equals zero. In this particular situation—and for a low molecular weight solute—the concentrations equilibrate in both sides of the dialyzing membrane [10].

The optimal recovery of any metabolite should be 100%; that is, the information provided by the MD catheter should accurately reflect the composition of the extracellular space. Hutchinson et al. analyzed the influence of various methodological aspects on the recovery of analytes, such as glucose, lactate, pyruvate, and glutamate in brain neurosurgical patients [11]. These authors confirmed that the concentrations of these metabolites obtained from adjacent catheters were practically identical [11].

In the same study, when the influence of dialysis membrane length was analyzed, metabolite recovery was found to be much higher if 30 mm dialysate membranes were used instead of 10 mm. The authors also verified that the perfusion rate of the dialysate fluid had a significant influence, with 0.3 μL/min performing best. Using

a dialysis membrane of 10 mm and an infusion rate of 0.3 μL/min, these authors obtained an approximate recovery of 70% of all the metabolites studied [11]. Coinciding with these results, Ungerstedt et al. observed that with a flow rate of 0.3 μL/min and a membrane length of 30 mm, the recovery was almost 100% [3].

Another important aspect reported in the Hutchinson et al.'s study was that the samples analyzed at the bedside (online analysis with the CMA-600 analyzer) showed an excellent correlation, with minimal differences in absolute values, with off-line determinations using chromatographic techniques [11]. Likewise, the freezing of the microdialysis samples at a temperature of −70 °C over a period of 3 months also did not significantly alter the determinations obtained, confirming that the differences in all the elements studied were less than 5%. Finally, these authors also confirmed that the use of Ringer solutions without lactate or isotonic saline did not influence the final concentration of glucose, lactate, pyruvate, or glutamate [11]. However, Ungerstedt et al. recommend the use of Ringer without lactate as a fluid to be perfused, based on the fact that the use of saline causes a depletion of calcium and potassium that can alter neurotransmission in the areas near the implanted catheter [3].

7.4 How to Implant a Cerebral Microdialysis Catheter

For placement in the brain of MD catheters, stereotaxy techniques were initially used. However, these techniques, which might be ideal in certain experimental studies, constitute an important limitation in the clinical context of neurocritical patients. At present, CMD catheters are inserted by placing them under direct vision during surgical procedures or through a burr hole in the operating room, through cranial multilumen bolts (Fig. 7.2), or percutaneously by a twist drill craniotomy [12].

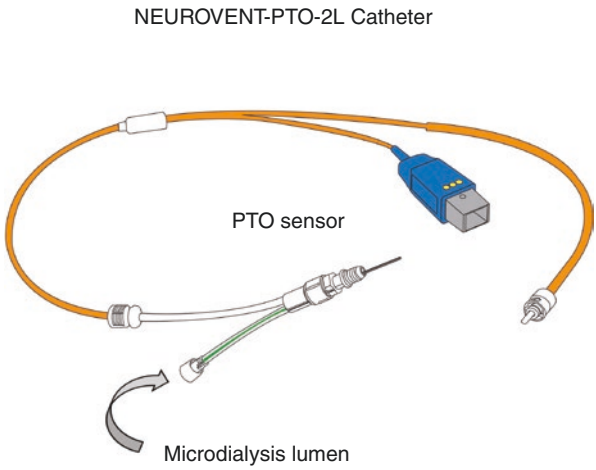

Fig. 7.2 Raumedic multi-lumen screw designed to insert a microdialysis catheter through one of its lumens (arrow)

Despite its greater ease, an important drawback of using bolts is that positioning of the catheter next to focal lesions can be difficult or impossible because bolts are manufactured to allow a fixed-length insertion of the catheter. Therefore, the implantation of catheters around focal lesions requires an independent burr hole to reach the target area. To simplify the insertion of cerebral microdialysis catheters, in our center, we use a percutaneous technique, similar to that used to implant an intraparenchymal ICP or $PtiO_2$ sensor without a bolt [12]. Like the implantation of other brain sensors used to monitor neurocritical patients, this technique can be performed at the bedside in the ICU.

The surgical technique for implanting CMD catheters involves a twist-drill craniotomy, with a small drill hole (2.7-mm in diameter), and subcutaneous catheter tunneling (Fig. 7.3). The patient's head is shaved and prepared. The craniotomy includes the outer and inner tables of the skull and is followed by a blind duramater perforation using a 14G needle. This maneuver ensures adequate patency of the craniotomy and opening of the dura. Then, a small stylet is inserted in the craniotomy and is introduced slightly into the opened dura to make a small puncture in the pia mater and ensure smooth insertion of the microdialysis catheter. Next, the stylet

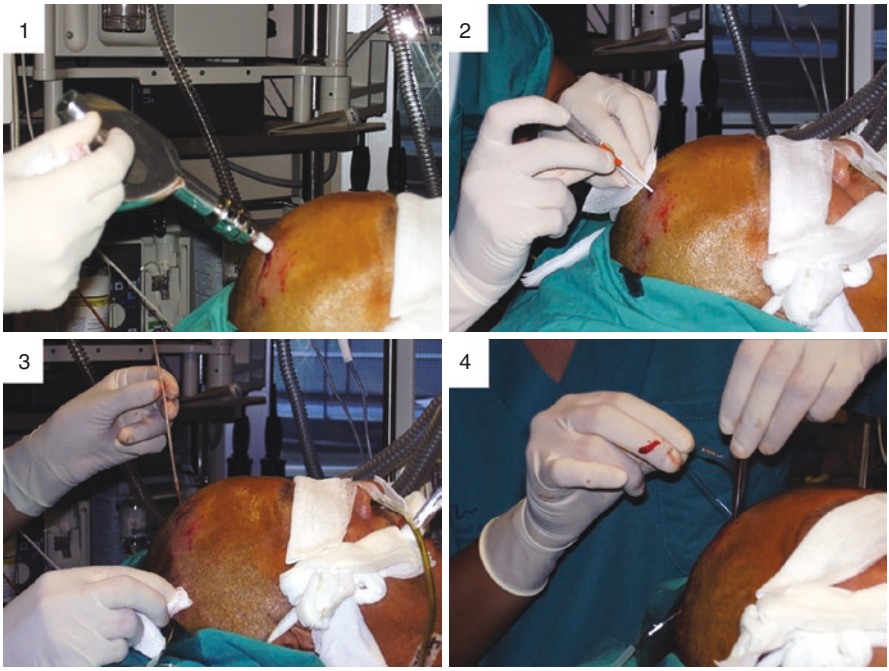

Fig. 7.3 Graph summarizing the steps for the implantation of a brain microdialysis catheter using a percutaneous technique: (1) a small drill hole (2.7-mm in diameter) was carried out, (2) the duramater was perforated using a 14G needle, (3) the microdialysis catheter was placed within the protective sheath and tunneled, (4) the distal part of the microdialysis catheter was guided toward the white matter. Finally, the microdialysis catheter was fixed on the scalp and covered by a semipermeable membrane, which remained in place throughout the monitoring period

is removed, and the MD catheter is introduced into the craniotomy following the route created by the stylet. Finally, the dialysis membrane was positioned in the subcortical white matter, the skin is sutured, and the catheter is fixed to the scalp by additional sutures [12]. As with other cranial sensors, CMD catheters are only implanted when coagulation parameters are considered to be normal (platelet count > 100,000, prothrombin time < 14 s, and partial thromboplastin time < 50 s), without the use of antibiotic prophylaxis. Routine precautions against infection are taken during sensor insertion and daily care.

7.5 Where Should the Cerebral Microdialysis Catheter Be Placed? The Importance of Radiological Control

As in other local monitoring systems, in CMD, clinicians must decide where the catheter should be implanted to obtain the most useful information for the clinical management of the patient. The implantation of a catheter in the "healthy" tissue offers the possibility of monitoring the tissue with greater chances of recovery, while offering us information that we can extrapolate globally to the rest of the uninjured brain. On the other hand, the placement of a catheter in the "penumbra" areas allows the monitoring of potentially recoverable brain regions. We consider ischemic or traumatic "penumbra" as a brain region of normal macroscopic appearance around the ischemic core or traumatic cerebral contusions or hemorrhages with no changes in brain tissue attenuation in a noncontrast CT scan (Fig. 7.4); these regions had to be at least 20 mm away from any brain region with parenchymal abnormalities [10]. The traumatic penumbra is also considered when the probe is located in the brain immediately below any significant extra-cerebral hematoma. To resolve this conflict, and ideally, in the focal lesions, two microdialysis catheters should be implanted in the brain parenchyma, one in healthy tissue and the second in the area of the penumbra. In diffuse lesions, however, the placement of a single cerebral catheter is sufficient. In our patients, we have found that in the focal or ischemic lesions, the information provided by two brain MD catheters can be very different, confirming the pathophysiological complexity of the cerebral lesions (Fig. 7.5).

An essential aspect of this type of monitoring is to know the exact position of the MD catheter (e.g., gray matter, white substance, and specific brain territory). Initially, the MD catheters were not radiopaque or equipped with radiological markers, so it was impossible to determine the exact position of the catheter. As an additional difficulty, if we wanted to place the dialysate membrane in a cortical position, the flexibility and small caliber of the catheters favored their migration to the subarachnoid space. At present, there is a consensus in locating the dialysate membrane in the white subcortical matter, and the CMD catheters incorporate a tiny piece of gold at its distal end, which is perfectly visible in radiological controls (Fig. 7.5). Also, the information we obtain can be interfered with by the presence of blood or air around the catheter (Fig. 7.6), so for a proper clinical interpretation of the results, we must rule out these facts.

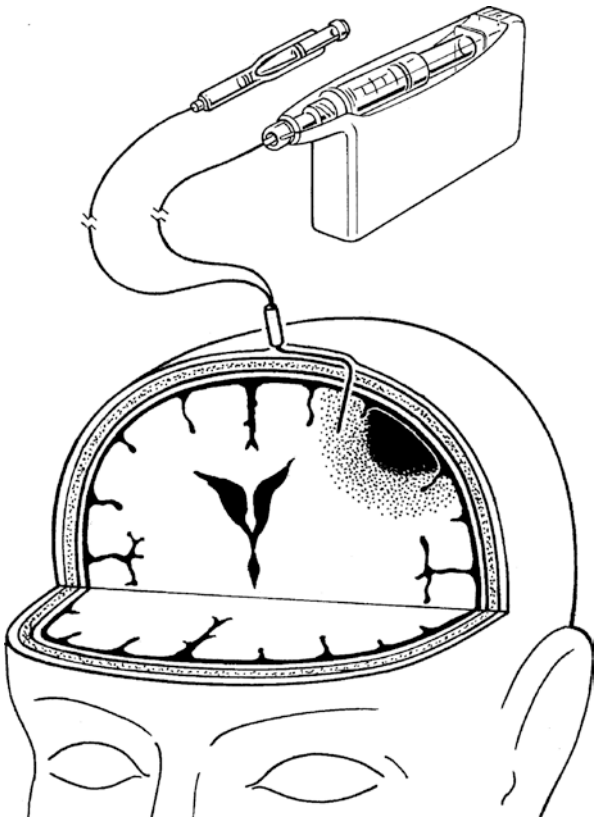

Fig. 7.4 A microdialysis catheter implanted in a traumatic "penumbra" region (brain region with normal macroscopic appearance around cerebral traumatic contusions or hemorrhages with no changes in brain tissue attenuation in a noncontrast CT scan). These regions had to be at least 20 mm away from any brain region with parenchymal abnormalities

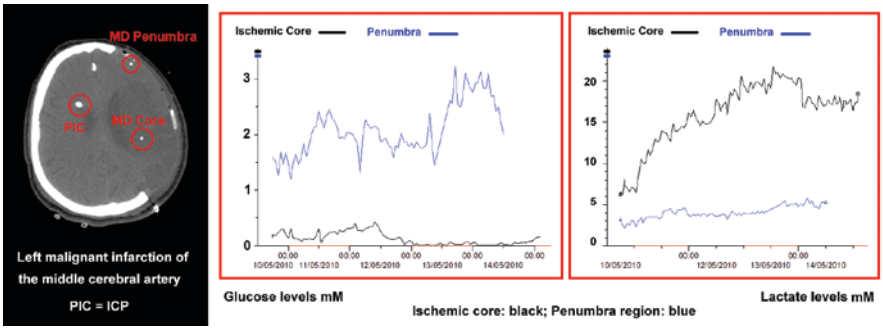

Fig. 7.5 CT scan of a patient with malignant infarction of the middle cerebral artery. Two microdialysis catheters were implanted in the ischemic hemisphere: in the ischemic core and in the penumbra region. Both catheters have a gold tip. Note how the information offered by the two catheters is very different depending on the tissue in which they are inserted

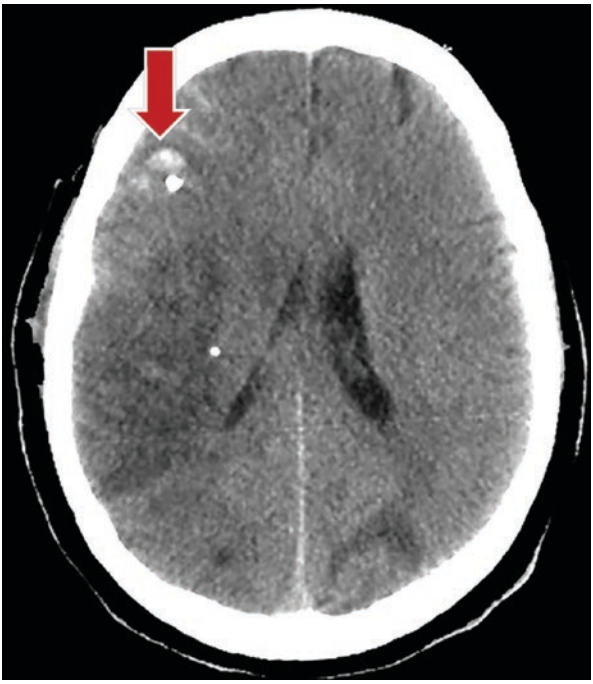

Fig. 7.6 CT images of a patient with a minute blood collection (less than 1 cc) resulting from the implantation of a cerebral microdialysis catheter. This hemorrhage is not clinically relevant but might invalidate the information of the microdialysis catheter

7.6 Metabolites to Be Determined: Neurotransmitters, Markers of Ischemia, and Tissue Injury

Although CMD catheters allow a large number of molecules and ions to be obtained, neurochemical monitoring at the bedside is limited to the sequential quantification of four to six metabolites, the maximum number allowed by the analyzers used in the ICU. The standard analyzer equipment (CMA-600) allows the quantification of four analytes per patient and the monitoring of three simultaneous patients. The ISCUSflex, the third generation of MD analyzers, allows the monitoring of up to eight simultaneous patients, with a batch analysis capacity of 16 samples, and the use of six available reagents: glucose, lactate, pyruvate, glycerol, glutamate, and urea. However, if the microvials are preserved at the appropriate temperature (−70 °C), subsequent determinations of additional analytes can be made, with the only limitation being the residual volume of dialysate fluid that the microvial contains.

Glucose is the metabolite most frequently determined in MD. Glucose constitutes the fundamental energy substrate of the brain. Its extracellular concentration depends on the concentration of peripheral blood glucose, local capillary flow, and cell uptake. The latter can vary when cellular metabolism shifts from an aerobic to

an anaerobic pathway. The simultaneous use of an MD catheter located in the subcutaneous tissue provides continuous information on the systemic availability of glucose and therefore information for the correct interpretation of brain glucose levels. Thus, when the glucose in the brain descends parallel to the brain tissue O_2 ($PtiO_2$), with peripheral glucose being preserved, we can affirm that there is a decrease in capillary blood flow [3]. In other situations, to correctly interpret the metabolic events that take place, the simultaneous quantification of several metabolites in the brain is required [3]. Several studies have established that brain glucose levels are lower than plasma levels [13, 14]. Reinstrup et al. established the traditional clinical upper threshold for MD brain glucose at 0.3 μL/min in awake patients—using the ±1.96 SD method—at 3.5 mmol/L [15]. This upper limit was similar to the values found in our awake and anesthetized patients at the same perfusion rate [14].

In the brain, interstitial *lactate* arises as an intermediate metabolite in aerobic glycolysis and is generated in large quantities in anaerobic glycolysis, in an attempt to increase the production of ATP through a less efficient metabolic pathway. Therefore, when high levels of lactate are found in the brain, it can come from an increase in aerobic metabolism (situation of cellular hypermetabolism) or from a situation of tissue hypoxia, ischemic or nonischemic, in which glycolysis is fundamentally anaerobic. In patients with spontaneous SAH, Oddo et al. found that brain lactate elevations (>4 mmol/L) were more often caused by cerebral hyperglycolysis than by brain hypoxia and that hypoxic lactate was associated with increased mortality, whereas hyperglycolysis was a predictor of a good outcome [16]. The differential diagnosis between these situations, conceptually opposed, can be made with the simultaneous determination of pyruvate and the calculation of the *lactate/pyruvate ratio* (LPR). An increase in lactate parallel to an increase in pyruvate, with a normal LPR, indicates a situation of cellular hyperglycolysis. In contrast, an increase in lactate accompanied by a decrease in pyruvate and an increase in the LPR are indicators of ischemic or nonischemic brain hypoxia or mitochondrial dysfunction [17]. According to the results of our study of reference levels in CMD [14], a pragmatic upper limit for the LPR in both awake and anesthetized patients appears to be 35, and not the limit of 25 that we have used in a classical way [17].

Glycerol is one of the structural components of the lipid bilayer of the cell membrane. Located in the outermost part of the cell membrane (hydrophilic portion), glycerol emerges from this structure in situations of lack of cellular energy, constituting a biochemical marker of tissue injury [18]. In situations of excitotoxicity, mediated by massive glutamate releases in the synaptic cleft, or in a situation of lack of energy, uncontrolled entry of calcium into the cell occurs. Intracellular calcium activates certain phospholipases and generates the formation of free radicals of O_2, which are responsible for the phenomenon of lipid peroxidation. Lipid peroxidation destroys the cell membrane, with the consequent release of fatty acids and glycerol. In clinical practice, there are several situations that can generate cellular "suffering," such as increases in ICP (Fig. 7.7). However, it is not clearly established whether the increase in glycerol is associated with the destruction of the cell membrane, with secondary death of the cell, or if it constitutes a marker of "cell suffering," with the

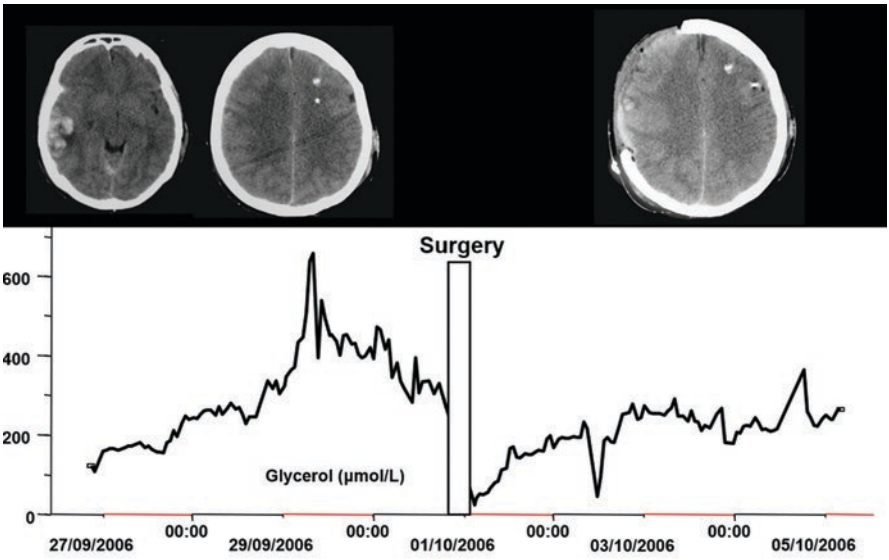

Fig. 7.7 Image showing elevated glycerol values in the context of intracranial hypertension. See how the values of this metabolite are drastically reduced after evacuating a brain lesion, and the values of intracranial pressure are normalized

possibility of reversal of the process, without destruction of the cell. In a small cohort of TBI patients, Peerdeman et al. found that values of glycerol >150 µmol/L in the normal-appearing regions of the brain had a positive predictive value of 100% for an unfavorable outcome [19]. In a series of patients, we found a significant increase in cerebral glycerol in both the ischemic and traumatic core, but the glycerol levels were always below the upper reference threshold in both the normal-appearing brain and the traumatic penumbra. Our findings reinforce the idea that glycerol is a marker of tissue injury [10]. However, some studies have pointed out that maneuvers as simple and routine as the application of a glycerol enema in a patient can greatly increase the concentrations of this substance, which might raise questions about its validity as a marker element of tissue injury and leads us back to the need for systemic information to properly interpret the information offered by CMD catheters [20].

Glutamate is the most abundant excitatory neurotransmitter in the mammalian nervous system, followed in importance by aspartate. Glutamate is distributed practically throughout all brain regions, and its action is essential in normal neuronal transmission. When the neuron is depolarized, glutamate is released into the synaptic cleft, exerting its action on a variable set of receptors. The function of this neurotransmitter depends fundamentally on the type of receptor on which it acts. In severe TBI, there are certain situations (e.g., hypoxia, ischemia, mechanical injury with rupture of cell membranes, and the release of blood content) in which large amounts of glutamate and aspartate are released into the extracellular space. In

these circumstances, both neurotransmitters, although especially glutamate, can exert a repeated and uncontrolled exciting action on neurons, leading them to a state of repetitive depolarization that can condition cellular self-destruction (*excitotoxicity phenomenon*). Since ischemic phenomena cause a massive release of this neurotransmitter, its determination can also be used as a marker of tissue injury.

As with any high-precision technique and on which clinical decisions might be based, in CMD, it is essential to have a system capable of identifying artifactual information that might be included among valid values. Ronne-Engstrom et al. [21] proposed the use of *urea* to detect problems in the recovery of MD catheters, since this molecule acts as an endogenous reference compound. An endogenous reference compound is a substance naturally present in the organism that, once synthesized, is not metabolized and can diffuse freely through biological membranes, reaching a similar and stable concentration in all systemic fluids. Urea is a molecule of low molecular weight (60 Da) and polar structure, but without an electric charge, characteristics that make it suitable for use as an endogenous reference compound [22], provided there is a sufficient period to allow a homogeneous distribution of the molecule.

In mammals, urea is the main end product of nitrogen catabolism. Almost all the urea present in blood and urine is synthesized in the liver and excreted through the kidney, without its concentration showing sharp oscillations. Assuming that the concentration of urea is similar in the extracellular space fluid of the brain and subcutaneous tissue, the ratio between cerebral urea and subcutaneous urea of MD samples constitutes a good quality control in the application of this technique. The ratio between cerebral and subcutaneous urea usually ranges between 0.5 and 1 in different patients. This variability is due to the different physicochemical and physiological conditions that occur in the tissue in which each catheter is inserted and that directly affects the amount of urea collected by each of the catheters [23]. However, the value of the urea ratio brain/subcutaneous measured between a pair of specific catheters should be constant in a given patient. Thus, if the ratio of cerebral urea versus subcutaneous urea is constant, it can be said that the two MD catheters are functioning correctly. When the ratio is constant, the oscillations in the concentration of the other analytes studied simultaneously would be a correct reflection of the real oscillations of these analytes in the interstitial space. An increase or decrease in the ratio between cerebral urea and subcutaneous urea will indicate dysfunction of one of the two catheters. Urea should not be used as a reference substance in cases of renal insufficiency, since in this situation, its concentration may suffer sharp oscillations [21].

7.7 Reference Values of Brain Metabolites

One of the fundamental problems of MD lies in establishing the normal values of different metabolites. Given the ethical and methodological impossibility of monitoring normal subjects, the reference values should be obtained from experimental

Table 7.1 Reference levels of brain metabolites determined by microdialysis neuromonitoring

Metabolite	Reinstrup[a] mean ± SD	VHUH study[b] Anesthetized median (RI)	VHUH study[b] Awake median (RI)	VHUH study[b] ZFM method median (RI)
n (patients)	9	15	17	16
Glucose (mmol/L)	1.7 ± 0.9	1.25 (0.68–3.11)	1.55 (0.43–2.94)	1.57 (1.15–4.13)
Lactate (mmol/L)	2.9 ± 0.9	1.40 (1.11–3.63)	3.41 (1.64–5.50)	2.01 (1.3–5.31)
Pyruvate (μmol/L)	166 ± 47	73.8 (39.0–137.1)	137.1 (86.1–188.7)	80.0 (54.4–197.0)
LPR	23 ± 4	23.3 (13.1–34.3)	24.9 (18.3–33.5)	27.5 (15.6–39.2)
Glycerol (μmol/L)	82 ± 44	53.8 (25.3–202.9)	79.8 (31.7–338.7)	49.9 (23.6–227.3)
Glutamate (μmol/L)	16 ± 16	–	–	–

[a]Reinstrup et al. study [15]
[b]Sanchez-Guerrero et al. study [14]
LPR lactate/pyruvate ratio, *SD* standard deviation, *RI* reference interval (lower-upper values), *VHUH* Vall d'Hebron University Hospital, *ZFM* zero-flow rate method

studies or from patients with intracranial pathology, with the limitations that this implies. The reference values of the different elements or metabolites studied that we have used for years were obtained from neurological and neurosurgical patients, awake and anesthetized, inserting the cerebral catheter into uninjured tissue [15]. In most cases, these patients had benign tumors of the posterior fossa, and the catheter was implanted in an uninjured frontal region without cerebral edema [Table 7.1] [15]. Other authors have reported brain metabolite levels in the normal brains of patients with central nervous system tumors [24], in awake epileptic patients [13, 25], and in patients with spontaneous SAH [26].

Nevertheless, the true reference limits of the different metabolites that we usually monitor in clinical practice are still unknown. Recently, we published the results of an in vitro and a human study in which the reference limits for glucose, lactate, pyruvate, and glycerol were determined in a cohort of 19 patients who were observed twice: while anesthetized and while fully awake [14]. In anesthetized patients, the extrapolation to the zero-flow rate method was used. In awake patients, we employed perfusion at a constant infusion speed of 0.3 μL/min, as recommended by a recent consensus conference on neuromonitoring [27]. The reference intervals reported in this study provide additional support for the thresholds suggested by the most recent consensus conference on MD neuromonitoring [27], highlighting the importance of lactate in brain energetics and raising the need to reconsider traditional definitions of metabolic disturbances observed in neurocritical patients. This study emphasizes the importance of using different thresholds for patients that are awake and those under anesthesia or deep sedation [14]. Table 7.1 summarizes the main results of this study.

7.8 Clinical Indications of Cerebral Microdialysis and Evidence-Based Medicine

Although CMD has been used in the monitoring of patients with epilepsy, brain tumors, and different types of neurosurgical interventions, at present the clinical applications of this technique mainly focus on the neuromonitoring of patients with a severe TBI, SAH, or brain injury of ischemic origin.

In the latest edition (4th) of the clinical practice guidelines of the Brain Trauma Foundation, the authors recognize that the goal of the medical management of severe TBI is to ensure that nutrient delivery to the brain is optimized through the period of abnormal physiology and brain swelling that follows the injury, and that the only way to be assured that this is being achieved to the greatest extent possible is to measure brain metabolites, which provide reassurance that the needs of oxidative metabolism are being met [28]. Another statement is that the use of advanced monitoring techniques, such as CMD, in tandem with ICP and CPP monitoring, adds to the assessment of brain metabolic needs and the effects of therapies to meet them [28]. However, they only offer recommendations (with a level III of evidence) on the use of jugular bulb monitoring of arteriovenous oxygen content difference [28]. Of the 51 new studies on all advanced monitoring tools that are reviewed in this latest edition, methodological limitations eliminate 42, and of the nine remaining, only one refers to MD. This corresponds to the Chamoun study in which it is observed that patients with glutamate levels that tend to normalize within 120 h of trauma have lower mortality than those in which glutamate remains high [29]. Therefore, indications and recommendations on the use of CMD are based only on the result of expert consensus conferences.

In agreement with the conclusions of an expert panel meeting in the Karolinska Institute in Stockholm in 2002, published in 2004 [30], the patients who will derive the greatest benefit from the inclusion of CMD in neuromonitoring are those with a severe TBI or SAH. In both types of patient, the aim of MD monitoring is the same: the early detection of metabolic changes suggesting the development of tissue ischemia and monitoring of the effect of the therapeutic maneuvers applied to treat the ischemia. In TBI, one or more brain catheters should be applied according to the type of lesion. In diffuse lesions, the implantation of a single brain catheter in the right frontal region was recommended. In focal lesions, two catheters were recommended, one in the macroscopically nonlesioned region and the other in the "area of penumbra" (the brain area surrounding a focal lesion, which is considered at greatest risk). The consensus conference concluded that the information that might be provided by placing an additional catheter in an established lesion does not add important information for patient management. In patients with SAH, a single brain catheter was recommended, although it should be implanted in the vascular area at greatest risk. The analytes recommended, and the relative importance of each, in

both entities were as follows: (a) in SAH, glutamate and the lactate/pyruvate ratio and (b) in TBI, lactate/pyruvate ratio, glucose, glycerol, and glutamate.

In the second consensus conference on neuromonitoring in neurocritical patients made by the NICEM (Neuro-Intensive Care and Emergency Medicine), a section of the ESICM (European Society of Intensive Care Medicine) [31], the expert panel concluded that:

- Despite the increase in the application of cerebral microdialysis in the clinical management of patients with a severe TBI, class I evidence on the routine use of this technique is lacking.
- MD is the only technique that allows continuous monitoring of the biochemical characteristics of the extracellular space of the brain parenchyma. This information is much more reliable than any other biomarker obtained from peripheral blood.
- MD can help in the differential diagnosis of the distinct types of nonischemic hypoxia.
- High-resolution CMD allows the recovery of additional substances contained in the extracellular space, such as cytokines, interleukins, and other inflammatory molecules, which will allow a greater understanding of the physiopathology of acute neurological lesions.
- This technique is ideal to obtain direct information on the passage of drugs through the blood–brain barrier and on their metabolic repercussions, which will allow studies of neuroprotective drugs to be more rational and effective.

In 2015, the conclusions of the last consensus statement from the 2014 International Microdialysis Forum were published [27]. In this document, regarding the clinical indications of CMD, the conclusions are very similar to the previous recommendations. The most obvious change is the recommendation of where to place the MD catheter or catheters. In patients with SAH, two situations are considered: (1) when the patient does not present a risk for any specific vascular territory, in which case the catheter would be placed in the watershed anterior cerebral artery–middle cerebral artery territory (frontal lobe) and (2) when the monitoring is implanted in a deferred way in a patient who has deterioration, in which case the catheter should be placed in the vascular territory of risk of infarction [27]. In TBI, a distinction is made between diffuse lesions (in which a single catheter would be placed in the frontal region of the nondominant hemisphere) and focal lesions (in which one or more catheters could be placed, depending on what is of interest to monitor: area of penumbra or macroscopically normal brain tissue) [27]. In this consensus conference, additional recommendations were made about methodology, interpretation of CMD, and core data reporting required in the publication of microdialysis papers [27]. The conclusions of this consensus conference are summarized in Table 7.2.

Table 7.2 Part of the recommendations from the 2014 International Forum on Microdialysis – the 2014 consensus statement [27]

Clinical indications of CMD	
Traumatic brain injury (TBI)	Subarachnoid hemorrhage (SAH)
In *diffuse TBI*: MD catheter in nondominant frontal lobe In *focal TBI:* there are different options for catheter placement that depend on whether the goal is to monitor tissue at risk or normal brain. Multiple catheters are an option in focal TBI.	As a *primary monitoring device* in mechanically ventilated ("poor-grade") patients: catheter location in the watershed ACA-MCA territory (frontal lobe) on the same side as the maximal blood load seen on CT or the ruptured aneurysm. If the blood load is symmetrical, they recommend nondominant frontal lobe placement. In patients with a *secondary neurological deterioration*, catheter location should be guided by local practice to identify tissue at risk. Multiple catheters are an option in SAH.
Tiered approach to the clinical value of substances (TBI and SAH): *Tier 1*: glucose and LP ratio/*Tier 2*: glutamate/*Tier 3*: glycerol	
Methodological recommendations of CMD	
Catheters should be inserted according to local institutional protocols either by twist drill hole, transcranial bolt, or at craniotomy. The first hour of microdialysate collected should not be used for clinical monitoring due to unreliable results caused by insertion trauma and the pump flush sequence. To monitor glucose, pyruvate, lactate, glycerol, and glutamate catheters with a 20- or 100-kDa cut-off are available. A flow rate of 0.3 μL/min with hourly sampling is recommended, which is the flow rate most commonly used in the cerebral microdialysis literature.	
Core data reporting required in the publication of MD papers	
Publication of microdialysis data should include the following information (core data reporting): Catheter type Catheter location based on post-insertion imaging Flow rate Membrane length Perfusion fluid composition Time from ictus to monitoring	
Interpretation of cerebral microdialysis	
Chemistry should be interpreted in the context of the clinical condition of the patient and in conjunction with other monitored parameters including ICP, CPP, $PbtO_2$, PRx, and systemic parameters. Microdialysis is a focal technique. Therefore, brain chemistry should be interpreted according to catheter location in relation to focal injury based on CT/MRI imaging.	

ACA anterior cerebral artery, *$PbtO_2$* brain tissue oxygen, *CMD* cerebral microdialysis, *CPP* cerebral perfusion pressure, *CT* computed tomography, *ICP* intracranial pressure, *LP* lactate/pyruvate ratio, *MCA* middle cerebral artery, *MD* microdialysis, *MRI* magnetic resonance imaging, *PRx* pressure reactivity index

7.9 Limitations and Complications

Among the *limitations* of CMD, it should be noted that it is a local monitoring system, which might not detect metabolic events that take place at points away from the location of the catheter. Also, depending on the duration of the monitoring, local

inflammation phenomena have been described that might hinder the passage of molecules from the interstitial space to the MD catheter [23]. However, it has been confirmed that this phenomenon has no clinical relevance during the first week of monitoring [23]. Another limitation of the technique is the type of molecules that can be determined from the use of catheters with dialysis membranes of 20 kDa. However, this limitation has been largely resolved, since, at present, there are already cerebral catheters equipped with dialysate membranes with pores of 100 kDa. These catheters make it possible to determine larger molecules related to neuroinflammation phenomena and other processes involved in the pathophysiology of certain acute neurological lesions.

The *complication* rate attributed to this monitoring system in the different published series has been much lower than that associated with the placement of an ICP sensor [32]. Brain MD catheters are extremely thin (0.62 mm), which minimizes the possibility of brain injury. No significant hemorrhagic complications or infections attributable to CMD have been described, probably because it is a closed circuit that is not manipulated (except for the exchange of microvials) for the duration of the monitoring. In our series [12], no clinically significant hemorrhages were observed after catheter implantation in 122 implanted MD catheters. In only four of these 122 MD catheters, the follow-up CT scan showed minute blood collections around the tip of the catheter (Fig. 7.6). These findings cannot be considered as true hemorrhagic complications. However, they might affect the validity of the information we obtain from the catheter. In this series, there were no instances of meningitis, empyema, or brain abscess that could be attributed to MD monitoring [12]. Moreover, the rates of complications and catheter malfunction observed after using our percutaneous technique to implant CMD catheters were also very similar to those reported by other studies in which these catheters were implanted using bolts or conventional burr holes [33–35]. Fractures of the catheter or microdialysis membrane are almost always due to poor system manipulation and decrease at the end of the learning curve of each center.

7.10 The Future: Cerebral Microdialysis with High-Resolution Membranes

The appearance of 100 kDa MD membranes (also called “high resolution” membranes) has allowed the recovery, directly from the brain extracellular space in vivo, of larger molecules such as cytokines, interleukins, and matrix metalloproteases, which until now had been detected only in postmortem studies. These molecules are key to understanding and deepening the neuroinflammatory processes that have been observed in the context of the neurotraumatic patient, patients with a massive infarction of the middle cerebral artery, or in other neurocritical patients. These molecules are actively involved in the formation of cerebral edema, disruption of the blood–brain barrier, and in the expression of adhesion proteins and tissue infiltration, events involved in the appearance of secondary brain lesions that can exacerbate the neurological damage of the patient. These membranes have allowed MD

to become a powerful tool for the development of translational research projects in neurosciences and other scientific disciplines interested in a wide variety of analytes.

Despite its advantages, some technical limitations associated with the 100 kDa MD membranes that affect the recovery of larger molecules must be considered in the clinical setting. Although their molecular weights are below the nominal cut-off of the membrane, and therefore are potentially recoverable, each molecule has unique physicochemical characteristics (e.g., tertiary/quaternary structure of the molecule, polarity, and hydrophobicity) that will condition its diffusion through the dialysis membrane. On the other hand, preliminary observations made in our unit by scanning electron microscopy of implanted CMD membranes have objectified depositions and adhesions of biological components (protein exudate) that cover the membrane and occlude the pores (Fig. 7.8). The formation of this bioplate (the biofouling phenomena) could also affect the recovery of the membrane progressively throughout the days in which the catheter is implanted. These findings demonstrate the need to perform recovery experiments for each analyte if the aim is to extrapolate the actual concentration in the brain parenchyma.

The importance of the use of this neuromonitoring technique has become evident in the multitude of recent studies that include MD as a fundamental tool to determine the concentrations of various drugs inside the central nervous system [36–40].

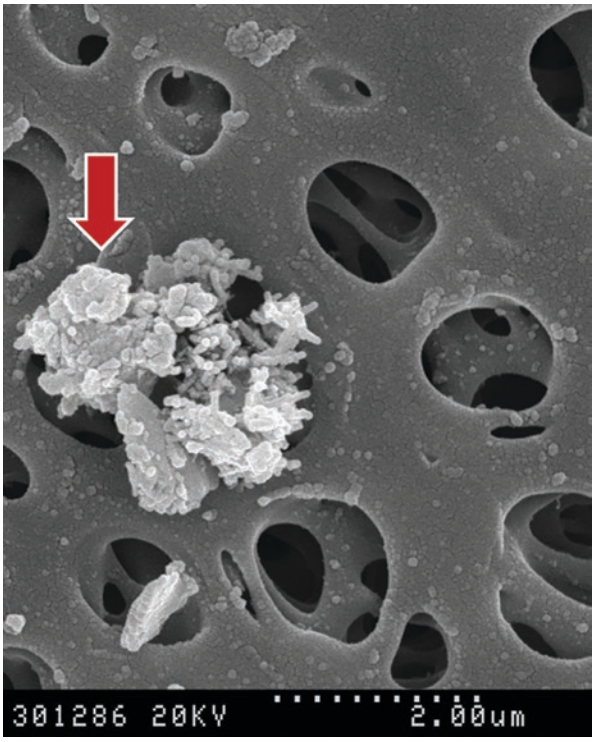

Fig. 7.8 Electron microscopy image showing the pores of an explanted dialysis membrane. Note the debris attached to the surface of the membrane (arrow), which can interfere with the passage of substances through it

7.11 Final Considerations

CMD is an extremely sensitive technique that can provide early metabolic information on the development of a brain lesion. The information provided by this technique is superior to that provided by any other monitoring system. Given its undeniable current position in research, in all probability, its use will become widespread in the clinical setting in the next few years, providing new knowledge on the physiopathology of neurocritical patients, as well as guidance on the more effective and personalized treatment. However, the introduction of this monitoring system involves a learning curve and requires human and technical resources, which currently limit its use to certain neurocritical units.

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Chapter 8
Jugular Bulb Oximetry

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8.1 Introduction

Patients with acute spontaneous or traumatic neurological injuries are susceptible to secondary brain damage. Episodes of hypotension, hypoxia, increased intracranial pressure, and local inflammatory cascades are the main events involved. Minimizing secondary insults is the main objective of the medical team [25]. However, to do so, such insults must first be detected. Older technologies allowed continuous monitoring of systemic variables, including blood pressure and oxygen saturation, which were then applied to brain physiology. Technological developments have allowed the brain to be directly monitored with catheter implantation that permits, in addition to continuous monitoring of intracranial pressure, monitoring of brain temperature, tissue pressure, and, more recently, brain microdialysis [22, 25]. Cerebral venous flow oxygen saturation (SjO2) has been investigated as a neuromonitoring parameter for over 50 years. The first works on jugular bulb oximetry are from 1930 to 1940 [17, 18]. SjO2 currently provides an indirect assessment of brain oxygen use and is used to guide physiological management decisions in a variety of clinical settings [33]. This chapter is an overview of SjO2 monitoring and an update on its clinical applications.

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8.2 Anatomy

The internal jugular veins drain practically all the blood from the brain. The drainage veins of the telencephalic and diencephalic structures direct their contents to the venous sinuses. Superior sagittal sinus, inferior sagittal sinus, straight sinus, and occipital sinus unite at the confluence of the sinuses (Herophili torcular) [15]. From this point, the venous blood is directed to the right and left transverse sinuses and sigmoid. These two sinuses pass through their jugular foramina at the base of the skull and dilate to form the jugular bulb—the dilated cephalic part of the internal jugular vein. A small proportion of effluent brain blood can drain through the vertebral venous plexus, which is most pronounced when in the upright position [35].

The jugular bulb receives drainage from both intracranial and extracranial compartments, and it is located posterolaterally within the pars vascularis of jugular foramen [39, 40]. The tributaries vein include: the middle thyroid vein, superior thyroid vein, lingual vein, facial vein, pharyngeal vein, and inferior petrosal sinus, apart from the vertebral venous plexus, venous plexus of the hypoglossal canal, posterior condylar emissary vein, and veins along the petroclival fissure [41, 42].

Anteriorly, the jugular bulb is limited by the internal carotid artery, cochlear aqueduct, inferior petrosal sinus, meningeal branch of the ascending pharyngeal artery, lower cranial nerves, and posterior meningeal artery. The posterior limits of the jugular bulb include the sigmoid sinus, occipital bone, and facial nerve, while the superior limits of the jugular bulb include the external auditory canal, middle ear, posterior semicircular canal (SCC), vestibule, and internal auditory canal [45, 46].

The upper limit of the jugular bulb is commonly found under the hypotympanum within the middle-ear cavity, and an atypical presentation of the jugular bulb may be visualized as an upward extension of the bulb that invades into the hypotympanum. Sasindran et al. define this extension of jugular bulb presenting in the middle-ear space with a thin or nonexistent bony septum as a high-riding jugular bulb (HRJB), which has been previously subclassified as “with dehiscence” or “without dehiscence.” An alternate definition of an HRJB has been proposed when it is observed above the tympanic annulus or no greater than 2 mm from the IAC. Singla et al. postulated the jugular bulb as high riding when the distance of the summit of the jugular fossa from the round window or IAC was less than or equal to 2 mm or if there is no distance between the jugular fossa and the slit on which the endolymphatic sac opens [47].

8.2.1 Classifications of Jugular Bulb

Shao et al. [52] classified jugular bulbs as (1) grade 1, jugular bulb located less than 1 mm above the lower border of IAC; (2) grade 2, jugular bulb between 1.5 and 3 mm above the lower border of the IAC; and (3) grade 3, jugular bulb greater than

3 mm above the lower border of the IAC. We believe that these anatomical boundaries of the jugular bulb and extent of the bulb itself are not evolving forms, and hence the term "classification" seems to be more appropriate than "grading."

Park et al. subclassified HRJB into two types based on axial CT images: type 1, in which the bulb dome reaches above the inferior part of the round window; and type 2, when the dome is higher than the inferior edge of the IAC. It is apparent that there is no consensus on the exact definition of HRJB, and multiplanar structures that define the critical microsurgical boundaries (SCC, IAC, round window, and endolymphatic sac) of the skull base cannot often be analyzed based only on limited standard axial CT sections of temporal bone, without reconstruction [39].

The current proposal of the Manjila and Semaan classification accounts for the relationship of the IAC, posterior SCC, and presence or absence of dehiscence into the middle ear or IAC. This straightforward and practical classification system with easy subcategorization based on local skull base landmarks would be extremely useful in preoperative planning of surgical corridors and thus achieve satisfactory clinical outcomes.

8.2.2 *Manjila and Semaan Classification of Jugular Bulb Location*

Type 1 No jugular bulb
Type 2 Below inferior margin of posterior SCC
Type 2a Without dehiscence into the middle ear
Type 2b With dehiscence into the middle ear
Type 3 Between inferior margin of posterior SCC and inferior margin of IAC
Type 3a Without dehiscence into the middle ear
Type 3b With dehiscence into the middle ear
Type 4 Above inferior margin of IAC
Type 4a Without dehiscence into the IAC
Type 4b With dehiscence into the IAC
Type 5 Combination of dehiscence

8.2.3 *Development of the Jugular Bulb*

The jugular bulb develops during childhood, particularly when the child has gained the ability to stay upright around 2 years of age. The jugular bulb continues to develop through childhood and becomes stable in adulthood. Once an erect posture is attained in life, the ascending negative pulse waves originating from the right atrium are postulated to be transmitted rostrally into the jugular sinus leading to the dilation or formation of the jugular bulb. Consequently, an HRJB is also considered

a risk factor for jugular bulb dehiscence. Because there is growth and plateauing of jugular bulb development with age, there is debate on the role of temporal bone pneumatization and the orientation of SCCs in determining the location of the jugular bulb.

8.3 Normal and Physiopathology

The concept of obtaining information on brain oxygen status from measuring oxygen saturation in mixed cerebral venous blood is based on the following assumptions derived from the Fick principle. Fick's principle states that the amount of oxygen transported to a tissue compartment minus the amount of oxygen consumed is equal to the amount of oxygen exiting this tissue compartment through the venous circulation. Therefore, jugular bulb blood saturation is related to cerebral blood flow (CBF), arterial saturation, brain oxygen extraction, and cerebral oxygen metabolism (CMRO2) (Spiss 1998; [48]). In other words, the cerebral oxygen supply (DO2) is described by the following equation (CaO2 arterial oxygen content):

$$\mathrm{DO2} = \mathrm{CBF} \times \mathrm{CaO2}$$

Where CaO2 = (% saturation × 1.34 × Hb) + (arterial or venous O2 tension × 0.003).

While brain oxygen consumption (CMRO2) is described by the equation (CjvO2 jugular venous blood oxygen content):

$$\mathrm{CMRO2} = \mathrm{CBF} \times \left(\mathrm{CaO2} - \mathrm{CjvO2}\right)$$

The difference in oxygen content between arterial and jugular venous blood is expressed by the term (CaO – CjvO2) or AjvDO2. Rearranging the above equation, it is evident that:

$$\mathrm{AjvDO2} = \mathrm{CMRO2} / \mathrm{CBF}$$

Usually, AjvDO2 is stable in 4–8 mL O2/100 mL blood [44, 55]. If CMRO2 remains constant, changes in AjvDO2 should reflect changes in CBF. If AjvDO2 is ±4 mL O2/100 mL blood, the oxygen supply is assumed to be greater than the demand (i.e., exuberant). An AjvDO2 ~ 8 mL of O2/100 mL of blood suggests that demand exceeds supply (i.e., ischemia) [48]. As the hemoglobin (Hb) level is practically constant between arterial and venous circulation and dissolved oxygen is negligible, it can be observed that CaO2 varies with saturation. Thus, SjO2 is a function of arterial saturation, CMRO2, and CBF. There is a debate about what the normal range of SjO2 is, but most studies assume that 50–54% is the lower limit of normal and 75% is the upper limit. Different methods for defining normality have caused controversy over the exact lower limit of normal SjO2, with some authors assuming 50% [21, 53] and 54% [7, 8, 31]. None of them are wrong, as shown in a recent

article comparing SjO2 monitoring with brain tissue oxygenation (PtiO2) [27], where PtiO2 values of 8.5 ± 11.0 mmHg (although with large variability) corresponded to 50 ± 54% SjO2 values.

It is noteworthy that in certain pathological situations, such as cerebral infarction, Sjv02, or AjvDO2 itself may not accurately reflect the presence of cerebral ischemia or hypoxia. With the onset of cerebral infarction, regional CMR02 may be decreased, leading to normal Sjv02 or AjvDO2, despite substantial impairment of cerebral perfusion. In such cases, the determination of the lactate oxygen index is a valuable complement to jugular venous bulb oximetry. It is a measure of the ratio between the amount of anaerobically metabolized glucose and the amount that is aerobically metabolized.

The lactate oxygen index is calculated as follows: lactate oxygen index (LOI): –(arterial–jugular bulb lactate concentration)/AjvDO2. If the LOI is less than 0.08, a normal AjvDO2 indicates that the brain is flow coupled with metabolism. If this number increases above 0.08, ischemia is likely to be present [49]. The extent of the impact of a given brain region on Sjv02 depends on the size of that particular region and its regional CMR02. Both factors determine the absolute amount of oxygen extracted from the arterial blood.

Therefore, small brain regions with high CMR02 can contribute as much as large brain regions with a lower CMR02 to the total amount of oxygen that is consumed during aerobic metabolism. These considerations are of great importance when interpreting changes in Sjv02 and their relationship to clinical events. In general, monitoring of Sjv02 is useful whenever we expect a mismatch between oxygen supply and consumption, which may be short-lived or even avoided if recognized in advance. Some situations where there is a mismatch between supply and consumption are:

- Oxygen supply drop: Cerebral ischemia: systemic hypotension, increased intracranial pressure, vasospasm, hyperventilation, internal carotid artery occlusion (for intraoperative monitoring situations)
- Drop-in arterial oxygen content: hypoxemia (ARDS), anemia, carbon monoxide poisoning, and hemoglobinopathies
- Increased consumption (metabolism): Seizure and hyperthermia

8.4 Which Side to Choose?

The choice of which cannular jugular bulb can potentially influence outcomes. The jugular bulb cannot be assumed to contain exclusively cerebral venous blood, as it may be contaminated by extracranial drainage. According to Shenkin et al. [54], in eight patients without cerebrovascular lesions in which dye was injected into the external carotid artery demonstrated that up to 6.6% (with an average of 2.7%) of blood in the jugular bulb was derived from extracranial sources. This is because the frontal veins and emissary veins drain into the sagittal sinus beyond the connection

of the cavernous sinus to the sigmoid sinus and the jugular bulb through the petrous sinuses [43]. The primary source of potential contamination is the facial vein that joins the internal jugular vein a few inches below the jugular bulb. Experiments show that the rate of blood withdrawal from the jugular bulb affects the composition of the sample. A rate of 1 ± 2 mL per minute is ideal so that venous blood is not aspirated from the facial vein [43].

It is observed that the composition of the jugular bulbs is not equal. Cortical tissue drains into the superior sagittal sinus, while subcortical tissue drains into the rectum sinus. These join together to form the confluence of the breasts (Torcular Herophili) that divides into the two transverse sinuses that eventually drain into the jugular bulb through the sigmoid sinuses. The mixing of blood from the cortex and deeper brain regions is incomplete; the lateral sinus is more significant to the right in 62%, left in 26%, and equal in 12% of individuals [23]. In an autopsy study, Gibbs et al. [17] found that blood from subcortical areas draining from the right sinus tended to flow to the left lateral sinus, while blood from cortical tissue draining from the sagittal sinus flowed mainly to the right lateral sinus. Shenkin et al. [54] suggested that two-thirds of the contents of the internal jugular vein are from the ipsilateral hemisphere and one-third from the contralateral hemisphere. Simultaneous sampling of right and left jugular bulbs in healthy subjects showed that oxygen saturation at the level of the internal jugular vein is equal on both sides [18].

On the other hand, according to Stoccheti et al., in a study with 32 patients with head trauma, in which both jugular bulbs were cannulated, and 171 blood samples were collected. Differences in the saturation of parallel samples were approximately 5%. Probably, in healthy individuals, there is no difference in saturation between the right and left sides, but there are differences in patients with head trauma [57]. In clinical practice to test the dominant side, compression of the right and left jugular vein can be performed and to evaluate that it generates a more significant increase of intracranial pressure [1, 11]. The side with the highest increase in ICP drains most of the blood and thus allows SjO2 monitoring of the largest vascular territory of the brain. If there is no difference between the two sides, the right side is commonly used in diffuse lesions, as it is more likely to be the dominant anatomical side [29]. In diffuse lesions, other authors recommend measuring the jugular foramen dimensions to choose which side to cannulate [34, 38].

8.5 Cannulation Technique

Retrograde cannulation of the internal jugular vein is a simple and safe procedure in experienced hands [20]. The jugular vein may be punctured more distally between the two heads of the sternocleidomastoid muscle [37] or more proximal at the cricoid ring level [1]. The patient is positioned horizontally, always aware of the ICP values so that they do not exceed 20 mmHg, if possible. The head should be laterally contralateral to the side of the puncture and slightly deflected. Routine antiseptic measures, as with all other invasive catheterization techniques, are required. The

carotid artery is palpated medially to the sternocleidomastoid muscle at the lower edge level of the thyroid cartilage. Lateral to the carotid artery, a 21 G needle with a coupled syringe containing normal saline is advanced at a 30° angle toward the ipsilateral external acoustic meatus. Blood aspiration should occur at a depth of approximately 4 cm from the skin. A 5 fr (french) introducer is placed using the Seldinger technique and fixed in position. After a preinsertion calibration, the fiber optic catheter is inserted through the introducer into the internal jugular vein and advanced to the base of the skull (approximately 15 cm). After feeling the resistance of reaching the bulb, the catheter is pulled for about 1 cm. To prevent increases in intracranial pressure that occur when the head is down (to facilitate puncture), there is a description of cannulation in the raised head position with the aid of a needle with an in situ Doppler probe [50].

The catheter tip should be above the C1/C2 disc to minimize facial vein contamination; therefore, the position of the catheter tip should be checked by X-ray to ensure accurate measurement and reduce complications. An over penetrated lateral radiograph is the simplest and most reliable X-ray type [24]; alternatively, anteroposterior radiographs may be preferred [2].

8.6 Clinical Indications

8.6.1 General Principles

Jugular bulb oximetry is the first continuous and bedside brain monitoring method estimating cerebral perfusion adequacy. The fact that most of the regulatory mechanisms of cerebral perfusion are failing in patients suffering from severe neurologic lesions explains the growing interest in monitoring cerebral perfusion adequacy in these critically ill patients. Moreover, brain ischemia has been observed in not less than 80% of all patients dying from severe head injury, illustrating the frequent occurrence of brain ischemia after severe head injury.

An important mainstay of the intensive management is accordingly to avoid the occurrence of cerebral ischemia. A distinction is often made between primary and secondary ischemia, with primary ischemia considered as resulting from the ischemic insults that occurred at the scene of the accident and secondary ischemia as the ischemic insults occurring during the further intensive care management. To avoid secondary ischemia during the intensive care management, monitoring of the cerebral perfusion state seems obligatory [36].

8.6.2 Outline in Detecting Physiological Insult

In acute brain injuries, multimodal monitoring is critical. These include pulse oximetry, electroencephalogram, intracranial pressure, blood pressure, tissue oxygen pressure, cerebral perfusion pressure, and not least oxygen saturation of the jugular

bulb. This is an integral component with significant contributions to clinical management, driving effective therapeutic strategies. SjO2 monitoring has applications in neurosurgery, neurointensive, cardiac surgery with cardiopulmonary bypass, and hypothermia [56]. Jugular venous oxygen is an indirect assessment of brain oxygen use. In a simplified way, when demand exceeds supply, the brain extracts more oxygen, resulting in lower oxygen saturation of the jugular bulb. If cerebral blood flow (CBF) decreases, a point is finally reached at which the brain can no longer fully compensate for decreased CBF by an additional increase in oxygen extraction. At this point, oxygen consumption decreases, and anaerobic metabolism with lactate production occurs when brain oxygen supply exceeds demand, jugular bulb oxygen saturation increases [33, 48]. If CMRO2 increases without an increase in CBF, the brain draws more oxygen from the blood, and there is a decrease in oxygen content of venous blood saturation of the brain. Jugular venous oxygen saturation is usually approximately 55–75% [19], which is lower than mixed venous systemic oxygen saturation.

If hemoglobin concentration is stable, arterial oxygen saturation is approximately 100%, and the amount of dissolved oxygen in plasma is physiological, SjVO2 is a direct correlation with AjvDO2. As SjVO2 is a global measure, SjVO2 monitoring has high specificity but low sensitivity to ischemia, that is, normal saturation may not reflect focal areas of ischemia, but low saturation is indicative of low flow. If SjVO2 is less than 50%, therapies directed at increasing brain oxygen supply and decreasing demand should be initiated. The decrease in hemoglobin (Hb) to deficient levels resulted in a decrease in CMR02 with an unchanged Sjv02 [9].

This observation indicates that cerebral oxygen extraction may be limited in these situations, that is, decreased Hb causes a decreased oxygen supply to the brain that cannot be compensated for by extracting more oxygen from arterial blood. Briefly, the main objective is to detect and treat cerebral hypoperfusion to minimize secondary insults. In acute brain injury, low values are indicative of increased cerebral oxygen extraction as a result of systemic arterial hypoxia, low cerebral blood flow from systemic hypotension, vasospasm, or increased intracranial pressure with low cerebral perfusion pressure (CPP). Chan et al. [5] demonstrated a reduction in SjO2 when PPC falls below 70 mmHg. Fever and seizures (which may not be correctly diagnosed in sedated patients) also result in low SjO2 due to increased brain metabolic needs. On the other hand, an increase in SjO2 may be the result of hyperemia [4] or failure of oxygen extraction. Another possibility exists in patients with high SjO2 who may have a very low CPP due to a high ICP as a preterminal event with arterial blood deviation [12] Fig. 8.1.

The fact that SjvO2 provides only information about global and nonregional disorders of brain oxygen consumption may lead to misinterpretation of typical SjvO2 values. In cases where posterior circulation is compromised, the brainstem oxygen supply is threatened. Posterior circulation contributes a small amount of drainage to the jugular bulb, and impaired brainstem oxygenation may go unnoticed with normal SjvO2 levels.

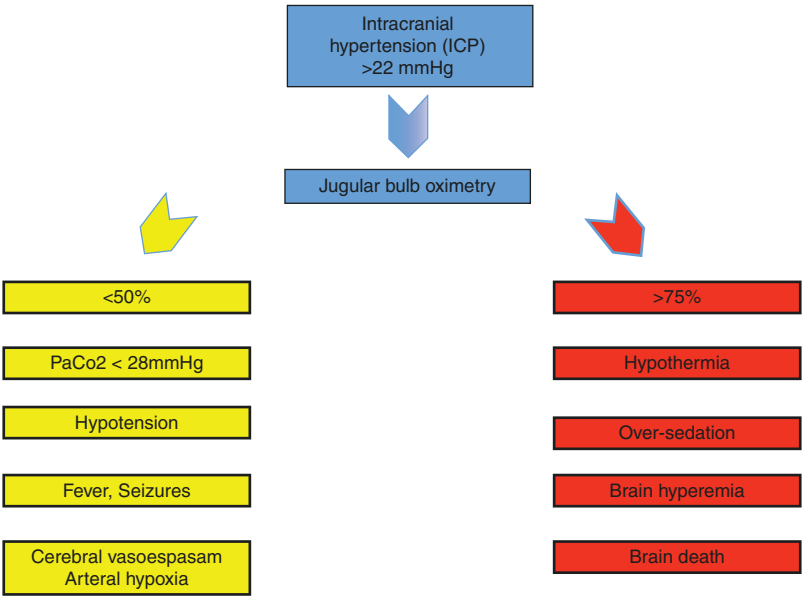

Fig. 8.1 Flowchart for evaluating jugular bulb oximetry results

8.6.3 Head Trauma

Traumatic brain injury (TBI)—the "silent epidemic"—contributes to death and disability worldwide more than any other traumatic insult. Sixty-nine million (95% CI: 64–74 million) individuals are estimated to be victims of head injury annually. One of the leading causes is auto-accidents. The proportion of TBIs resulting from traffic crashes is highest in Africa and Southeast Asia (both 56%) and the lowest in North America (25%). The overall incidence of TBI per 100,000 people is highest in North America (1300: 100,000) and Europe (1012: 100,000) [14]. According to Lewis et al. [31] in patients with acute blunt head injury, it is possible to safely detect episodes of cerebral venous desaturation mainly caused by hypocapnia in 45% of all observations, hypoperfusion in 22%, increased ICP in 9%, or a combination of any of these events by 24% [31]. These results demonstrate that these patients are at risk of a mismatch between oxygen supply and consumption and that most of the triggering factors can probably be avoided. Early monitoring after the initial injury is essential because many subsequent events occur in this early period. The most unstable period is usually in the early days when many episodes of jugular bulb desaturation were demonstrated. Eighty-three percent of these events occurred within 48 hours of injury [12, 13]. CBF is at its lowest level during the first 12 h after injury [3]. Many studies consider that CPP is more critical than ICP and that CPP should be maintained above 70 mmHg to prevent cerebral ischemia, evidenced by a low SjO2 [5].

Besides, as acute events noted, the brain's self-regulating mechanisms do not function properly, and SjO2 monitoring becomes an even more critical tool for guiding therapy. An example is a fact that mannitol may initially reduce brain oxygenation. This can be detected early by SjO2 monitoring and treated when PaCO2 is increased [28]. In addition to confirming the deleterious effects of low CPP or systemic desaturation, SjO2 can be used to guide interventional therapies. The initial active treatment for a high ICP is to "hyperventilate" the patient to lower PaCO2 levels and thus decrease ICP via cerebral vasoconstriction. It is impossible to know the PaCO2 threshold for each patient before cerebral ischemia occurs unless SjO2 is monitored [49]. This is because an individual's PaCO2 threshold depends on their CPP, steady-state PaCO2, and comorbid factors such as atherosclerosis. SjO2 monitoring allows therapeutic hypocapnia until SjO2 is near the lower limit of normal.

Extreme hyperventilation is harmful in severe intracranial lesions. Cruz et al. showed a reduction in SjO2 when hypocapnia was induced for ICP control. Therefore, hyperventilation as a therapeutic maneuver is a strong indication for SjO2 monitoring. In its absence, hyperventilation with a minimum PaCO2 is restricted to 30 mmHg [32]. We point out that in recently published guidelines, prophylactic hyperventilation is not recommended, and there is no evidence to justify that jugular bulb oxygen saturation as an auxiliary method for how hyperventilation can be performed. Although there is no evidence for measuring SjVO2, there is no contrary evidence either. Another author describes hyperoxia as another therapeutic maneuver to allow the lowest possible PaCO2, preserving global oxygenation as monitored by SjO2. Other studies do not corroborate such measures, and recent studies are demonstrating that hyperoxia increases mortality in head injury patients [10].

8.6.4 Subarachnoid Hemorrhage

One of the leading causes of morbidity and mortality in subarachnoid hemorrhage (SAH) is vasospasm. Patients suffering from intracerebral or subarachnoid hemorrhage had a 90% chance of developing episodes of cerebral venous desaturation during their disease, as opposed to just 50% in head trauma patients [49]. Despite this, jugular venous oximetry is occasionally used in aneurysmal subarachnoid hemorrhage as a tool to identify changes in cerebral oxygen metabolism. The use of transcranial Doppler (DTC) to diagnose vasospasm has become quite common. One of the difficulties with TCD is distinguishing hyperemia from vasospasm, and the management of these two conditions is markedly different. SjVO2 may be used in this setting because patients with hyperemia would demonstrate marked venous oxygen saturation, while in severe vasospasm, saturation would be decreased [59]. Von Helden et al. demonstrated that SjvO2 could be valuable for monitoring cerebral ischemia in SAH. They described a patient who had a 60% SjvO2 initially with a fall to 55% when TCD demonstrated an increase in flow velocity consistent with

vasospasm. Later, the flow velocity increased. Further, it was noted that SjvO2 fell below 50%.

The patient suffered a heart attack and died [58]. Fandino et al. also confirmed the ability of the jugular bulb oximetry to detect cerebral oxygenation patterns in vasospasm and differentiate them from nonvasospastic conditions that may also occur in SAH. They evaluated SjvO2 before, during, and after intra-arterial papaverine infusion, with or without balloon angioplasty, in patients with symptomatic vasospasm. Twenty-three vascular territories in 10 patients were treated. A significant improvement in SjvO2 was observed in all cases, with an improvement in brain oxygenation after endovascular vasospasm treatment ($P = 0.005$).

In their study, there was no attempt to use jugular venous oximetry as an aid to detect or predict vasospasm. Few studies have been performed demonstrating the AVDO2 baseline observed correctly in SAH before vasospasm, and the results were neither consistent nor clear. Gibbs et al. studied 50 normal young men and found a SvjO2 average of 61.8%, with a range of 55–71%. Kawamura et al. [26] studied nine patients with SAH and demonstrated that in the prevasospasm stage, the brain was relatively hyperemic, with CBF close to regular and smaller than usual CMRO2, compared to the vasospasm stage when CMRO2 decreased in parallel with CBF. The study by Heran et al. confirmed the jugular oximetry ability to predict the onset of clinical vasospasm in a small group of patients. In the four patients who developed vasospasm, a significant increase ($P < 0.001$) of cerebral AVDO2 was demonstrated on average, 26 hours before clinical changes were noted. This was not observed in patients who did not develop clinical vasospasm.

8.6.5 Ischemic Stroke and Children

In patients with an ischemic stroke, there are few studies with inconclusive results, and routine monitoring of venous saturation of the jugular bulb is not indicated. At present, there is no evidence to support that monitoring SjvO2 in children would have any additional prognostic benefit over other established prognostic predictors such as cerebral perfusion pressure, and GCS. Given the potential risk in children (thrombosis, infection, etc.), the benefit of using SjvO2 monitoring is undetermined. Additional studies on the overall value of monitoring jugular venous saturation to guide therapy in children are needed before widespread use is recommended.

8.6.6 Jugular Bulb Oximetry and Clinical Outcomes

SjO2 abnormalities were associated with a poor outcome compared with patients who did not demonstrate this physiological disorder. In a study of more than 100 patients admitted to intensive care after traumatic brain injury, Gopinath et al. reported a correlation between SjvO2 desaturation and final neurological prognosis

in case of brain injury. A poor final neurological prognosis was obtained in 90% of patients with recurrent SjvO2 desaturation events. In patients who had no SjvO2 desaturation events, the poor neurological prognosis was found in only 55% of these patients [21]. Cormio et al. reported that in 450 patients with severe head trauma treated at the intensive care unit, 25.6% of patients with increased SjvO2 had a better outcome (functional recovery, moderate disability), 25.6% recovered with severe disability, and 48.8% died or remained a vegetative state. In other prognostic models, as shown by Senapathi et al. [51]. Desaturation episodes measured in the jugular bulb and FOUR scores were considered significant predictors of mortality. Sharf and El-Gebali also reported that GCS ($P = 0.008$) and SjvO2 ($P< 0.001$) were significant predictors of mortality.

In a series of 50 patients with severe head trauma followed in 42% by multiple injuries, who were promptly treated were transferred to hospital, some aspects such as age, tomographic findings and clinical severity (as judged by the Glasgow Coma Scale, pupillary reactivity, and APACHE score), showed no statistically significant correlations with the outcome. Only the occurrence of two or more episodes of jugular venous desaturation correlated with clinical outcome. The nature of the population studied, and the relatively small number of patients may, however, have influenced the results. On the other hand, high values of SjO2 were also associated with poor results [16].

In general, even though studies in adults show the importance of measuring jugular oximetry mainly in trauma and subarachnoid hemorrhage, there are methodological limitations of the studies that do not allow absolute conclusions to use this monitoring method as a prognostic tool. It is observed that the more extensive discussion related to the diagnostic methods and prognostic estimation is influenced by the actions taken from the obtained results.

8.7 Complications

As with any invasive procedure, iatrogenic lesions may occur, the incidence of which is reduced if standard cannulation techniques are followed. The main complications relate to puncture and length of stay of the catheter. Some studies reported increased intracranial hypertension, but such findings were not corroborated. In a study with pediatric patients, Goetting measured intracranial pressure in 28 patients with jugular bulb catheters and found that neither cannulation nor the presence of in situ catheters further increased pressure [20]. In an observational study of 44 patients with jugular bulb catheters, Coplin et al. [6] concluded that complications related to catheter insertion were rare and clinically insignificant and that the risk of catheter-related bacteremia was negligible. However, on ultrasound, the incidence of subclinical thrombosis of the internal jugular vein after monitoring the jugular bulb catheter was up to 40% with in situ catheters for up to 6 days. Patients with proven thrombus had no symptoms.

Regarding infection in a study by Latronico et al., 73 catheters used in the study population and 11 (15%) cultures revealed colonization (Staphylococcus epidermidis, nine patients, Staphylococcus aureus, two patients). In two patients, *S. aureus* bacteremia was documented; however, microorganisms were isolated in the jugular and subclavian vein catheters [30]. In a risk balance, considering insertion complications and invasive catheter-related infections, monitoring the jugular bulb oximetry is a safe procedure with a low infection rate.

8.8 Conclusions

There is abundant evidence to support the fact that physiological insults secondary to the injured brain result in further brain damage. Monitoring jugular bulb saturation provides early warning of cerebral ischemia due to systemic disorders such as hypotension and hypoxia, and allows therapeutic maneuvers to be performed safely without inducing cerebral ischemia. The benefits far outweigh the risks associated with the technique. After years of enthusiasm, interest in jugular saturation has waned, and more modern methods such as tissue oxygen monitoring are now available. Jugular saturation monitoring has low sensitivity, with the risk of losing low saturation but high specificity. In addition, it is inexpensive when used with intermittent sampling. SjO2 monitoring should be considered, mainly if associated with other diagnostic methods such as ICP monitoring, transcranial Doppler, PtiO2 monitoring, brain microdialysis as well as imaging methods (tomography and resonance). In this context, the final neurological damage represented by cerebral ischemia may have minor clinical consequences.

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Chapter 9
Transcranial Doppler: Practical Applications

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9.1 Introduction

Transcranial Doppler (TCD) was developed in Switzerland by Aaslid et al. [1]. The technique uses a low-frequency probe to evaluate cerebral hemodynamic (2 MHz) [2, 3]. The method is noninvasive and cost-efficient and can be performed at bedside with the possibility of monitoring in real time the hemodynamic changes in different diseases and its response to therapy. TCD is used not just for clinical purposes. Also in clinical research, it has been used as a valuable tool to study cerebral hemodynamic's physiology and pathophysiology [1, 4].

The main clinical applications of TCD in child and adults are as follows:

- Study of the functional aspects of cerebral circulation including use of reactivity tests such as breath-holding test (reactivity to CO_2), cerebral perfusion pressure estimation [5, 6]
- Monitoring of cerebral hemodynamic in specific pathologies: vasospasm following subarachnoid hemorrhage (SAH), traumatic brain injury, and intracranial hypertension secondary to acute brain injury [7, 8]
- Evaluation of patients with cerebrovascular diseases: detection of intracranial stenosis, evaluation of collaterals, response to reperfusion therapies, detection of spontaneous embolism, and evaluation of hemodynamic repercussion of arteriovenous malformations [3, 9]

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- Evaluation of the cerebral hemodynamic impact of systemic diseases (e.g., sepsis and liver failure) [10]
- Evaluation of sickle cell disease to determine the stroke risk [11]
- Assessing and confirming cerebral circulatory arrest in brain death [12]

9.2 Technical Aspects of TCD

The low-frequency probe used in TCD passes through the cranial bone window reaching different depths. Reflected wave of the ultrasound represents red blood cell speed and is converted into a velocity graph with systolic and diastolic velocity (SV and DV) that are the products of the cardiac cycle during the time (Fig. 9.1) [13, 14].

To assess intracranial and extracranial vessels of cerebral circulation, the following windows (with respective vessels insonated) are used in a TCD exam (Fig. 9.2) [15].

- Temporal window: middle cerebral artery, anterior cerebral artery, distal carotid artery, anterior, and posterior communicating artery
- Orbital window: ophthalmic artery, carotid siphon (lower limb, genu, and upper limb), and homolateral anterior cerebral artery
- Transforaminal window: the distal portion of vertebral arteries and basilar artery
- Submandibular window: the distal portion of the internal carotid artery

Arteries are registered at 2 mm intervals [2, 15]. Artery is then identified through the chosen window according to the angle of probe, the direction of the signal, depth, and pattern of the spectral wave [16, 17]. Table 9.1 shows the classification of different arteries according to the characteristics mentioned above.

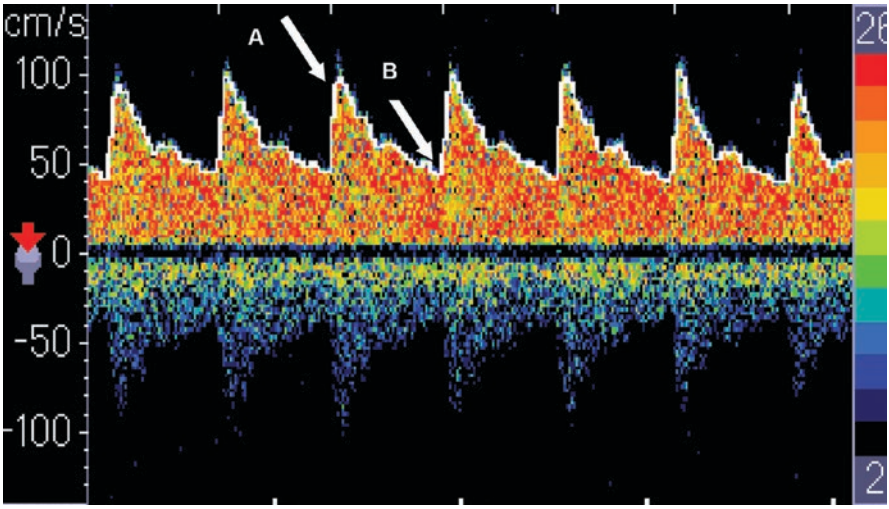

Fig 9.1 Spectral wave graph with systolic peak and end-diastolic velocity (A & B, respectively)

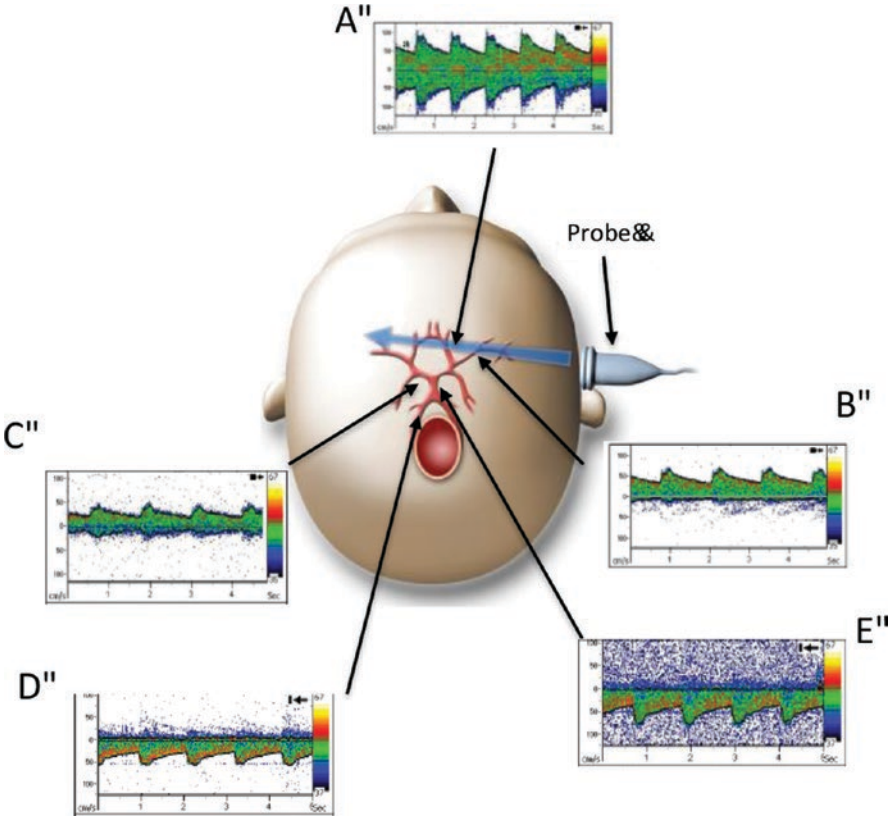

Fig. 9.2 Circle of Willis and vessels insonated by the transtemporal and suboccipital window. (a) Anterior cerebral artery (negative waveform); (**b**) medium cerebral artery, (**c**) posterior cerebral artery; (**d**) vertebral artery; and (**e**) basilar artery

Table 9.1 Main TCD parameters of the basal arteries

Artery	Window	Depth (mm)	Flow direction	Resistance	Mean velocity (cm/S)
$ICA_{extracranial}$	Retromandíbular	45–50	Retrograde	Low	21–39
MCA	Transtemporal	30–65	Orthograde	Low	43–67
ACA	Transtemporal	60–75	Retrograde	Low	39–61
PCA (P1)	Transtemporal	60–70	Orthograde	Low	29–49
PCA (P2)	Transtemporal	60–70	Retrograde	Low	30–50
BA	Transforaminal	80–120	Retrograde	Low	31–51
VE	Transforaminal	60–75	Retrograde	Low	28–48
OA	Transorbital	45–55	Orthograde	High	16–26
ICA_{siphon}	Transorbital	65–80	Bidirectional	Low	30–52

ICA, internal carotid artery; MCA, medium cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; VA, vertebral artery; OA, ophthalmic artery

9.2.1 Hemodynamic Index Evaluated by TCD

The índices evaluated by TCD are obtained through the analysis of the different parts of the wave spectra, which are further described in Table 9.2. These índices are used to characterize the normal and pathological patterns of the cerebral circulation. The most important are: mean velocity (MV), systolic velocity (SV), diastolic velocity (DV) pulsatility index (PI), resistance index (RI), Lindegaard index (LI), and Soustiel index (SI) [15, 16].

Mean velocity is one of the main parameters analyzed and is calculated by the formula: MV = SV + (DV × 2)/3 [17]. Mean velocity changes according to some physiological variables such as age, gender, temperature, partial pressure of CO_2, mean arterial blood pressure, hematocrit, pregnancy, and among others. Mean velocity is also influenced by some metabolic states like infection and the use of drugs such as anesthetics/sedatives. Usually, MV increases within the first 10 years of life and decreases after that during life [18, 19].

Pulsatility index is the relation of systolic, diastolic, and mean velocity and may represent the cerebral blood flow resistance in some circumstances with no impairment in cardiac output. The formula calculates the pulsatility index: SV -DV/MV with average values among 0.6–1.2 [20]. In stenosis or occlusion of the proximal portion of the cerebral circulation (extra or intracranial), the PI decreases in segments distal to the occlusion, in a pattern described as low resistance (blunted peak systolic and diminished SV/DV difference due to arteriolar vasodilatation). On the other hand, distal occlusions of cerebral circulation lead to an increase in PI due to increased resistance in proximal vessels caused by the occlusion. Cerebrovascular diseases with high flow, such as arteriovenous malformation, may determine high flow velocity with low vascular resistance as evaluated by PI, which is usually below 0.5 [21, 22]. The PI may also reflect changes in intracranial pressure (ICP) with an increase of ICP above the limits of cerebral compliance; the cerebrovascular resistance starts to increase with increasing in PI [23].

The increase in cerebral blood flow velocity (CBFV) can be secondary to focal stenosis or secondary to a global hyperdynamic state (e.g., hyperemia). In order to differentiate both conditions, it can be performed the ratio of intracranial/extracranial artery's velocity, which is named Lindegaard index (LI). LI ≥ 3 means that

Table 9.2 Hemodynamic index

Index	Formula
Medium velocity (MV)	MV = SV + (DV × 2)/3
Pulsatility index (PI)	PI = SV – DV/MV
Resistance index (RI)	RI = SV – DV/SV
Lindegaard index (LI)	LI = MCA MV/$ICA_{extracranial}$ MV
Soustiel index (SI)	SI = BA MV/VA MV

MCA, medium cerebral artery; BA, basilar artery; VA, vertebral artery; SV, systolic velocity; DV, diastolic velocity; MV, mean velocity

there is high velocity in the intracranial vessel without a parallel increase in the feeding extracranial artery that corresponds to focal stenosis. LI < 3 means that both intracranial and extracranial vessels have increased in CBFV that is compatible with hyperemia [24, 25]. There is another indix applied to posterior circulation with the same principles of LI that is called the Soustiel index, and represents the ratio of the basilar artery and extracranial vertebral artery. Like LI, SI is applicable to detect posterior circulation vasospasm, and the cut-off value is 2 (values >2 means basilar vasospasm). Both indexes are important not only to confirm the diagnosis but also to evaluate the severity of the disease (Table 9.2). [25].

9.2.1.1 Vasomotor Reactivity Tests

Vasomotor reactivity (VMR) tests the capacity of arterioles to vasodilate in response to external stimuli [26]. One stimulus that can be used is the breath-holding or apnea maneuver that calculates the breath-holding index (BHI). The mean velocity calculates the index before breath-holding (baseline) and at the end of 4 s of breathing after 30 s of breath-holding [16, 26, 27] (Formula 9.1).

When BHI is >0.69 means that the VMR is preserved, and values below this cut-off value mean impairment of VMR [26]. Impairment of VMR may represent an increased risk of ischemic lesions secondary to the hemodynamic mechanism [28].

9.2.1.2 Noninvasive Estimation of Intracranial Pressure

Studies have demonstrated that the TCD measurement of CBFV is an alternative noninvasive method to estimate the intracranial pressure (ICP) with good positive predictive value [29]. Three methods can be used to try to estimate ICP: (1) methods based on PI; (2) methods based on noninvasive calculation of cerebral perfusion pressure (nCPP); and (3) methods based on complex mathematical models [30].

PI can correlate positively with increases in ICP and may be used to monitor ICP. However, PI is influenced by many other parameters arterial blood pressure—ABP (ABP, CO_2, cerebrovascular resistance). Thus, in some circumstance, the increase in PI does not necessarily reflect an increase in ICP, and that is the reason why this method could not be replicated in many studies [30]. The methods that use nCPP mainly estimate the relation among the ABP and CBFV in especial diastolic and medium flow velocity. These methods were studied with different accuracy values. Finally, the methods that use more sophisticated mathematical models to

$$BHI = \frac{CBFV_{baseline} - CBFV_{end}}{CBF_{baseline}} \times \frac{100}{\text{Seconds of breath-holding}}$$

Formula 9.1 Breath Holding index formula; CBFV, cerebral blood flow velocity

estimate ICP use transfer function analysis of the relation of ABP and CBFV to predict ICP [30].

The estimation of noninvasive cerebral parameters as ICP and CPP has been extensively investigated. This noninvasive approach is useful for patients with contraindication to invasive procedures (e.g., hepatic insufficiency with coagulopathy) and also may help in the indication of invasive monitoring [23]. As TCD is a nonexpensive exam with real-time resolution and portability, it seems to be a good option for noninvasive studies. However, the different methods still have a wide confidence interval of results in comparison with invasive ICP (especially PI method), and further validation should be carried out to be applicable for clinical practice [30].

9.3 Subarachnoid Hemorrhage (SAH)

Patients with SAH may have changes in blood flow and metabolic alterations in the brain that may lead to increased intracranial pressure and ischemia [31]. Three hemodynamic phases can be identified in this context: hyperemia, oligemia, and vasospasm. With the recognition of these phases by TCD, the neurologist may optimize treatment [32].

9.3.1 Oligemia Phase

In general, there is a global decrease in cerebral blood flow (CBF) within the first 24 hours, which may be due to two mechanisms: increased intracranial pressure associated with decreased CPP and intense microvascular constriction associated with low nitric oxide (NO). These phenomena can trigger tissue hypoperfusion, decreased tissue O_2 supply, and consequent ischemia [32]. The identification of this phase by TCD help decisions in clinical evaluation, such as (1) the management of the most appropriate mean arterial pressure (MAP); (2) to avoid hyperventilation which in turn will cause hypocapnia, vasoconstriction, and further reduction of CBF; and (3) to avoid states that increase brain tissue metabolic demand (e.g., fever, seizure, and among others), [33, 34].

9.3.2 Hyperemia Phase

Brain microcirculatory vasodilation leads to global CBF increase. Encephalic hyperemia states may indicate impaired neurovascular coupling and autoregulation due to encephalic or systemic tissue acidosis and usually occur 24 hours after the

oligemia state [35]. TCD may identify the cerebral circulatory hyperdynamic and, consequently, guide the management of patients' hemodynamic conditions in order to avoid brain swelling. In this phase, conditions that worsen brain hyperemia such as hypercapnia, systemic arterial hypertension, anemia, and brain hypermetabolic states (e.g., seizures) should be avoided.

In this phase of SAH, cerebral autoregulation (CA) impairment should be suspected. With intact CA, the cerebral blood flow does not change even with a wide change in ABP; however, with impaired CA, cerebral blood flow variates with ABP variation, and tight control of this parameter is essential. TCD can identify CA impairment through the relationship between CBFV and ABP oscillation (spontaneous or induced). This analysis is performed through mathematical modeling used in signal analysis, requiring the use of specific software for this purpose. Thus, TCD can assist in identifying the most appropriate pressure range in the compromised states of CA at this phase of SAH [36].

9.3.3 Vasospasm Phase

Vasospasm in SAH is a significant cause of late cerebral ischemia. Therefore, early recognition is mandatory in the clinical management of neurocritical patients. TCD can detect vasospasm before neurologic symptoms. Thus, clinical treatment of vasospasm may be instituted early, before the onset of neurological deficits [32].

Several factors determine vasospasm-related late cerebral ischemia in SAH: (1) vasospasm intensity; (2) occurrence in multiple arteries or sequential/tandem vasospasm; (3) presence or absence of activated collateral circulation; (4) associated tissue hypermetabolism; (5) tissue mitochondrial dysfunction; (6) presence of intracranial hypertension; (7) associated circulatory oligemia; and (8) impaired brain microcirculatory reserve [37].

TCD can detect vasospasm in the middle and basilar cerebral arteries with high sensitivity and specificity [38]. Classically, vasospasm may occur 4–14 days after the bleeding, and in some cases (13% of patients) may be detected early within the first 48 hours or late after the 17th day. Therefore, periodic TCCD examinations are recommended at this stage [39]. The possibility of monitoring the vasospasm severity and its evolution may help in the patient's clinical management. In severe vasospasm, the conjunction of other hemodynamic factors also observed by the TCD determines the indication of adjunctive therapies, such as vasoactive drugs or endovascular interventional treatment. The monitoring of response to treatment is also an essential benefit of TCD at this stage. Table 9.3 shows the diagnostic and classification criteria for vasospasm severity by TCD using MV and LI/SI.

Table 9.3 TCD vasospasm diagnosis criteria

Vasospasm severity (MCA)	MV (cm/s)	LI
Mild	120–130	3–3.9
Moderate	131–180	4–6
Severe	>180	≥6
Vasospasm severity (BA)	**VM (cm/s)**	**SI**
Mild	70–85	2–2.49
Moderate	>85	2.5–2.99
Severe	>85	≥3

MCA, Middle Cerebral Artery; BA, Basilar Artery; MV, Mean Velocity; LI, Lindegaard Index; SI, Soustiel Index

9.4 Traumatic Brain Injury (TBI)

Intracranial circulation abnormalities often occur in patients with TBI [40, 41]. Ischemic brain injury can be identified in about 90% of patients who die after severe TBI [42, 43], suggesting that changes in systemic or brain blood flow dynamics are frequent reasons for ischemia and unfavorable outcomes. Also, hyperemic phenomena are most frequently found in patients after severe TBI [42].

9.4.1 Brain Hemodynamic Phases After Severe TBI

As in SAH, there are three brain hemodynamic phases after severe TBI: oligemia, hyperemia, and vasospasm. The oligemia phase may occur on the day of TBI (day 0) and is characterized by reduced CBF. The hyperemia phase usually occurs on days 1–3 and is characterized by increased CBF. The vasospasm phase usually occurs from days 2 to 6 after TBI and CBF may be reduced [2, 44].

9.4.1.1 Oligemic Phase

The oligemic phase of TBI is characterized with TCD as blood flow velocity and increased PI in the intracranial arteries [44]. At this stage, TCD is useful in guiding therapeutic management. The reduction in blood flow velocity to TCD in the brain arteries may also be due to brain hypometabolism that may be associated with severe brain injury and poor prognosis [2]. Other causes of reduction in CBFV in TBI are: low ABP with impaired AR, hypocapnia, post-traumatic thrombosis of proximal vessels, and intracranial hypertension (primarily if associated with increased PI).

9.4.1.2 Hyperemia Phase

Usually, hyperemia is detected in about 30% of patients during the first weeks after severe TBI. It is associated with severe brain swelling and increased intracranial pressure. TCD exam can identify patients with post-traumatic brain hyperemia at the very early stages of brain swelling, which allows the institution of therapies aimed at minimizing neural tissue damage secondary to ICH, such as determining the best mean arterial blood pressure range for the patient or determining the best PCO_2 for a patient on mechanical ventilation [2]. Persistent hyperemia may be associated with unfavorable neurological prognosis.

9.4.1.3 Vasospasm Phase

TCD studies on TBI estimate the occurrence of vasospasm in 50% of patients. Although it is lower than spontaneous SAH, vasospasm with severe hemodynamic repercussion is associated with an unfavorable neurological prognosis.

In case of post-traumatic basilar artery vasospasm, the risk of unfavorable prognosis is duplicated when compared with patients without vasospasm. [2].

Vasospasm duration in TBI patients tends to be shorter than in SAH due to noninflammatory nature. Possibly, its origin is associated with the stretching of the arteries during trauma, and the peak incidence usually occurs between the fifth and seventh day after trauma, although a duration similar to SAH is observed in some cases [2].

9.4.2 Other Applications of TCD in TBI

Among other applications of the TCD in severe TBI, it is worth mentioning:

1. Detection of cerebral circulatory changes secondary to ICH
2. Assessment of CA and VMR to predict prognosis
3. Provide evidence of post-traumatic dissection or thrombosis of the arteries supplying the brain, allowing early investigation and measures to prevent brain infarction
4. Monitoring of cerebral hemodynamic changes in response to instituted treatments

9.5 Intracranial Hypertension (ICH)

TCD is important for assessing the effects of ICH in brain circulation, especially when invasive ICP monitoring is contraindicated. The most common finding disclosed by TCD in patients with ICH is the elevation of PI with progressive reduction of mean and diastolic blood flow velocities [30].

In general, changes in PI occur when brain perfusion pressure is less than 70 mmHg [2]. When ICP equals diastolic systemic blood pressure, diastolic blood flow velocity reaches zero, characterizing the absence of cerebral perfusion during the diastolic phase of the cardiac cycle [23, 45].

In other situations, TCD is important to be used in conjunction with invasive ICP monitoring to evaluate, in real-time, the effectiveness of therapeutic measures used to treat ICH. For instance, in some cases, TCD may reveal that increased ICP may be associated with cerebral circulatory hyperdynamic due to impaired CA. In this case, increasing ABP will lead to the worsening of ICH.

TCD also allows for the assessment of intracranial compliance by simultaneously compressing the internal jugular veins and increasing mean arterial pressure. Under normal conditions, this maneuver causes a slight increase in brain blood volume, followed by increased ICP. In patients with decreased intracranial compliance, venous compression would lead to increased PI and reduced mean cerebral blood flow velocities [46].

9.6 Cerebrovascular Disease

The use of TCD in ischemic cerebrovascular disease is essential to investigate the pathophysiological mechanisms involved in ischemic injury, to plan targeted therapeutic strategies aimed at protecting and recovering the penumbra zones, and preventing further episodes of cerebral ischemia. TCD may identify patients with arterial occlusions or critical stenoses in the proximal segments of the brain arteries in the acute phase of stroke, both in the anterior and posterior cerebral circulations. It may help in the indication of further treatments such as rescue therapies [47–50]. Besides, TCD can detect and evaluate collateral circulation in the intracranial arteries after acute arterial occlusions [51, 52]. Furthermore, the detection of emboli by TCD in the occluded artery region during recanalization therapies may be indicative of initial recanalization.

In the subacute phase of ischemic cerebrovascular disease, TCD assesses the hemodynamic repercussion of extracranial carotid disease through VMR tests and the presence and hemodynamic repercussion of intracranial stenosis [53–57]. Another utility of TCD is real-time embolus detection. Embolic activity in a single intracranial arterial territory may suggest an embolic source originating from the cervical carotid artery or ipsilateral intracranial artery and is suggestive of an increased risk of recurrence of the ischemic event. When the embolic activity is detected in multiple intracranial arterial territories such as bilaterally carotid and vertebrobasilar system, the embolic source is probably cardioaortic or paradoxical embolism.

Another application of TCD in acute ischemic stroke is the identification of right-to-left shunts. By infusing saline with microbubbles (small gas particles) in the peripheral vein, TCD can detect the passage of these microbubbles into the brain

circulation, allowing the diagnosis of venous to arterial communication, such as patency of the foramen ovale or pulmonary fistula [58, 59].

In summary, TCD in ischemic cerebrovascular disease enables the following:

1. Detection of intracranial arterial stenoses and occlusions
2. Evaluation of the cerebral hemodynamic effects of extracranial and intracranial occlusive diseases
3. Assessment of the pattern and effectiveness of brain collateral circulation
4. Quantification of the cerebral vascular reserve using VMR tests
5. Detection of real-time embolic activity and right-to-left shunt
6. Monitoring of spontaneous recanalization or secondary to therapies in the acute phase of ischemic stroke [2]

9.7 Transcranial Doppler in Systemic Conditions

9.7.1 Liver Cirrhosis with Encephalopathy and Liver Failure

Several studies show that CBF is impaired in patients with acute or chronic severe liver disease, especially in the presence of hepatic encephalopathy (HE) [60]. In this condition, impairment of CA occurs and, consequently, the variation in MAP may be associated with changes in CBF [61]. Although hyperammonemia is the leading cause of hepatic encephalopathy, recent evidence suggests that abnormalities in CBF may also have some relationship in the pathophysiology of this disease [60].

There is a hypothesis that cirrhotic patients with encephalopathy have more pronounced cerebral vasoconstriction and, consequently, progressive elevation of PI, RI, and reduction of BHI with more severe disease. The more severe the encephalopathy, the more changes in cerebral hemodynamics are observed [60, 61]. Significant complication of severe hepatic encephalopathy is intracranial hypertension (ICH). This is due to three main mechanisms: (1) brain swelling secondary to the cytotoxic effect of hyperammonemia (astrocyte swelling); (2) breakdown of the blood–brain barrier; and (3) brain hyperemia secondary to loss of cerebral autoregulation. TCD can provide information regarding the dynamics of CBF in patients with ICH and detect CA impairment, which can guide therapeutic management [61, 62].

9.7.2 Sepsis and Sepsis-Associated Encephalopathy

Hemodynamic impairment is a fundamental feature of sepsis. The cerebral microcirculation may be gradually compromised and consequently cause significant changes in the CBF. These factors play an important role in the etiology of

sepsis-associated encephalopathy (SAE) [29]. SAE is a frequent brain dysfunction that occurs in 50% of intensive care units (ICU) patients and is one of the most common causes of delirium in ICU. Also, SAE is associated with increased mortality [10, 29, 63].

In the early phase of sepsis, there are progressive increases in MV and PI over time, which are evident 24 hours after onset. At this stage, cerebral autoregulation may remain unchanged. In contrast, in the later phase of sepsis (patients with severe sepsis or septic shock), there are progressive reductions in MV and PI, as well as impairment of cerebral autoregulation. The elevation of PI associated with increased cerebrovascular resistance has been correlated with a higher prevalence of delirium and coma [10, 64].

Many of the factors leading to CBF changes (such as changes in cerebral vascular reactivity and impaired cerebral autoregulation) are often the result of microcirculation dysfunction due to the release of inflammatory mediators [64]. The use of TCD to assess cerebral hemodynamic patterns has some clinical advantages: (1) TCD can be used to identify sepsis cerebral hemodynamic patterns that may precede systemic hemodynamic signals; (2) increased PI in confused patients may be an early sign of sepsis and help shorten the time to diagnosis; and (3) the identification of cerebral hemodynamic changes and correlation with systemic hemodynamic changes may improve the management of blood pressure and blood volume in septic patients [10, 64].

9.7.3 Sickle Cell Anemia

Cerebral infarcts are frequent complications in sickle cell anemia. In this disease, a fibrous proliferation of the arterial intimal layer may cause detectable stenosis of the TCD. Mean blood flow velocities greater than 200 cm/s in intracranial carotid arteries, middle, and anterior cerebral arteries are associated with significantly increased risk of stroke in neurologically asymptomatic children. In this group, prophylactic blood transfusions reduce the risk of stroke [65]. Since September 1997, the National Institutes of Health of the United States has recommended routine TCD tests in children 2–16 years of age in order to identify those most at risk for stroke. For children with typical results is recommended to perform TCD exams every 6 months. This approach was established because the Stroke Prevention Trial in Sickle Cell Anemia (STOP) demonstrated a relative 90% reduction in the relative risk of stroke in children aged 2–16 years treated with prophylactic blood transfusion based on TCD results [11, 66]. A previous publication has shown that blood transfusion therapy reduces the risk of stroke, including silent strokes, in children with abnormal TCD results [67]. These findings reinforce the need for routine use of TCD in the clinical and therapeutic evaluation of children with sickle cell anemia [11]. STOP was the most successful clinical trial in demonstrating the importance

of TCD in preventing stroke in children with sickle cell anemia. Importantly, in this study, research was discontinued before termination due to the great benefit that blood transfusion, based on TCD results, offered to these patients. The application of TCD for stroke prevention in children with sickle cell anemia was considered adequate, with class I of recommendation and level A of evidence [68].

9.8 Brain Death

In many countries, brain death is defined by the total and definitive cessation of all brain functions [69]. TCD is a validated method for the diagnosis of intracranial circulatory collapse and is considered in the medical literature the exam of choice for this purpose due to portability, noninvasiveness, and possibility of repetition [2]. The sensitivity of TCD for brain death diagnosis reaches values greater than 95% and specificity of 100% [70, 71].

The TCD shows absence of bilateral blood flow in the arteries of the intracranial carotid system and vertebrobasilar system. The criteria of circulatory collapse are (1) the presence of oscillatory flow (systolic velocity equal to reverse diastolic velocity – zero final flow) or (2) systolic spicules or (3) disappearance of intracranial flow [70].

False-negative results may occur in some patients undergoing decompression craniectomy, ventricular cerebrospinal fluid shunts, or in patients with significant brain atrophy. In these cases, the maximum elevation of intracranial pressure to cause circulatory collapse is difficult to establish, and electrical methods can diagnose brain death earlier [2].

9.9 Conclusion

Cerebral circulatory changes are often found in the intensive care unit's daily practice and may lead to secondary tissue damage. Either brain damage such as hypoxia, intracranial hypertension, trauma brain injury, or systemic conditions such as kidney, liver failure, and sepsis may impair cerebral autoregulation. The impairment of CA makes the cerebral circulation more susceptible to changes in ABP. Thus, monitoring with TCD patients who has one or more of the situations mentioned above can help to adjust CBF to meet cerebral metabolic demands.

The TCD has the advantage of allowing bedside access to cerebral hemodynamic changes, both intermittently and continuously. The disadvantage of the method is that it is operator dependent and requires long and intensive training so that it can be applied in practice by highly trained physicians.

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Chapter 10
Electroencephalogram in the Neurosurgical Intensive Care Unit (When a Single EEG Is Not Enough)

Luiz H. Castro

10.1 Introduction

The last two decades have witnessed technological advances that made continuous digital EEG monitoring (cEEG)—with or without vídeo—feasible, and allowed remote interpretation of records. cEEG allows recognition of previously undetectable nonconvulsive seizures (NCSzs), that occur more commonly than previously recognized, and are associated with worse outcome. NCSzs risk factors include coma and decreased level of consciousness, history of clinical seizures, specially when occurring prior to coma, brain infection, tumors, autoimmune disease, recent neurosurgery, and presence of periodic EEG patterns. Most NCSzs will be detected in the initial 24 hours of cEEG recording in noncomatose patients. Longer periods are required in patients in coma, or in patients that present periodic EEG patterns. Interpretation of periodic and rhythmic EEG patterns commonly seen in this patient population, however, remains incompletely understood. cEEG helps characterizing paroxysmal spells, and also allows assessment of sedation level. Quantitative cEEG analysis of long-term EEG trends can aid in early detection of cerebral ischemia, before permanent neuronal damage ensues, and may allow prevention of brain infarction [1–4].

Indications for cEEG include not only detection of nonconvulsive seizures but also characterization of possible clinical seizure correlates and to aid in outcome prognostication. Additionally, guidelines on treatment of NCSzs and periodic EEG patterns in this patient population are still lacking [1–4].

This chapter will review cEEG nomenclatures, the clinical relevance of the findings of EEG patterns in critically ill patients, and the clinical and therapeutic implication for patient management in the intensive care unit (ICU) setting.

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10.2 Continuous EEG Terminology and Interpretation of EEG Patterns

With increasing use of continuous video-EEG recording in critically ill patients, particularly in patients with encephalopathy and coma, abnormal findings such as periodic discharges (PDs) and rhythmic delta activity (RDA) were increasingly recognized. Interpretation of these findings, however, was fraught with subjectivity regarding nomenclature, interpretation, and clinical implications of the various EEG patterns that were recognized in these patients.

10.2.1 American Clinical Neurophysiology Society Standardized Definitions and Classification of Electroencephalographic Rhythmic and Periodic Patterns

The American Clinical Neurophysiology Society (ACNS) proposed standardized definitions and classification of electroencephalographic rhythmic and periodic patterns in 2005. Terms were objective, reproducible, and well-defined. Diagnostic terms and treatment implications such as "triphasic waves (TWs)" were excluded (yet described, if appropriate), and terms such as "ictal," "interictal," and "epileptiform" were avoided. ACNS definitions and classifications were revised in 2011 and in 2012, and are currently adopted in centers worldwide.

The final version was published in 2013 as an official ACNS guideline. The latest version of the nomenclature can be found at http://www.acns.org. Unified terminology has enabled advances in the understanding of the underlying pathophysiological process, potential epileptogenicity, as well as clinical significance of these patterns. Interrater reliability of most of the proposed terms has been established, providing a solid research basis. Researchers are currently able to cooperate investigating diagnostic and therapeutic algorithms to these patterns. This may soon result in scientific evidence that will guide clinicians in patient management [5].

The main standardized terms used for EEG patterns are [5]:

- Descriptors 1: Generalized (G), Lateralized (L), Bilateral independent (BI), and Multifocal (Mf)
- Descriptors 2: Periodic discharges (PDs), rhythmic delta activity (RDA), and Spike-Wave that includes Sharp-Wave (SW) (Fig. 10.1).
- Modifiers: Persistence, duration, frequency, sharpness, amplitude, and also if patterns are stimulus-induced or spontaneous, evolving, fluctuating, or static.

Plus (+) are additional features that indicate that a pattern is more ictal-appearing than the usual term without the plus (Figs. 10.1, 10.2, 10.3, and 10.4)

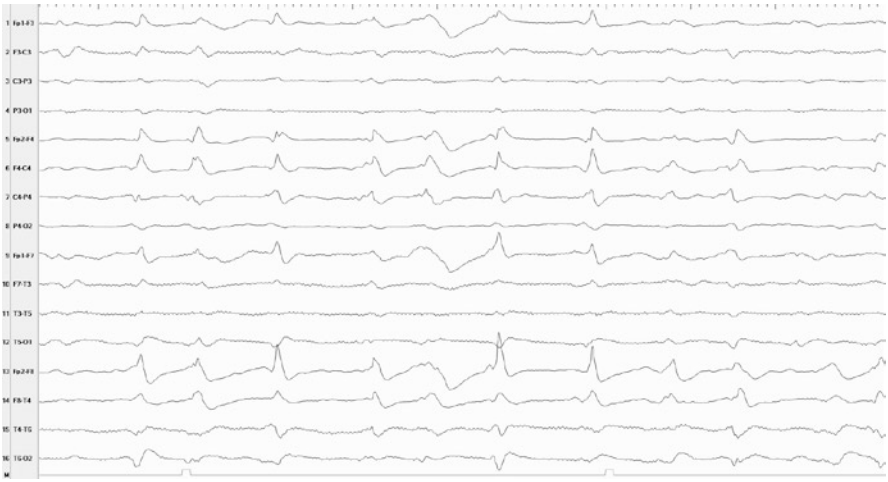

Fig. 10.1 Lateralized periodic discharges (LPD)—1.0 Hz periodic discharges (sharp waves) in the right frontal regions, in a comatose patient post right frontal meningioma resection. (Courtesy Dr. Eliana Garzon)

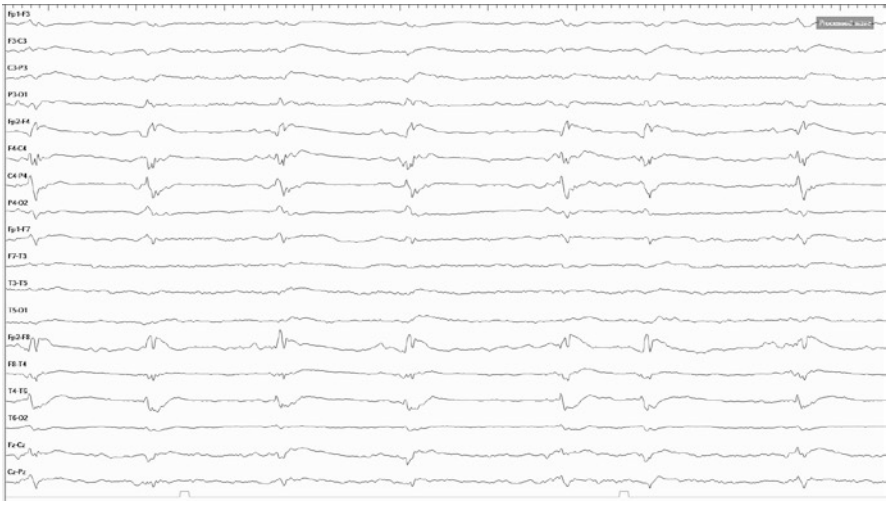

Fig. 10.2 Lateralized periodic discharges plus (LPD+)—0.5–1.0 Hz discharges in the right hemisphere, in a comatose patient with a stroke and a generalized seizure. (Courtesy Dr. Eliana Garzon)

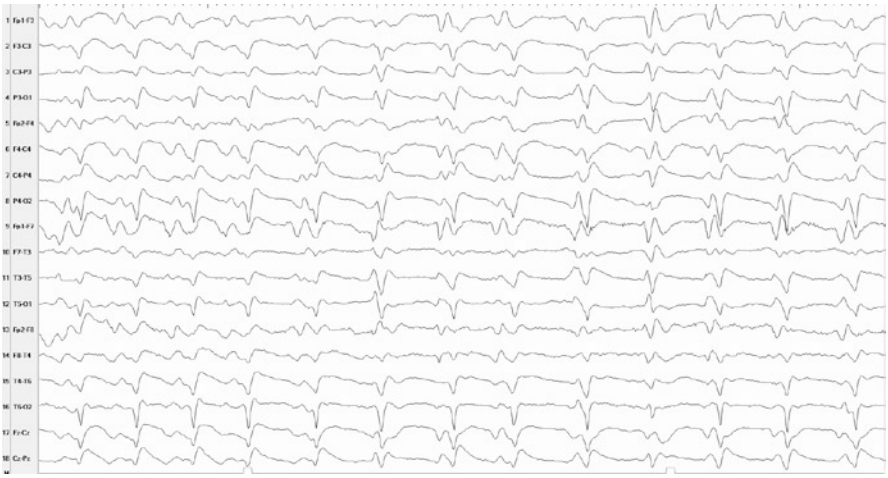

Fig. 10.3 Generalized periodic discharges (GPD)—1 Hz—in a patient with Jacob–Creutzfeldt disease. (Courtesy Dr. Eliana Garzon)

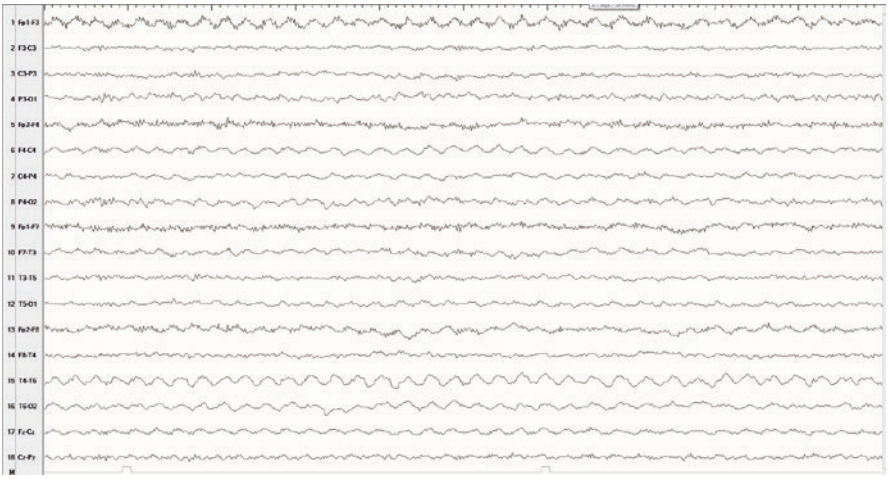

Fig. 10.4 Generalized rhythmic delta activity—in a patient with anti-NMDA encephalitis. (Courtesy Dr. Eliana Garzon)

10.2.2 Interrater Agreement

Interrater agreement for the published American Clinical Neurophysiology Society (ACNS)-approved version of the critical care EEG terminology (2012 version) was evaluated by 49 independent readers, who assessed if a pattern corresponded to an

electrographic seizure, pattern location (main term 1), pattern type (main term 2), and regarding presence and classification of other key features ("plus" modifiers, sharpness, amplitude, frequency, number of phases, fluctuation and evolution, and presence of "triphasic" morphology). Interrater agreement (kappa values) was almost perfect (90–100%) for seizures, main terms 1 and 2, +S modifier (superimposed spikes/sharp waves or sharply contoured rhythmic delta activity), sharpness, absolute amplitude, frequency, and number of phases. Agreement was substantial for +F (superimposed fast activity) and + R (superimposed rhythmic delta activity) modifiers (66% and 67%, respectively), moderate for triphasic morphology (58%), and fair for evolution (21%) [6] .

10.2.3 EEG Criteria for Nonconvulsive Status Epilepticus

Before the establishment of a unified EEG terminology, and of evidence-based EEG criteria, ability to diagnose nonconvulsive status epilepticus (NCSE) was limited due to poor interrater reliability. Therefore, diagnostic criteria were proposed for the diagnosis of nonconvulsive seizures, based on the standardized EEG criteria in critically ill patients.

The diagnosis of nonconvulsive status epilepticus (NCSE) is now largely established based on electroencephalographic (EEG) findings [7, 8].

10.2.3.1 Clinical Criteria for Nonconvulsive Status Epilepticus

Clinical criteria for nonconvulsive status epilepticus were defined as:

In patients without known epileptic encephalopathy nonconvulsive status epilepticus was defined as:

- Epileptiform discharges at a rate greater than 2.5 Hz or
- Epileptiform discharges at a rate less than 2.5 Hz or rhythmic delta or theta activity (greater than 0.5 Hz) and one of the following: EEG and clinical improvement after intravenous antiepileptic drug administration or presence of subtle clinical ictal phenomena concomitant with the above-described EEG patterns or typical spatiotemporal evolution in the EEG pattern.

In patients with a previously known epileptic encephalopathy nonconvulsive status epilepticus was defined as:

- An increase in prominence or frequency of the EEG features described above (compared to baseline EEG), and observable change on clinical status is required or improved clinical status or EEG patterns after intravenous drug administration [7] (Fig. 10.5a, b).

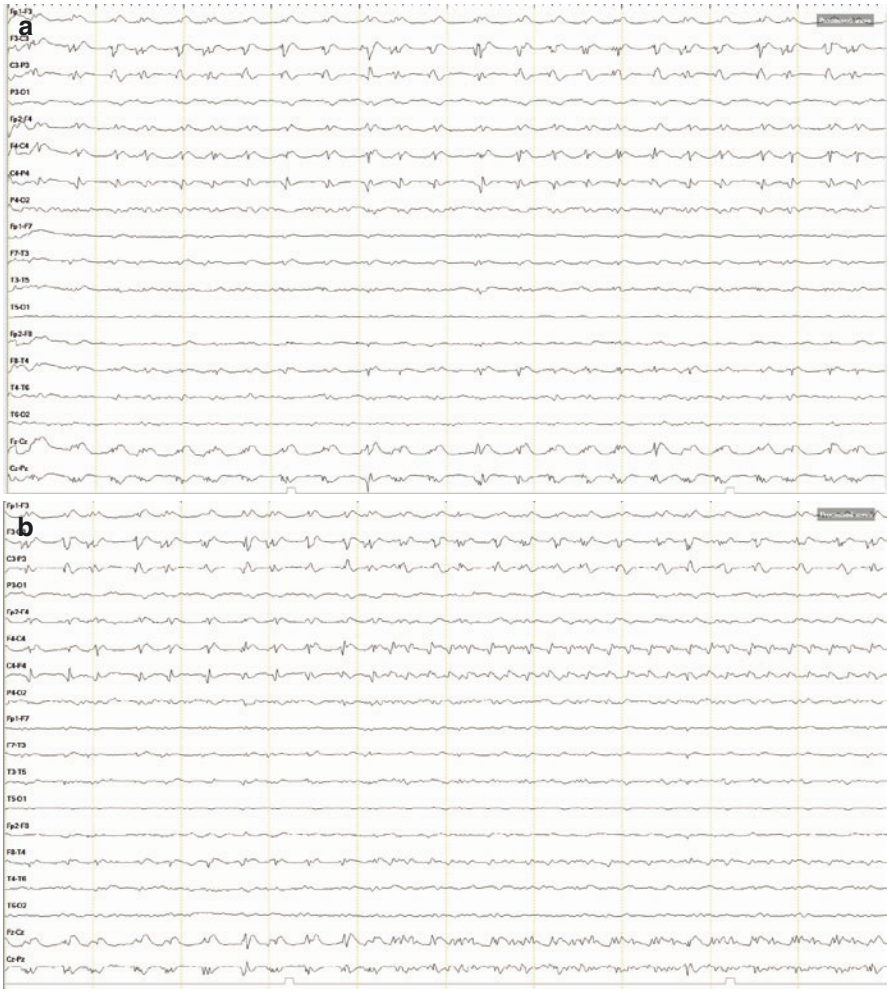

Fig. 10.5 (**a**) Rhythmic spike and sharp waves (>2 Hz) over the parasagittal regions in a patient in barbiturate coma for focal epileptic status, (**b**) Same; note temporal evolution on EEG pattern. (Courtesy Dr. Eliana Garzon)

10.2.3.2 Nonconvulsive Status Epilepticus: Electroclinical and Etiologic Classification

Based on EEG features and clinical settings, nonconvulsive status epilepticus (NCSE) can be further classified according to [8]:

NCES Type (Electroclinical Classification)

NCSE in patients in coma/stupor. NCSE may present with decreased level of consciousness, but subtle clinical findings, such as muscle twitching, conjugate eye deviation, or nystagmus may be present.

NCSE without coma/stupor:

1. Generalized onset (absence status epilepticus: typical, atypical, and myoclonic absence status epilepticus),
2. Focal onset (with or without impairment of consciousness, aphasic nonconvulsive status epilepticus [NCSE]),
3. Unknown whether focal or generalized (e.g., autonomic SE).

Etiology

Symptomatic (known etiology) and cryptogenic (unknown etiology).

Symptomatic cases can be further classified as:

1. Acute,
2. Remote,
3. Progressive,
4. Nonconvulsive status epilepticus in age-related electroclinical syndromes.

10.3 EEG Patterns: Clinical Significance

10.3.1 Generalized and Lateralized Periodic Patterns

Generalized periodic discharges (GPDs) are increasingly recognized on continuous EEG monitoring, but their relationship to seizures and prognosis remains unclear.

In a case control study that evaluated 200 adult patients with generalized discharges from 1996 to 2006 matched to controls by age, etiology, and level of consciousness, generalized periodic discharges were strongly associated with nonconvulsive seizures and nonconvulsive status epilepticus. Nonconvulsive status epilepticus was independently associated with worse outcome, generalized periodic discharges were not after matching for age, etiology, and level of consciousness [9].

While generalized periodic discharges (GPDs) are associated with nonconvulsive seizures, triphasic waves (TWs), a subtype of GPDs, have been described in relation to metabolic encephalopathy, and not felt to be associated with seizures. Eleven experts in continuous EEG monitoring scored 20 cEEG samples containing GPDs using standardized critical care EEG terminology. While interrater agreement for the terms "generalized" and "periodic" was high, it was only fair for TWs. EEG interpreted as TWs entails similar seizure risk as GPDs without triphasic appearance. GPDs are commonly associated with metabolic encephalopathy, but "triphasic" appearance is not predictive. The authors concluded that association of "triphasic waves" with specific clinical conditions, such as hepatic or other metabolic encephalopathies, may lead to inaccurate EEG interpretation [10].

Another study evaluated the association of periodic and rhythmic electroencephalographic patterns and risk of seizures in critically ill patients. The authors reviewed cEEG recordings from 4772 critically ill adults in three academic medical centers to determine association of periodic and rhythmic patterns and certain features, such as pattern frequency, presence of a plus modifier, prevalence, and stimulation-induced patterns and the association with seizure occurrence. Lateralized periodic discharges (LPDs), lateralized rhythmic delta activity (LRDA), and generalized periodic discharges (GPDs) were associated with seizures. Generalized rhythmic delta activity (GRDA) was not associated with seizures [11].

Lateralized periodic discharges were associated with seizures regardless of frequency or association with a plus modifier. LRDA and GPDs were associated with seizures at frequencies 1.5 Hz or faster or in association with a plus modifier. Increased frequency of pattern occurrence was associated with increased seizure risk for LPDs and GPDs. Stimulus-induced patterns were not associated with increased risk of seizures [11].

10.3.2 Brief Potentially (Ictal) Rhythmic Patterns—B(I)RDs

Another pattern, brief potentially ictal rhythmic discharges, termed B(I)RDs, was also evaluated in critically ill patients. The most commonly seen pattern consisted of brief—1–3 second—runs of sharply contoured theta activity, without spatial or temporal evolution. The authors concluded that brief potentially ictal rhythmic discharges (B[I]RDs) in critically ill patients were highly associated (75%) with electrographic seizures, and could represent a predictor of seizures on subsequent monitoring [12].

10.3.3 Sensitivity and Duration of cEEG for Seizure Detection in Critically Ill Patients

Although continuous EEG has become standard of care in patients in the ICU setting that present with neurologic impairment, the duration of cEEG recordings to detect seizures remains unclear. A recent study evaluated seizure risk factors based on clinical history and on EEG findings, in order to create a scoring system associated with seizure risk in acutely ill patients.

The authors evaluated data from a prospective multicenter (Emory University Hospital, Brigham and Women's Hospital, and Yale University Hospital) database that contained clinical and electrographic features on 5427 cEEG recordings from 4772 critically ill patients [13].

The final model, 2HELPS2B, included six variables: (1) brief ictal rhythmic discharges (B[I]RDs) (two points); (2) lateralized periodic discharges, lateralized rhythmic delta activity, or bilateral independent periodic discharges (one point); (3) seizure prior to recording (one point); (4) sporadic epileptiform discharges (one point); (5) any periodic or rhythmic pattern with a frequency greater than 2.0 Hz (one point); and (6) occurrence of "plus" features (superimposed, rhythmic, sharp, or fast activity) (one point). The probable seizure risk for each score was: 5% for score 0, 12% for score 1, 27% for score 2, 50% for a score 3, 73% for score 4, 88% for score 5, and greater than 95% for scores 6 or 7 [13].

Rational and optimized use of cEEG in the ICU setting requires study that determines optimal duration of monitoring. Another recent study analyzed 665 consecutive patients cEEG recordings, and used clinical and EEG data over 72 hours to predict time to seizure emergence. Clinical factors were used for baseline (pre-EEG) risk. EEG risk state was defined by epileptiform patterns.

The clinical variables that had the greatest predictive value were coma (31% had seizures) and history of seizures, remotely or acute illness related (34% had seizures). If there were no epileptiform findings on EEG, 72-hour seizure risk ranged from 9% (absent clinical risk factors) to 36% (coma and history of seizures). If epileptiform findings emerged, seizure incidence ranged from 18% (absent clinical risk factors) and 64% (history of seizures and coma). If epileptiform EEG abnormalities were absent, monitoring duration needed for a < 5% seizure risk was between 0.4 hours (for patients who were not comatose and without a prior seizure) and 16.4 hours (comatose and with prior seizure). The authors concluded that the initial risk of seizures on cEEG is related to a prior history of seizures and occurrence of coma. The risk of seizures on cEEG is <5% by 24 hours if there are no epileptiform EEG, independent of initial clinical risk factors [14].

A multicenter retrospective medical record review study analyzed clinical and EEG data from adult patients undergoing cEEG for 12 hours or longer who were receiving consecutive cEEG in order to assess the validity of the 2HELP2B score in predicting seizures in patients undergoing cEEG [15].

The 2HELPS2B score calculated on the first hour of EEG (in patients without seizures during that hour) allowed stratification of patients into three risk groups: low (2HELPS2B = 0; <5% risk of seizures), medium (2HELPS2B = 1; 12% risk of seizures), and high-risk (2HELPS2B, ≥2; risk of seizures, >25%). Each category was associated with a minimum recommended duration of EEG monitoring to achieve at least a less than 5% risk of seizures: 2HELPS2B score of 0 at 1-hour screening EEG, 2HELPS2B score of 1 at 12 hours, and 2HELPS2B score of 2 or greater at 24 hours [15].

10.3.4 Quantitative cEEG

Quantitative cEEG softwares allow faster processing of prolonged EEG recordings. Accuracy of seizure detection may represent a major limitation to use these softwares to detect electrographic seizures.

The sensitivity of quantitative EEG (qEEG) for identification of electrographic seizure in the intensive care unit was evaluated in the following manner: 6-hour EEG epochs from 15 patients were transformed into qEEG displays. Each epoch was reviewed in three ways: raw EEG, raw and qEEG, and qEEG only. Additionally, epochs were analyzed with a seizure detection software. Raw EEGs were reviewed by nine neurophysiologists in order to identify seizures, serving as the gold standard. Nine other neurophysiologists experienced in qEEG evaluated the qEEG formats, with and without concomitant raw EEG. Mean sensitivity for seizure identification ranged from 51 to 67% for qEEG-only and 63–68% for qEEG + raw. False positive rates averaged 1.0/hour for qEEG-only and 0.5/hour for qEEG + raw. Seizure probability software mean sensitivity was 26.2–26.7%, with a false positive rate of 0.07/hour. Epochs with highest sensitivities had frequent, intermittent seizures. Lower sensitivities were seen with slow-frequency, low-amplitude seizures, and epochs that included rhythmic or periodic patterns. Median review times were shorter for qEEG (6 minutes) and qEEG with raw analysis (14.5 minutes) compared to raw EEG (19 minutes).

The authors concluded that a panel of qEEG trends allows experts to reduce EEG review time for seizure identification with acceptable sensitivity and low false positive rates. The high prevalence of false detections confirms that raw EEG must be reviewed in conjunction with qEEG. The study provided Class II evidence that qEEG with raw interpretation by experts has a sensitivity of 63–68% and false positive rate of 0.5 seizures per hour to identify seizures in patients in the ICU [16].

Compressed displays of EEG frequency spectra, such as spectral array, facilitate bedside interpretation of continuous EEG allowing untrained medical and nursing personnel to observe evolving patterns over time.

10.4 cEEG Indications in Different Clinical Scenarios

The Critical Care Continuous EEG Task Force of the American Clinical Neurophysiology Society developed expert consensus recommendations regarding the use of CCEEG in critically ill patients (adults and children).

The consensus panel recommended cEEG for the diagnosis of nonconvulsive seizures and nonconvulsive status epilepticus, of other paroxysmal events, as well as for assessment of therapeutic efficacy for seizures and status epilepticus. The consensus panel suggested that cEEG should be used for identification of ischemia in patients at high risk for developing cerebral ischemia, for assessment of level of consciousness in patients undergoing intravenous sedation or pharmacologically-induced coma, and for prognostication in patients that suffered cardiac arrest. For each the consensus panel also described the utility of video recordings and quantitative EEG trends, timing and duration of cEEG, as well as frequency of review and interpretation [17].

10.4.1 cEEG in the Neurological, Medical, Surgical, and Pediatric ICU

10.4.1.1 cEEG in the Pediatric ICU

Seizures, mainly nonconvulsive seizures, were also commonly encountered during cEEG in critically ill children (in 44% of patients). Half of the seizures are detected in the first hour of recording, while 20% are detected after more than 24 hours of recording. Periodic lateralized epileptiform discharges and absence of reactivity on cEEG were associated with seizures [18].

10.4.1.2 cEEG in the Medical ICU

In a retrospective study of 201 consecutive patients admitted to the medical ICU setting that were monitored with cEEG, nonconvulsive seizures and the finding of periodic discharges were frequently seen, more commonly in patients with sepsis. Seizures were mainly nonconvulsive. Seizures and periodic discharges were associated with worse outcome (death or severe disability at hospital discharge) [19].

10.4.1.3 cEEG in the Surgical ICU

In the surgical ICU setting, of 154 patients admitted after abdominal surgery (36%) and liver transplantation (24%), sepsis developed in 100 (65%) patients. Patients underwent cEEG monitoring for altered mental status. Sixteen percent had

nonconvulsive seizures, including 5% with nonconvulsive status epilepticus; 29% had periodic discharges. All eight patients with nonconvulsive status epilepticus were septic. Clinical seizures prior to cEEG and coma were more common among patients who developed nonconvulsive seizures or nonconvulsive status epilepticus. Nonconvulsive seizures and periodic discharges were independently associated with poor outcome [20].

10.4.2 Continuous EEG Monitoring in Patients with Subarachnoid Hemorrhage

Patients that suffer subarachnoid hemorrhage (SAH) are at increased risk for seizures and vasospasm, resulting in delayed cerebral ischemia. These complications can be detected with continuous EEG monitoring (cEEG). EEG allows ischemia to be detected still at a reversible stage. cEEG is probably most useful in patients with poor grade SAH, since the neurological exam is of limited use in stuporous or comatose patients. Seizures have been detected in 19% of SAH patients undergoing cEEG. The vast majority (95%) of these seizures are nonconvulsive and without any perceptible clinical correlate [21].

Quantitative cEEG analysis, measuring relative alpha variability and poststimulation alpha/delta ratio allows detection of ischemia resulting from vasospasm. EEG changes often precede changes in the clinical exam and in other noncontinuous monitoring techniques by up to 48 hours. In patients at risk for cerebral vasospasm, cEEG monitoring, preferably with associated quantitative EEG analysis, should be started early, and maintained for up to 14 days after SAH. cEEG findings may have therapeutic implication (e.g., antiepileptic medication initiation or adjustment, hypertensive therapy, angioplasty) or may allow indication for additional diagnostic interventions (angiography, CT, or MRI). cEEG monitoring also provides independent prognostication for patients with poor-grade SAH, after controlling for clinical and radiological findings. Findings of periodic epileptiform activity, nonconvulsive status epilepticus, absence of sleep architecture are associated unfavorable outcomes [22].

10.4.3 cEEG in Postcardiac Arrest Coma

cEEG patterns can help to prognostiate outcome in postcardiac arrest comatose patients treated with hypothermia.

In a prospective cohort of 100 consecutive patients undergoing hypothermia after cardiac arrest anoxia, clinical and 5-min EEG clips were analyzed at 6, 12, 24, 48, and 72 hours after return of spontaneous circulation and related to outcome. EEG background was classified according to the American Clinical Neurophysiological

Society critical care EEG terminology. Clinical outcome was classified as good (Glasgow outcome scale 4 or 5, low to moderate disability) or poor (Glasgow outcome scale 1 to 3, severe disability to death.

Cardiac arrest secondary to nonventricular fibrillation/tachycardia, longer time to return of circulation, absent brainstem reflexes, extensor posturing or absent motor response, acidosis (lower pH and higher lactate), hypotension requiring two or more vasopressors, and lack of EEG reactivity were associated with poor outcome. Regarding EEG patterns, all patients with suppression-burst at any time or a low voltage (<20 μV) EEG at 24 hours had a poor outcome, with a false positive rate of 0%. Normal background voltage without epileptiform discharges at any time had a positive predictive value >70% for good outcome [23].

10.5 Intracortical cEEG

Scalp EEG does not allow good spatial resolution, and is often contaminated by muscle and movement artifact. Bedside placement of intracortical multicontact electrodes allows improved monitoring of cortical electrical activity in critically ill neurological patients. Intracortical EEG provides accurate intracranial EEG recordings in the intensive care unit, and is able to detect ictal discharges not apparent on scalp EEG. Intracortical EEG can also identify early brain activity changes associated with neurological complications [24].

Intracortical electroencephalography with quantitative EEG analysis was also used to detect vasospasm in poor-grade subarachnoid hemorrhage patients. Decline in intracranial EEG alpha to delta ratio was able for predicting angiographic vasospasm, and occurred one to 3 days before angiographic confirmation of vasospasm [25].

10.6 Treatment

10.6.1 Treatment of Convulsive Status Epilepticus

Convulsive status epilepticus constitutes a medical emergency that is associated high mortality and morbidity. The operational definition of convulsive status epilepticus is defined as a convulsive seizure that lasts for more than 5 minutes or occurrence of consecutive seizures without recovery of consciousness.

Successful management of convulsive status epilepticus relies on rapid administration of antiepileptic drugs. The choice of a specific antiepileptic drug is less important than early treatment and rapid consideration of potentially reversible causes of status. According to current guidelines, benzodiazepines are first-line treatment in convulsive status epilepticus. Midazolam is considered safe and

effective in prehospital or home settings, when administered intramuscularly (best evidence), buccally, or nasally. Buccal or nasal midazolam possibly acts faster than intramuscular, however, with lower evidence levels. Regular use of home rescue medications (nasal/buccal midazolam) by patients or caregivers for prolonged seizures and seizure clusters may prevent status epilepticus, emergency room visits, and positively impact on quality of life, and decreased health care costs. Phenytoin is traditionally the most used second-line agent in convulsive status epilepticus, but its use is limited by hypotension, arrhythmias, allergies, and phlebitis. Intravenous valproate is a safe and effective option to treat convulsive status epilepticus. Valproate can be rapidly and safely loaded intravenously rapidly, has broad-spectrum efficacy for different seizure types, and fewer acute side effects. Other well tolerated antiepileptic drugs are levetiracetam and lacosamide. These drugs present fewer drug interactions, allergic reactions, and contraindications. Older adults, adults, and children with established status epilepticus present a similar response to phenytoin, fosphenytoin, levetiracetam, and valproate, with treatment success rates in approximately half of patients. These drugs are considered a first-choice or second-line drug for benzodiazepine-refractory status epilepticus. Ketamine is probably effective in treating refractory status epilepticus, but further evidence is needed [26–28].

Convulsive status epilepticus should be managed quickly and aggressively. Treatment success must be confirmed with electroencephalographic (EEG), since occurrence of nonconvulsive status epilepticus after initial treatment for convulsive status epilepticus is common. EEG should be continued for at least 24 hours if the patient does not fully recover consciousness [26].

10.6.2 Treatment of Nonconvulsive Status Epilepticus

Evidence based recommendations for treating refractory nonconvulsive status epilepticus, intermittent nonconvulsive seizures, and EEG patterns associated with high seizure risk are still lacking.

While some specialists argue that refractory nonconvulsive status epilepticus, especially when associated with acute brain injury, causes additional dependent brain damage. In that scenario, treating to EEG patterns to burst-suppression would be the fastest and most effective option to treat nonconvulsive status epilepticus. Treating EEG to burst-suppression is commonly associated with risks that could theoretically be minimized with expert ICU management. Other authors suggest that treatment of nonconvulsive status epilepticus with coma-inducing medication carries significant risk and high mortality rate, usually associated with iatrogenic complications. These authors argue that it is still unclear if nonconvulsive seizures are associated with permanent neuronal damage. Therefore, nonconvulsive seizures should be diagnosed and treated, avoiding coma-inducing treatments in most cases [29].

10.6.3 Treatment of Refractory Status Epilepticus

Treatment of refractory status epilepticus usually requires intravenous continuous infusion of anesthetic doses of antiseizure medications. If an auto-immune or paraneoplastic etiology is possible or if etiology of status epilepticus is not identified (such as in cryptogenic new onset refractory status epilepticus, NORSE), early treatment with immuno-modulatory agents is now recommended by many experts [26].

10.6.4 Impact of cEEG Monitoring on Treatment of Seizures

A retrospective cohort study evaluated changes in antiepileptic drug therapy based on the electroencephalographic findings in 300 consecutive continuous electroencephalographic monitoring studies, performed on 287 individuals in intensive care units and neurological wards. cEEG findings led to a change in antiepileptic drug (AED) prescribing in 52% of all studies with initiation of an AED therapy in 14%, modification of AED therapy in 33%, and discontinuation of AED therapy in 5% of all studies. Detection of electrographic seizures led to a change in AED therapy in 28% of all studies [30]. Similar results had been previously reported in a study that reviewed cEEG findings in 200 patients in a neuroscience intensive care unit: cEEG had a "decisive" impact on clinical management in 54% of patients and contributed to decisions in another 32% [31]. Another small study reported that cEEG affected management on just under 50% of monitoring days [32].

Discovery of nonepileptic seizures previously believed to be epileptic seizures in the critically ill is also an underappreciated benefit of cEEG. In one prior series, 9.5% of patients on cEEG were found to have nonepileptic spells [33].

cEEG is costly and labor intensive. Healthcare providers have questioned if cEEG is really necessary and proposed that this question should be resolved soon, before clinicians get used to using cEEG and are unwilling to practice without it, despite the fact that proof of its benefit is still lacking, as with other diagnostic tools, such as pulmonary artery catheters. The key question that remains, which is more important, to be responded is if cEEG benefits patients.

10.7 Highlights

1. Prolonged cEEG use in critically ill patients is rapidly spreading and becoming standard practice.
2. Many encephalopathic or comatose patients with different underlying diagnoses are found to have electrographic seizures, most of which lack an obvious clinical correlate ("subclinical" or "nonconvulsive" seizures).

3. Standardized terminology has enabled advances in the understanding of the clinical significance of EEG patterns frequently seen in critically ill stuporous and comatose patients.
4. Lateralized periodic discharges (LPDs) on EEG are associated with seizures regardless of frequency or association with a plus modifier. Lateralized rhythmic delta activity (LRDA) and generalized periodic discharges (GPDs) are associated with seizures at frequencies 1.5 Hz or faster or in association with a plus modifier.
5. Generalized rhythmic delta activity (GRDA) on EEG is not associated with seizures
6. cEEG can be useful to adjust antiepileptic drug regimen in comatose patients presenting nonconvulsive seizures and in nonconvulsive status epilepticus, and to detect early signs of vasospasm and brain ischemia in patients with subarachnoid hemorrhage.
7. The exact use of cEEG in different clinical scenarios requires further studies that should also evaluate the role of cEEG to support clinical decisions that guide therapeutic interventions in critically ill patients, and also evaluate the role of cEEG in improving neurologic outcomes in different clinical settings.

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Chapter 11
Radiological Evaluation of Postoperative Complications of Intracranial Surgery

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11.1 Introduction

Imaging plays a crucial role in the evaluation of postoperative patients. Both computed tomography (CT) and magnetic resonance imaging (MRI) can be useful tools for evaluating these patients [1].

In the first few days of postsurgery, CT is widely the most commonly used method. It is a cheap and fast technique, compatible with most of the life-support devices currently used in the postoperative period, and it can be used even in patients under severe distress and requiring intensive care. Portable CT scanners are already in use in large centers: the in loco examination avoids transportation of the patient and minimizes related complications, such as accidental extubation. Moreover, CT is a technique that is very effective in displaying some of the possible significant complications in the postoperative period, such as fluid collections, pneumocephalus, hemorrhages, expansive effect lesions related to the surgical site, and herniations [2, 3]. However, it is not very sensitive to acute stroke or minimal foci of ischemia. Another advantage of CT is that a scan is so rapidly obtained, sometimes in just a few seconds, which even a patient that is not under profound sedation can be examined since he can collaborate until the scan is completed.

In some cases, radiation is not a significant problem when compared to the potential significant possible postoperative complications. In other cases, however, multiple scans can be the source of a massive load of radiation, with potential harms,

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cumulative and adverse effects for the patients in the course of their lives, especially the young ones. Some studies suggest that the lifetime risk of carcinogenesis attributable to radiation exposure in the first year post a major trauma can reach 3.5% [4, 5].

MR, on the other hand, does not use ionizing radiation, so it can be repeated as many times as needed for patients in whom multiple scans would be required [6]. Although MR may not be compatible with many of the life support equipment commonly used in the postoperative period, it is a very sensitive technique. It can be an essential tool for the diagnosis and monitoring of some conditions. For example, it is the gold standard imaging technique when searching for strokes or areas of acute ischemia, as well as for diagnosis and monitoring of the treatment of infections [7, 8]. It is also the best technique for detecting small fluid collections and empyema [8]. In these cases, the risks of performing a long MR scan (which usually lasts for 20–30 min) in a critically ill patient needs to be considered together with the information that this scan can provide.

Both CT and MR have restrictions. Metallic surgical materials, such as clips and implants, can cause substantial image degradation and limit its interpretation [9]. In some cases, a device that is not compatible with the magnetic field of the scanner can be a contraindication for the procedure, such as older pacemakers, certain aneurysm clips, cochlear implants, and specific intensive care unit (ICU) devices (such as a *Swan-Ganz* catheter). For unconscious or sedated patients, orthopedic implants that may heat under MR stimulation may be a relative contraindication.

In both techniques, contrast media can be used for better visualization of the vascular structures or to search for sites of pathological impregnation due to blood–brain barrier disruption. There are some remarkable differences between iodinated contrast media, as used for CT, and gadolinium-based contrast media, as used for MR. Iodinated contrast media can produce kidney dysfunction, which can be demonstrated by creatinine level fluctuations after contrast use. Basic questions for the assessment of the risk of renal disease are proposed, such as the Choyke questionnaire. Creatinine renal clearance should always be obtained before the exam for patients with risk factors for kidney disease. Although moderate kidney dysfunction is not a contraindication for the use of iodinated contrast media, in these cases, the risks and benefits should always be carefully weighed [10].

Gadolinium-based contrast media, however, does not cause kidney dysfunction. There is, though, a rare disease that can be caused by the use of contrast media in patients with known renal dysfunction: nephrogenic systemic fibrosis. This condition can cause progressive fibrosis of soft tissues and is related to gadolinium-based contrast media (primarily linear structured ones) in patients with end-stage renal insufficiency [11]. The American College of Radiology discriminates the gadolinium-based contrast media in three groups. Every facility that uses gadolinium-based contrast media should always classify their products in one of those groups. For groups 1 and 3, the risks are higher; for group 2, extremely low or nonexistent [12].

This chapter aims to review the most critical surgical-related findings that can be assessed by imaging, so that the attending physician can be familiar with the typical appearance of those procedures and materials. Still, examples of the most common and critical postoperative complications that can be evaluated by CT and MR will be depicted.

11.2 Main Findings

11.2.1 Burr Holes

11.2.1.1 Normal Findings

In the postoperative period, small burr holes are drilled throughout the bone. Burr holes, for example, can be used for inserting drain, intracranial monitors, or for draining extra-axial fluid collections or hematomas. Frequently burr holes are part of the craniotomy procedure. Those bone defects can be more easily depicted through CT, but MR can also demonstrate them. Sometimes different materials are used to fill the bony gap, including metallic prosthesis, fibrin glue, a mixture of bone and dust, or a preformed titanium cover that can also be used. The typical appearance of a burr hole includes a defect that extends from the inner to the outer table of the calvaria (Fig. 11.1), sometimes filled with fluid or with any of those material replacements. It is a normal finding to see enhancement in the borders of the burr hole, or enhancement in the entire hole, both in CT or MRI [1].

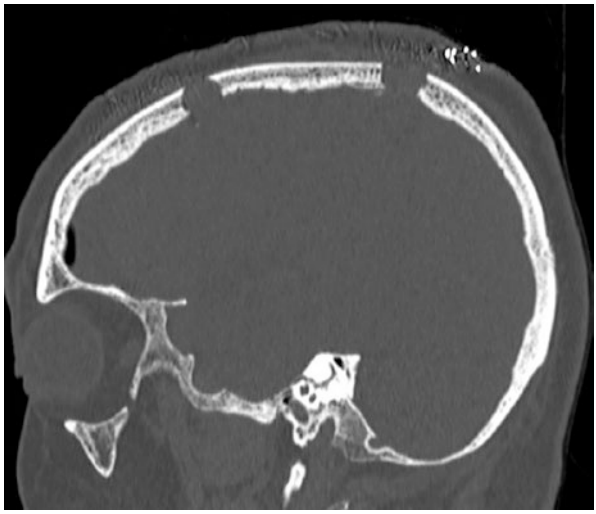

Fig. 11.1 Sagittal CT scan shows frontal and parietal burr hole and frontal pneumocephalus

11.2.1.2 Complications

Complications such as bone fracture, infections, and hemorrhages can be associated with all kinds of surgical procedures, and so are with burr holes (Fig. 11.2). One of the most harmful possible complications of burr holes is the unwanted penetration of the drill in the dural compartment and, if further, in brain parenchyma. There are reports of brain hemorrhages, extradural hematomas, subarachnoid hematomas, cortical contusions, or even intraventricular hemorrhages. This complication takes place more often with manual drills, and less often with automatic and more modern drills. Another significant complication of burr holes is the "growing" burr hole. In this situation, which occurs more frequently in pediatric patients, an enlarging pseudomeningocele insinuates through the bone defects and creates a cystic cavity inside the meningogaleal complex, which can be easily depicted both by CT or MRI [13].

11.2.2 Craniotomies

11.2.2.1 Normal Findings

This procedure is performed when the exposure of a more extensive area of the brain is needed. Craniotomies are programmed to avoid the need for excessive brain dislocation. There are at least six standard places where the craniotomies can be performed: pterional, subtemporal, anterior parasagittal, posterior parasagittal, median suboccipital, and lateral suboccipital (Figs. 11.3 and 11.4) [14].

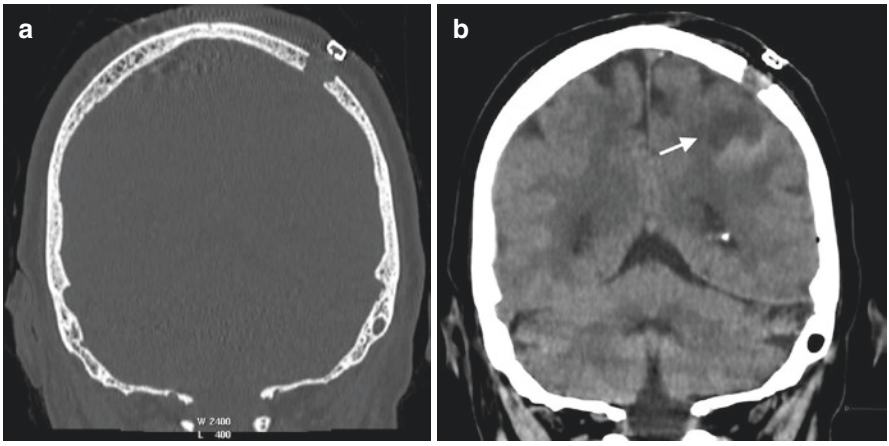

Fig. 11.2 Burr hole complication with venous stroke in a 45-year-old woman, 2 weeks after stereotactic biopsy of a brain tumor. Coronal CT scan (**a**, **b**) obtained with a bone algorithm (**a**) shows frontal burr hole. Parenchyma hypoattenuation (**b**) adjacent to the frontal burr hole, represent a venous stroke (arrow)

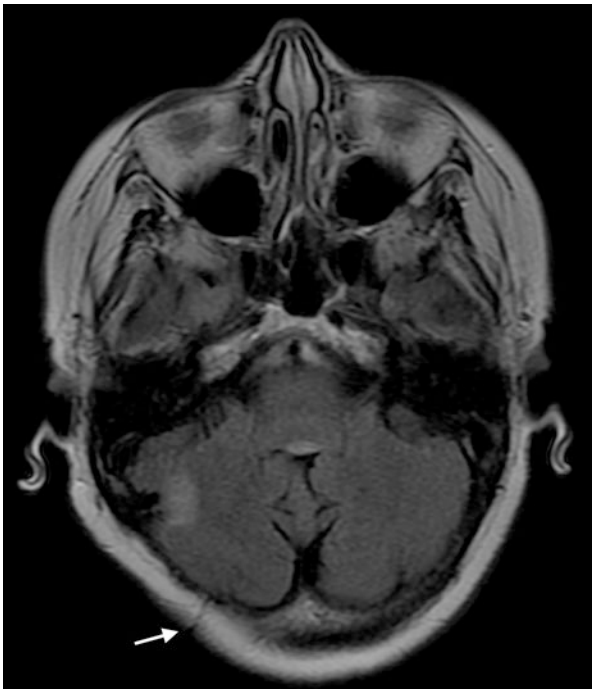

Fig. 11.3 Right lateral suboccipital craniotomy in an 8-year-old boy 1 year after debulking of a right cerebellar pilocytic astrocytoma. Axial T1 MR image shows a lateral suboccipital craniotomy (arrow)

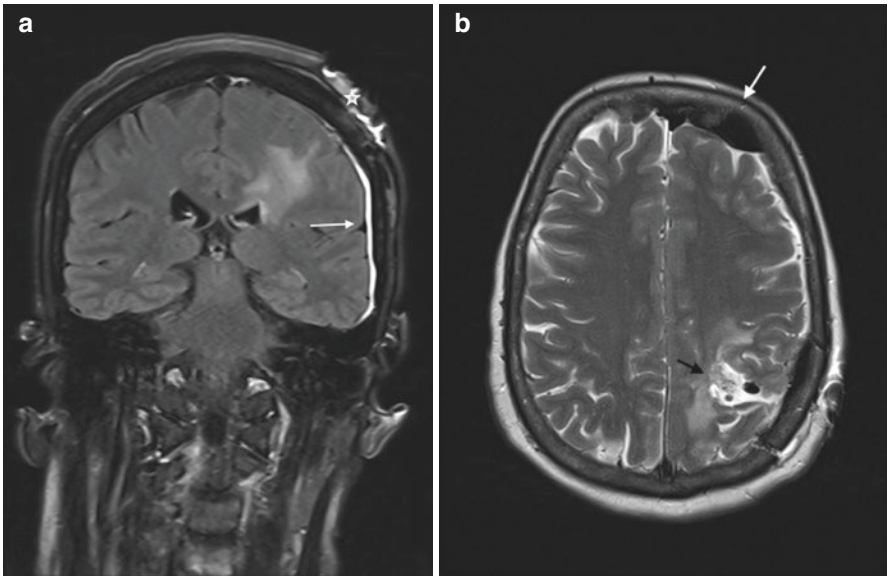

Fig. 11.4 Subdural fluid collection in a 41-year-old man 2 days after a craniotomy for debulking of a parietal glioblastoma. Coronal FLAIR post-contrast MR image (**a**) shows a posterior parasagittal craniotomy (☆) and a hyperintense subdural fluid collection (arrow). Axial T2 MR image (**b**) shows a frontal pneumocephalus (white arrow), under the craniotomy the resection cavity is characterized (black arrow)

The steps needed to perform the craniotomy can help to understand the most typical findings in the postoperative period. As the surgeon needs to remove a skin flap bigger than the bone flap, it is usual to see fluid collections accumulated in the subgaleal space, mixed with air, blood products, and sometimes Cerebrospinal fluid (CSF) (Fig. 11.4). It is also a typical finding to have the same type of fluid in the space underneath the bone flap. Often it is hard to distinguish if the fluid collection lies in the subdural or extradural space. Most frequently, it resides in the extradural space.

The bone flap habitually has sharp edges in the first months of the postoperative period. Over the months, the edges can become fused to the external marginal bone, or can become progressively rounded, sometimes with decreased bone density, finding that can be better illustrated in CT than in MR. The autologous bone place may be replaced immediately at the same surgical time. Sometimes, however, the bone flap needs to be cryopreserved and replaced in a second time (autologous cryopreserved cranioplasty). The bone fusion is slightly faster in the immediate replacement group than in the cryopreserved group, especially in the first months [15].

It is also a standard finding to have enhancement close to the craniotomy (Fig. 11.5). It can be detected as early as in the first 10 hours after the procedure, can last for up to 40 years afterward, and can be identified by MR more clearly than by CT.

Another normal finding postcraniotomy is pneumocephalus (Fig. 11.6). After supratentorial craniotomy, all patients demonstrate pneumocephalus on CT within

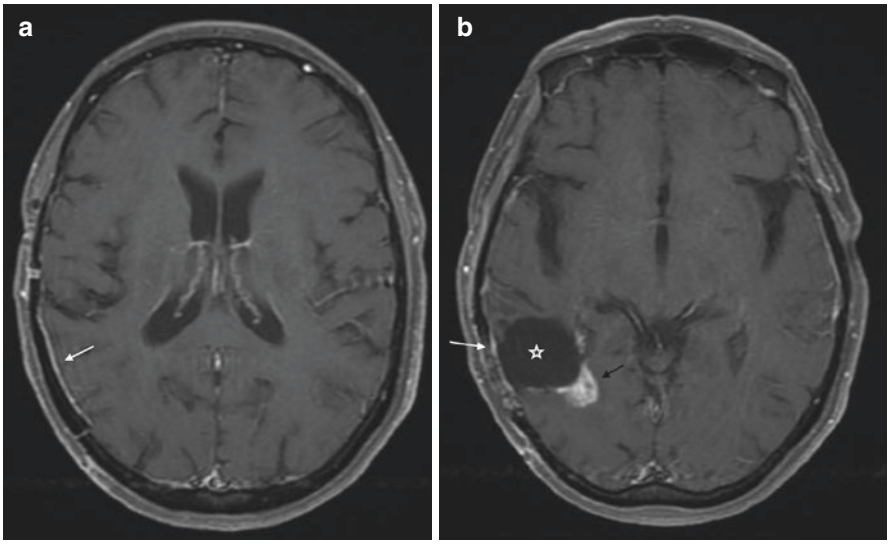

Fig. 11.5 Dural enhancement in a 54-years-old woman, 6 months after a craniotomy for debulking of a fronto-parietal glioblastoma multiforme (GBM). Axial post-contrast T1 MRI (**a**) and (**b**) shows smooth enhancement of the thickened dura mater (arrow) beneath the craniotomy flap. The (☆) represents the resection cavity (**b**), with enhancement lining the posterior and medial aspects (black arrow) of the resection cavity, representing tumor regrowth

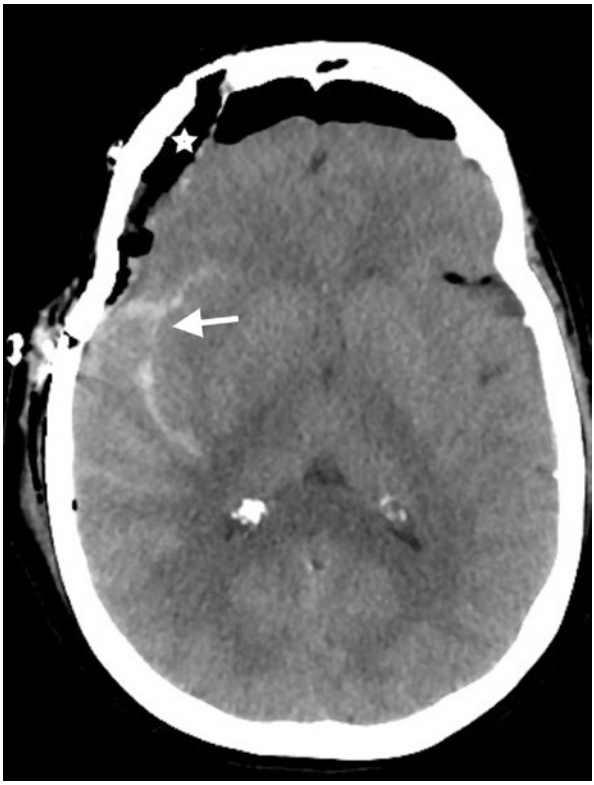

Fig. 11.6 Subarachnoid hemorrhage and pneumocephalus in a 57-year-old man 1 day after craniotomy for meningioma resection. Axial CT scan shows subarachnoid hemorrhage (arrow), note also the pneumocephalus (☆) and soft tissue scalp edema

the first two postoperative days; 75% show pneumocephalus 1 week after the surgery, but in 26% of the patients it can persist until 3 weeks postoperatively [16]. It can be detected more clearly by CT (by measurement of its negative Hounsfield Units), but can also be detected by MR (by its magnetic susceptibility effect).

MR can also depict signs of CSF hypotension after craniotomies. The most common signs of this condition are pachymeningeal thickening and enhancement, dural venous sinus ectasia, and pituitary turgescence. Although rare, in more severe cases, a "sagging brain sign" of the brainstem or the closure of the premesencephalic angle cistern may be present. Almost invariably, in these cases, there is an active or occult CSF drainage [17, 18].

11.2.2.2 Complications

Tension Pneumocephalus

This complication is a neurosurgical emergency, so it needs to be quickly recognized and treated. Although this condition has a classic radiological appearance (the "Mount Fuji sign") (Fig .11.7), the same aspect can be observed in asymptomatic

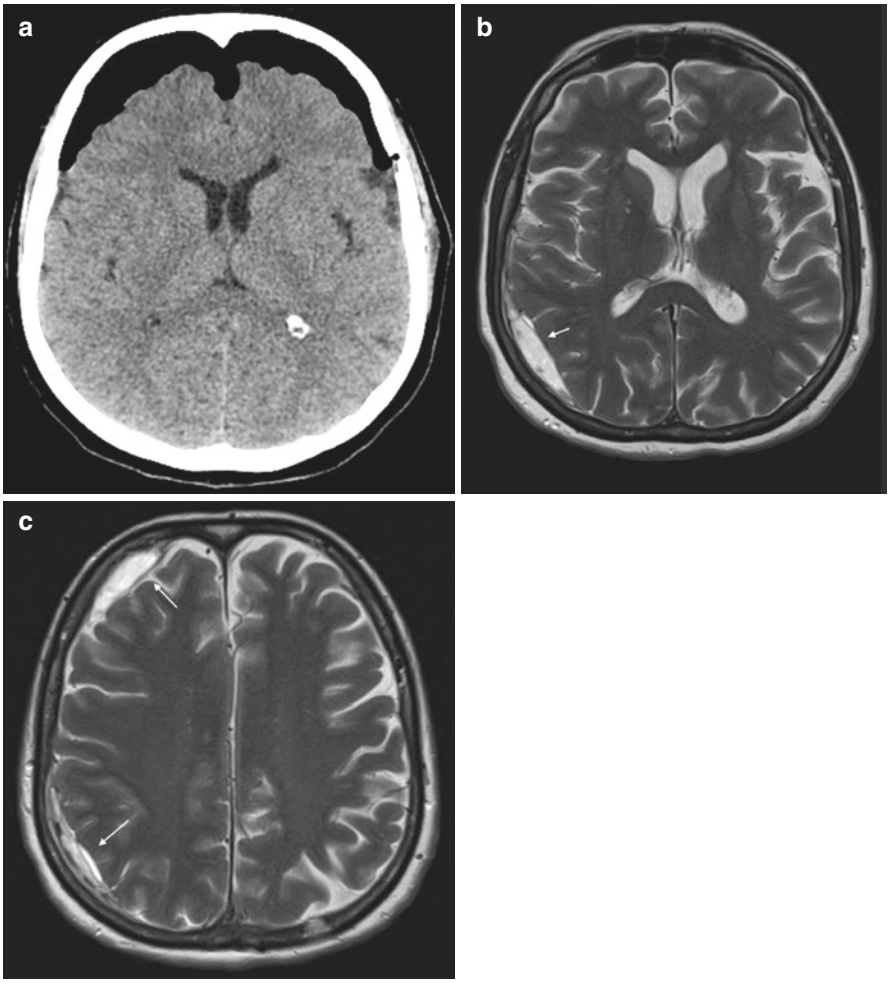

Fig. 11.7 Tension pneumocephalus in a 47-year-old man status after debulking of a meningioma located inside the superior sagittal sinus and subdural hygromas after few months of the craniotomy. Axial CT image (**a**) shows pneumocephalus along the bifrontal convexities with mass effect on the frontal lobes and displacement of the frontal lobes from the falx cerebri, also known as the "Mount Fuji Sign." Follow-up axial T2 MRI (**b**, **c**) shows subdural hygromas, extra-axial fluid collections with T2 hypersignal, over the right parietal and (**c**) frontal subdural spaces (arrows)

patients. Therefore, in these cases, a strict clinical–radiological correlation is required. This condition is more often found in situations where nitrous oxide is administered in patients with previously known pneumocephalus and is more commonly found in posterior fossa surgeries. Treatment can be conservative (administer 100% oxygen) or surgical, depending on the symptoms [1, 16, 19].

Surgical Site Infection

Craniotomy-related infection can occur in the soft tissues or the bone flap. Although usually suspected clinically, CT and MR play an essential role in establishing how deep it extends. When limited to the extracranial tissues, enhancement and possibly small fluid collections in the subcutaneous space may be found. The subgaleal space is usually spared. Sometimes, however, the infection can be located in the intracranial compartment, and if so, CT and MR can detect augmented dural or leptomeningeal enhancement, and sometimes fluid collections. When there is an infected fluid collection, MR can be much more specific in defining its nature: an empyema is usually identified by its restricted diffusion. The Apparent diffusion coefficient (ADC) map in the diffusion sequence is a very reliable tool for the identification of infection inside a fluid collection in the preoperative period. In the postoperative period, however, it lacks both sensitivity and specificity during the first 3 months postoperatively, regaining the power to detect empyema after that period [8].

Dural sinus infections may eventually be detected as complications of intracranial infection, a finding that should evoke a septic thrombosis and is life-threatening. Although soft tissue craniotomy-related infections usually are no tough diagnosis, defining if there is osteomyelitis in a bone flap can be quite challenging. The sign of infection in a bone flap in CT can be either bone reabsorption, sometimes with osteolytic lesion within, or can also be sclerosis of the flap. The problem is that uninfected bone flaps can display the same appearance. For this reason, the condition of the bone flap in CT scans cannot define if it is infected or not. Signs of infection should be searched in the vicinity of the bone flap, for example, edema of the fat, new or growing collections, or even an apparent source of infection, such as fistulas with the intracranial compartment or with the nasal cavities. It is also more common to see osteomyelitis when there is a penetrating injury. On MR, the signs of infection are also not very reliable (Fig. 11.8). High signal intensity in T2 sequences due to edema can sometimes be seen, but it can also be observed in asymptomatic patients [1, 20].

Extradural Abscess and Subdural Empyema

Although some signs of infection are usually seen, fever and headache appear only in a minority of cases. Clinical signals tend to be more indolent and may present months after surgery. In CT, there is usually a fluid collection adjacent to the bone flap, but sometimes it extends through the extra-axial space. It is typically hypodense but of a higher density than CSF, and with peripheral enhancement. On MR, extradural abscesses and subdural empyemas tend to show a more hyperintense signal than CSF on T1, more hypointense than CSF on T2, and more hyperintense than CSF on FLAIR. Edema and enhancement of the underlying brain parenchyma may indicate cerebritis. The classic finding of an intracranial abscess is the restricted diffusion in its central component. However, in the postoperative phase, this is not always true. In many cases, an empyema or an extradural abscess can exist without

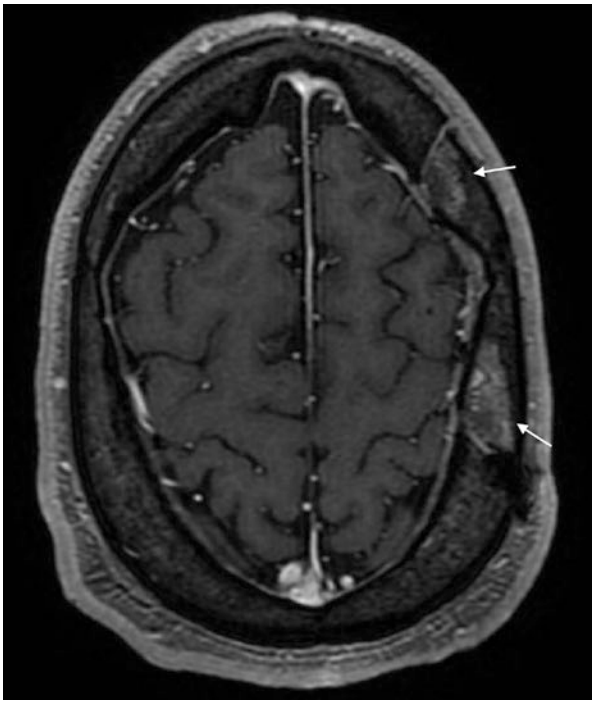

Fig. 11.8 Craniotomy complication with clinical signs of osteomyelitis in a 30-year-old man 2 years after debulking of a GBM. Axial SPGR post-contrast MR image shows enhancement in the anterior parasagittal craniotomy (arrow)

restricted diffusion, and this is quite frequent, though, especially in those cases where there is no contrast enhancement. Moreover, in some cases, blood products can simulate restricted diffusion, which may make the diagnosis even more challenging [1, 20, 21].

Extradural Hematomas

They can be regional hematomas (just below the bone flap, which account for the majority of the cases) or they can be remote (in a location distant to the site of craniectomy) (Fig. 11.9). For all of those hematomas, the risk factors are similar: coagulation disorders, rapid decompression of hydrocephalus, and low intracranial pressure in the postoperative period [22].

Remote Cerebellar Hemorrhage

This complication is thought to be related to the drainage of high volumes of CSF. Although it can be quite symptomatic, usually displaying cerebellar signs, it is a relatively benign condition, most of the times with complete remission. It can easily be demonstrated by CT as an area of high density (blood) interspersed in between the cerebellar fissures, a finding described as the "zebra" pattern [23] (Fig. 11.9).

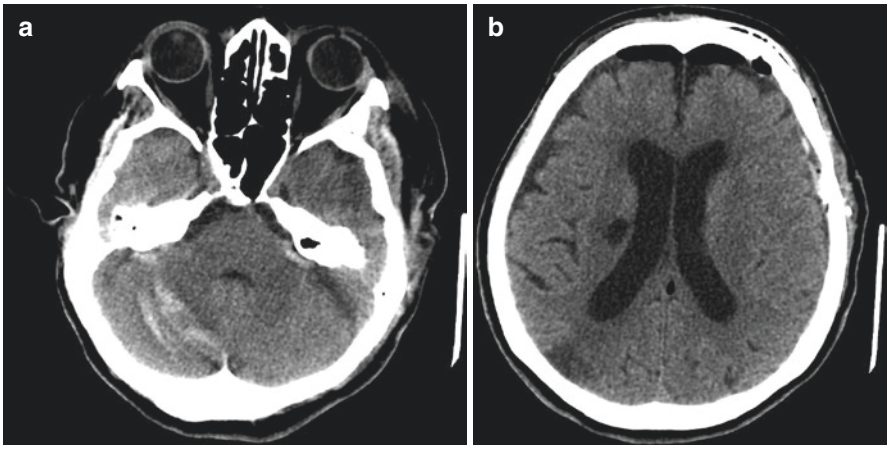

Fig. 11.9 Remote cerebellar hemorrhage in a 55-year-old man 1 day after a left pterional craniotomy for clipping of an aneurysm. Axial CT image (**a**) shows curvilinear streaks of acute hemorrhage (arrows) in the folia and sulci of the right cerebellar hemisphere. Axial CT image (**b**) shows a frontal pneumocephalus, an extradural hematoma just below the bone flap, also characterized an acute infarct of the right posterior cortical border zone

Intraparenchymal Hemorrhage

Despite the fact that the presence of some blood in the surgical site is a common finding (Fig. 11.10), hematomas with mass effect in the surgical site are fortunately a rare condition. Most often, it occurs in cases of incomplete tumor resection or incomplete homeostasis of the surgical bed, and in cases of blood dyscrasias. In CT, intraparenchymal hemorrhage can be very hyperdense in the initial days (Fig. 11.11) and become isodense to brain parenchyma after around 10 days. On MR, the signs of intraparenchymal hematomas follow a very complicated transition of phases in both T1 and T2 sequences, but all of them exhibit very low signal in Susceptibility weighted magnetic resonance sequences (SWI) and T2* sequences [22, 24].

11.2.3 Craniectomies

11.2.3.1 Normal Findings

This technique consists of leaving the bone gap without the bone flap after performing a craniotomy. This can be the indicated approach for removing infected bone flaps (Fig. 11.12), for decompressing hematomas or malignant middle cerebral artery stroke, and can be the chosen technique for posterior fossa lesions, to avoid the risks of postsurgical posterior fossa hypertension.

The craniectomy can be bilateral or unilateral, depending on the size, location, and nature of the underlying lesion. Moreover, the dura can be left closed, but for a

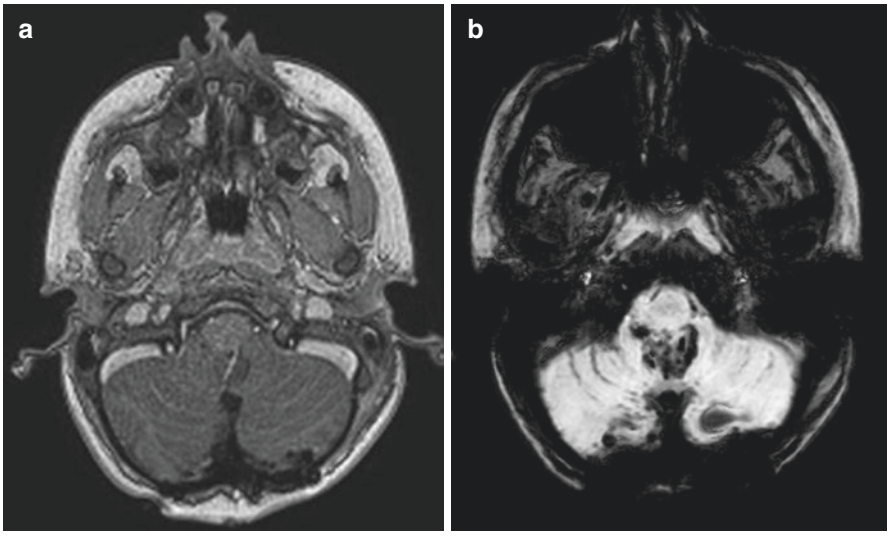

Fig. 11.10 Normal post-operative appearance. Axial post-contrast SPGR MRI (**a**) at the level of the posterior fossa shows occipital craniectomy, and magnetic susceptibility sequence (**b**) demonstrated an amount of blood products along craniotomy and in the subarachnoid space, in (**a**) a profoundly hyposignal component

better decompression, the dura may be left open or managed by duroplasty. The typical appearance (Fig. 11.12) may be a slim meningogaleal complex, in which there is a sum of the dura mater and the galea. Sometimes, however, there may be a line of fluid between these two layers. Sometimes (more often in posterior fossa craniectomies), there may be a protrusion of the subarachnoid space through the bone defect, producing a pseudomeningocele [1, 14].

11.2.3.2 Complications

Extracranial Herniation

This complication is very common. It can occur when there is a disproportion between a large ingurgitated intracranial content and a relatively small skull defect. Some harmful consequences of this herniation may occur: in up to one-third of the cases, contusions in the borders of the craniectomy or venous infarcts in the margins of the herniated parenchyma. On CT, these fluid collections usually show low attenuation [1, 22, 25].

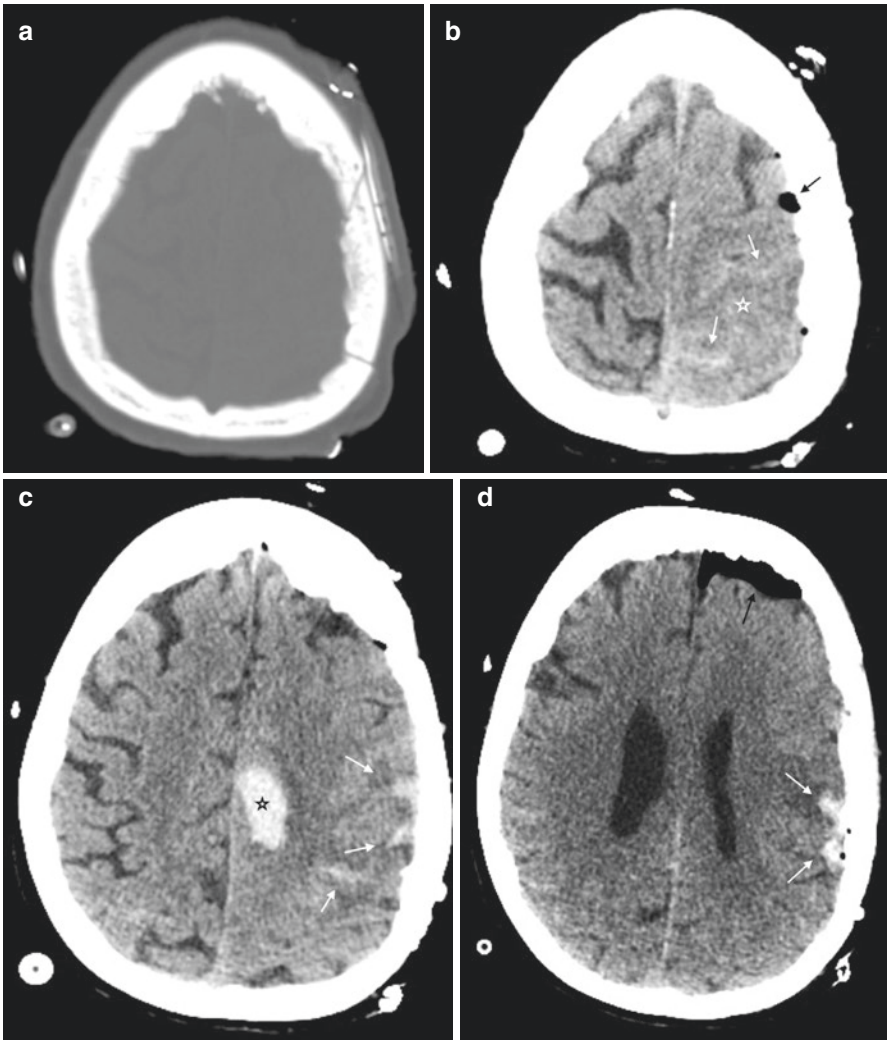

Fig. 11.11 Subarachnoid and intraparenchymal hemorrhages in a 34-years-old woman, after debulking of a meningioma. Axial CT scan (**a**) shows a frontoparietal craniotomy. Axial CT scans (**b–d**) show subarachnoid hemorrhage (white arrow) over the left frontal and parietal lobes associated with loss of gray–white differentiation, from combined cytotoxic and vasogenic edema (**b**) in the left convexity (☆) and pneumocephalus (black arrow). Foci of intraparenchymal hemorrhage (**c**) along the left gyrus cinguli (☆)

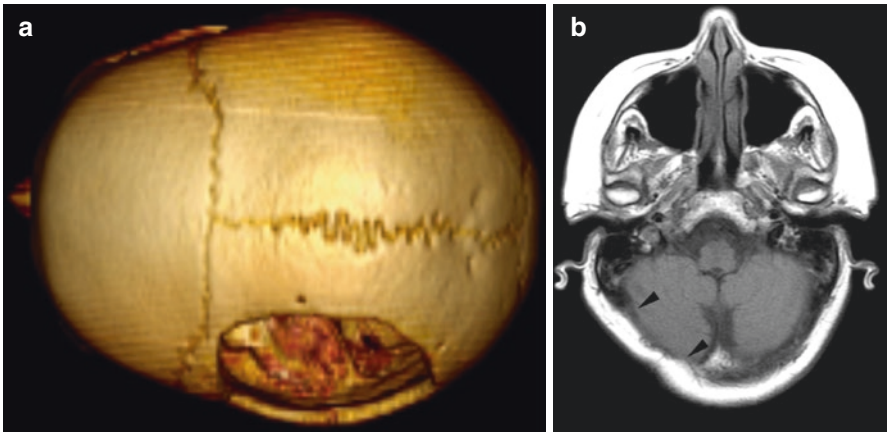

Fig. 11.12 (**a**) Subtemporal craniectomy in a 37-years-old man for removing infected bone flap. Volume-rendered CT image (**a**) shows subtemporal craniectomy. (**b**) A suboccipital craniectomy in an 85-year-old female, as demonstrated by a gap in the calvaria in an axial T1 sequence

Hygromas

Fluid collection can occur in the subdural or the subgaleal regions. They can be regional and adjacent to the craniectomy, or they can be in remote areas, for example, in the interhemispheric fissure. They can be related to CSF homeostasis disturbances, such as CSF hypotension. On rare occasions, pressurized fluid collections can cause external brain tamponade, a situation in which there is neurologic deterioration, mass effect, and clinical recovery after drainage of the collection. These collections are usually hypodense and may produce a bulge externally at the site of craniectomy [1, 22, 25].

Trephine Syndrome

It is also known as the "sinking skin flap syndrome." In late stages postcraniectomy, atmospheric pressure disrupts the Monro–Kellie model and can create a compression over the brain parenchyma, decreases cerebrospinal fluid tension and blood flow, which progressively shrinks to the inside of the cranial vault. Symptoms may be nonspecific. Neurological symptoms include motor, cognitive, and language deficits that improves with cranioplasty [26].

Paradoxical Herniation

This acute complication has a relation to the atmospheric pressure similar to that of the trephine syndrome, sometimes referred as late stage of the trephined syndrome. In these cases, a CSF drainage can predispose the acute pressure imbalance, brain

sag, and, ultimately, descending or transtentorial brain herniation. Most often, it occurs from 2 weeks to 2 months postsurgery. Symptoms can be focal neurologic deficits, autonomic dysfunction, or signs of brainstem dysfunction. At imaging, those cases demonstrate a midline herniation away from the craniotomy, together with the sunken meningogaleal complex. Treatment is a neurosurgical emergency. Calvarial defect coverage stops CSF leakage and is sometimes needed to increase intracranial pressure, altogether with placing the patient in a Trendelenburg position [27].

11.2.4 Cranioplasty

The term cranioplasty describes the repair of a cranial defect with autologous or prosthetic materials (Fig. 11.13). It can be used to cover congenital defects, bone gaps that result from a craniectomy, or be the result of tumor resection, for example. The use of autologous bone graft is one of the most classic techniques. The autografts can be the calvarial bone flap previously stored in the abdominal subcutaneous fat or can be a fresh autograft obtained from a rib or the calvarial bone [1, 28]. The rates of infection in the bone stored flaps is more significant than that of the fresh grafts, especially if the bone flaps have been previously autoclaved or irradiated [29]. The appearance of a bone flap is usually the same as that of a craniotomy. As time goes by, resorption can happen at a faster rate than that of a craniotomy. Cranioplasties can also be made from prosthetic materials, such as titanium mesh or acrylic. As a point

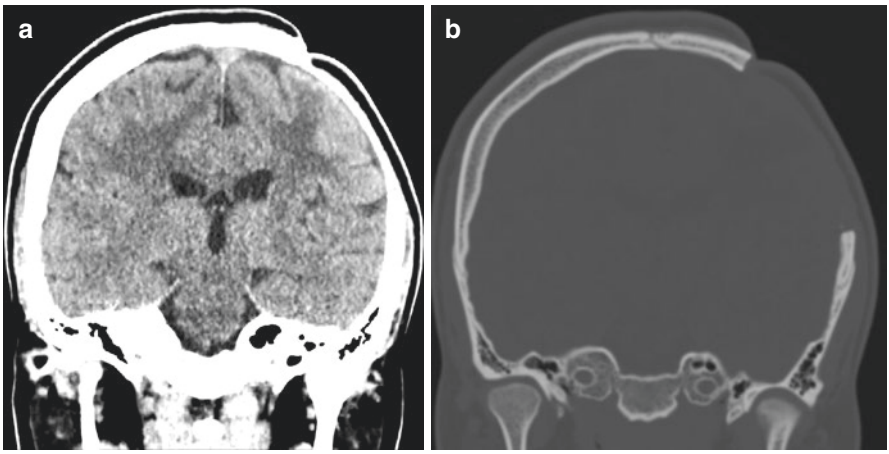

Fig. 11.13 Acrylic cranioplasty in a 16-year-old girl after evacuation of an intracerebral hematoma caused by an arteriovenous malformation. Axial CT image obtained with brain window settings (**a**) shows the cranioplasty as a smooth region of high attenuation that is thinner than the calvaria. Axial CT image obtained with bone window settings (**b**) shows that the cranioplasty has lower attenuation than bone

to remember, the acrylic cranioplasties usually have bubbles of gas in their inside, which should not be confused with infection [30]. Cranioplasty is a procedure that has a relatively high incidence of adverse outcomes. Among the many possible complications, there are draining sinus, exposure of the reconstruction material, resorption of graft, thermal sensitivity, migration of reconstruction material, among others. All of those complications can be detected both in CT as in MR. If there is metallic material being used, such as titanium, then imaging artifacts can be expected. In CT, there is a bean hardening artifact, and in MRI, there is the magnetic susceptibility artifact. Both of them can limit the diagnostic accuracy of the images severely [31].

Moreover, contrast enhancement in the margins of the cranioplasty is a normal postoperative finding for both infected or uninfected cranioplasty, so it cannot be used for this differentiation. Clinical and evolutive correlation is usually very useful in establishing the diagnosis of cranioplasty-related infection. Fluid collection is a common finding postcranioplasties (Fig. 11.14). Although most of the fluid collections are uninfected, sometimes CT and MR can help to detect signs of infection, such as contrast enhancement, peripheral edema, and sometimes restricted diffusion (Fig. 11.15). The diffusion sequence can help. If restricted diffusion is found in the fluid collection alongside the cranioplasty, there is a higher probability of infection [1, 28, 31, 32].

11.2.5 Ventricular Shunts

There are two main types of ventricular catheters. They can be internalized internal ventricular shunt (IVD) or externalized External ventricular shunt (EVD). External ventricular catheter (EVC) is commonly used in the ICU setting, sometimes inserted through external landmarks. They are commonly inserted through a frontal burr hole, with extremity aimed to be anterior to the Monro foramen. Alternatively, the ECD may be inserted through a parietal burr hole. The typical findings in the postoperative period include edema at the margins of the catheter, a thin line of supratentorial dural enhancement (related to the reduction of CSF volume), as well as blood products along its trajectory [33, 34].

Many complications can be attributable to ventricular shunts. Shunt infections are reported with a variable incidence, from 3 to 28% of cases. *Staphylococcus epidermidis* is the most common pathogen. Infection signs usually begin from 1 to 3 months after the shunt. Both CT and MRI can depict enhancement in the ependymal lining of the ventricular system (Fig. 11.16), and sometimes on the surface of the subarachnoid space, but MRI's sensitivity for infection is almost always superior [22, 33, 35]. Shunt obstruction is also possible, although the catheters usually have multiple perforations. The most common places of obstruction are the tip of the catheter, sometimes due to trapping of choroid plexus inside of the shunt, followed by obstruction at the valve. Clinical and imaging signs of hypertensive hydrocephalus can often be detected, such as ballooning of the lateral and third ventricles and, sometimes, less profound cortical sulci. If a shunt obstruction is suspected, comparison to previous exams always yields essential information [33]. Overdrainage

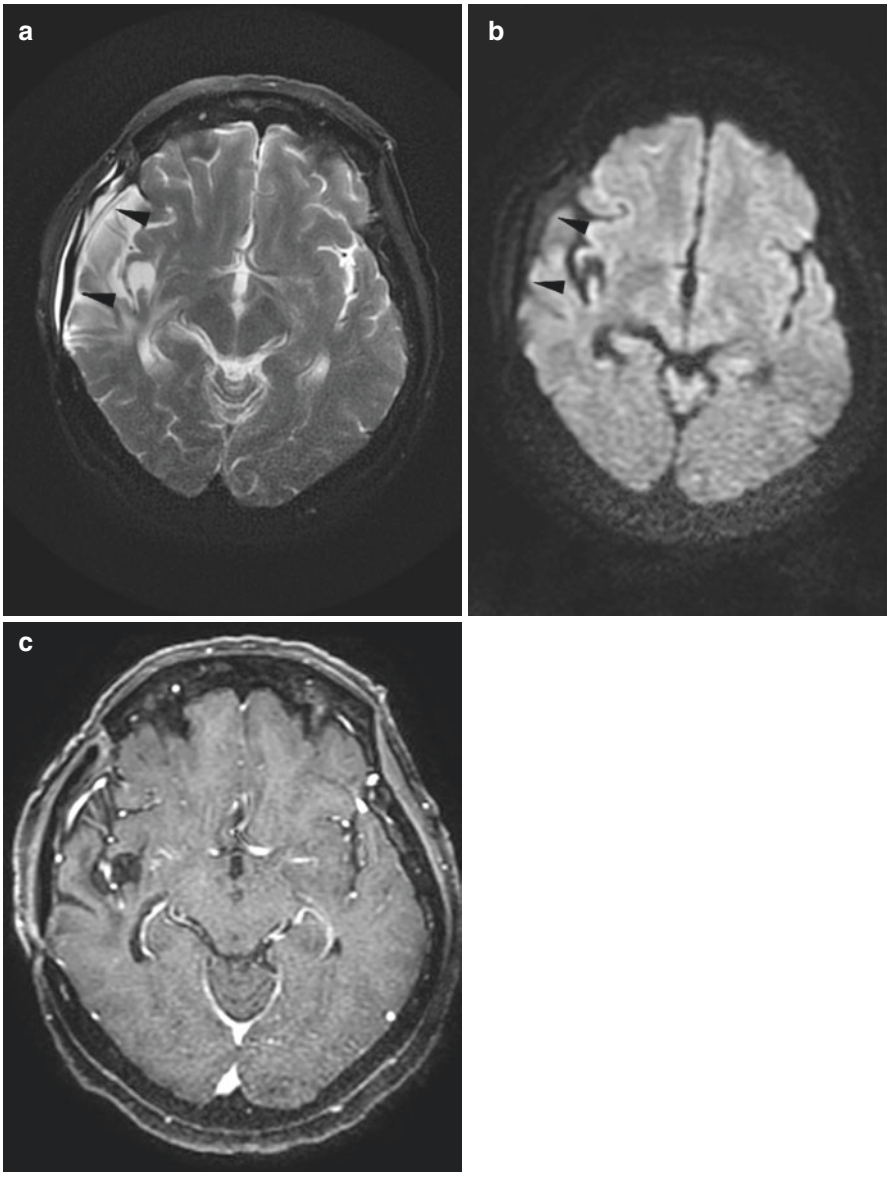

Fig. 11.14 Noninfected fluid collection surrounding cranioplasty. There is a fluid collection in the subgaleal and extradural compartments that shows a signal similar to liquor both in T2 (**a**), diffusion (**b**) and without marginal contrast enhancement (**c**)

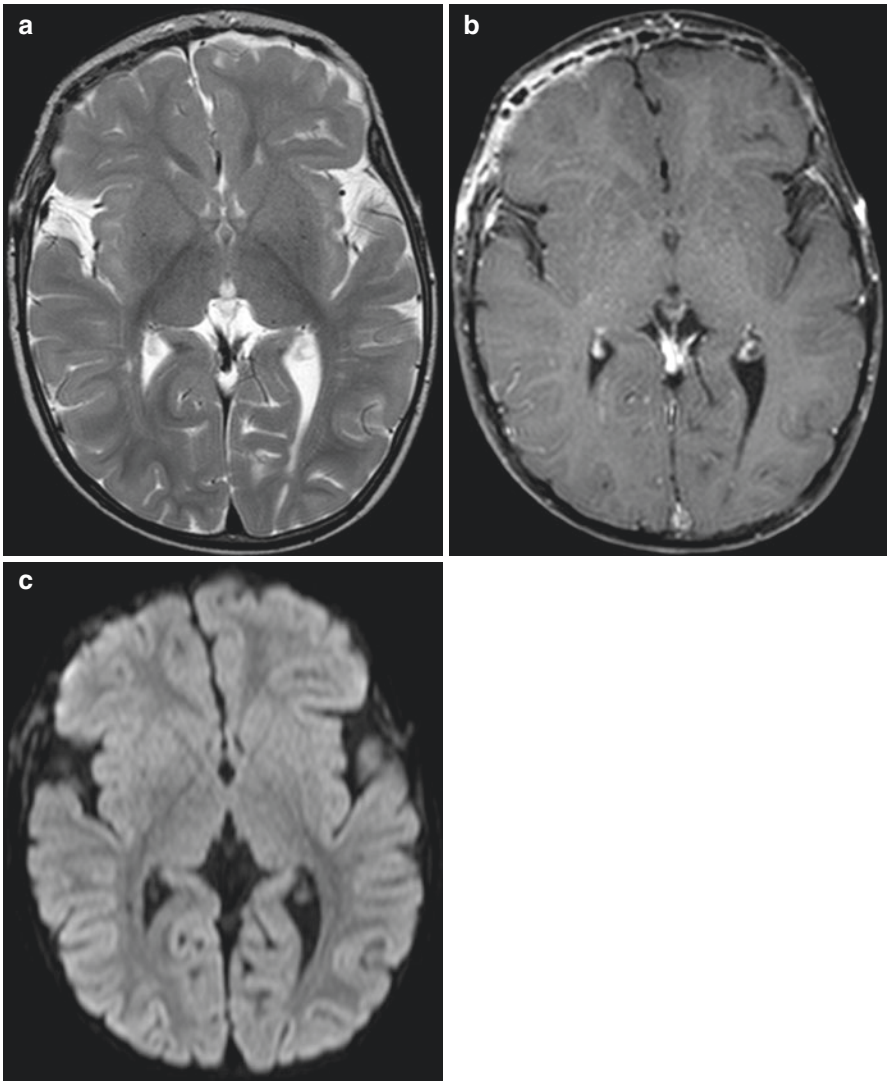

Fig. 11.15 Infection in a cranioplasty in a 7-year-old girl. There was a clinical diagnosis of infected cranioplasty. In the T2 sequence (**a**), there are no significant findings other than the cranioplasty itself. The post-contrast image, however, shows a strong contrast enhancement (**b**, **c**) both in the intra and in the extracranial compartments. In the diffusion sequence, however, there is no significant restricted diffusion, which shows the limited utility of the diffusion sequence to this objective

occurs when the catheter drains more CSF than necessary; it is usually a chronic finding. The most common findings are the collapse of the ventricles, as well as pachymeningeal thickening and enhancement. If the overdrainage progresses further, benign fluid collections can be formed in the extra-axial space, which can be

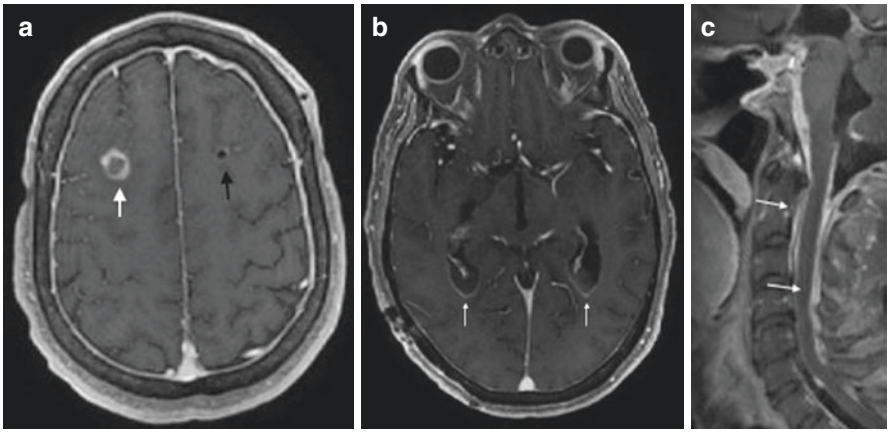

Fig. 11.16 A patient with a history of type 2 diabetes mellitus and hydrocephalus, external ventriculostomy catheter placement presents, 10 days after ventriculostomy placement with fever, headache, and altered mental status, the catheter was removed and a new one in the other side was placed. Axial SPGR post-contrast MRI (**a**, **b**) shows (**a**) an exuberant enhancement on the path of the removed catheter (white arrow), (**b**) ependymal enhancement of the lateral ventricle (arrow). Sagittal T1 post-contrast (**c**) shows in the cervical spine enhancement on the surface of the subarachnoid space and nerve roots (arrow). These findings are consistent with ventriculitis with extension to the meninges and cervical nerves

either hygromas or chronic subdural hematomas. Other signs of CSF hypotension can appear, such as turgescence of the dural sinuses and the pituitary. The "sagging" of the brainstem can also be found in more extreme cases (Fig. 11.17).

On the other hand, some patients may have less drainage than expected. In these cases, postoperative imaging studies depict the failure to correct the hydrocephalus. The "slit ventricle syndrome" is a condition where there is a shunt malfunction due to ventricle collapse. Clinically this can be suspected when there are intermittent signs of CSF hypertension, such as elevated measured pressure or papilla edema on fundoscopy, with small ventricles [33, 36]. Another complication of ventricular shunts is the misplacement of the catheter, which can be located inside the brain parenchyma or in the choroid plexus, for instance (Fig. 11.18). In those cases, the postoperative CT can easily detect the misplacement.

Compartmentalization is another complication. It is most common in cases where there was a previous infection, hemorrhage, or inflammatory process in the ventricular system. Membranes can develop and can cause the ventricular system to become compartmentalized. As the ventricular drainage progresses, those compartmentalized places fail to reduce their volume. Those cases usually show a reserved prognosis. Some of them are treated with multiple endoscopic fenestrations, or sometimes with numerous shunts placement, but usually, there is not a fully functional drainage [37]. A paradoxical herniation is a very uncommon complication of the ventricular shunt. It happens when there is a craniotomy, and the atmospheric pressure pushes the brain, resulting in subfalcine herniation toward the shunted side. Both CT and MR easily detect these situations.

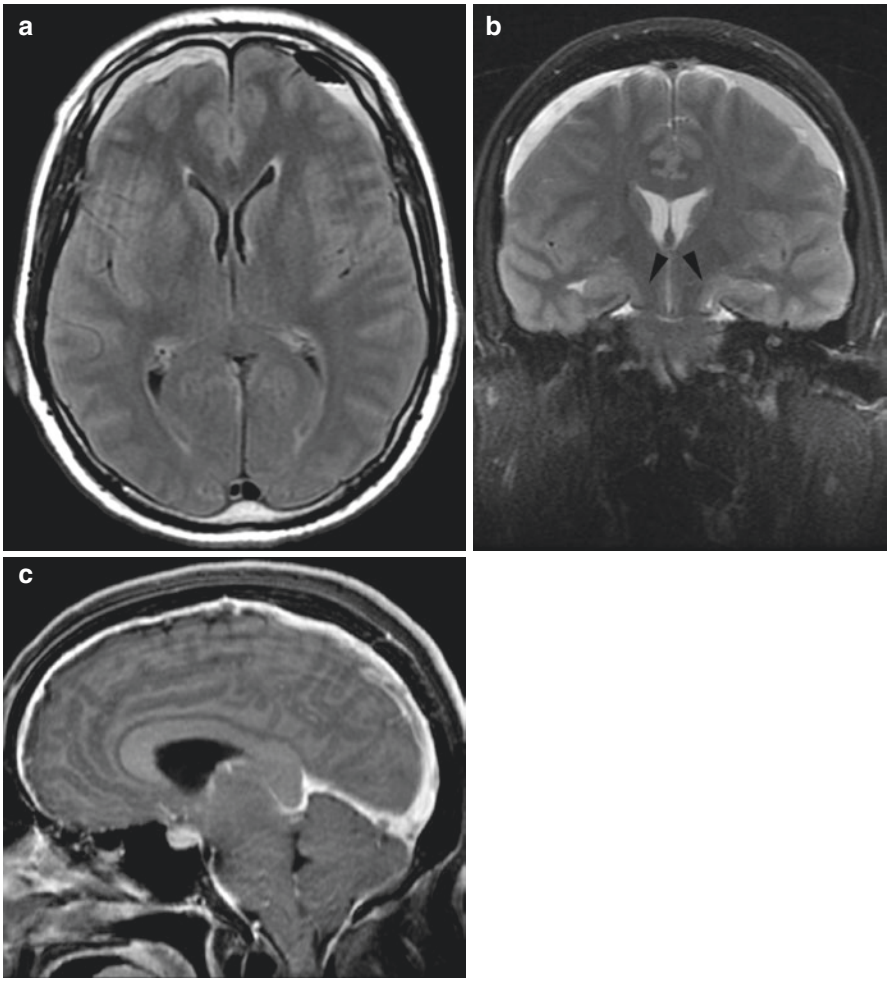

Fig. 11.17 Signs of liquoric hypotension in MR imaging. Axial FLAIR image (**a**) shows hygromas in both frontal regions and small sized ventricles. Coronal T2 image (**b**) demonstrates the same fluid collection, but also signs of sagging brain with herniated uncus bilaterally. Sagittal post-contrast T1 image shows diffuse post-contrast pachymeningeal enhancement, as well as pituitary turgescence and liquor paucity in the basal cisterns with signs of sag of the brainstem

11.2.6 Tumor Resection

Tumor resection can produce an extensive set of complications that include infections, hemorrhages, vasogenic edema, among others [38]. It is useful to know the normal evolution of a postoperative cerebral surgical site. During the first 24–48 hours postsurgery, there is cytotoxic edema at the margins of resection. This is a standard finding in the early postoperative time and should not be confused as a stroke (Fig. 11.19). As time goes by, the area of restricted diffusion becomes

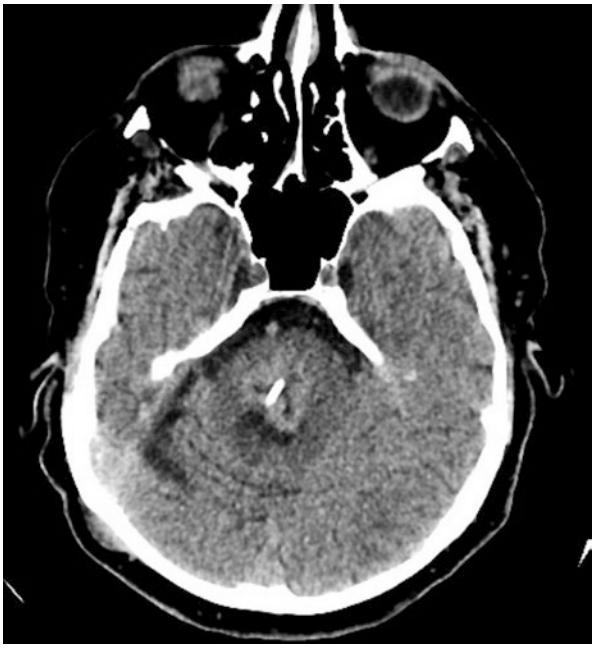

Fig. 11.18 Catheter misplacement. Axial CT at the level of the midbrain shows a catheter in the middle of the pons

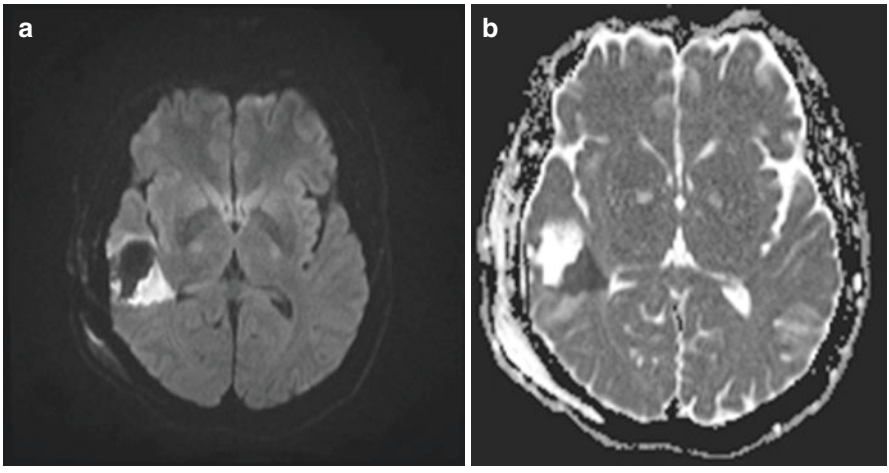

Fig. 11.19 Cytotoxic edema after debulking of a metastasis in a 78-year-old man. Axial trace DW image (**a**) shows a hyperintense lesion and a low ADC (**b**) indicating restricted diffusion

impregnates, and diffusion sequence starts to show facilitated diffusion. This period is critical, for those imaging findings can easily be confused with surgical site infection or viable tumor (Fig. 11.20).

Resection of gliomas often shows complications in the postoperative period, and they are more frequent following incomplete tumor resection. Postoperative

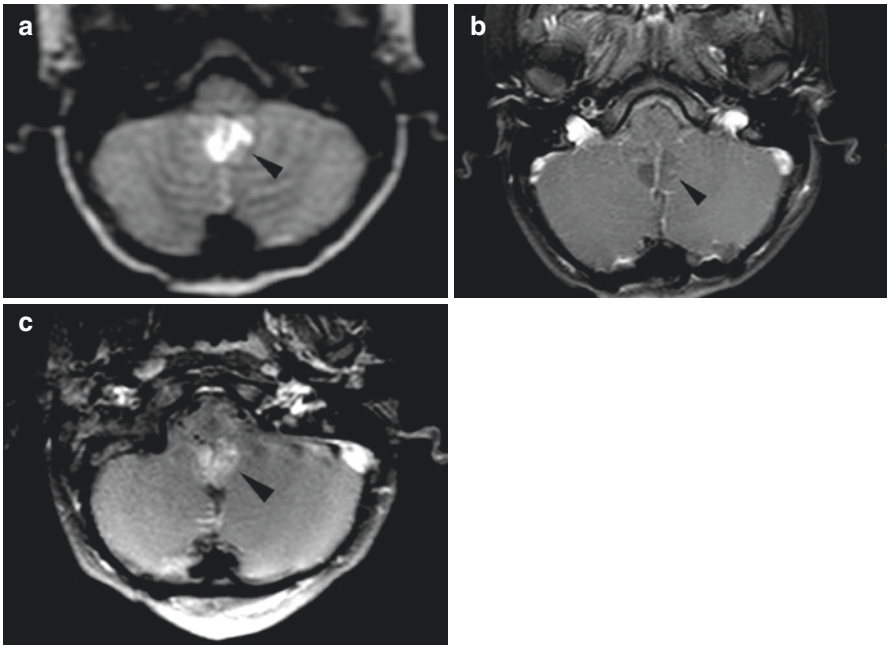

Fig. 11.20 Post-surgical site after complete removal of an ependymoma. In the first post- operative day, there is restricted diffusion at the margins of the surgical cavity (**a**). There is no impregnation in this site (**b**). After 2 weeks, there is impregnation at this same place, attributable to reparative processes

hemorrhages are one of the most critical possible complications (Fig. 11.21). In the "wounded glioma syndrome," extensive edema and hemorrhages can occur after partial glioma resection, which can be located both at the surgical site or remote to the surgical site. Another complication of the glioma resection is dural sinus thrombosis, with a cumulative risk of around 20% in the first-year postsurgery. Posterior fossa tumor is susceptible to some specific complications, such as CSF fistulas, pseudomeningocele, and hydrocephalus, all of them can be easily detected by both CT and MR. Resection of extra-axial tumors can also have some specific complications, such as sinus thrombosis and venous infarcts. Although sinus thrombosis can be demonstrated both by CT and MR, venous infarcts can be much better detected by MR, especially by diffusion-weighted imaging [1, 8, 25, 39]. Surgical site infection is also a possible complication in the management of brain tumors. As previously discussed, the infection can begin in the skin and meninges, and in these sites, the inflammatory signs, such as edema and enhancement in the margins of the surgical site may be very helpful in establishing the diagnosis.

Although MR can depict signs of meningeal inflammation in the more established and severe cases, liquor plays a central role in establishing this diagnosis. In the evaluation of postoperative brain abscess, however, MR plays a pivotal role. At the beginning of the infection process, cerebritis starts at the margins of the surgical site (Fig. 11.22). Usually, there is edema that can be detected as a developing

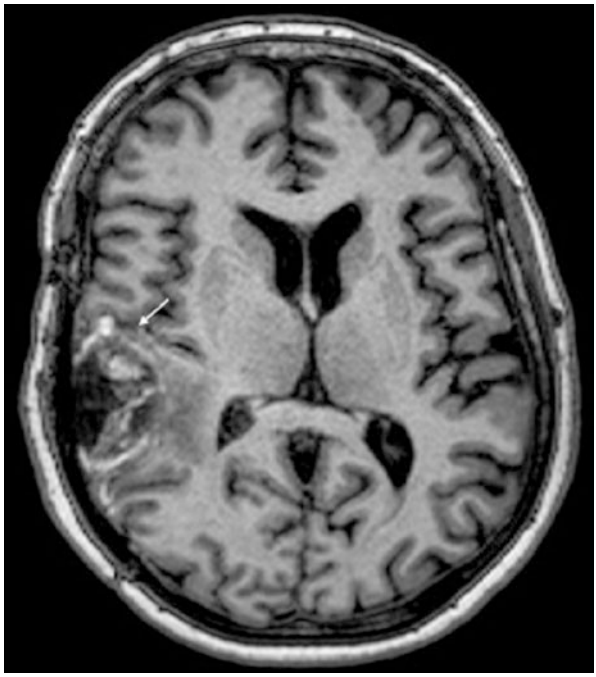

Fig. 11.21 Hemorrhage on the border of the resection cavity 2 weeks after debulking of a glioma. Axial T1 MRI shows a hemorrhagic component on the border of the resection cavity (arrow)

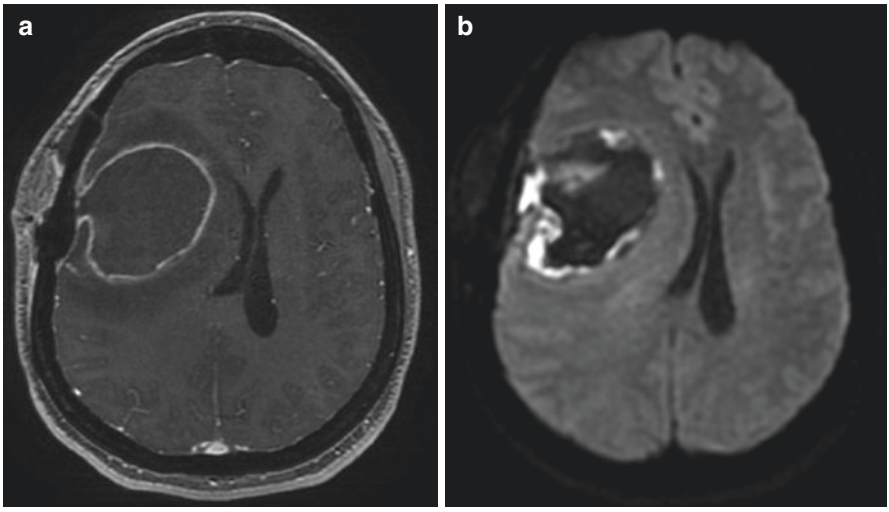

Fig. 11.22 Initial infection at the margins of a low-grade glioma resection. Axial trace DW image (**a**) show a hyperintense lesion with a low ADC indicating restricted diffusion. (**b**) Post-contrast SPGR T1 image demonstrates irregular impregnation at the same area where there is restricted diffusion

hypodense halo around the surgical site at the CT or can be represented as a halo of hyper signal in FLAIR at MR. As the infection progresses, restricted diffusion and impregnation can be seen in the margins of the surgical cavity (Fig. 11.21). The fluid inside the cavity initially may show hyper signal in FLAIR, due to hyper protein content, but at the end of the process usually shows a very high signal in the diffusion sequence, due to thick fluid with restricted diffusion to the water molecules. Almost half of the cases are due to *Staphylococcus aureus* [8, 22, 40].

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Part II
General Management

Chapter 12
Management of Intracranial Hypertension

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12.1 Introduction

The concept of a pressure–volume relationship inside the skull and, therefore, the understanding of how this relationship affects the intracranial pressure (ICP) was first mentioned in 1783, by Alexander Monro, and supported by Monro's student George Kellie in 1824. The Monro-Kellie doctrine [1] states that the human skull is a rigid compartment with a fixed volume and with three main components within: brain parenchyma, blood, and cerebrospinal fluid (CSF). These three components are in a dynamic equilibrium, and an increase in any of them or the appearance of any space-occupying lesion is followed by a decrease in the other components without any significant increase in ICP [2]. However, this equilibrium mechanism is maintained until a threshold is reached where the ICP increases exponentially with any increase of volume inside the skull [1, 3].

A dynamic, non-linear relationship exists between the intracranial volume and ICP (Fig. 12.1). Initially, in this curve, in the segment I, an excellent compensatory mechanism can prevent significant increases in ICP despite rising in intracranial volume. In segment II, a poor autoregulatory mechanism is present, when buffering capabilities are being exceeded, with a near-linear ICP response to the increases in volume, until a critical threshold (segment III) is reached, when autoregulation fails [4].

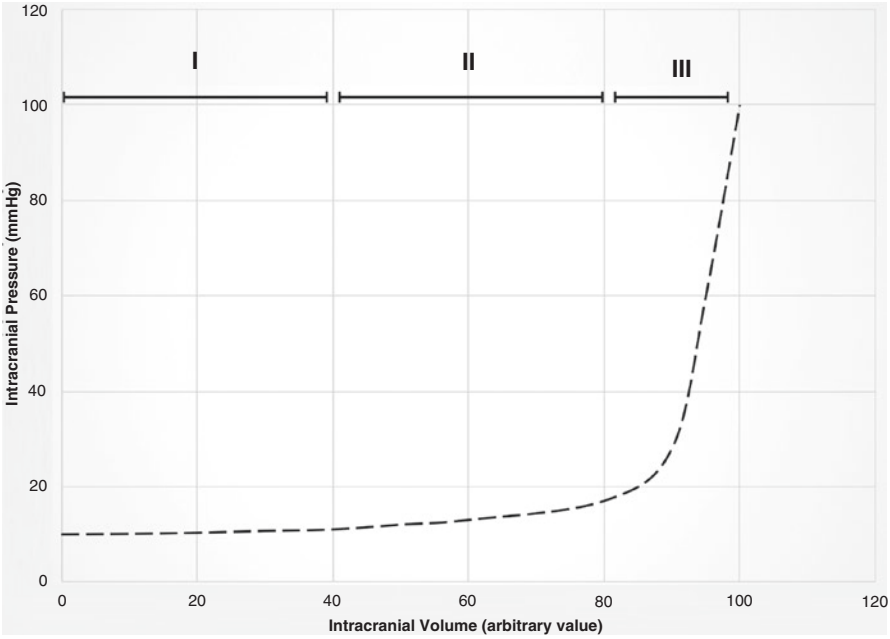


Fig. 12.1 Pressure volume relationship

Intracranial hypertension (IH), sustained or not, is harmful leading to secondary brain injury, herniation, and possible brain death if untreated [5]. Therefore, aggressive treatment should be provided as soon as possible. For many years the cutoff for diagnosing IH has been debated. The last edition of Brain Trauma Foundation guidelines established that sustained ICP > 22 mmHg diagnosis IH [4]. However, recent evidence suggests that more important than a single cutoff value is the ICP dose [5, 6].

Intracranial pressure dose represents the time spent over the threshold and its intensity (area under the curve ICP x Time), and together with cerebral perfusion pressure (CPP) should be considered when treating a neurocritical patient [7, 8].

The earliest reports of ICP monitoring are from Guillaume and Janny in 1951, and Lundberg in 1960, in which ICP estimation was done from backpressure of CSF in a tube manometry. More accurate and safer methods for continuous monitoring of the ICP are available today [3].

Intracranial pressure monitoring offers more than a continuous pressure value. It allows continuous monitoring of the cerebral perfusion pressure (CPP), which is equal to mean arterial pressure (MAP) – ICP. Also, it will enable evaluation of the pressure-reactivity index, which estimates cerebrovascular reaction and ICP waveform. Since IH is a heterogeneous and complex disease, the more information is gathered from the ICP monitoring more tailored and assertive can the neurocritical care management be [4].

Despite the strong correlation between IH and mortality, other factors such as metabolic disarrangements might be present before any significant ICP elevation. This understanding leads to the concept of multimodal neuromonitoring strategies, considering other variables, together with ICP values, to guide the clinical decision [4, 8].

12.2 Clinical Presentation

Clinical symptoms of IH are diverse and depend on the underlying etiology and time of installation (acute or chronic), being more clinically evident in acute cases [4, 9]. Most of the time, clinical manifestations are related to global or hemispheric dysfunction rather than focal findings [4].

These symptoms include headache, decreased level of consciousness, nausea, vomiting, diplopia, and sixth cranial nerve palsy. The Cushing's triad (bradycardia, hypertension, and irregular breathing or apnea) with all its three components is an uncommon feature occurring most frequently with high and acute increases in ICP and late phases of intracranial hypertension (herniation syndrome and brain dead) [3, 4, 9].

Although intracranial hypertension is a global phenomenon most of the time, in some situations, it might be a compartmentalized syndrome due to intracranial anatomical landmarks, such as falx and tentorium cerebelli. In these situations,

herniation can occur from those points of higher to points of lower pressure [9]. Common herniation syndromes are subfalcine, uncal, and foraminal.

Transtentorial or uncal herniation is the prototype of these syndromes and is marked by acute loss of consciousness, ipsilateral pupillary dilatation, and contralateral hemiparesis. These clinical manifestations are related to compression of ascending arousal pathways, oculomotor nerve, and corticospinal tract, respectively. Ipsilateral cerebral infarction can be present due to occlusion of the posterior cerebral artery [9].

12.3 Physical Examination

Unfortunately, physical examination alone has low sensitivity for the diagnosis of IH [9]. A decreased level of consciousness has very low specificity. It may be present in many other clinical conditions, especially in the setting of a prior known neurologic disease, such as traumatic brain injury (TBI). Abnormal motor posture (Glasgow coma scale motor score ≤3) has both low sensitivity and low specificity. Pupillary dilation has low sensitivity, but it is more specific, although it is a late sign of elevated ICP, as well as are other clinical signs seen in herniation syndromes.

12.4 Imaging

Computed tomography (CT) is the most widely available imaging method for the evaluation of neurocritical patients and is extremely useful when IH is suspected. It allows the diagnosis of underlying pathologies and is helpful for non-invasive evaluation of the presence of IH. A recent meta-analysis showed that compression or effacement of the basal cisterns (Fig. 12.2) has good sensitivity (85.9%) but low specificity (61%) for the diagnosis of elevated ICP. The presence of any midline shift also has good sensitivity, especially if 5–10 mm or >10 mm [9].

The optic nerve sheath diameter (ONSD) measurement using ultrasound is a reproducible easy to perform non-invasive method to detect elevated ICP with a steep learning curve [10]. It evaluates the retrobulbar segment of the optic nerve, which is surrounded by subarachnoid space, which distends with increased ICP. There are different cut-offs described in the literature that provide different sensitivity and specificity. There is no consensus about the optimal threshold to detect elevated ICP, with values <5 mm probably not associated with increased ICP and values >6 mm highly associated with increased ICP [11]. Its dynamic variation, however, might be of limited interpretation given the nerve sheath might remain enlarged for a variable and undetermined period after an episode of increased ICP. Another concern is the variable response to therapeutic interventions. For this reason, it has a limited role in patients with known intracranial hypertension. However, it is useful as a fast screening method after neurological worsening [10].

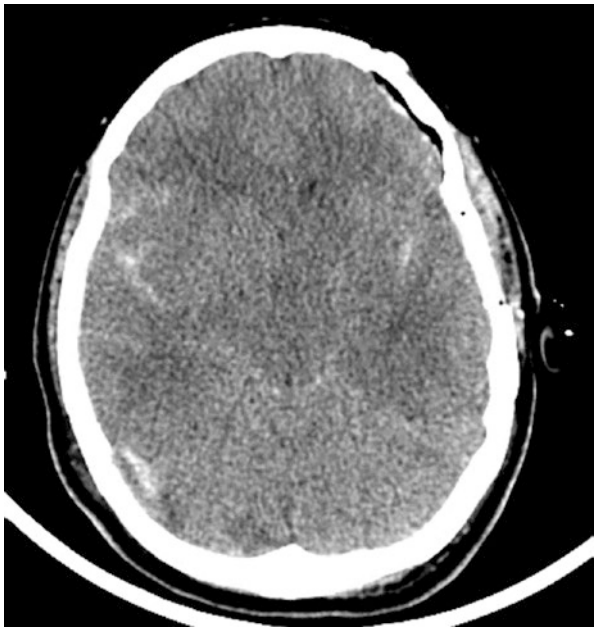


Fig. 12.2 Compressed basal cisterns

Transcranial doppler indices (pulsatility index and methods derived from flow velocity) have low accuracy in estimating ICP and are not recommended in the diagnosis of intracranial hypertension [12, 13].

Invasive ICP monitoring should be considered in patients at risk for intracranial hypertension [4, 14]. However, there are possible complications for this invasive procedure, and there are settings where it may not be readily available. In these scenarios, physicians should gather information from physical examination, head CT, and non-invasive methods to diagnosis increased ICP. Individually, none of these are sufficiently accurate in diagnosing IH when compared to invasive monitoring. Physicians should use a combination of these findings, along with pre-test probability, to interpret them adequately.

12.5 Etiology

As discussed, the clinical presentation of IH is variable and depends on its etiology and time of installation [4, 9]. The initial symptoms and clinical findings such as headache, nausea, vomiting, and diplopia are unspecific, and other diagnostics should be considered. These initial symptoms may be accompanied by clinical findings, which may suggest a specific etiology. Some clinical pictures may be archetypal. For instance, acute onset of headache, nausea, vomiting, fever, and neck stiffness is suggestive of meningitis.

Table 12.1 Common intracranial hypertension etiologies

Traumatic brain injury (TBI):
Epidural hematoma
Subdural hematoma
Intracerebral hematoma
Contusion
Brain swelling
Vascular:
Subarachnoid Hemorrhage
Ischemic stroke (large vascular territories: carotid or medial cerebral artery)
Spontaneous Intracerebral Hemorrhage
Cerebral venous thrombosis
Infectious:
Meningitis
Encephalitis
CNS abscess
Neoplastic:
Primary CNS Tumors
CNS metastasis
Others:
Hydrocephalous
Hepatic failure
Convulsive/non convulsive status
Anoxic encephalopathy

Therefore, it is essential to know that the initial presentation of a patient with IH may be unspecific, and any suspicion should guide further investigation. The physician must go through two different steps during the diagnostic process. The first one is the diagnosis of IH, and the second is its etiology (Table 12.1). At initial presentation, the differential diagnosis of headache, nausea, and vomiting are numerous.

When facing a patient with likely IH in a more advanced stage, it is essential to know that there is a common pathway for all the pathologic processes leading to an impaired level of consciousness. We can divide the diagnosis of the reduced level of consciousness into two groups: those with focal neurologic signs and those without (Table 12.2).

The first group (with focal neurologic signs) of differential diagnosis comprises central nervous system structural lesions and some exogenous intoxications. In this situation, an urgent head CT scan is paramount for diagnosis. The second group (without focal neurologic signs) comprises toxic metabolic causes, including most of the exogenous intoxications, inflammatory, and infectious diseases. Patients in this group are more likely to have systemic conditions, so a thorough clinical history and physical examination are paramount. Also, in this group, a head CT scan and an electroencephalogram (EEG) are helpful, since mass effect lesions (e.g., diffuse cerebral edema) or EEG abnormalities may also be the cause or symptoms.

Table 12.2 Differential diagnosis of impaired level of consciousness

I. With neurologic focal signs:
Mass effect lesions: infarcts/ischemia, hemorrhage, neoplastic, abscess.
Brain stem lesions: infarcts/ischemia, hemorrhage, neoplastic, abscess.
Exogenous intoxications: opioids, cholinergic (organophosphates, carbamates), anticholinergic and stimulants (scopolamine, tricyclics, caffeine, cocaine, amphetamines).
Others: postictal, convulsive status, nonconvulsive status.
II. Without neurological focal signs:
Metabolic disturbances: uremia, hepatic failure, hyperglycemic states (hyperosmolar coma, ketoacidosis), hypoglycemia, myxedematous state, adrenal insufficiency.
Infectious: sepsis, CNS infections (meningitis, encephalitis).
Exogenous intoxications: anesthetics, sedatives, anticonvulsants, antihistamines, antipsychotics, gases.
Mass effect lesions.
Others: postictal, convulsive status, nonconvulsive status, hypothermia, delirium

12.6 Treatment

12.6.1 Initial Treatment

Despite the myriad of therapeutic interventions for treating IH, success is heavily dependent on the two cornerstones [4]: early removal of surgically treatable lesions and early and continuous correction of anatomic and physiologic derangements that can worsen cerebral edema.

When IH is documented or suspected (based on clinical–radiological findings), surgically treatable space-occupying lesions should be removed as soon as possible, and any delays increase the secondary injury to the brain parenchyma.

Correction of underlying anatomic and physiologic disorders that can worsen both cerebral edema and secondary injury is of pivotal importance. Secondary brain injury is any factor that occurs immediately after the primary injury and worse neurological outcomes [15], for example, hypoxia, hyperthermia, and hypoglycemia. Avoiding secondary injury is also one of the cornerstones of the care of neurocritical patients, and its prognostic impact is independent of its effect on intracranial pressure. For example, in patients with traumatic brain injury, a systolic blood pressure <90 mmHg increases unfavorable outcomes by an odds ratio of 3.5 [16].

Intracranial hypertension is often refractory when these physiologic alterations are not under close control. Additionally, specific treatments for refractory intracranial hypertension, such as hyperventilation, barbiturates, induced hypothermia, or decompressive craniectomy, have significant side effects [17], however, their benefit might not be apparent for all patients.

It is essential to make sure all these initial targets (Table 12.3) are reached as soon as possible in all patients with suspected IH before escalating to a sequential stepwise approach.

Table 12.3 Initial management of patients with suspected intracranial hypertension

Head of the bed elevated (30–45°)
Head and neck in neutral position
Avoid hypoxemia (maintain oxygen saturation between 94% and 98%
Arterial CO_2 between 35 and 40 mmHg
Cerebral perfusion pressure target of 60–70 mmHg (if ICP monitoring)
Mean arterial pressure target of 90–100 mmHg (without ICP monitoring)
Normothermia (36–37 °C)
Serum sodium 140–150 mEq/L
Glucose control target 140–190 mg/dL
Avoid anemia (hemoglobin target >9–7 mg/dL)

The goal in this initial approach is to avoid any factors that increase the likelihood of secondary brain injury or might affect either the ICP or the CPP [18]. Known risk factors for secondary brain injury such as hypoxia, hypoglycemia, hyperthermia, hypotension, and decreased CPP must be corrected. Therefore, one should aim to achieve the values summarized in Table 12.3 [4]. For patients with invasive ICP monitoring, the CPP is 60–70 mmHg, however for patients with suspected IH without invasive ICP monitoring, the mean arterial pressure target (MAP) target is 90–100 mmHg. For patients with invasive ICP monitoring is possible in some situations to tailor the CPP target according to the intracranial pressure response, with the use of cerebral autoregulation surrogates, such as the pressure reactivity index (for details on this topic, see Copplestone and Welbourne, 2018).

However, if the ICP persists >22 mmHg after these initial measures, we suggest an orderly sequential stepwise approach to guide treatment. We choose to divide this approach in conventional treatment and options for refractory intracranial hypertension based on the scope of evidence available for each therapy.

12.6.2 Conventional Treatment

The interventions described below must be performed in a stepwise approach following the order: cerebrospinal fluid drainage (when applicable), optimizing sedation, hyperosmolar therapy, neuromuscular blockade, and transitory induced hypocapnia [3].

12.6.3 Cerebrospinal Fluid (CSF) Drainage

The CSF drainage can only be performed in patients with external ventricular drainage (EVD) placed, which is most of the time inserted together with an ICP monitor [4]. One should not drain CSF through a lumbar puncture (except in specific

situations), which might lead to downward herniation. The EVD can be used as a therapeutic and monitoring tool. In situations of increased ICP, the drainage of small volumes of CSF can lead to a significant decrease in ICP since most of these patients are in the segment III of the intracranial pressure–volume curve (Fig. 12.1).

There are some concerns that continuous CSF drainage trough the EVD might lead to ventricular collapse and EVD obstruction (which might lead to an increase in ICP), however, a continuous drainage strategy is recommended by the Brain Trauma Foundation since it is an efficient way to reduce ICP in trauma patients. Therefore, proper functioning of the EVD must be guaranteed, and additional drainage might be necessary in situations of persistent increase in ICP.

12.6.4 Sedation

Appropriate analgesia should be a priority in acute neurologic ill patients. Once pain is resolved, a higher dose of analgesics usually does not confer an additional benefit on controlling the ICP [4, 19].

The use of sedatives with the goal of deep sedation (burst suppression) does not confer any benefits in the long-term prognosis of the acute neurologic ill patient without IH. Furthermore, heavy sedation lengthens the duration of mechanical ventilation, which increases the risk of adverse events such as nosocomial infections. Also, it might reduce cerebral perfusion pressure and decrease the sensitivity of clinical neurologic monitoring.

However, if IH persists after the initial treatment (Table 12.3) and cerebrospinal fluid drainage if there is a ventricular drain in place, sedation and mechanical ventilation are recommended to decrease the ICP. Propofol or midazolam are the most used drugs; both act on the gamma-amino-butyric acid (GABA) receptor and decreases brain metabolism. Sedation should be titrated to avoid agitation and consequently increase in cerebral oxygen consumption and to control the IH, but not necessarily to induce coma in all acute neurologic ill patients. We suggest using the least amount of sedation to achieve two practical goals in patients with IH: Richmond Agitation-Sedation Scale (RASS) <1 and intracranial pressure <22 mmHg.

In some cases, higher sedatives doses are needed to accomplish both targets, especially to control the ICP, leading in these patients to more profound sedation (sometimes RASS – 5).

We suggest using propofol (maximum dose 5 mg/kg/h) as first-line sedative due to its short half live, allowing constant neurologic reevaluation and titration. Midazolam is an option in patients at risk for the propofol-infusion syndrome (young male patients and/or use of propofol for >72 h), patients with severe systolic dysfunction, or needing high-dose vasopressors.

12.6.5 Hyperosmolar Therapy

Mannitol and hypertonic saline are the next steps if IH persists despite optimized sedation (RASS – 5) and pain control [20, 21]. While both are effective in reducing the ICP, hypertonic saline has less frequent serious adverse events. Mannitol-induced polyuria can reduce cerebral perfusion pressure and titrate the mannitol dosing is challenging since the osmolar gap is not routinely measured in the majority of intensive care units, also using mannitol in oliguric patients can cause acute pulmonary edema. We recommend infusions of hypertonic saline if ICP persists >22 mmHg with maximal dosing titrated by serum sodium targeting serum sodium 140–155 mEq/L. There is no consensus on which concentration is better. Therefore, different concentrations (3%, 7.5%, 20%) can be used. We suggest 0.5 mL/kg sodium chloride 20% in 10 minutes in cases of cerebral herniation.

12.6.6 Neuromuscular Blockade

In selected cases of IH, especially in patients with uncontrolled shivering despite the usual treatment (extremities warming, opioids, magnesium, and others), a trial of neuromuscular blockade might help to decrease the ICP. Also, the use of neuromuscular blockade might lower the intraabdominal pressure and facilitate ventilation and CO_2 control. We suggest a trial of cisatracurium 0.2 μg/kg IV push. If a sustained decrease in ICP is observed, continuous infusion until control of other factors associated with increased ICP might be beneficial [22].

12.6.7 Induced Hypocapnia

In situations of acute elevation of ICP or herniation syndrome, controlled hypocapnia targeting an arterial CO_2 between 30 and 35 mmHg decreases the ICP allowing a safe time to adjust other therapies and image evaluation. However, this hypocapnia must be controlled in both its intensity and duration, since hypocapnia leads to cerebral vasoconstriction and consequently decreases cerebral blood flow [23].

12.6.8 Imaging

In situations of acute unexplained neurologic deterioration (decrease in GCS by two or more points, new anisocoria, herniation syndrome, or any other significant new neurologic alteration) or unexplained increase in ICP, it is advisable to consider obtaining new image of the brain, to exclude surgical treated causes alongside with acute treatment to control ICP.

The series of interventions mentioned are called first and second tiers therapy and are described in Algorithms 1 and 2 for patients with and without ICP monitors, respectively.

12.6.9 Treatment Options – Refractory Measures

For patients with refractory ICP elevation despite first and second tiers describe above, rescue therapy strategies such as decompressive craniectomy, barbiturates, or mild hypothermia might be useful.

12.6.10 Barbiturates

Barbiturates (thiopental and pentobarbital) have potent effects on cerebral metabolic demand and cerebral blood flow, inducing a state of cerebral metabolic suppression [24]. These drugs have serious side effects, like hypotension, long half-life (jeopardizing neurological examination in the meanwhile, eventually even delaying brain death diagnosis), paralytic ileus, potassium shift disturbances, and increased risk of pneumonia. Loading doses of three are followed by 1–4 mg/kg/h. We suggest administration in 10 minutes and close hemodynamic during loading dose. Patients should be monitored with continuous electroencephalography to achieve a burst-suppression pattern, also an indication of its maximal effect. Other sedatives are then ceased. Hypokalemia may occur with induction and hyperkalemia as a rebound when the infusion is suddenly stopped. Despite the impact on ICP reduction, there is no convincing evidence that barbiturates improve outcomes in patients with severe TBI, possible due to harmful side effects (hypotension adversely affecting cerebral perfusion and increased risk of infection). Its use should be considered when ICP is measured invasively, and intracranial hypertension is refractory to first and second-tier treatments. In that scenario, one must individualize its use either as a therapeutic bridge to surgical decompression or, knowledgeable of its severe side effects, when surgery is not the best option.

12.6.11 Hypothermia

Therapeutic hypothermia decreases cerebral metabolism, lowering oxygen consumption, and CO_2 production, which may lead to ICP reduction. It has severe side effects, such as metabolic acidosis, electrolyte disturbances (mainly hypokalemia), arrhythmias and bradycardia, coagulopathy, and increased risk of infections. There are various methods to induce hypothermia. Most commonly, cold intravenous infusion, gastric lavage, and surface cooling blankets are used, but other automated

devices are also available. The induction phase should be fast, followed by a sustained maintenance phase for 24–48 hours; then, the rewarming phase must be slow and controlled (maximum of 0.5°C per hour) due to the risk of rebound intracranial hypertension and sudden metabolic disturbances (hyperkalemia). During induction, patients may present shivering, which increases CO_2 production. It can be managed through warming of the extremities and boluses of opiates and sedatives; eventually, neuromuscular blockers are necessary. Continuous core temperature monitoring is essential to avoid sudden and frequent temperature changes and adequate induction and rewarming speed. Despite its theoretical protective effects, clinical trials have failed to show that hypothermia improves outcomes in patients with intracranial hypertension.

The Eurotherm3235 [25] trial assigned patients with TBI and ICP >20 mmHg despite first-tier treatment to receive either hypothermia between 32 and 35 °C or standard therapy. Trial recruitment was suspended for safety reasons, indicating worse outcomes (GOS-E at 6 months) in the hypothermia group. Recently, the POLAR [26] trial evaluated the role of early prophylactic hypothermia in severe TBI. Patients were enrolled both out-of-hospital and at emergency departments and assigned to hypothermia between 33 and 35 °C for at least 72 hours or normothermia (target of 37 ± 5 °C). There was no difference in neurologic outcomes (GOS-E) in 6 months.

Given these recent results with even a signal of harm from a trial, therapeutic hypothermia is not currently recommended as a standard treatment in intracranial hypertension. Its use should be limited to selected cases of ICP refractory to first and second-tier therapies. In our practice, a target core temperature of 36–37 °C is the usual goal of treatment.

12.6.12 Decompressive Craniectomy

Craniectomy is an effective therapy in reducing and even normalizing ICP by removing a large segment of the skull, thus increasing cranial vault volume for allowing brain tissue swelling (according to Monro–Kellie Doctrine) without or with lower impact on the ICP. When performed, it should be of sufficient size (at least 10–12 cm in diameter), involving temporal and parietal bones (unilateral or hemicraniectomy), including middle cranial fossa. A large proportion of ICP reduction is achieved through durotomy.

Randomized clinical trials showed that decompressive craniectomy is effective in reducing ICP and possibly increases patient's survival, but it does not improve long term functional outcomes. In the 2011 DECRA trial [27], patients with severe TBI and early refractory ICP (ICP >20 mmHg for 15 minutes within 1 hour) despite optimized first tier therapies (sedation, normocapnia, hyperosmolar therapy, and external ventricular drainage) were randomized within 72 hours of injury to undergo bifrontotemporoparietal decompressive craniectomy or continuing standard care. Early surgical intervention decreased ICP and length of stay in the ICU but was

associated with unfavorable neurological outcomes (worst Extended Glasgow Outcome Scale GOS-E), with no difference in 6 months mortality.

Later, the RESCUEicp trial [28] studied craniectomy as a rescue maneuver. In this study, patients with TBI and refractory ICP elevation (>25 mmHg for 1–12 hours), despite first and second-tier therapies (sedation, mild hypocapnia, hyperosmolar therapy, blood pressure augmentation, external ventricular drainage, and mild hypothermia) were randomly assigned to surgery (either hemicraniectomy or bifrontal craniectomy, at the discretion of neurosurgeons) or continuing medical therapy, with the option to add barbiturates. Again, the surgical group achieved lower ICP values, but this time with lower 6 months mortality (26.9% × 48.9%) but higher rates of vegetative state, lower severe disability, and upper severe disability. Rates of favorable outcomes (moderate disability and good recovery) were similar between groups.

Nowadays, craniectomy is considered a salvage therapy in the context of large middle cerebral artery infarction and severe traumatic brain injury. It could be a therapeutic alternative to barbiturates and mild hypothermia in the management of intracranial hypertension refractory to first and second-tier measures, but no late enough that harmful effects of prolonged elevated ICP can no longer be avoided. The decision to perform this procedure should be individualized and consider the patient's values and preferences through family members' perspective, the timing of the procedure and patient's age, considering it may increase survival, but it does not improve long term neurologic outcomes.

12.7 Complications

Intracranial hypertension and its effects on intracranial physiology, if left untreated, may lead to brain death, permanent neurological dysfunction, or devastating neurological outcomes. On the other hand, the treatment for IH itself poses substantial side effects.

Some risks are inherent to the treatment. Since all patients with IH are under invasive mechanical ventilation, there is a risk for ventilation associated pneumonia (VAP) and ventilator-induced lung injury (VILI). The same for central line-associated bloodstream infections. The sedation used for reducing brain oxygen consumption might lead to hemodynamic instability in different degrees, depending on the dose and agent used. Osmolar therapy to minimize brain edema leads to fluid depletion and may cause dehydration and hydroelectrolytic disturbances in the case of mannitol or hypernatremia and fluid overload when using hypertonic saline. Induced hypocapnia causes cerebral vasoconstriction and may lead to brain ischemia.

In advanced stages, if left untreated, independent of the cause of the IH, a common pathway is seen. The increase in the ICP leads to compression of brain stem structures and brain herniation. Breathing pattern alterations may then occur

depending on the herniation, leading to a gasping pattern and possible cardiovascular collapse, culminating in cardiorespiratory arrest.

Metabolic suppression with barbiturates causes hemodynamic instability, hypokalemia, and might increase the risk of infection. Hypothermia causes severe electrolytic disturbances and may increase the risk of infection. Surgical treatments such as the use of EVD or decompressive craniectomy also may increase the risk of infection. Vasopressors are frequently used to achieve MAP targets and might cause arrhythmias and increase the risk of vascular ischemia.

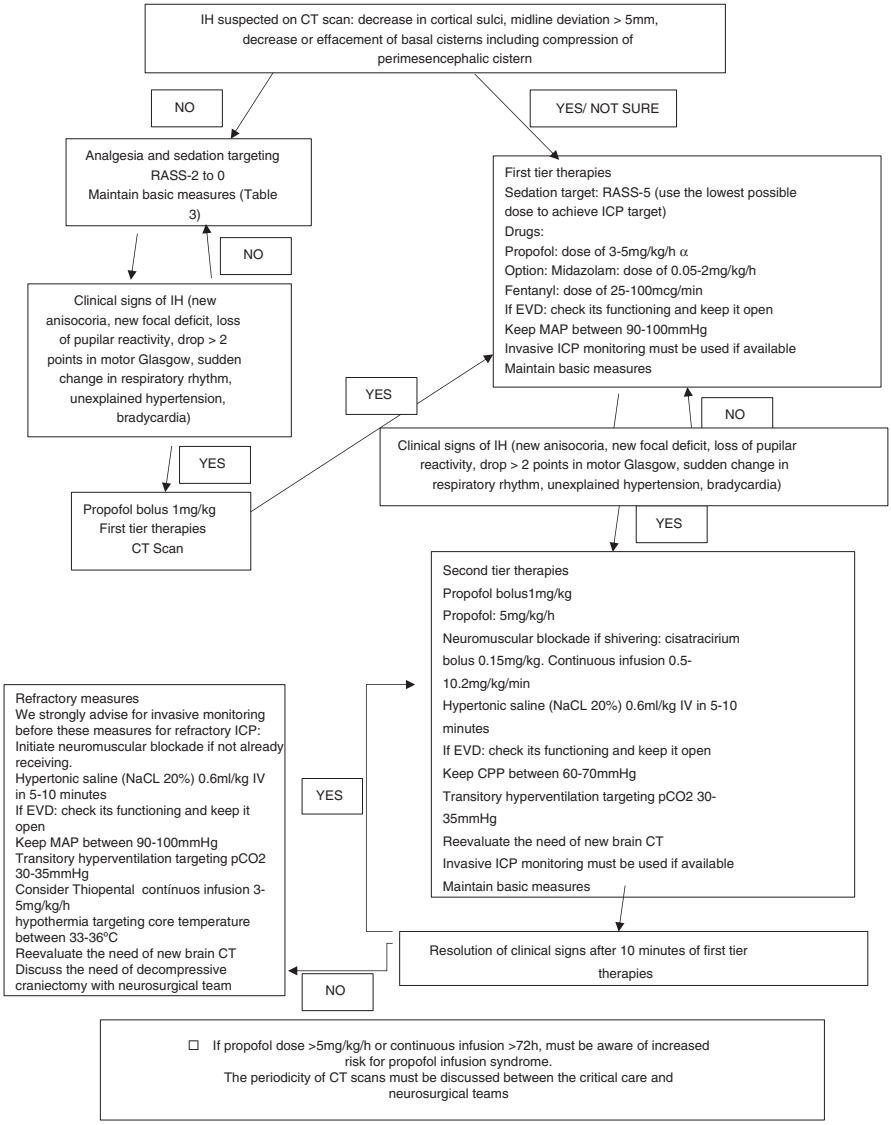
The occurrence of seizures, convulsive, or nonconvulsive status is not uncommon in patients with acute neurological insults and are associated with worse neurological outcomes. Therefore, seizure prophylaxis is indicated for selected patients. Some patients might develop central diabetes insipidus and other sodium disturbances (cerebral salt wasting syndrome and syndrome of inappropriate antidiuretic hormone secretion) may also be present and should be treated accordingly. Patients with IH have increased risk for upper gastrointestinal bleeding, and stress ulcer prophylaxis is recommended in the acute phase.

Therefore, when managing a patient with IH, it is paramount to be aware of the most common complications. Due to its severity and frequency of poor neurological outcomes, patients with IH require an aggressive management strategy. A comprehensive plan, weighting the pros and cons of each conduct, with precisely timing interventions, is the best tool for managing patients with IH.

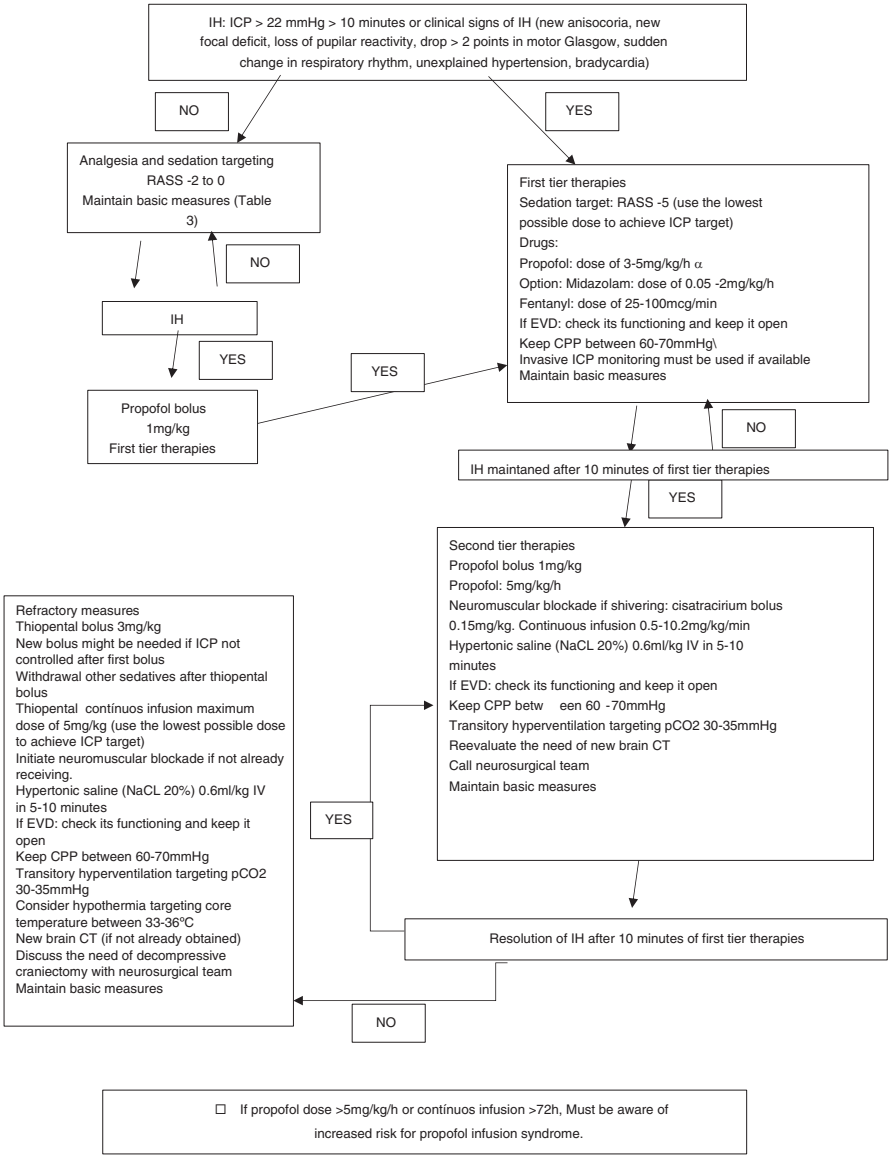
Pearls/Tips

- When managing IH without direct ICP monitoring, a well-structured clinical/imaging protocol is necessary. The criteria for acquiring a new head CT must be low. Optic nerve sheath diameter (ONSD) measurement is a useful triage tool is this setting.
- When IH is suspected or documented, aggressive treatment must be provided even before acquiring a new CT image or installing invasive ICP monitoring.
- If available, we recommend invasive intraventricular ICP monitoring with EVD in patients with suspected IH.
- Despite the myriad of therapeutic interventions for treating IH, success is heavily dependent on two cornerstones: early removal of surgically treatable lesions and early and continuous correction of anatomic and physiologic derangements that can worsen cerebral edema (Table 12.3).
- If IH is refractory to these initial maneuvers, a stepwise approach is suggested: cerebrospinal fluid drainage (when applicable), optimizing analgesia and sedation, hyperosmolar therapy, neuromuscular blockade (when indicated), and mild induced hypocapnia. We suggest propofol as first line sedation agent and hypertonic saline for hyperosmolar therapy.
- If IH is refractory to initial maneuvers and to conventional treatment, rescue therapy strategies include metabolic suppression with barbiturates, mild hypothermia, and/or decompressive craniectomy.

Algorithm 1 – For Patients Without ICP Monitoring



Algorithm 2 – For Patients with ICP Monitoring



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Chapter 13
Neuroprotection in Brain Injury

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13.1 Introduction

Neuroprotection entails the preservation of the structural and functional integrity of neurons due to traumatic brain injury (TBI), stroke, or neurodegenerative disorders. It can involve measures employed to limit the loss of brain cells in ongoing degenerative conditions or to halt the degeneration of secondary tissue in acute TBI. Also, neuroprotection is geared toward improving central nervous system (CNS) functions in various instances, such as in cerebral lesions, whether traumatic or nontraumatic, in brain ischemia and intracranial hemorrhage [1].

Various medical problems can result in neurological damage and progressive degeneration, including acute brain injury, ischemic stroke, and increased intracranial pressure (ICP), among others. Although the injuries and symptoms that result from CNS disorders present in different ways. Pathophysiological mechanisms associated with the neurodegeneration include an increase in oxidative stress, high excitotoxicity, mitochondrial dysfunction, accumulation of iron, inflammatory effects, and protein aggregation [1, 2].

The most targeted issues in neuroprotective treatment are the glutamate excitotoxicity and oxidative stress because they are the most common etiological mechanisms in nervous system disorders, primarily leading to brain cell death, mainly because the two phenomena work in synergy, thus accelerating the degeneration. This chapter is focused on the most common causes, mechanisms of neurodegeneration, as well as objectives of and the primary approaches to neuroprotection.

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13.2 Causes and Mechanisms of Neurodegeneration

Several conditions lead to the loss of neurons, thus affecting brain structure and function. Diverse studies have been conducted in this area that provide extensive data on the pathophysiology and treatment options for these conditions [1–3]. Acute brain injury is highly associated with both short-term and long-term morbidity and mortality, with approximately 52,000 deaths resulting from TBI in the USA every year. Similar statistics are evident in other parts of the world, such as in Europe, where about 7.7 million people suffer from disabilities associated with a brain injury each year [1].

The causes of TBI vary, but the leading ones include road accidents [1]. TBI is a direct insult to the brain that results in mechanical damage, which may progress to secondary neuro-injury or delayed non-mechanical damage. TBI is among the most common causes of morbidity and mortality for people below 45 years old [1, 4].

The initial trauma leads to focal damage from the contact injury that may entail contusion, hemorrhage, laceration, and diffuse cerebral damage, which could entail brain swelling or axonal injury. As Werner and Engelhard (2007) [2] argued, the primary insult is only sensitive to preventive measures but not to treatment. In other words, it would be possible to prevent an accident from occurring and, therefore, avoid a head injury, but once the event happens, the primary damage occurs.

For a patient who has suffered a primary injury, doctors should focus on limiting the progression to secondary insult, which includes various processes that begin from the moment the trauma occurs and may have delayed clinical manifestation. Therefore, health care providers should focus on the secondary mechanism of brain injury to prevent further neurological degeneration, which often presents as intracranial hypertension and cerebral ischemia [2–4]. Fortunately, at the secondary stage, therapeutic interventions may be effective.

Ischemic stroke is another cause of brain injury and a major cause of death and disability globally, with a significant impact on the life span of those affected. Stroke refers to various neurological deficits and brain injuries that result from problems in vascular integrity and functions. It is initiated by either ischemia or hemorrhage, with the former representing 87% of the cases [4]. The problem occurs when a blood vessel that perfuses an area of the brain is damaged or blocked, thereby failing to supply that region, which subsequently dies.

Another cause of neural degeneration is elevated ICP, which refers to the increase in the pressure within the brain and the cerebral spinal fluid (CSF). Research indicates that this problem results from diverse conditions, including TBI, cerebral infarction, intracerebral hematoma, and generalized brain swelling [5]. The prognosis for increased ICP is often poor, with 55.6% of patients presenting with an ICP of 40 mmHg dying as compared with 18.4% of those with an ICP of below 20 mmHg [6]. It is often imperative that secondary brain damage that may result from raised ICP is prevented. This goal should be the focus of neuroprotection in intensive care.

Various drugs, whether medical or recreational, have the potential to cause neurotoxicity. For instance, Moratalla et al. [7] found that amphetamine-related

products, including methamphetamine and methylenedioxymethamphetamine (MDMA), lead to neuroinflammation and neurotoxicity, especially in overdose. These substances target the serotonergic and dopaminergic neurons, with adverse outcomes observed in rodents and non-human primates. Victims may suffer neuronal damage with severe neurological and neuropsychological effects [7]. Other drugs with neurotoxicity include antiepileptic drugs, especially sodium channel-blockers, when used together with lacosamide [8]. Therefore, doctors should closely monitor patients placed under these medications to avoid such adverse implications.

The advances in aneurysm surgery and the management of patients presenting with aneurysmal subarachnoid hemorrhage (aSAH), delayed cerebral ischemia remains a significant morbidity. Delayed cerebral ischemia many times is a result of vasospasm of the proximal intracranial vessels, and vasospasm as a surrogate for functional outcome. However, there is a dissociation between angiographic vasospasm and outcome and more recent data suggest that other mechanisms of injury such as microvascular dysfunction and complex neuronal-glial interactions may influence the development of delayed ischemic deficit following aSAH [8, 9].

13.3 The Mechanisms of Neurodegeneration

The neurodegeneration mechanisms are diverse, some of which are discussed in sections above, such as neuroinflammation and neurotoxicity in drug-related brain damage. Most of the secondary outcomes of brain injury and CNS disorders, which are the primary focus of neuroprotection, result mainly from excitotoxicity and oxidative stress. Zadori et al. [9] observed that neuroinflammation and glutamate excitotoxicity are closely associated with mitochondria dysfunction, which results in a reduction in the production of ATP and subsequent initiation of oxidative damage.

In TBI, there is an impairment of metabolism in the brain that is closely associated with poor regulation of cerebral blood flow (CBF), with subsequent lactic acid accumulation due to anaerobic respiration, as well as edema that results from high permeability of the brain membranes. This process depletes the ATP-stores, thus influencing energy production in the brain [2, 10].

During the second stage, a high depolarization of the membranes occurs, which leads to an elevated release of the excitatory neurotransmitters glutamate and aspartate. The activation of the voltage-dependent calcium and sodium channels occurs after an influx of Ca2+ and Na+ ions. The rise in the concentration of these ions increases intracellular catabolic processes, which result in apoptosis (self-destruction of brain cells) [10]. Other post-traumatic effects include the distortion of blood vessels, vasoconstriction due to elevated prostaglandins, and a decrease in cholinergic neurotransmitters and nitric oxides, all of which lead to ischemia due to hypoperfusion of affected brain tissues. In retrospect, post-traumatic ischemia may be followed by hyperemia since hyperperfusion is a common occurrence in the early stages of brain injury.

These pathological processes are as destructive as ischemia and hypoperfusion since increased CBF leads to vasoparalysis and increased ICP [10]. Another primary mechanism of neural injury is oxidative stress, which results from neuroinflammation among other etiological processes. It is a significant occurrence in cerebral ischemia and various degenerative diseases, such as Alzheimer's disease, Parkinson's disease, and lateral sclerosis [9].

Doctors should have a clear understanding of these causes and mechanisms of neural damage while treating a patient with brain injury to ensure the best approach to prevent further neuronal loss.

13.4 Objectives and Approaches to Neuroprotection

As earlier stated, neuroprotection is primarily focused on salvage and regeneration of neurons and it prevents further secondary damage. This goal can be theoretically achieved through the halting of glutamate excitotoxicity, reducing oxidative stress, and addressing other issues such as hypo or hyperperfusion.

The neurochemical agents of progressive brain damage are diverse. However, doctors can effectively limit damage and even trigger regeneration by focusing on the most common modulators, which are usually glutamate neurotransmitters, sodium and calcium voltage-channel ions, and free oxidative radicals [11].

To define the most relevant objective in the treatment of a brain injury patient, doctors should identify the actual pathological issue, whether ischemia, hypoperfusion, hyperperfusion, or ICP. For instance, Ropper [11] identifies raised ICP as a common symptom in most acute brain diseases, which should be treated using specific approaches such as hyperosmolar therapy. In ischemia, Stocchetti et al. [1] identify reperfusion as the primary objective that is focused on preventing cell death and enhancing recovery by restoring blood flow to areas that can still be salvaged.

Moreover, in the case of sepsis, it is crucial to focus on maintaining brain perfusion since brain dysfunction is frequent during this condition, and it is associated with high mortality and long-term cognitive impairment [1].

Neuroprotection entails any strategy geared toward interrupting or slowing down the molecular and biochemical sequences that could have irreversible effects on the nervous system of the victim. The success of neuroprotective measures depends on the type of injury and the extent of damage, which explains the need for prompt action in TBI, ischemic stroke, drug overdose, and other degenerative CNS conditions [12].

Researchers have identified various quite effective approaches to neuroprotection. For instance, Stocchetti et al. [1] identify the use of intravenous thrombolytic drugs to achieve reperfusion in ischemic stroke. The authors further consider the application of "intra-arterial thrombolysis, mechanical thromboembolectomy, ultrasound-enhanced thrombolysis and various combinations of these approaches" [1] .

Barreto and Alexandrov (2012) [13] proposed alternative measures that may also be used as adjuncts to the major treatment options mentioned here, and they include hemodilution and increased oxygen delivery to the brain. Choi et al. (2018) identified hemodynamic augmentation therapy as another practical approach in ischemic stroke, which may entail the use of antihypertensive drugs, such as angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACE) to diminish the progression of the vicious cascade that follows the stroke, including endothelial dysfunction, vascular damage, inflammation, and oxidative stress [14].

Stocchetti et al. (2015) [1] cite a large-scale randomized trial that found the use of alteplase, the intravenous recombinant tissue plasminogen activator, leading to a considerable improvement in brain functions when administered 3 hours following the onset of an ischemic stroke. However, the reperfusion therapies have been shown to have quite serious disadvantages, such as the risk of ICH, increased complications during catheterization, and reperfusion injury (Stocchetti et al., 2015) [1].

Nevertheless, the benefits associated with the thrombolytic agents significantly outweigh the risks and, therefore, warrant their use in ischemic stroke, especially when used within 3–6 hours of the onset [15]. Perfusion can also be restored through selective targeting of the blocked artery using IV thrombolysis for patients who are contraindicated for systemic IV thrombolysis or whose symptoms have stayed for over 4.5 hours [16] . Mechanical thrombectomy can also be used to achieve the same effects.

Various approaches have been advanced for preventing secondary insults after TBI. Stocchetti et al. (2015) emphasized that prompt removal of large hematomas to ease compression on the brain is a crucial intervention. This fact indicates that early surgery may be an effective strategy of neuroprotection. It is well-known that shortening the time that elapses before surgery is conducted to remove an epidural hematoma in a patient who suffers from brain trauma has shown to enhance good outcomes (Stocchetti et al., 2015) [1–3].

In addition to hypoperfusion, the traumatized brain may suffer hypotension and hypoxia, and effective measures should be taken to prevent further damage. Some of the approaches include the use of isotonic saline and hypertonic fluids, as well as prehospital intubation, all of which have demonstrated favorable results [17]. In general, timely detection and prompt intensive therapy are crucial for the most desirable outcomes.

Since excitotoxicity is a major mechanism of secondary brain injury, methods used to halt this process are vital to neuroprotection therapy. Primarily, the target should be inhibition of excess glutamate neurotransmission, thus thwarting the effect of increased and uncontrolled calcium channel activation that has a disruptive effect on various physiological processes and leads to the destruction of lipids, proteins, and the DNA [18].

Previous treatment options have involved the use of glutamate receptor inhibitors, specifically the N-methyl-D-aspartate (NMDA) antagonists, but their efficacy has been detected, thus necessitating the exploration of other measures [19]. For example, NA-1 is a peptide used to block the chemical interaction of NMDA receptors with neuronal nitric oxide synthase (nNOS), thus decreasing the production of

noxious nitric oxide (NO). This intervention prevents the progression of the deleterious effects of glutamate-associated excitotoxicity. There are other treatment options for excitotoxicity, such as targeting the activation of glutamate NR2B subunit to prevent the apoptosis associated with the interaction between NR2B and DAPK1 [19].

This coupling can be inhibited either through direct targeting or by disrupting the downstream pathways of activation such as p53, and this intervention is crucial in the prevention of infarction or reduction of an already formed infarct, thus promoting satisfactory neurological results [20, 21]. Neuhaus et al. (2017) argued that this downstream targeting of the excitotoxicity modulators is further associated with reduced side effects of direct inhibition of glutamatergic neurotransmissions, such as increased psychotic episodes and neurological complications [19, 20].

The reduction of oxidative stress is another fundamental approach to neuroprotection. Manzanero et al. (2013) stated that the ischemic cascade that follows brain injury, especially after a stroke, is characterized by an influx of free radicals, which include reactive oxygen and nitrogen compounds (ROS and RNS) [21].

Preventing the excessive production of the oxidative species or enhancing antioxidant strategies could ameliorate the secondary damage associated with ischemia-reperfusion. Most of the agents that have been used in the past to achieve this goal, including the free radical scavenger NXY-059, have mainly proved to be inefficient [19]. Another compound utilized with this purpose with proved effectiveness in limiting neurological damage is edaravone, but it has been used mainly in Asia [21].

The failure of most of the antioxidant treatments can be explained by the fact that the temporal cause of the imbalance between oxidants and antioxidants following traumatic brain injury has not been determined, despite the identification of the enzymes associated with oxidative stress. Effective measures against oxidative stress can significantly limit the progression of neurodegeneration by preventing apoptosis, which occurs when free radicals destroy DNA, RNA, and various cellular proteins.

Another approach to neuroprotection is the management of hemoglobin [1]. Anemia is identified as a common problem in patients suffering a severe brain injury, and it results in poor outcomes, especially in TBI, intracranial hemorrhage, acute ischemic stroke, and aneurismal subarachnoid hemorrhage (SAH). In such cases, provided the patient does not present with a serious cardiac disease, doctors usually perform restrictive red blood cell transfusion to increase hemoglobin levels [23]. However, doctors should be careful not to increase the Hb to levels that may have adverse effects on the patient due to the sensitivity of the compromised cerebral tissue. The control of Hb is crucial since studies have demonstrated that low levels increase the risk of infarctions related to vasospasms [1].

This observation is more frequent in patients suffering from aneurismal SAH. Care should also be exercised due to the possibility of such individuals developing pulmonary embolism and thrombosis while receiving blood transfusion. The benefits of transfusing patients with red blood cells are only considered to outweigh the risks if there are such serious physiologic indicators as tissue hypoxia and metabolic distress. For instance, in TBI patients with both anemia and compromised

oxygenation of the brain tissue, there are higher chances of poor outcomes unless the Hb levels are brought to optimal [1].

Neuroprotection is crucial during sepsis since the condition is often associated with brain dysfunction, with increased mortality or long-term impairment of cognitive abilities. Other causes of the reduced brain perfusion in sepsis could be the use of sedative agents, as well as hypocapnia resulting from hyperventilation. Nevertheless, researchers have found that sepsis leads to impaired autoregulation of blood flow in the brain, particularly in patients presenting with shock consider regulation of carbon tension in the arteries as a potential remedy to poor brain perfusion in sepsis. The authors further identify the maintenance of an optimal blood pressure threshold as another potential remedy to low cerebral perfusion [1, 25].

As aforementioned, increased intracranial pressure is an outcome of most forms of brain injury and, therefore, its regulation is a major focus of neuroprotection. As Ropper (2012) states, any condition that causes the brain to increase in volume leads to a rise in intracranial pressure. For instance, an increase in intravascular blood or cerebrospinal fluid would lead to an automatic rise in ICP unless there is a corresponding decrease in another component [26].

The author further states that a continued rise in ICP to 50–60 mmHg results in widespread cerebral ischemia and eventual brain death (Ropper, 2012). Therefore, detecting and correcting high ICP is crucial to the survival of patients of brain injury. According to Treggiari et al. (2007), the goal of doctors in neuroprotection is to maintain the ICP between 20 and 25 mmHg, which is the safe range. Ropper (2012) advances the application of hyperosmolarity as a strategy for reducing brain volume and, thus, controlling the ICP [5, 6, 26].

In this approach, the administration of hypertonic solutions intravenously is effective in causing a drop in the CSF pressure. Since the brain parenchyma has high water content, specifically 80% of the mass, it is more highly sensitive to changes in the water concentration than other organs. Therefore, the use of any suitable osmolar agent, such as sodium or mannitol, which induce osmotic gradient between the cerebral tissue and the blood, is an effective way of reducing intracerebral blood volume and consequently lowering ICP [25].

For the application of hyperosmolar therapy to be effective, the blood–brain barrier must be intact. Therefore, it may not be useful in cases where the barrier is damaged, such as in traumatic contusion. Applying this strategy in such a situation would mean reducing the pressure within the normal cerebral tissue while having no significant effect on the brain edema associated with the lesion [25]. The other option for reducing ICP is the application of forced hyperventilation, but its effects are not as consistent and long-term as those of the hyperosmolar therapy. However, the doctor should carry out a pertinent assessment of the patient's condition to determine which of these techniques to use.

Another focus of neuroprotection is brain temperature. The cerebral temperature exceeds the measured temperature of the rest of the body by 1–2 °C. Studies have revealed that in acute brain injury, fever is usually associated with undesirable outcomes [25]. As a result, several studies have been conducted to investigate the effect

of lowering the body temperature in a controlled setup to prevent secondary damage, including reperfusion insults, following acute brain injury [1].

Animal studies have shown the potential effectiveness of therapeutic hypothermia (TH) in the prevention of reperfusion injury in ischemia, as well as reduction of cerebral edema. In a meta-analysis, Crompton et al. (2017) found that therapeutic hypothermia is a potentially effective neuroprotective approach for adults, but it cannot be applied safely in children [22–25].

The results of the treatment appear to be time-dependent, with the use of TH for the treatment of acute TBI for short periods failing to exhibit desired outcomes, while applying the strategy for prolonged periods appear to have better results [28]. In general, hypothermia therapy is still an area under investigation, and the results of the clinical application are not yet conclusive.

Finally, neurorepair is an alternative strategy for the treatment of brain injury. While neuroprotection is majorly focused on preventing secondary damage, neurorepair is used when destruction to crucial brain structures has already occurred and, therefore, doctors must focus on rectifying the damage [19].

In some instances, the commencement of treatment may take too long such that the standard therapeutic window is exceeded and, therefore, the death of brain cells at affected regions occurs. In such instances, it is possible to initiate remedial treatment approaches to repair the damage tissues. These approaches are mostly experimental. The treatment can be either through exogenous measures or by inducing endogenous processes to initiate repair. Neurogenesis and repair of destroyed cells have been stimulated in animal models through pharmacological and cellular treatment options, with considerable functional recovery and reduced extent of infarction when the measures are applied 24 hours after experimental stroke [19].

Neurons that have been lost through apoptosis following delayed treatment of brain injury can be repaired to give patients better survival odds. Kalladka et al. (2016) stated that some allogeneic neural stem cells are under phase I clinical trials, thus indicating that the approach is safe and could be beneficial. Stem cell therapy for exogenous neural regeneration can be done by integrating cells into the CNS or by using neurotrophic factors from donor cells. Also, the growth of neurons can be promoted by inactivating the major inhibitors of this process [3].

13.5 Conclusion

In conclusion, there are different approaches to neuroprotection for various causes and mechanisms of brain injury, with differing levels of clinical applicability, efficacy and safety. The primary focus of neuroprotective strategies is to limit secondary damage to the brain following the initial insults, whether from TBI, ischemic stroke, SAH or degenerative CNS disorders. Among the most critical objectives of neuroprotection is to halt the effects of excitotoxicity, oxidative stress, elevation of ICP, and hypoperfusion.

The most prevalent secondary degenerative processes of brain injury is excitotoxicity resulting from increased glutamate neurotransmission with an influx of calcium and sodium ions, which leads to high activation of the voltage channels with neural destructive effects. Treatment of this phenomenon is focused on antagonizing the chemical interactions involved in this cascade. On the other hand, oxidative stress is treated using various antioxidant or radical scavenging agents, although the success rate of most of these substances is below optimal. Another approach to neuroprotection is the control of ICP, where hyperosmolar therapy has demonstrated quite a significant efficacy in achieving the desired outcomes.

Moreover, the maintenance of hemoglobin levels is a crucial consideration in brain injury since most patients present with anemia following cerebral insults. Controlled transfusion with red blood cells has been the most effective approach, although stringent care should be applied to avoid adverse events.

During brain injury, cerebral temperatures are generally higher than the core body temperature, which makes it necessary to employ measures such as controlled hypothermia to prevent escalation of adverse effects resulting from fever. In situations where treatment has been delayed to the extent that significant secondary damage has occurred to the brain, neurorepair is an alternative to neuroprotection, and it can be done through exogenous means or by inducing endogenous processes to stimulate neural regeneration.

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Chapter 14
Decompressive Craniectomy: Breaking Skepticism

Leonardo C. Welling, Nícollas Nunes Rabelo, and Eberval Gadelha Figueiredo

14.1 Introduction

The World Health Organization estimates that more than five million people die from trauma annually. Among traumatic injuries, those that affect the brain are related to death and long-term neurological sequelae. Recent studies show that 60% of neurosurgical interventions performed annually are caused by trauma and cerebrovascular diseases. There are about 6.2 million neurosurgeries for trauma and 2.8 million for cerebrovascular disease each year [1].

The removal of different parts of the skull, associated with the dura mater opening and enlargement with aponeurotic galea, or other synthetic graft, is widely performed on head trauma and cerebrovascular disease patients. In addition to these classic indications, cranial decompression may be applied by neurosurgeons who evaluate that the brain is swollen and "tightened" after primary lesion removal. This procedure allows the brain parenchyma expansion and consequently minimizes the intracranial hypertension increase [2, 3].

Although it has been documented that decompressive craniotomy (DC) does not change the primary injury (which has already occurred at the time of the injury, whether traumatic or spontaneous), it reduces the secondary injury damage that lasts for hours and days [4].

Most neurotraumatology studies focus on closed cranial injuries, but the experience acquired in war scenarios, in which decompressive craniotomy was used as "damage control," allowed its application to be disseminated to countries where gunshot injuries are observed in urban settings [4].

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DC is usually indicated in two scenarios. The first, also known as a primary or prophylactic DC, is defined as extensive bone removal after intracranial surgery. It is not intended to intracranial hypertension control but is done prophylactically to prevent the intracranial pressure to increase. Its indication is based on the findings of cerebral edema or on situations in which the brain tomographic findings suggest the possibility of a significant intracranial hypertension in the postoperative period. Some authors also indicate the primary DC in the treatment of brain contusions, acute subdural hematoma (ASDH), or in low-income countries where neurocritical care resources are deficient [5, 6].

Secondary DC (Sec-DC) is the procedure performed on patients who have not responded to first and second-line therapies for intracranial hypertension control. The concept of convert a closed box with finite volume into an open box minimizes the damage secondary to intracranial hypertension, improves cerebral perfusion pressure (CPP), and prevents the occurrence of cerebral herniation with brainstem compression [4].

Skepticism concerning DC is influenced by the opinion of several neurosurgeons, that despite the intracranial pressure (ICP) control, the functional results do not improve and still account for neurological and neurosurgical complications in the short-, medium-, and long-term outcome. In this context, this chapter aims to demonstrate, in the light of current knowledge, what are the benefits, complications, and possible harms of cranial decompression in traumatic and cerebrovascular events. As quoted by Kjellberg in 1971 [7]:

> "We have presented our appraisal of the case material (bifrontal decompressive craniectomy), not so much as proof of its superiority over other methods, but rather as a provocation for further critical appraisal of its use."

14.2 Historical Aspects

The first evidence of cranial trepanation dates back to 10,000 BC at the beginning of the Neolithic period. Later, in the Greek Era, Hippocrates described more elaborate cranial interventions. At the Medical School of Alexandria, scientist Aulus Aurelius Cornelius Celsus indicated trepanation in all symptomatic patients after head trauma, regardless of the identification of any fracture [8, 9].

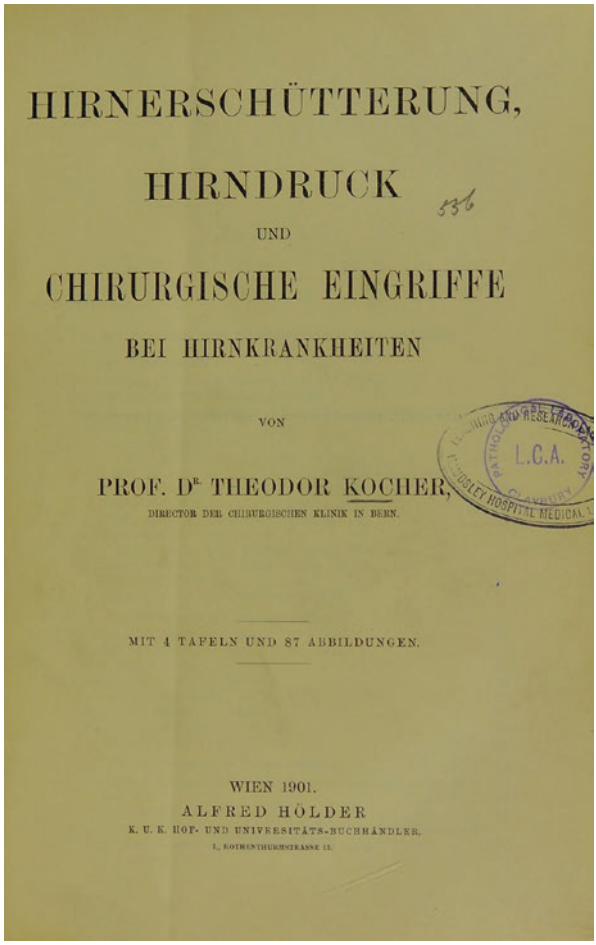
During the Roman Empire, Galen indicated trepanation for cases of open fractures, fractures with hematoma, and comminution fractures. In the Early Medieval era, knowledge about the importance of the skull and dura mater as a natural barrier has increased, and neurosurgical procedures at the time have been discredited. Interest in cranial surgery resurged in the eleventh century at the Salerno Medical School in Italy when some procedures had begun to be performed [10].

However, it was Berengario da Carpi, a doctor and professor at the University of Bologna who made, in 1518, one of the most beautiful descriptions. The "Tractatus de calve sive cranei fracture," inspired by the treatment offered to Lorenzo de Medici after an occipital gunshot, can be considered as one of the first step by step

descriptions of a successful craniotomy. Also, this author reported three cranial injuries cases that were operated on and had at least a 1-year follow-up. One of which experienced a decompressive craniotomy [11].

Despite the uncertainties of who was the first modern-era neurosurgeon to perform the first DC, the first description was made by Annandale in 1894. Spiller et al. were the first to report a case series of decompressive craniotomy.

In the late nineteenth century, most DCs were palliative measures in patients with inoperable tumors. In the early twentieth century, Kocher proposed decompressive craniotomy in patients with symptoms of intracranial hypertension. Its manuscript (Fig. 14.1) describes therapeutic measures to intracranial hypertension control, as well as indications for trepanation whenever there are intracranial hypertension doubt and "temporary" hemicraniectomy for those whose trepanation was not useful [4].


HIRNERSCHÜTTERUNG,

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CHIRURGISCHE EINGRIFFE

BEI HIRNKRANKHEITEN

VON

PROF. Dr THEODOR KOCHER,

DIRECTOR DER CHIRURGISCHEN KLINIK IN BERN.

MIT 4 TAFELN UND 87 ABBILDUNGEN.

WIEN 1901.

ALFRED HÖLDER

K. U. K. HOF- UND UNIVERSITÄTS-BUCHHÄNDLER.

Fig. 14.1 Kocher's article where the decompressive craniotomy has been proposed

In 1905, after visiting and learning with Theodor Kocher in Bern, the American neurosurgeon Harvey Cushing, through a detailed report, described the subtemporal decompression technique for intracranial hypertension relief in patients with an expansive lesion [4]. At that time, it was possible to observe that the ICP control, along with mortality reduction, was responsible for lower morbidity among survivors when compared with those who did not undergo surgery.

Cushing's indications about DC are secondary to his observations in 250 cranial perforating injuries treated during the First World War. In his observations, the watertight dural closure was already recommended [12]. In subsequent years, poor results caused DC to fall into disrepute quickly. Between the 1960s and 1980s, only 22 studies evaluating cranial decompression after skull trauma were published. Besides, mortality in these studies ranged from 46 to 96% regardless of the operative technique used.

Still, in the 1970s, two studies defined operative techniques for decompression that are references to the present day. Firstly, the bifrontal DC proposed by Kjellberg and Prieto [7]. In the same year, Ransohoff et al. described unilateral DC in acute subdural hematoma patients. The survival of his series of 35 patients was 35% [13]. In the following 2 years, Morantz et al. analyzed tomographic changes after decompression and observed that patients in whom the deviation from the midline had improved presented a better survival [14].

Despite the mortality reduction, functional outcomes remained poor. In 1968, Moody et al., in an animal model, demonstrated lower mortality, but their "quality of survival has not been good" [15]. In 1979, Cooper et al. demonstrated in animal models that cryoinduced lesions have higher volumes after cranial decompression than in those who were not submitted to intervention. In parallel, clinical and surgical observations pointed out that cerebral edema was evident after decompression [16]. Based on these studies and others that demonstrated functional outcomes were inferior, DC was practically banned from the neurosurgery textbooks written at that time [17, 18].

At the beginning of the twenty-first century, there was an improvement in prehospital care, as well as the development of well-established protocols, knowledge of neurological injury pathophysiology, and other pharmacological measures for intracranial hypertension treatment. In this current context, DC has been extensively investigated in neurocritical patients. More specifically, in the past 10 years, two large multicenter studies have been published. DECRA evaluated the bifrontotemporoparietal craniotomy efficacy in patients with diffuse brain lesions who did not respond to first-line clinical measures to intracranial pressure (ICP) control [19]. On the other hand, RESCUEicp evaluated the effectiveness of DC after first- and second-line measures to raised ICP control in severe TBI patients [20].

14.3 Decompressive Craniotomy

A primary decompressive craniotomy is an act of not replacing the bone flap after evacuating any mass-effect injury. It can be an epidural, subdural, intraparenchymal hemorrhage, or hemorrhagic contusion. It is supposed that there will be an ICP increase in the postoperative period.

When we analyze patients, who have been submitted to epidural hematoma removal, which corresponds to only 2% of traumatic cranial injuries, it is observed that the vast majority present themselves as isolated injuries and the chances of intracranial hypertension secondary to cerebral edema are very small [21].

Patients undergoing removal of an acute subdural hematoma can be treated with craniotomy (and replacement of the bone flap) or with DC. Acute subdural hematomas (ASDH) correspond to about 65% of patients who are submitted to intracranial trauma surgery [22]. Unlike epidural collections, ASDHs are often associated with intraparenchymal contusions and cerebral swelling. The surgical indications proposed by the current guidelines are the cases in which the computerized tomography (CT) scan shows 10 mm hematoma thickness or midline deviation greater than 5 mm (Fig. 14.2), regardless of the Glasgow Coma Scale Score (GCS score). In cases where the hematoma is less than 10 mm thickness and the midline deviation

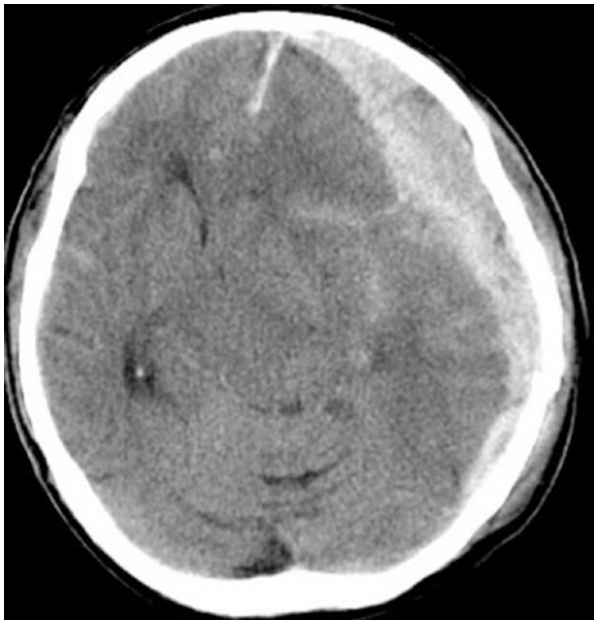

Fig. 14.2 Acute subdural hematoma with surgical indication

is less than 5 mm, but the patient lowers the GCS score by two points or more, surgical removal is also indicated. Although the indications are clear that the hematoma should be removed by craniotomy, the bone replacement is not defined [23]. According to Miller et al., two-thirds of ASDH patients submitted to surgery develop intracranial hypertension in the postoperative period [24]. Wilberger et al. observed that 43% of patients undergoing acute subdural hematoma removal had sustained raised ICP that did not respond to the currently recommended measures. Mortality in this group of patients was higher than 95% [25].

The results of studies comparing patients undergoing primary DC versus bone replacement after ASDH removal are controversial. There is still possibly a selection bias since patients undergoing primary DC have baseline characteristics that suggest that TBI is more severe, such as greater hematoma thickness, more significant midline deviation, low admission GCS score [26].

In an attempt to elucidate responses, the RESCUE-ASDH Trial was developed in which the craniotomy and primary DC will be compared. This study currently includes all patients (463 patients in 4.5 years). The primary outcome was the Glasgow Outcome Scale-Extended (GOS-E) at 12 months. Secondary outcomes were GOS-E at 6 months, quality of life (EQ-5D) after ICU discharge, 6 and 12 months after injury, ICU length of stay, discharge destination, mortality, hydrocephalus requiring shunt insertion, as well as clinical complications during and after hospitalization, and the economic costs involved. The results will come out soon and many answers are awaited [26, 27].

Furthermore, many times, neurosurgeons face it with brain injury, not being trauma. There are numerous situations in which intraoperative complications occur. Sinus vein thrombosis, bleeding tumors, ruptured arteriovenous malformations are situations where these changes can challenge the surgeon to take rapid decisions. There is no standard recommendation for doing DC in those cases but it is recommended to individualize each case.

14.4 Secondary Decompression Craniotomy

The raised intracranial hypertension is the most frequent cause of morbidity and mortality in patients suffering from severe TBI. Despite advances in the treatment and intracranial pressure monitoring, poor outcomes are still prevalent. In situations of brain swelling and without mass lesions with surgical indication, the use of barbiturates, hypothermia, and other pharmacological measures have few benefits. In this context, secondary decompression craniotomy is well indicated. The drop in ICP is promptly observed after cranial decompression. According to Aarabi et al., in his series of 40 patients with intracranial hypertension submitted to DC, ICP decreased from 24 to 14.6 mmHg (average) after surgical decompression [28]. Also, numerous other studies show a decrease in ICP and CPP improvement. On the other hand, the functional results are not always good, and most of the observational studies show controversial results, possibly due to heterogeneous population.

In addition, outcomes evaluation did not follow a model and time standardization [29–32].

The first large multicenter randomized study in the adult population was DECRA, with its results published in 2011. A total of 155 adults with diffuse lesions who developed intracranial hypertension (greater than 20 mmHg) for more than 15 minutes and refractory to first-line therapies were randomized. The intervention was a bifrontal DC (bDC), and the primary outcome was GOS-E 6 months after injury (Fig. 14.3). Patients submitted to DC had less time with ICP above 20 mmHg, fewer interventions to ICP control, and shorter ICU stay. However, ICP control did not translate into a better clinical outcome. Mortality was the same in both groups, and GOS-E was higher in the group that underwent surgical intervention [19].

One of the criticisms of the work was that in the group undergoing DC, there was a higher proportion of patients with both non-reactive pupils ($p = 0.04$). After post hoc adjustment for pupillary reactivity, there was no difference in GOS-E between both treatment groups (surgical vs. conservative) [19].

This study should be evaluated with caution, as its definition of refractory ICP (20 mmHg for 15 minutes) is very strict, and currently, higher ICPs are tolerated, especially if CPP is above 60 mmHg and the cerebrovascular reactivity index (PRx) is adequate. Therefore, it is estimated that several patients received DC

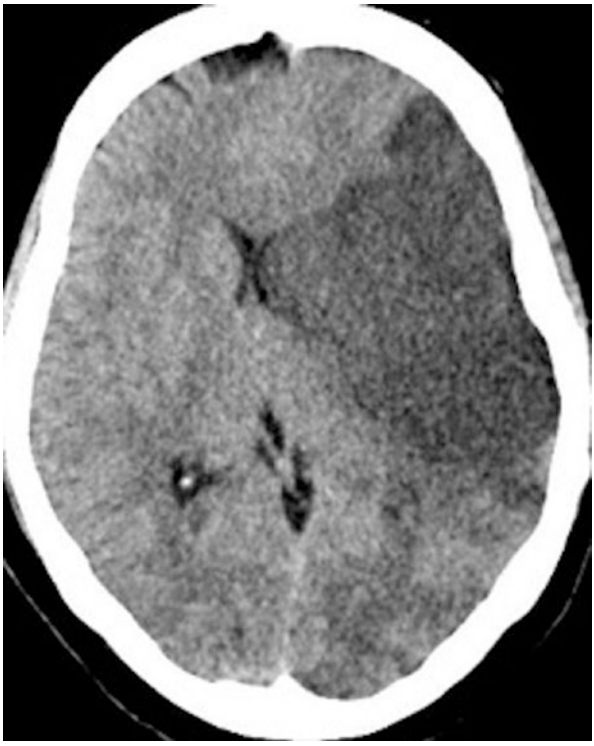

Fig. 14.3 Malignant middle cerebral artery infarction

unnecessarily. Another criticism is the operative technique chosen when the surgeon does not cut the brain scythe [33]. Some authors report that bDC is related to poor functional results, especially when the brain scythe is not sectioned, as the frontal lobes advance and are injured against the dural fold. These patients may have late cognitive deficits. The study shows that bDC is not a good technique to be used and that is why bilateral craniectomy is preferable to bifrontal [33].

RESCUEicp is another multicenter, randomized study that compared last-tier secondary DC with continued medical management for refractory intracranial hypertension after TBI. It included patients with head trauma between 10 and 65 years of age, with tomographic abnormalities, who maintained high ICP despite all clinical measures. Surgical treatment could be a bifrontal decompressive craniotomy or unilateral frontotemporoparietal craniectomy (Figs. 14.4a–d and 14.5). The primary assessment was 6-month GOS-E. A total of 408 patients were randomized, and there were no differences between both groups in their baseline characteristics.

The surgical intervention group had lower mortality (26.9 vs. 49.9%). However, there was a higher number of patients in a persistent vegetative state (GOS-E 2), lower severe disability (GOS-E 3), and upper severe disability (GOS-E 4).

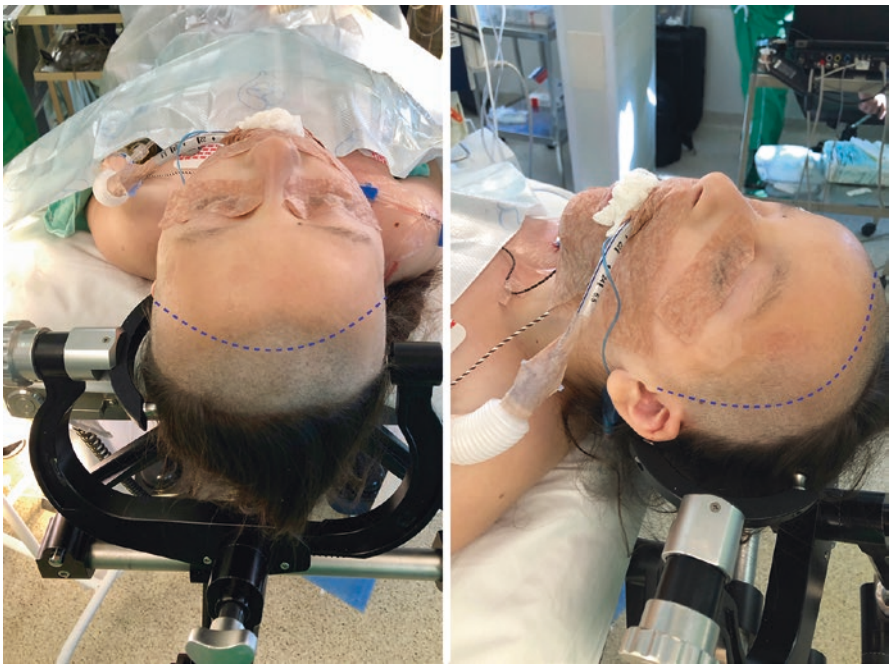

Fig. 14.4 Preoperative planning—bifrontal decompressive craniotomy

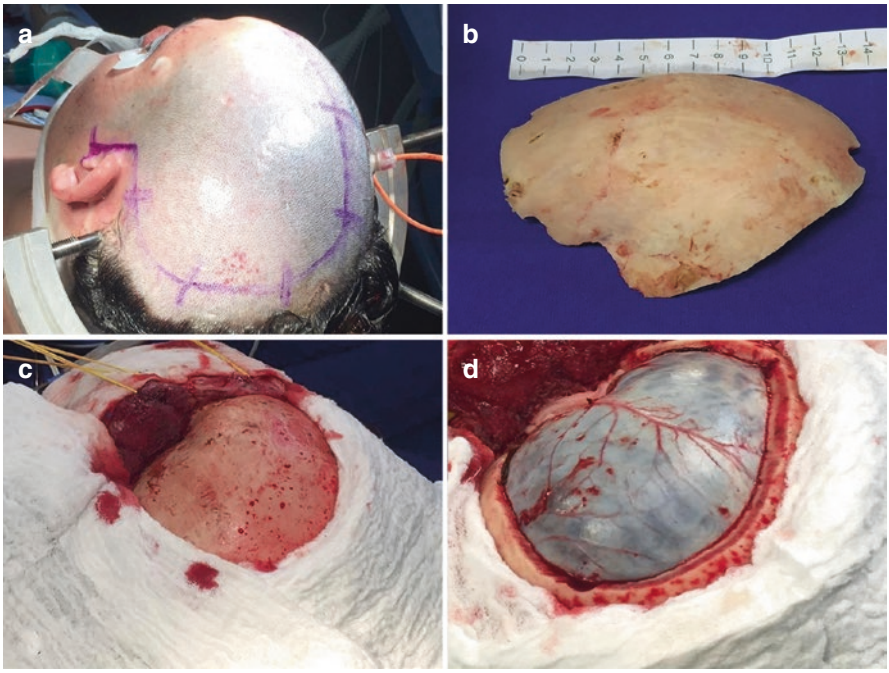

Fig. 14.5 Unilateral hemispheric decompressive craniotomy. (**a**) Skin planning. (**b**) Bone exposure. (**c**) Bone size (bone flap). (**d**) Dural exposure

Chestnut et al. recently conducted a multicenter study (BEST Trip Trial) in which the results were compared between two groups of patients with severe traumatic brain injury. In the first group, therapy was guided by ICP values. In the second, the treatment was guided by images and serial physical examination. They observed that there was no outcome difference. In both groups, conservative measures were applied to ICP control, and 30% of patients in each arm were submitted to DC [34]. This result does not change the basic concept that all situations of intracranial hypertension (whether measured by an ICP monitoring or indirectly supposed by imaging tests) should be treated rigorously.

More important than ICP monitoring is to understand how to interpret their values. It should be noted that isolated episodes of raised ICP do not justify the DC indication. For eligibility, there must be sustained increase in ICP, and other parameters such as physical examination, neuroimaging, other monitoring variables analysis must be included before surgical indication. Also, an escalation in conservative treatment must be achieved, unless a severe neurological deterioration indicates surgery anticipation [26].

14.5 Decompression Craniotomy in Stroke

The occlusion of the internal carotid or middle cerebral artery can cause significant cerebral ischemia. This event occurs in approximately 10% supratentorial ischemic stroke cases [35]. Hypodensity that affects more than 50% of the middle cerebral artery (MCA) territory in the first 48 hours indicates life-threatening ischemia. It is also called malignant middle cerebral artery infarction (MMCAI) (Fig. 14.3) [36]. Neurological deterioration usually occurs in the first 5 days, but in most severe cases, the deterioration occurs earlier, and death occurs due to transtentorial herniation [36–38]. Not all patients with middle cerebral artery occlusion will develop MMCAI. One of the main predictors for MMCAI is high admission NIHSS, arterial hypertension in the first 12 hours after ictus, female sex, and young patients [36, 38, 39]. Without any neurosurgical intervention, mortality from this type of stroke can reach 80% [40, 41].

To date, there are eight randomized clinical trials with their published results that assess DC in the MMCAI. The first three were published between 2007 and 2009 (DESTINY, DECIMAL, and HAMLET) [40].

Vahedi et al. carried out a pooled analysis of these three initial studies and observed significant benefits in all previously defined subgroups (age below and above 50 years, time until randomization less and greater than 24 hours, dominant vs. non-dominant hemisphere). The number need to treat (NNT) was 4 for an adverse outcome, classified using the modified Rankin Scale (mRS) from 4 to 6. For survival assessment, an NNT of 2 was observed. The chance of surviving with mRS of 4 increased tenfold, the survival chances with an mRS of $\leq$3almost doubled. The chances of survival with severe sequelae, in the case of mRS of 5, remained the same in the conservatively and surgically treated group [42].

Several criticisms arose in the included patients' age since the majority of stroke studies the patients are older. In DESTINY II, the mean patient's age was 70, and the study had to be suspended earlier due to the clear evidence of decompressive craniotomy benefits [43]. Another Japanese cohort also found no difference in the outcomes of patients older than 60 years who underwent DC [44].

When asked about the decompression side, the pooled analysis observed that the benefit is independent of the presence of aphasia. Kastrau et al. evaluated aphasic patients who underwent DC. Aphasia improvement was achieved by more than 90% patients. Early decompression and patient age were predictors of better evolution [45].

Patients who were randomized 48 hours after the onset of the symptoms presented worse functional and mortality results when compared with patients operated before 48 hours [42]. In a medical database with more than 1300 patients (who were not included in any study protocol), it was observed that 56% of the patients underwent surgical intervention before 48 hours, but the poor outcomes were only noticeable if the surgery was postponed for more than 72 hours after ictus [46].

Some studies advocate ultra-early DC, with an average of 4.25 hours after the onset of symptoms. Analyzing comparatively with another group that the

decompression was done approximately 68 hours after the ictus, the ultra-early group showed much lower mortality (8% vs. 38%). Despite the beneficial results, this should be interpreted with caution, as there may be an over indication of DC and, consequently, unnecessary surgery [47].

Therefore, there is robust evidence obtained from multicenter studies that CD reduces mortality and improves the neurological outcome in patients with extensive ischemia regardless of age and the side affected.

14.6 Operative Technique

There are several techniques described for cranial decompression. Among the variations observed is the amount of bone removed, whether unilaterally or bilaterally, dura mater opening, as well as bifrontal decompression [29–32].

In diffuse lesions and refractory intracranial hypertension, a bifrontal decompressive craniectomy is indicated (Fig. 14.4). No studies that prove whether the removal of the bone that covers the upper sagittal sinus and its ligation in its most anterior portion aiming at a more considerable decompression influence the outcome that has been published. Alternatively, bilateral hemicraniectomy may be indicated [26].

When opting for unilateral decompression, there are two types of skin incisions described in the literature: one with an inverted question mark, or Becker type, also recognized as trauma flap, and the other with a T-shaped incision described by Ludwig Kempe. At the time of bone removal, wider craniectomy (12 × 15cm) than that usually used in contusions is indicated (Figs. 14.5 and 14.6). In the Becker incision, any attempt to increase this incision behind the ear can cause skin necrosis [48, 49].

In this context, the ‘T’ incision may be an alternative [48]. This type of incision allows safe access to the frontotemporoparietal regions and extensive bone decompression. The bone resection should include the inferior part of the squamous bone, as this is where the basal cisterns compression by the mesial temporal lobe (uncus) occurs. The next step, after craniotomy, is dural opening followed by autologous (aponeurotic galea) enlargement. There are several techniques for incision and repair of the dura mater. At this point, it should be noted that whatever technique is chosen, a homogeneous expansion of brain tissue is essential. For grafting and dural enlargement, synthetic grafts can be used, but pericranium is a great low-cost alternative. A watertight dural suture is essential [29, 30].

Two clinical trials assessed whether the size of the craniotomy influenced the outcome. Both compared 12 × 15 cm standard frontotemporoparietal craniotomies with smaller temporoparietal craniotomies (8 × 6 cm). Standard craniotomies were related to lower mortality, better clinical outcome, lower incidence of late hematomas, and lower incidence of CSF fistula [31, 32].

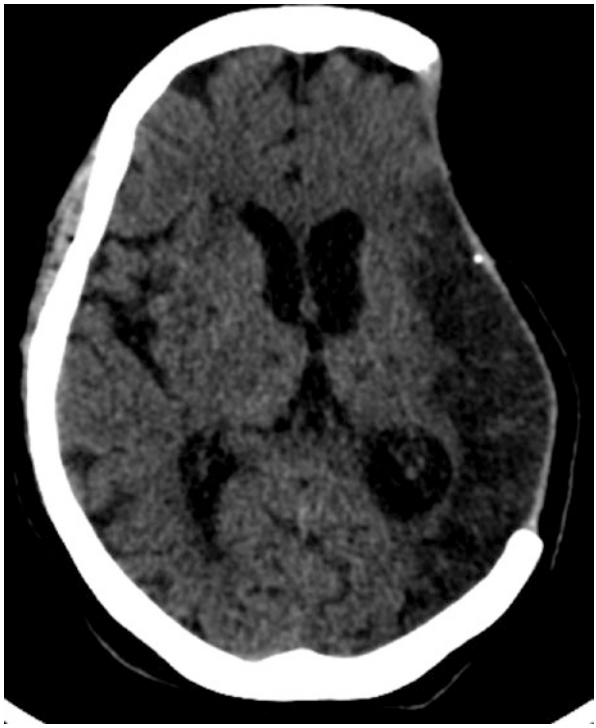

Fig. 14.6 Unilateral hemispheric decompressive craniotomy. Posoperative CT scan

14.7 Hinge Craniotomy

In the past 10 years, a variation of decompressive craniotomy is being used and tested. Hinge craniotomy (or Tucci flap), consists of a neurosurgical procedure in which the bone flap is replaced and fixed only on a bone border. This technique allows the brain to expand without meeting the resistance of a fixed bone flap. Other titanium plates are placed on the flap, but the edges of the skull are not fixed, in order to protect eventual sinking inward toward the brain [50–52].

There are retrospective studies that include TBI and stroke patients, which demonstrate ICP control comparable to conventional DC. Besides the ICP control, there is a lower infection incidence and other complications in the hinge craniotomy group [52].

Horsfall et al., in a systematic review, with 15 studies (211 patients), only nine patients had their surgeries converted to conventional DC. Despite the attractive results, there is no randomized clinical trial, and further studies are needed for any definitive conclusions [53].

14.8 Complications

14.8.1 Post-traumatic Hydrocephalus

Post-traumatic hydrocephalus (PTH) is defined as the appearance of new neurological symptoms in a patient with traumatic cerebral injury history and compatible radiological findings [54–56]. The diagnosis is often difficult since hydrocephalus symptoms can coexist with neurological deficits caused by brain damage.

There is little published data on cranial reconstruction impact on post-traumatic hydrocephalus incidence. One of the main controversies is the cranial reconstruction moment and those performed three months later are more likely to have PTH [57].

Another issue involves the timing of shunt placement. When cranioplasty is performed in conjunction with the shunt, the chances of postoperative subdural hygroma are lower when compared with patients who underwent cranioplasty at first and shunt afterward [58].

14.8.2 Subdural Hygroma

Subdural hygromas are CSF collections found in many neurosurgical contexts, whether after elective or emergency surgery. There are several level III evidence studies that describe the occurrence of subdural hygromas after DC, with indirect evidence that CSF hydrodynamics imbalance precipitates post-TBI hygroma formation [56, 59].

Some studies correlate the occurrence of subdural hygromas with post-traumatic hydrocephalus development. Lu et al., in a systematic review, analyzed nine studies that altogether included 1010 TBI patients who underwent decompressive craniotomy. Altogether post-traumatic hydrocephalus was identified in 27% of cases, and subdural hygromas occurred in 44% of cases. Pooling multivariate-derived HRs indicated that subdural hygroma was a significant, independent predictor of PTH. Despite the real correlation, there is no causal link so far, and some authors suggest that subdural hygroma and post-traumatic hydrocephalus are a spectrum of the same disease with the CSF hydrodynamic disturbance. Regardless of these studies' findings, it is observed that in patients with subdural hygromas, often occurring early after decompression call attention that post-traumatic hydrocephalus may occur [56].

14.8.3 Sinking Flap Syndrome

The sinking flap syndrome (SFS) is a DC complication. Its exact incidence has not been well established. One of the diagnostic criteria is sudden neurological worsening after an interval of improvement following craniectomy [60]. The introflexion of the skin flap, with a concave aspect, is observed. The contralateral motor deficit, accompanied by progressive mental confusion, cognitive dysfunction, slurred speech, lethargy, and even death, may occur [61]. Since the first descriptions, many SFS synonyms have been described. In the literature 'syndrome of the trephined,' 'sinking skin flap syndrome,' 'sinking scalp flap syndrome,' 'sunken brain and scalp flap syndrome,' and 'motor trephine syndrome' are synonymous.

Its pathophysiology has not been clarified, and most of the literature reports are isolated cases, with only a few published series thus far.

Yamaura et al. [62] described their observations in 33 SFS patients and 30% of these improved after cranioplasty. The most interesting data from this study were CSF dynamics analyzes performed before and after reconstruction surgery. It was observed that the lumbar opening pressure normalized after cranioplasty.

Fodstad et al. reported 22 SFS cases. Headache, vertigo, and hemiparesis were the most prevalent symptoms. All of them improved after cranioplasty [63]. Stiver et al. observed 10 SFS cases among 170 patients submitted DC. They have described the motor syndrome, known as reversible hemiparesis, which, as the name says, fully resolved after cranial reconstruction. The main tomographic characteristics observed were hygromas, ventriculomegaly, and changes in regional blood flow measured by CT perfusion. All described changes disappeared after cranioplasty [64].

Di Rienzo et al. followed 393 DCs in a single-center series. Among these, 40 met diagnostic criteria for SFS. In this study, one of the most relevant data was that the decompression area was directly related to the chances of SFS appearance. Also, if the decompression is closer to the midline, more likely it is to develop SFS, probably because very large craniotomies may reduce CSF resorption capacity due to arachnoid granulations blockage. It can occur by blood, cortical scars, or collapse of the drainage veins to the superior sagittal sinus [65].

Regardless of the causes, SFS is not a rare event. Its treatment should be instituted as soon as possible.

14.9 Cranial Reconstruction

Cranial reconstruction, also called cranioplasty, aims to restore local aesthetics, improve the CSF flow dynamics, and promote brain tissue protection. Despite being considered a routine procedure in neurosurgery, it is associated with high morbidity [66].

Surgical planning begins with skin inspection. In situations in which primary closure will not be possible, especially in those with sinking skin flap syndrome, the use of expanders should be preferred.

After the initial decompression surgery, the temporal muscle is inferiorly retracted. The previous interposition of the skin flap directly on the dura mater may create adhesions at the time of dissection. At this point, careful manipulation is necessary to avoid damage to the dura or cerebral cortex. Besides, CSF fistula may occur and predisposes secondary local infection. To avoid adherence, some authors recommend, at the time of decompression, the interposition of non-absorbable materials between the dura and the subcutaneous tissue. In addition, some perform temporal muscle marking with colored sutures in order to identify them better later on [66].

Cranioplasty has a higher complication incidence when compared with other elective neurosurgeries. Walcott et al. reported that previous surgeries, ventriculoperitoneal shunt, and cardiovascular diseases are predictive factors for complications after trauma and hemispheric stroke. Skin complications, such as dehiscence, are related to preoperative clinical conditions, and there is no correlation with biomaterials used for reconstruction [67].

When comparing unilateral hemispheric with bifrontal reconstruction, it is observed that the last has a higher infection incidence, possibly due to paranasal sinuses communication, longer operative time for reconstruction, and the absence of temporal muscle protection. In infected cases, bone or synthetic graft removal is recommended until the infectious process resolved. The development of resistant materials to bacterial colonization may be very helpful [66].

The hydrocephalus occurrence varies from 10% to 45% after decompression craniotomy and, the broader percentage can be explained by the diagnostic criteria used. Its management has not been precisely defined yet. The controversies are when to perform cranioplasty, the necessity of CSF diversion, and if the bone or synthetic graft presence itself is not enough to restore the CSF flow dynamics.

According to Nasi et al., when evaluating patients in the 6-month post-decompression, CSF diversion was necessary in 91% of cases (in 130 patients series). Of these, 76% had their shunt performed after, 14% at the time and 8.8% before cranial reconstruction [57].

The hydrocephalus disappearance after cranioplasty is also documented. In some situations, when the hydrocephalus bulges the skin flap, the placement of ventricular or even external lumbar drainage allows cranial reconstruction minimizing the risk of brain parenchyma injury.

The ideal moment of cranioplasty is controversial. The early cranioplasty concept itself is not defined, with some authors referring to reconstructions performed in 4 weeks, while others even consider it as an early procedure even when performed within 12 weeks [68]. Reconstructions performed 14 days after DC carries the highest infection incidence. On the other hand, some authors advocate for ultra-early cranioplasty, performed 15–30 days after decompression. According to them, this moment minimizes infection incidence, seizures, and autologous flap absorption.

Archavlis et al. emphasized that the functional outcome is better if cranioplasty is performed before 7 weeks or between 7 and 12 weeks when compared with reconstruction surgery after 12 weeks. At the same time, patients with comorbidities such as diabetes, pulmonary thromboembolism, and resistant bacteria colonization are more likely to become infected susceptible to infection when reconstruction is done before 7 weeks [69].

Opinions about the benefits of early cranioplasty diverge. Some authors attribute a lower risk of hydrocephalus and others report that the functional outcomes do not change according to the surgical moment. However, the available studies are of low evidence [68].

14.10 Ethical Dilemmas

Based on outcomes 6 months after cranial decompression, it is clear that DC is a life-saving measure. When considering what life means, the controversy starts. What degree of functional impairment is tolerated by an individual? [68, 70] Patients submitted to decompression craniotomy after a hemispheric stroke had their satisfaction evaluated and whether the surgery would be acceptable initially. It was observed that 80% of patients would consent to undergo DC again [71]. It should be observed that patients classified as mRS > 4 are the ones who mostly would give retrospective surgical consent.

Possibly these patients were able to adapt and accept their neurological disability. Perceptions of quality of life are ultimately patient-specific, with perceptions of whether life is realized as "worth living" depends on the particular context [72].

Follow-ups should be long since, in 6 months, the assessment of neurological rehabilitation can still be considered early. It is evident in severe traumatic brain injury, in which the recovery time can extend beyond 2 years [68]. Larach et al. observed that one point in the GOS-E increased between 6 and 18 months after decompression. Among 59 patients with a considerable poor outcome at the sixth-month evaluation, 25% progressed to a good functional result at the 18th-month evaluation [73]. In the study by Gouello et al., 11% of DC patients obtained functional improvement from the third to the 24th month after surgery [74].

For the quality of life after TBI, evaluations beyond 3 years after trauma are recommended. Besides, there is a patient subgroup that worsens their cognitive and executive capacities due to progressive structural dysfunctions.

Patients must discuss their life support preferences with their closest relatives, who will be able to assist in decision making. Information exchange regarding clinical and surgical options must be emphasized. The possible functional results and real quality of life goals after recovery need attention, also. Patients should be aware that in the absence of any consent, especially after severe TBI or stroke, the surgery may be performed at the discretion of the surgeon/health care team [68].

14.11 Conclusions

The DC is a popular neurosurgical option used in traumatic brain injury and cerebrovascular diseases. Its primary objective is ICP control. It can be performed prophylactically (primary DC) or when clinical measures to avoid intracranial hypertension are not sufficient. Despite being used for more than a century, there are still many ethical dilemmas involved and disbelief in its real outcome benefits. Recently published work shows hopeful results. Despite the decompression inherent complications, the observed benefits justify, until now, its use in daily neurosurgical practice.

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Chapter 15
Sedation and Analgesia in Neurocritical Patients

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15.1 Introduction

Pain, anxiety, agitation, and delirium are frequent in intensive care unit (ICU) patients and associated with adverse outcomes [1]. Analgesia-based sedation approach is necessary for many of the general critical care population, especially in the neurocritical intensive care unit (NICU) [1–3].

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [4] or "an aversive sensory and emotional experience typically caused by, or resembling that caused by actual or potential tissue injury" [5]. The actual medical perception is that pain is considered as the "fifth vital sign."

Anxiety is a multisystem response to a perceived threat or danger. Agitation is an excessive, purposeless cognitive and motor activity or restlessness, usually associated with a state of anxiety. Delirium is a change in mental status accompanied by inattention. Delirium may be either hyperactive (restlessness and agitation) or hypoactive (lethargy and motor slowing).

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Population-specific protocols to manage analgesia and sedation in NICU increase the use of the analgesic, decrease sedative use, and reduce the medication-associated costs. The present standards advocate for multimodal analgesic and sedative regimes, including setting realistic pain expectations, identifying psychosocial factors that may affect self-report of pain, monitoring high-risk patients, and implementing prescription drug monitoring programs [6].

The clinical approach should be individualized to the severity of neurologic illness, prevention of chronic pain, posttraumatic stress disorder, and post-intensive care syndrome and monitoring systemic therapeutic targets (ICP, CBF, CPP, $CMRO_2$) aiming to optimize analgesia and minimize sedative drug dosage, ventilation length, and NICU stay.

15.2 Epidemiology of Pain at NICU

Pain, anxiety, agitation, and delirium are highly prevalent in critically ill neurosurgical and neurological patients [7]. Pain causes suffering and stress which is attributed to painful procedures, inability to communicate due to endotracheal intubation, interruption of sleep, hallucinations, and nightmares, which is related to the "post-intensive care syndrome" and posttraumatic stress disorder, observed in up to 25% of the ICU patients.

Many neurological conditions cause discomfort in NICU patients: intracranial tumors, hydrocephalus, central nervous system infections, hemicraniectomy, post-craniotomy pain, endovascular interventions, spinal procedures, surgical wound infections, subarachnoid hemorrhage, traumatic and nontraumatic intracranial hematomas, cranial fractures, ischemic stroke, and pituitary apoplexy, among others. However, a considerable number of patients present chronic pains not necessarily related to the by which they are admitted to the NICU.

Additionally, NICU patients present new non-neurological painful illness caused by starvation, drug side effects, immobilization syndromes, urinary disorders, pulmonary complications, and numerous distinct disturbances commonly observed in general ICU patients [8, 9].

Usually, NICU discomforts and pains are observed during routine procedures, as endotracheal suctioning, nasogastric tube insertion, bladder catheterization, drain removal, arterial or venous puncture, respiratory and motor physiotherapy, patient mobilization, complex wound care, and cerebrospinal fluid sampling [10].

Most patients describe moderate to severe pain in the first 48 h following NICU admission, especially during the first 12 h in those submitted to surgical interventions [11].

Post-craniotomy and posttraumatic headaches are very common [12]. The 2013 "International Headache Society Classification" includes in chapter "Headache Attributed to Trauma or Injury to the Head and/or Neck" acute or persistent

headaches attributed to whiplash, craniotomy, or traumatic injury to the head [13]. Up to 80% of post-craniotomy patients experience moderate to severe pain, being nearly 70% on the first postoperative and 48% on the second postoperative days [14], and more than 30% still endure pain for many days after this initial period [14]. Moderate to severe headache starts immediately or during the first 24–48 h in 50–90% of the patients after craniotomy [14]. Post-craniotomy pain is typically nociceptive and results from tissue lesion and is usually superficial and localized on the same side of the trauma or craniotomy, on the injury site, or the surgical scar [15]. Commonly, post-craniotomy headache differs from preoperative headache and may have characteristics of a tension-type headache [15]. Thibault et al. [16] observed that 76% from 299 patients who underwent craniotomy experienced moderate to severe postoperative pain, usually described as pulsating or pounding and less frequently as steady and continuous. Up to 22% of post-craniotomy patients report a dramatic impact of pain on their quality of life [17].

Several characteristics and surgical risk factors may influence the incidence and severity of acute postoperative pain as sex, preoperative diagnosis, and surgical approach. Acute pain experienced after craniotomy predominates in female and young people and in patients who required opioid analgesics preoperatively [18]. Pfund et al. [19] observed that 41% from 279 patients undergoing craniotomy for resection of brain tumor did not complain preoperative headache. Preoperative headache was more common in patients with metastatic brain tumors, astrocytoma, or tumors localized in the infratentorial space or cerebral ventricles.

Frontal craniotomies are associated with lower pain scores, while skull base surgeries, particularly for resection of posterior fossa tumors including acoustic neuromas, are associated with a higher incidence of disabling postoperative headache [20]. Schessel et al. [21] observed severe pain in 30 to 67% of patients following suboccipital craniotomy aiming resection of acoustic neuroma [21]. They also described that 63.7% of patients who had undergone the suboccipital approach but who did not undergo the translabyrinthine approach for neuroma excision experienced significant discomfort localized at the craniotomy site or headache. Vijayan [22] observed that while 42% of the patients with acoustic neuroma had no presurgical or minor headache, 75% experienced headache after the surgery.

Patients undergoing osteoplastic craniotomy or cranioplasty for posterior fossa procedures presented less postoperative headache than patients undergoing craniectomy. Koperer et al. [23] observed that at the discharge time from the hospital, 69% out of 16 patients undergoing craniectomy and just 31% out of 13 patients undergoing craniotomy presented post-craniotomy pain and that 3 and 12 months postoperatively, the pain was less frequent in the patients who had undergone osteoplastic craniotomy or cranioplasty. Similarly, Harner et al. [24] observed that post-craniotomy headache was complained by just 4% of patients treated with cranioplasty after posterior fossa excision of acoustic neuroma and by 17% of those treated with craniectomy without cranioplasty.

The incidence of chronic post-craniotomy headache ranges from 0% to 65% [15, 17, 25]. According to the Headache Classification Committee of the International Headache Society, chronic post-craniotomy headache must onset within 7 days after the surgery and persist longer than 2–3 months since other diagnoses are excluded [13]. Harner et al. [26] graded chronic pain following craniotomy at 3 months post-procedure as Grade 1 (relatively minor annoyance), Grade 2 (present almost every day), Grade 3 (patient requiring medication every day), and Grade 4 (patient feels incapacitated). The incidence of chronic post-craniotomy pain is higher after posterior fossa approach aiming acoustic neuroma resection (33–44%) [27] than after supratentorial craniotomy (17.5–29.3%) [17, 26] and reduces with time. Also, the translabyrinthine approach for resection of acoustic neuromas is associated with a less chronic postoperative headache than the retrosigmoid approach [21, 26].

Severe or prolonged postoperative acute pain and postoperative complications predict the development of chronic post-craniotomy headache [28]. Gee et al. [29] observed that 82% from 107 patients who underwent craniotomy had prolonged resolution of post-craniotomy headache which disappeared gradually, and none required major medical intervention. Batoz et al. [25] observed that more than 50% of their patients experienced chronic headache and 25% presented neuropathic pain at the second month after craniotomy.

Often post-subarachnoid hemorrhage headache is severe. Headache was more frequent in patients having perimesencephalic subarachnoid hemorrhage (88%) than with spontaneous subarachnoid hemorrhage in the absence of perimesencephalic subarachnoid hemorrhage (66%) [30]. Glisic et al. [31] evaluated retrospectively 77 patients with subarachnoid hemorrhage and concluded that severe headache (VAS scores 8 or higher or need for three or more different analgesics and analgesic use lasting 2 or more days) was complained by 73% of patients at the end of the second week post-hemorrhage; in 58% when Hunt and Hess was Grade I, in 88% when Grade 1., and in 56% when Grade 3;, and in 56% of patients with Hijdra score ranging from 0 to 10, in 86% with Hijdra score ranging from 11 to 20, and in 76% with Hijdra score ranging from 21 to 30. The pain was more common in females (73%) and young patients [31]. Morad et al. [32] reported severe pain (VAS ranging from 7 to 10) in 89% and very severe pain (VAS = 10) in 63% from 46 patients with subarachnoid hemorrhage. The pain was primarily placed in the head in 76% of the patients but also in the back, neck, limbs, and eyes and more frequent in females.

Pain is also very common in traumatic brain injury (TBI) patients [33]. Headaches persisting more than 2 months after the craniocerebral trauma are usually referred to as chronic posttraumatic headache [33]. Chronic posttraumatic headache may reach a prevalence of 32% and 75% in patients with mild and moderate to severe traumatic injury, respectively [34]. The reported 1-year populational prevalence of persistent posttraumatic headache in Norway was 0.21%, and the lifetime prevalence in Denmark was 4.7% in men and 2.4% in women [35]. Craniotomy for treatment of intracranial traumatic lesion may also lead to chronic headache. With time, these patients may present complaints compatible with chronic tension-type headache or occasionally migraine-like attacks. Pain becomes chronic more frequently in females and young people [36].

15.3 Consequences of Unsatisfactory Treatment of Pain, Anxiety, Agitation, and Delirium

Pain and discomfort may cause suffering, anxiety, fear, anger, depression, delirium, agitation, and sleep disturbances. Also, systemic responses as increased blood pressure, heart and respiratory rates, chest pain, myocardial infarction, lung atelectasis, constipation, deep venous thrombosis, infection, and fever, among others, are documented [37, 38].

Pain interferes with respiratory muscle functions, prolongs mechanical ventilation days and NICU stay, increases the number of deaths, and causes many other complications after extubation [38]. The physical and psychological stress responses and neurovascular reactions to pain may harm recovery from neurologic illnesses [39].

Pain, delirium, agitation, and long-term cognitive, psychological, neuromuscular, and functional deficits are also risk factors for "post-intensive care syndrome," posttraumatic stress disorder, and reduced quality of life after the discharge [40]. There are also evidences that undertreated acute pain may play a significant role in the development of chronic pain [41].

15.4 Physiopathology of Pain

Nociception is the neurological process that encodes nociceptive stimuli, which actually or potentially may cause tissue damage [42]. The first step in the occurrence of nociception in normal people is the transduction of intense thermal, mechanical, or chemical stimuli in nociceptors present in type C and A-delta afferent fibers [43]. Na^+, Ca^{++}, and K^+ ion channels, proton-sensitive receptors (ASICs), transient receptor potential vanilloid type channels (TRPVs), and G protein-coupled receptors, among others, are present in the surface of nociceptors. Nociceptors may be activated by specific or varied stimuli (polymodal nociceptors) or are "silent," being sensitized by inflammatory molecules as neurotrophins, platelet-activating factor, protons, K^+, acetylcholine, bradykinin, histamine, nitric oxide (NO), serotonin (5-HT), substance P (sP), ATP, AMP, prostaglandins (PGs), prostacyclins, leukotrienes, thromboxanes, interleukins, TNF-α, glutamate, and endothelin [44, 45].

Trophic factors' activation of tyrosine-kinase receptors upregulate nociceptors and ionic channels and induce neuronal sprouting. Many visceral nociceptors are silent and become activated when sensitized by visceral inflammation, distension, torsion, or ischemia. Activated nociceptors release sP, calcitonin gene-related peptide (CGRP), neurokinins, somatostatin, and vasoactive intestinal peptide (VIP) that cause mast cell degranulation, vasodilation, and "neurogenic inflammation" enhancing nociception [45]. From nociceptors, sensory stimuli are carried through peripheral nerve afferent fibers mainly to the spinal cord dorsal horn (DH) laminae I, II, V, and X and the correspondent laminae of the trigeminal subnucleus caudalis

[45, 46]. The action potentials activate Ca^{++} channels present at the DH terminal endings of primary afferent fibers and induce intracellular Ca^{++} influx and thereafter, the release of sP, CGRP, cholecystokinin (CCK), ATP, somatostatin, VIP, and glutamate that bind to specific DH neurons (DHNs) [47].

Circulating blood cytokines from inflamed tissues also reach and sensitize the DHNs. Glutamate activates alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic (AMPA), N-methyl-d-aspartate (NMDA), kainate, and CGRP receptors. SP and neurokinins (NK) NK-A and NK-B bind to NK1, NK2, and NK3 receptors, and CGRP binds on G2,20 protein-coupled receptors. AMPA receptors induce Na^{+}, K^{+}, and Ca^{++} ions' neuronal influx and depolarize the neuronal membrane. In the presence of glycine, glutamate displaces Mg^{++} from the NMDA receptor enabling the cytoplasmic Ca^{++} and Na^{+} neuronal influx and K^{+} efflux. The stimulation of glutamate CGRP receptors generates inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 releases Ca^{++} from the endoplasmic reticulum and DAG activates protein kinase C [45–48]. Extracellular Ca^{++} ions added to those released into the cytoplasm from intracellular reserves trigger AMP synthesis. COX-2 induces intracellular PGs synthesis that is delivered in the DH extracellular interstitial environment self-stimulates and excites DHNs, facilitates the release of excitatory neurotransmitters, and reduces presynaptic bulbospinal inhibition. Activation of nitric oxide synthase (NOS) induces NO synthesis which flows through the neuronal membrane and increases the excitatory neurotransmitters' release from the primary afferents [47–49].

Activation of NMDA receptor, cumulative neuronal membrane depolarization, action potential bursting, and afterdischarges in DHNs following prolonged or intense noxious stimulation result in increase in nociceptive intensity over time and progressive increase in DHNs reactivity, the "wind-up" phenomenon, that is the initial process that induces CNS sensitization and amplification of receptive fields of DHNs, "secondary hyperalgesia" and "secondary mechanical allodynia" [47]. Activation of sympathetic neurons in the intermediolateral spinal cord gray matter increases the peripheral vascular resistance, causes urinary retention, and depresses the respiratory ciliary and intestinal and urinary activities. The activation of ventral spinal cord gray matter neurons causes muscle hypertonus resulting in postural abnormalities, muscle ischemia, "muscle energetic crisis," and myofascial painful syndromes. The long duration of nociceptive stimuli induces inhibitory DHNs apoptosis and DHNs neuroplastic changes, both related to pain chronification [49–51].

The convergence of information from various sources on wide dynamic range lamina V neurons results in "referred pain" phenomenon. Through the spinothalamic, spinoreticular, spinomesencephalic, spinosolitary, spinoparabrachial, spinohypothalamic, spinoamygdalar, spinocervical, and posterior funiculus, postsynaptic tracts from the DHNs inputs reach the dorsal reticular substance; the ventrobasal, ventromedial, ventrolateral, and intralaminar thalamic and brain stem gigantocellularis and parabrachial nuclei; the ventral and dorsal raphe subnuclei; the superior colliculus; and the periaqueductal gray (PAG) matter [52].

From these structures, the nociceptive inputs reach, activate, sensitize, and induce neuroplastic changes in the hypothalamus, primary (S1) and secondary (S2)

somatosensitive brain cortex, limbic areas (insula, anterior cingulum, amygdala), and associative cerebral cortex (prefrontal cortex) [53, 54], and reduce the dorsolateral prefrontal cortex and thalamus volume [55]. The neospinothalamic system and the SI and SII cortices are related to the sensorial-discriminative dimensions (localization, intensity, causative factor, duration) of nociception; the limbic and paralimbic areas (anterior cingulate and insular cortex) are related to the emotional and motivational dimensions of pain; the insula is related to the pain sensorial, emotional, and affective dimensions (depression), memory, thermal stimuli coding, and pain-related autonomous reactions; the frontal-orbital-thalamic-accumbens nucleus circuit is related to the affective dimension of pain, while the frontal cortex modulates the nociceptive neurons and limits the magnitude of their expression [56].

Nociceptive inputs may be inhibited in the peripheral and CNS by many neurotransmitters, as endogenous opioids (enkephalins, endorphins, A and B dynorphins, neoendorphins), endogenous endocannabinoids (anandamide, 2-AG), gamma-aminobutyric acid (GABA), monoamines (5-HT, Nadr), neurotensin, somatostatin, acetylcholine, and glycine [45, 57]. The opioid neurotransmitters bind to MOR or μ, DOR or δ, KOR or κ, and ε or epsilon receptors and inhibit presynaptically the primary afferents' excitatory neurotransmitter release in the DH and hyperpolarize postsynaptically and reduce the DHNs excitability [45, 49, 57].

Nociceptive, neuropathic, nociplastic, and mixed are the four main categories of "pathological" pains [58]. Somatic nociceptive pains usually are caused by trauma, rheumatic and musculoskeletal diseases, cancer, and other causes. Neuronal sensitization, neuroplastic and abnormal synaptic reorganization, glial activation, nociceptive inhibitory neurons' apoptosis, and abnormal autonomic nervous system activity are the main mechanisms of nociceptive pains [7]. Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system" [1]. Neuropathic pain results from sensitization of receptors, peripheral nerve fibers, sensory ganglia, and CNS neurons, neuronal ectopic activity, ephaptic currents, synaptic reorganization, glial activation, nociceptive neuron uninhibition, and autonomic nervous system hyperactivity [59]. Pain is classified as nociplastic when there is no evidence of a lesion or tissue injury threat as occurring in patients with fibromyalgia, irritable bowel and bladder syndromes, atypical facial pains, and primary headaches. However, as a rule, chronic pains, like osteoarthritic, oncologic, or visceral pains, are mixed and results from neuropathic, nociceptive, and nociplastic mechanisms [58].

15.5 Evaluation of Pain

Assessment of the adequacy of analgesia and sedation presents special challenges. Adequate analgesia requires pain assessment and titration guides. The ideal pain and sedation scales should be simple, provide data easily recorded, accurately describe the degree of analgesia and sedation within defined categories, guide the titration of therapy, and have validity and reliability in NICU patients. The pain

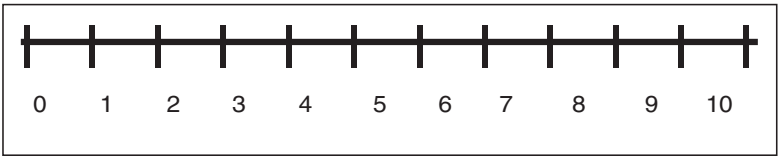
must be assessed and scored before treatment or sedation to choose the analgesic regimes and the sedation medications. In addition to evaluation of the suffering and assessment of analgesic regime efficacy, determination of the reasons for the occurrence of pain and the decreasing or discontinuation of the pain management should be appropriately documented.

Routine pain assessment improves the clinical outcomes, makes weaning from the ventilator more comfortable, and shortens the length of stay in NICUs population. Self-reporting is the most reliable and valid indicator for the presence and degree of pain. In the conscious, mentally normal, and oriented patient, the speaking or writing description of pain characteristics, as a quality of sensations, localization, intensity, duration, periodicity, exacerbating and relieving factors, associated symptoms, and results and adverse effects of present and past pain managements is very important to determine the best analgesic regime approach. The most widely self-rating pain scales used in adults are the Visual Analogue Scale (VAS), Numeric Rating Scale, and Four-Point Verbal Categorical Rating Scale [60], and for children older than 3 years, the Faces Pain Scale [61](Fig. 15.1).

However, even experienced nurses and clinicians often underestimate the pain severity in NICU, because neurologically ill patients may not be able to voluntarily complain or inform appropriately due to delirium or neurological diseases that alter the consciousness or the ability to express their feelings, or because there is limited possibility to verbal communication because they are intubated or a combination of all of them. Self-reporting scales are not appropriate for intubated, sedated, or unable to communicate and very young nonverbal children and very old, demented, confused, aphasic, or low cultural background patients.

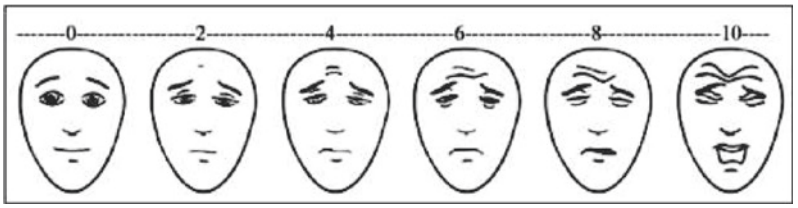
The disclosure and quantification of pain and the adequacy of analgesia in these patients may consist in the indirect signs and analysis of pain based on behavioral indicators as body language (muscle hypertonia, body posture, protective movements, restriction of movements, gait or mobility changes, noncompliance with ventilator), facial expressions (frown, sad, frightened face, grimacing, wrinkled forehead, closed or tightened eyes, distorted expression), sounds (sigh, moan, grunt, shout, noisy breathing, request for help), social interactions (aggressive, combative, resistive care, decreased social interaction, inappropriate sociability), changes in daily routines (food refusal, appetite change, sleep increase or decrease, rest pattern changes, cessation of common routines), emotions and mental status (crying, confusion, irritability, anguish, consolability), and neurophysiological findings (tachycardia, systemic hypertension, blood concentration of stress hormones, ICP elevation) [10]. Behavioral Pain Rating Scale (BPRS) [43], Behavioral Pain Scale (BPS) [62] (Table 15.1), Critical-Care Pain Observation Tool (CPOT) [10] (Table 15.2), Pain Assessment and Intervention Notation Algorithm (PAIN) [63], Non-Verbal Pain Scale [64], and Nociception Coma Scale [65] are the most reliable and valid pain assessment scales for noncommunicative or nonverbal populations. The Numerical Rating Scale is the preferred approach in alert patients, and the Behavioral Pain Scale and the Critical-Care Pain Observation Tool are preferred in subjects not able to respond. The Pain Intensity Scale, based on changes in vital signs as blood pressure, heart, and respiratory rate, facial expression (grimacing), and behavior

Visual Analog Scale



Visual Numeric Scale

Visual Categorial Scale



Faces Pain Scale

Fig. 15.1 Self-rating pain scales for conscious, mentally normal, and oriented patients. Visual Analogue Scale (VAS), Numerical Rating Scale, and Four-Point Verbal Categorical Rating Scale [43] for adults and the Faces Pain Scale [32].[135] for children older than 3 years. Faces Pain Scale. Permission for Use. Copyright of the FPS-R is held by the International Association for the Study of Pain (IASP) © 2001. This material may be photocopied for noncommercial, clinical, educational, and research use. For reproduction of the FPS-R in a journal, book, or web page, or for any commercial use of the scale, request permission from IASP online at www.iasp-pain.org/FPS-R. No permission is required for clinical, educational, or research use of the FPS-R, provided that it is not modified or altered in any way

(agitation), is feasible for caregivers. The analgesic goals may be evaluated with the Face, Legs, Activity, Cry, and Consolability (FLACC) behavioral scale [66] (Table 15.3).

Patient agitation and the level of sedation required must also be assessed. Sedation scales are used to evaluate arousal, depth of sedation, and response to stimuli. The most used sedation scales are the Ramsay Scale [67], Richmond Agitation-Sedation

Table 15.1 Behavioral scales for pain assessment in patients unable to communicate

Behavioral Pain Scale (BPS)		
Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Behavioral Pain Scale[248] and Critical Care Pain Observation Tool [14, 105] for adults and FLACC scale[208] for infants, young children, and adults
BPS scores range from 3 (no pain) to 12 (maximum pain): 4 = mild pain, 5–7 = moderate pain, > 7 = severe pain

Scale (RASS) [68] (Table 15.4), Riker Sedation-Agitation Scale (SAS) [69], Intensive Care Environment (ATICE) [70], and Motor Activity Assessment Scale (MAAS) [67]. The adequate interpretation of sedation results in the reduction of the number of sedatives, the number of days on mechanical ventilation, and hospital stay cost. For patients completely paralyzed, deeply sedated, or treated with neuromuscular blocking agents and unable to communicate, none of the scales is applicable. It was shown that the Quantitative Bispectral Index (BIS) may assess sedation levels and that its monitoring values are correlated with RASS scores in ABI patients [71]. However, the recent neurophysiological and neurofunctional CNS image acquisition methods were not validated to evaluate pain and delirium in NICU patients [65].

15.6 General Principles of Pain Management

Many neurocritical patients have impaired consciousness or clinical conditions that require sedation either to prevent further injury as to allow intubation to secure airways and normocapnic ventilation or to assist the management of ICP. Aggressive and prolonged analgosedation is recommended not only for the prevention and treatment of pain but also to avoid and treat increased ICP, status epilepticus, and paroxysmal sympathetic crisis [1]. Management and prevention of pain, anxiety, agitation, and delirium require a coordinated multidisciplinary interaction involving

Table 15.2 Critical Care Pain Observation Tool (CPOT) [105]

Indicator	Score		Descriptions
Facial expression	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Presence of frowning, brow lowering, orbit tightening, and levator contraction or any other change (e.g., opening of eyes or tearing during nociceptive procedures)
	Grimacing	2	All previous facial movements plus eyelid tightly closed (the patient may present with mouth open orbiting the endotracheal tube)
Body movements	Absence of movements or normal position	0	Does not move at all (doesn't necessarily mean absence of pain) or normal position (movements not aimed toward the pain site or not made for the purpose of protection)
	Protection	1	Slow, cautious movements, touching, or rubbing the pain site seeking attention through movement
	Restlessness/ agitation	2	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed
Compliance with the ventilator (intubated patients)	Tolerating ventilator movement	0	Alarms not activated, easy ventilation
	Coughing but tolerating	1	Coughing, alarms may be activated but stop spontaneously
	Fighting ventilator or no sound	2	Asynchrony: blocking ventilation, alarms frequently activated
OR			
Vocalization (extubated patients)	Talking in normal tone or no sound	0	Talking in normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Sighing, moaning	2	Sighing, moaning
Muscle tension Evaluation by passive flexion and extension of upper libs when patient is at rest or evaluation when patient is being turned	Relaxed	0	No resistance to passive movements
	Tense, rigid sobbing	1	Resistance to passive movements
	Very tense or rigid	2	Strong resistance to passive movements or incapacity to complete them
Total	_____**/8**		

CPOT score 0–2 = absence of pain, 3–4 = moderate pain, and > 4 = severe pain

Table 15.3 Face, Legs, Activity, Cry, and Consolability (FLACC) behavioral scale

Criteria	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering of the chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractible	Difficult to console or comfort

FLACC scale is scored in a range of 0–10. 0 = relaxed and comfortable, 1–3 = mild discomfort, 4–6 = moderate pain, > 6 = severe pain

nurses, physiotherapists, psychotherapists, pharmacists, and physicians. ABCDEF is the basic approach proposed by the Society of Critical Care Medicine representing an evidence-based guide for clinicians about the organizational changes necessary for optimizing ICU resources and patient care, recovery, and outcomes and for improvement of the interaction between NICU patients and better pain control [1].

The *ABCDEF* bundle includes the following: *A*ssess, Prevent, and Manage Pain, *B*oth Spontaneous Awakening Trials and Spontaneous Breathing Trials, *C*hoice of analgesia and sedation, *D*elirium: Assess, Prevent, and Manage, *E*arly mobility and Exercise, and *F*amily engagement and empowerment. However, little attention has been directed toward analgesia and sedation in NICU patients [72].

Minimal sedation and adequate drug selection decrease duration of mechanical ventilation, rate of delirium, and mortality rates. In stable mechanically intubated patients, spontaneous sedation interruption, followed by spontaneous breathing trials, decreases the duration of mechanical ventilation and medically induced coma and mortality. Early mobilization and optimization of the environment, reducing noise, optimizing the patient sleep-wake cycles, and stimulating early mobilization decrease the risk of delirium.

Analgosedation together with other specific measures, including controlled hyperventilation, cerebral perfusion pressure (CPP)-guided improvement, head-of-bed elevation, and osmotic agents, is the first-line preventive and therapeutic measure in the management of elevated ICP. The adequately sedated patients do not react to external stimulation, and their ICP does not fluctuate. Cerebral O_2 delivery needs may be compensated, reducing O_2 demand and increasing the doses of sedative and analgesic drug administration. Deep sedation is often necessary for the treatment of status epilepticus refractory to emergency and first-line therapies (benzodiazepines, anticonvulsants) [71].

Table 15.4 Richmond Agitation and Sedation Scale (RASS) [88] used to evaluate arousal, depth of sedation, and response to stimuli [73]

Richmond Agitation and Sedation Scale (RASS) [88]	
4	Combative, violent, danger to staff
3	Pulls or removes tube(s) or catheters; aggressive
2	Frequent no purposeful movement, fights ventilator
1	Anxious, apprehensive, but not aggressive
0	Alert and calm
−1	Awakens to voice (eye opening/contact) >10 seconds
−2	Briefly awakens to voice (eye opening/contact) <10 seconds
−3	Movement or eye opening. No eye contacts
−4	No response to voice, but movement or eye opening to physical stimulation
−5	Unarousable (no response to voice or physical stimulation)

Is patient alert and calm (score 0)?
Does patient have behavior that is consistent with restlessness or agitation (score 1–4 using the criteria listed above, under Description)?
If patient is not alert, in a loud speaking voice, state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score 1)
Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score 2). Patient has any movement in response to voice, excluding eye contact (score 3)
If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder. Patient has any movement to physical stimulation (score 4)
Patient has no response to voice or physical stimulation (score 5)

In patients with paroxysmal sympathetic activity, sedative agents may be considered to attenuate excessive autonomic activation and motor hyperactivity [71, 72]. The management of anxiety, agitation, and delirium should address reversible causes, provide for patient comfort, facilitate mechanical ventilation and neurologic examination, reorient the patient to the environment, optimize normal sleep patterns, and carefully titrate the administration of sedatives avoiding deleterious changes in intracranial and cerebral perfusion pressures [1].

Sedation consists of anxiolysis, hypnosis, and amnesia. Analgesia should be started before initiating sedation. Pain should be prevented and treated early and not when is out of control. However, the overall pain management in NICU usually is suboptimal [11]. Only in 38% from 27 studies addressing pain management in the NICU analyzed by Zeiler et al. [11], a validated pain assessment scale

was considered. A low proportion of NICU patients suffering from moderate to severe acute pain receive opioids [73], and procedures aiming prevention of pain in mechanically ventilated patients are implemented in less than 25% of the ICU population [74].

Acute pain, especially post-craniotomy pain, is usually undertreated and poorly managed in NICU [75]. The analgesic regime is inadequate in approximately 50% of patients undergoing craniotomy [75]. Numerous factors may contribute to inadequate pain management. Many neurosurgical patients are unable to self-report the pain due to altered levels of consciousness, use of mechanical ventilation, and administration of high doses of sedatives [74, 75].

No adequate physician training or patient education about opioid use concerns that opioids may preclude neurological evaluation or cause complications such as excessive sedation, hypoventilation, miosis, seizures, intracranial bleeding, and neurological deterioration, and the presumed lack about the need for analgesics due to non-assessment or unsatisfactory pain evaluation is one of the reasons that makes the implementation of effective analgesia difficult in NICUs. As acute pain can be a symptom of neurological deterioration, analgesic therapies have been withheld from patients with acute neurological disease [76].

According to old concepts, the use of analgesia and sedation might have a negative impact on patients, because it could interfere the ICU personnel's ability to perform neurologic examination; cause hemodynamic instability; increase the occurrence of pneumonia, ventilator dependency, days of mechanical ventilation, weaning time and ICU and hospital stays, and long-term cognitive decline; and impact morbidity and mortality [77, 78]. Otherwise, recent studies suggested that application of the appropriate analgesia-based sedation protocols helps to achieve better outcomes; increases the use of analgesics; decreases the amount and accumulation of sedatives, medication-associated costs, and need and duration of mechanical ventilation; shortens the length of NICU stays; and does not result in long-term cognitive decline [77, 78].

The change in neurological signs is one of the best ways to evaluate the clinical condition and to preview the progress of neurological abnormalities in NICU patients. Providing rapid periodic wake-up recovery, that is, daily withdrawal of sedation and sedation periods, from the analgesia and sedation effects without compromising ICP is necessary for neurological periodic assessment in NICU [79] to perform neurological wake-up tests in sedated neurological patients allows clinical monitoring the detection and progression of warning neurological signs [80], assessment, prevention, and management of pain and delirium, early mobility and exercises and engagement of rehabilitation team and family in the treatment, and may reduce the duration of mechanical ventilation, the need for tracheostomy and improve the clinical outcomes [71].

However, sedation interruption may have the risks of cerebral hemodynamic deterioration, ICP elevation, and brain tissue O_2 pressure ($PbtO_2$) and CPP lowering, especially during the first 4 days after acute brain injury, and may increase the circulating levels of cortisol and endogenous catecholamines that, by itself, may exacerbate secondary brain injury and the signs of adrenergic activation and increase in

ICP [80]. Skoglund et al. [81] observed that the mean ICP and CPP levels increased in severe TBI or subarachnoid hemorrhage patients with the discontinuation of propofol infusion.

CPP reduction due to increased ICP during the waking-up period observed in some of their patients might result in brain ischemia and in impairment of blood pressure autoregulation. Other authors did not observe differences in the duration and need of mechanical ventilation or ICU and hospital length of stay between both methods [78]. Furthermore, sedation interruption detected only new neurological signs in a very low number of wake-up tests [82]. There is a recommendation to avoid sedation interruption in patients with clinical and image signs of severe brain edema or cerebral herniation, and risk for or with ICP elevation, or undergoing treatment of refractory status epilepticus [31]. In these patients, sedation should not be stopped abruptly but progressively, titrating the sedation dose to ICP and $PbtO_2$ targets [82].

There is no clear guidance about the best drugs or procedures for analgosedation. Age, weight, obesity, hemodynamic status, renal and hepatic function, past use of licit or illicit drugs, and the need of hypothermia should be considered before selection of the analgesic and sedative drugs. The dose and type of drugs for analgesia and sedation should consider the requirement of the periodic neurological assessment [79]. The pharmacogenomic variability in the metabolism of these drugs or precursor molecules may determine their potential ineffectiveness and risk [82]. The promotion of adequate analgesia and sedation in patients with intracranial hypertension should be titrated based on multimodal monitoring aiming at recording and controlling ICP and $PbtO_2$ [71].

Systemic hemodynamic effects of analgosedation drugs are usually dose-dependent; therefore, to minimize the risk of hypotension and reduced CPP, it is important to carefully assess preload and ensure normovolemia in all patients, particularly in those with preexisting heart disease [71]. The titration of the analgesics and sedatives to a defined endpoint is recommended with periodic tapering of the dose or daily interruption with re-titration to minimize prolonged sedative effects. The improper use or too high or too low dosages of analgesics and sedatives may interfere in the neurological performance and lead to the wrong diagnosis. Overmedication may delay the weaning time duration from mechanical ventilation; raise the treatment costs; prolong intubation and ICU stay; interfere on the level of consciousness and, as a consequence, on the neurologic examination and on the degree of pain and delirium assessment; increase the risk of deep venous thrombosis and infection, as pneumonia, among other complications [83]. Treatable neurologic lesions in an overmedicated patient may be missed, and, consequently, the clinical condition may deteriorate and lead to prolongation of NICU stay. However, many substances including sedatives and analgesics may cause or aggravate delirium through intoxication or withdrawal. Additionally, neuromuscular blocks may compromise patient communication and the assessment of pain, anxiety, delirium, and other discomforts [84].

When pain is frequent, providing medication around the clock is a better option than under demand. Often, neurocritically ill patients present nausea and vomiting

that limit the use of oral medications and make the IV route the best way for analgesics and adjuvant drug delivery [85]. Patient-controlled analgesia (PCA) is an effective method of analgesia in awake cooperative patients. It is well tolerated, produces better analgesia, improves patient satisfaction, causes fewer side effects, and provides a PCA-titrated drug administration, allowing the patient to exert control over the pain management, reduction of overall opioid requirement, and alleviation of the psychological stress aggravated by pain [86]. However, PCA background dosing is associated with an increased risk for respiratory failure [87].

The current standards recommended multimodal analgesic regimens. Several pharmacological and non-pharmacological modalities for prevention and treatment of pain are available in NICU, including physical therapy (heat, cold, transcutaneous electric stimulation), acupuncture, simple analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), specific cyclooxygenase-2 (COX-2) inhibitors, typical and atypical opioids, dexmedetomidine, ketamine, antiepileptics, antidepressants, clonidine, ketamine, lidocaine infusion, anesthetic scalp and neuraxial blockades, and wound infiltration [88–90].

After ruling out other etiologies, sedation may be started with treatment of anxiety. The most used sedatives in NICU are opioids, propofol, benzodiazepines, clonidine, dexmedetomidine, barbiturates, and similar agents. Due to their rapid onset of action, midazolam and diazepam are recommended for rapid sedation in acutely agitated patients. However, diazepam has a long half-life and its effect is prolonged. CBF reduction is an adaptive phenomenon of diminished brain metabolism. These negative effects can be largely prevented if MAP is maintained. Propofol and dexmedetomidine have more desirable properties in target temperature management in comparison with benzodiazepines [91]. Propofol and dexmedetomidine are preferred when rapid awakening for periodic neurologic assessment or extubation is needed. Short-acting sedatives, e.g., thiopental, propofol, and etomidate, and the neuromuscular blockage (rocuronium or nondepolarizing agents) are recommended to suppress the autonomic activation induced by laryngeal stimulation. High bolus doses of opioids trigger cerebral vasodilatation in response to reductions in MAP and are associated with an increase in ICP and decrease of CPP.

Propofol is minimally affected by renal failure. Benzodiazepines such as diazepam and midazolam are associated with slower clearance and higher concentrations in case of hepatic dysfunction. Midazolam and propofol can induce hypotension and hemodynamic compromise, particularly in hypovolemic patients. Ketamine may reduce the need for benzodiazepines or propofol and reduce the risk of hypotension. In these patients, α-2-adrenergic agonists should be avoided because of the potential induction of hypotension or bradycardia [71].

The recommended doses and some pharmacokinetic characteristics of the most common analgesic and sedative drugs prescribed in NICU are presented in Tables 15.5, 15.6, and 15.7 and the effects of these drugs in ICP, CBF, and brain metabolism in Table 15.8.

Table 15.5 Recommended analgesics and sedatives according to clinical needs, intracranial pressure, liver and renal functions, hemodynamics conditions, and mental status of the patients in NICU

Indication	Fist-line analgesics	First-line sedatives	Options
No ICP elevation	Fentanyl Morphine	Sufentanil Remifentanil	Propofol Midazolam
Elevated ICP	Fentanyl Morphine	Sufentanil Remifentanil	Propofol Midazolam
Targeted temperature management	Fentanyl Morphine	Sufentanil Remifentanil	Propofol Midazolam
Status epilepticus	Fentanyl Morphine	Sufentanil Remifentanil	Propofol Midazolam
Liver dysfunction	Fentanyl Sufentanil Remifentanil	–	Propofol
Renal dysfunction	Remifentanil	–	Propofol
Hemodynamic instability	Fentanyl	Ketamine	Midazolam
Agitation and/or delirium	Fentanyl Morphine	Antipsychotics	α_2-Adrenergic agonists

15.7 Prevention of Pain in Neurosurgery

Surgical approach, especially the technique used for wound closure, may prevent the development of chronic post-craniotomy pain. Postoperative headache in patients undergoing retrosigmoid approach for resection of vestibular schwannomas may be lowered if the bone flap is replaced, fat grafting is used, duraplasty is made instead of direct dura mater closure, and fibrin glue or extensive drilling of the internal auditory canal is avoided [92]. Gabapentinoids and ketamine potentially prevent the occurrence of post-craniotomy pain [12].

15.8 Local Anesthesia and Intraspinal Regional Analgesia

Local anesthetics alone or associated with opioids are used for regional epidural, intrathecal, intercostal, and femoral nerve anesthesia but are not routinely recommended for pain control in the NICU setting. Preoperative nerve blocks may reduce intraoperative analgesic requirements and pain [20, 28] and prevent neuronal sensitization and the development of non-neuropathic post-craniotomy chronic pain [93]. Local anesthetic infiltration, at the cranial pin sites and of the surgical or traumatic wounds, application of patches containing 5% lidocaine to the skin of both sides of the surgical wound, and continuous lidocaine infusion are effective in the

Table 15.6 Main mechanisms of action, clinical pharmacodynamics, titration facility, special characteristics, main side effects, and recommendations about the use of analgesics and sedatives

Pharmacological class	Drug	Main mechanisms	Sedation	Analgesia	Fast onset	Fast recovery	Easily titration	Other indications	Side effects	Recommendations
Simple analgesics		COX-3 inhibition Opioidergic and cannabinoid systems								
	Acetaminophen			+				Fever	Hepatotoxicity	Patients with impaired liver function or on regular alcohol use should take less than 2.000 mg of acetaminophen daily
	Metamizole			+				Fever and GI, urologic, and gynecological visceral spams	Hypersensitivity skin reactions, such as rash, urticaria, or erythema Agranulocytosis rare	Contraindicated in patients with a history or presence of blood dyscrasia

NSAIDs				+					GI irritation, bleeding, and perforation, nephrotoxicity, hepatotoxicity, coronary artery disease	Avoid: renal dysfunction, ulcer, gastrointestinal bleeding, platelet abnormality, use of angiotensin-converting enzyme inhibitor, congestive heart failure, cirrhosis, asthma, bone graft and major intracranial and spinal cord surgeries
COX-1 and COX-2 inhibitors	Ketorolac Diclofenac Naproxen Ibuprofen	COX-1 and/or COX-2 inhibition		++						Avoid: in preoperative phase due to antiplatelet effect, in patients with gastritis, ulcer, and GI bleeding and in elderly
COX-2 inhibitors	Celecoxib Valdecoxib	COX-2 inhibition		+						Avoid: coronary diseases, myocardial infarction
Anticonvul-sants										

(continued)

Table 15.6 (continued)

Pharmacological class	Drug	Main mechanisms	Sedation	Analgesia	Fast onset	Fast recovery	Easily titration	Other indications	Side effects	Recommendations
	Carbamazepine	Voltage-gated Na^+ channel blocker		+++ (trigeminal neuralgia)				Anticonvulsant and antineuralgic	Nystagmus, dizziness, diplopia, light-headedness, lethargy, Stevens-Johnson syndrome, water retention, hyponatremia, GI and cardiovascular side effects, bone marrow depression, neutropenia, aplastic anemia, agranulocytosis, multiple drug interactions	
	Gabapentin Pregabalin	α2δ subunits of voltage-activated Ca^{++} channel modulation	+	+				Analgesic, anxiolytic, sleep inductor	Sedation, confusion, dizziness, and ataxia	
Opioids	Agonists							Analgesia, euphoria, and sedation	Reduced GI motility (constipation), nausea, vomiting, respiratory depression, pupillary constriction (except meperidine), addictive behavior, tolerance, and dependence	

	Tramadol	μ +; δ +; κ + activation 5-HT reuptake inhibition		++				Better side effect profile than most opioids	Dizziness Risk of seizures	No respiratory depression Caution in epileptic patients
	Tapentadol	μ +; δ +; κ + activation NA reuptake inhibition		++				Same	Same	Same
	Codeine	μ +; δ +; κ +		++				Antitussive, antidiarrheal	Constipation	Often used combined with acetaminophen or NSAIDs) Production of the same degree of respiratory depression as morphine, but this effect is limited
	Morphine	μ +++; δ+; κ_1 ++; κ_3+	+	+++				Antitussive, antidiarrheal	Accumulation with hepatic and renal impairment, active metabolite accumulation in renal failure, itching (histamine release)	

(continued)

Table 15.6 (continued)

Pharmacological class	Drug	Main mechanisms	Sedation	Analgesia	Fast onset	Fast recovery	Easily titration	Other indications	Side effects	Recommendations
	Fentanyl	μ +++; δ +	+	+++	+++	++	++	Less cardiovascular effects (hypotension) than morphine No histamine releasing Treatment of breakthrough pain. Can be used in PCA Inexpensive	Accumulation in hepatic impairment, high risk of respiratory depression with IV PCA	
	Remifentanil		+	+++	+++	+++	++	No accumulation in hepatic/renal failure	Opioid hyperalgesia Use ideal body weight if body weight > 130% Expensive	Bolus injection not recommended
	Sufentanil	μ +++; δ +; κ_1+						Treatment of breakthrough pain Can be used in PCA		
	Alfentanil	μ +++; δ +; κ+						Treatment of breakthrough pain Can be used in PCA		

	Hydromorphone		+	+++				Alternative in patients tolerant to morphine/fentanyl	Accumulation with hepatic/renal impairment	
	Methadone	μ +++; NMDAr inhibitor						Chronic pain treatment Relieving withdrawal symptoms and slow development of tolerance in escalation of opioid dosing requirements Maintenance of addicts Less euphoric effect than morphine	Accumulation may occur Unpredictable pharmacokinetics; unpredictable pharmacodynamics in opiate-naïve patients	Not recommended for IV infusion Slow recovery results in attenuated withdrawal syndrome because of long half-life
	Oxycodone	μ+++;? δ+								
	Butorphanol									
	Meperidine	μ ++; δ +; κ +						Treatment of acute pain and shivering	Anticholinergic effects Active metabolite (norpethidine) has stimulant effect	Risk of excitement, tremors, myoclonus, delirium, agitation, and seizures Interacts with monoamine oxidase inhibitors

(continued)

Table 15.6 (continued)

Pharmacological class	Drug	Main mechanisms	Sedation	Analgesia	Fast onset	Fast recovery	Easily titration	Other indications	Side effects	Recommendations
	Partial agonists									
	Buprenorphine	μ partial agonist +++; κ_1 ++ antagonist						Acute and chronic pain Relieving withdrawal symptoms Maintenance of addicts Less pronounced respiratory depression then morphine Useful in PCA		Not reversed by naloxone May precipitate opioid withdrawal
	Butorphanol									
	Agonists-antagonists									
	Nalbuphine	κ ++ agonist μ + antagonist						Less euphoria then opioid agonists		
	Antagonists									

	Naloxone	μ +++; δ ++; κ_1 ++, κ_3++ antagonist						Rapidly reversion of opioid respiratory depression, oral administration is effective in the treatment of opioid-induced constipation		Rapidly reversion of opioid-induced analgesia, precipitation of withdrawal symptoms in morphine-dependent patients
	Naltrexone	μ++; δ+; κ_1+++; κ_3++ antagonist						Treatment of addicts, compulsive eating, septic shock, and chronic itching. Reduction alcohol consumption		
α-2-Adrenergic agonists		Pre- and postsynaptic α-2-adrenergic agonist						Sedative, analgesic, anxiolytic, sympatholytic Minimal respiratory depression, neuroprotection	Arterial hypotension, bradycardia, cardiac arrhythmias, sympathetic rebound	

(continued)

Table 15.6 (continued)

Pharmacological class	Drug	Main mechanisms	Sedation	Analgesia	Fast onset	Fast recovery	Easily titration	Other indications	Side effects	Recommendations
	Clonidine		++	++				Treatment of opioid, alcohol and nicotine withdrawal, glaucoma hypertension, migraine, prophylaxis, vasomotor instability	Drowsiness, hypotension, edema, weight gain, rebound hypertension	
	Dexmedetomidine		++	++					Bradycardia, hypotension, hypertension with loading dose, loss of airway reflexes Expensive	Avoid IV bolus doses to minimize hypotension especially in hemodynamically unstable patients

Local anesthetics		PNS Na + channel blockade							Drowsiness, disorientation, convulsions, motor weakness, bradycardia, hypotension, cardiac bundle branch block, cardiac arrest Spinal blocks may also cause respiratory depression (action on phrenic nerve or respiratory center); avoided by minimizing cranial and urinary retention	
	Lidocaine			++				Used for local anesthesia and topically for treatment of incisional or neuropathic pains Used intravenously for treatment of ventricular arrhythmias		
	Bupivacaine								Greater cardiotoxicity than lidocaine	

(continued)

Table 15.6 (continued)

Pharmacological class	Drug	Main mechanisms	Sedation	Analgesia	Fast onset	Fast recovery	Easily titration	Other indications	Side effects	Recommendations
NMDA antagonists	Ketamine	NMDA antagonist	+++	+++				Anesthesia, sedation, analgesia, depression and attenuation of development of acute tolerance to opioids Not respiration depression, hemodynamic stability, neuroprotection	Cerebral activation, hallucinations, other psychological disturbances, seizures, ICP elevation?	
GABA agonist										
	Propofol	GABA agonist	+++	–	+++	+++	+++	Hypnotic, anti-seizure, treatment of delirium tremens, prevention of benzodiazepine withdrawal	Not analgesic, hypotension, respiratory depression, green urine Hypertriglyceridemia, pancreatitis,propofol infusion syndrome, anaphylaxis, sepsis, pain at venous site Expensive	Bolus dose not recommended IV loading only in patients in whom hypotension is unlikely to occur Discontinue if triglycerides >300
Diazepines		GABA receptor agonist							Respiratory depression, arterial hypotension, mental confusion, tolerance tachyphylaxis	Not adequate for continuous infusion

	Diazepam		+++	–				Anxiolytic, muscle relaxant, anticonvulsant	Prolonged sedation, long-acting active metabolite, prolonged sedation, especially in renal failure, cardiocirculatory side effects due to propylene glycol phlebitis	Not adequate for continuous infusion
	Lorazepam		+++	–	+	+	+	Anxiolytic, hypnotic, anticonvulsant Long effect duration Inexpensive	Hypotension, propylene glycol-related acidosis, nephrotoxicity, cardiocirculatory side effects due to propylene glycol	
	Midazolam		+++	–	+++	++	++	Hypnotic, anticonvulsant, short duration, water soluble Causes amnesia and little respiratory or cardiovascular depression	Hypotension, increasing delirium, mechanical ventilation prolongation Awakening unpredictable with prolonged infusion Moderate expensive	May accumulate in renal dysfunction Half-life (time for drug plasma concentration) decreases by 50% after cessation of a continuous infusion
Barbiturates	Pentobarbital								Immune suppression, adrenal dysfunction	

(continued)

Table 15.6 (continued)

Pharmacological class	Drug	Main mechanisms	Sedation	Analgesia	Fast onset	Fast recovery	Easily titration	Other indications	Side effects	Recommendations
Butyrophenones		Dopamine, nor-adrenalin, 5-HT, acetylcholine, histamine receptors blockers						Antipsychotic and antiemetic	Extrapyramidal syndromes, seizure threshold lowering, ECG QT prolongation	
	Haloperidol		+++	–				Preserves arousal level and airway reflexes Few anticholinergic side effects Psychomotor agitation and severe anxiety, nausea and vomiting, motor tics and intractable hiccup		
	Droperidol		+++	+				Analgesia (headache syndromes)		

COX cyclooxygenase, *NMDA* N-methyl-D-aspartate

Table 15.7 Drug classes and pharmacokinetics of analgesics and sedatives in neurocritical intensive care unit

Pharmacological classes and drugs	Dosage	Onset	Peak	Clinical effect	Half-life	Dose ceiling	Protein binding	Metabolism	Active metabolites
Simple analgesics									
Acetaminophen	PO starting dose: 325–1000 mg (20 mg/kg) q. 4–6 h; max dose	PO, PR: 30–60			PO/PR: 2–4 h	PO, IV: 3.2 g (60 mg/kg/day)		*Hepatic*	None
	Maintenance: 15 mg/kg (max 1 g) q. 4-6 h	IV: 5–10 min			IV: 2 h	PR: 5 g/day		Glucuronidation, sulfonation, and oxidation	
	PR: 40 mg/kg								
	Maintenance: 30 mg/kg (max 1 g) q. 4-6 h								
	IV bolus and maintenance: 650 mg q. 4 hrs or 1000 mg IV every 6 h								
Metamizole	PO,IM,IV: 500–2000 mg (10–15 mg/kg) q.6 h				2.6–3.25 h				
NSAIDs									
Ibuprofen	PO: 400 mg 10 mg/kg q. 4 h	PO:25 min			PO: 2.2–2.4 h	PO: 2.4 g/day		*Hepatic*	
	IV: 400–800 mg q. 6 h infused over >30 mins				IV: 5–7 h	IV: 3.2 g/day		Oxidation	
Ketorolac	IM/IV: 30 mg, then 15–30 mg q. 6 h up to 5 days	IM, IV: 10 min			2.4–8.6 h	120 mg/day		Hepatic	*None*
Antiepileptics						Maximum: 5 days		Hydroxylation and conjugation	

(continued)

Table 15.7 (continued)

Pharmacological classes and drugs	Dosage	Onset	Peak	Clinical effect	Half-life	Dose ceiling	Protein binding	Metabolism	Active metabolites
Carbamazepine	VO: 100 mg PO bid	VO: 4–5 h	*4–8 h*	*20–65 h*	Single dose: 25–65 h	1200 mg/day		Hepatic	*None*
	Maintenance: 100–200 mg q. 4–6 h;				Repeated doses: 12–17 h				
Gabapentin	PO starting dose: 100 mg q. 8 h Maintenance: 300–3600 mg/day in 3 divided doses	NA		*5–13 h*	5–7 h	3.6 g/day		Renal excretion	
Pregabalin	PO stating dose: 50 mg q, 12 h	*2 h*	*3 h*	*6*	12 h	600 mg/day		Renal excretion	
	Titrated q. 4 days up to 300–600 mg/day divided in 2 dose/day								
Local anesthetics									
Lidocaine					*2 h*				
Bupivacaine	Injected or dripped onto incision site at the end of surgery: 4 mg/kg 1x								
A-2-adrenergic agonists									
Clonidine	PO: 0.1 mg q. 8–24 h;	30–60 min	PO: 1–4 h	PO: 6–20 h)	12–16 h	PO: 0.6 mg	20–40%	Hepatic (50%)	
	Increase 0.1 mg/day q. 1–2 days up to 0.6 mg/day		Transdermal: 24 h	IV:2–4 h					

	Morphine detoxification 0.1–0.3 mg q.6–8 h		Epidural: 10 min (arterial)	Intrathecal: 3–5 h					
	Migraine prophylaxis 0,1 mg 2–4x		IV: 30–45 min						
	I		CSF: 30–60 min						
	IV: 0.1 mg (2 μg/kg) q8–24h up to 0.6 mg/day		>40 h in impaired renal function patients						
	Transdermal: 0.1 mg changed q. 7 days; increase to 0.2–0.3 mg each week								
	Epidural:								
	Adults:								
	Bolus: 75–700 μg (2–10 μg/kg)								
	Infusion:10–40 μg/h (0,2–0,8 μg/kg/h)								
	Children: 0.5 μg/kg/h titrated to response PCEA								
	Intrathecal analgesia:								
	Bolus: 15–150 μg (0.3–2 μg/kg)								

(continued)

Table 15.7 (continued)

Pharmacological classes and drugs	Dosage	Onset	Peak	Clinical effect	Half-life	Dose ceiling	Protein binding	Metabolism	Active metabolites
	Infusion: 2–8 μg/h (0,04–0,16 μg/kg/h)								
	Epidural:								
	Bupivacaine 0.0625% + fentanyl 2 μg/mL + clonidine 4.5 μg/mL								
	Intrathecal								
	Adult: bupivacaine 15 mg + clonidine 75 μg or bupivacaine 15 mg + clonidine 25 μg + morphine 250 μg								
Dexmedetomidine	IV bolus: 0.1 μg/kg/10 min, followed by 0.2–0.7 μg/kg/h	IV:5–15 min	3 min	10 min 2–6 h	1.8–3.1 h	Children: < 30 mg/day Adults: 200–300 mg/day	94%	Hepatic	None
	IV infusion: 0.2–0.7 ug/kg/h; up to 1.5 μg/kg/h as tolerated.							Glucuronidation CYP2D6	
	Preemptive 90–120 mg								
	Children 2–6 y.o.: 2.5–5 mg q. 4 h; 7,5 mg q. 6–8 h								

	6–12 y.o.: 5–10 mg q. 4 h; 15 mg q.								
	6/8 h								
	Epidural analgesia								
	Bolus: 100–500 μg (2–4 μg/kg)								
	Infusion: 10–40 μg/h (0,2–0,8 μg/kg/h)								
	Intrathecal analgesia								
	Bolus: 15–150 μg (0,3–2 μg/kg)								
	Infusion: 2–8 μg/h (0,04–0,16 μg/kg/h)								
	Epidural anesthesia:								
	Bolus: 150–500 μg (4–10 μg/kg)								
NMDA blockers									
Ketamine	Anxiolysis:	PO:15–30 min	3–8 h		2–3 h		47%	Hepatic	Norketamine
	PO/rectal:0,5–10 mg/kg	Nasal: 8–12 min						N-demethylation	
	Transdermal 0.24–0.37 mg/kg	IM: 3–4 min							
	Sedation: IV: loading: 0.1–0.5 mg/kg	IV: 30–120 sec							

(continued)

Table 15.7 (continued)

Pharmacological classes and drugs	Dosage	Onset	Peak	Clinical effect	Half-life	Dose ceiling	Protein binding	Metabolism	Active metabolites
	Maintenance: 0.05–0.4 mg/kg/h; followed by 0,25–0,5 mg/kg/5–10 min, and 1–5 mg/kg/ h	Epidural: 30 min							
	PCA: 2 mg/kg/day								
	Peridural: 0,2–1 mg/kg								
	Procedural sedation IV: 1–2 mg/kg/								
	1–2 minutes, followed by 0.25–0.5 mg/kg every 5–10 min								
Mg++	Presurgical IV: 50 mg/kg								None
	Intraoperative: 8 mg/kg/h								
	Intrathecal: 50 mg/3 ml saline								
	Hypothermia: IV: 4–6 g to achieve 3–4 mg/dL								
GABA-A agonists/ antagonist									
Propofol	Anesthesia	1–2 min	2–6 h	Single bolus: 5–8 min	Short-term infusion: 3–12 h		97–99%	Hepatic and extrahepatic	None

	Induction: IV 1–3 mg/kg			Continuous infusion: 10–15 min	Long-term infusion: 50 ± 18.6 h				
	Sedation			Recovery: 60 min longer after 12 h infusion)					
	IV bolus: 1–2 mg/kg/h								
	0.1–5 μg/kg/5–10 min followed by 0.2–0.7 μg/kg/h if hypotension is unlikely to occur; increased infusion by 5–10 ug/kg/min, q. 5–10 min to 25–100 ug/kg/min up to 2–4 mg/kg/h (5–300 ug/kg/min)								
	Maintenance:								
	5–200 μg/kg/min								
	Status epilepticus:								
	IV load: 2 mg/kg								
	Infusion: >5 m/kg/h (150–200 ug/kg/min)								
Diazepam	IV: 2 mg q. 30–60 min or 0.03–0.1 mg/kg q. 0.5–6 h prn	IV: 2–5 min	3–4 min		20–60 h		99%	Hepatic Oxidation	Desmethyl-diazepam, oxazepam, hydroxy diazepam

(continued)

Table 15.7 (continued)

Pharmacological classes and drugs	Dosage	Onset	Peak	Clinical effect	Half-life	Dose ceiling	Protein binding	Metabolism	Active metabolites
Lorazepam	IV bolus: 0.25–0.5 mg (0.02–0.06 mg/kg)/h up to 2 mg q. 1–4 h;	5–20 min	2–6 h	IV: 1–2 mg moderate deep sedation lasting 4–8 h	8–20 h		91–93%	Hepatic Glucuronidation	None
	IV infusion: 0.01–0.10 mg/kg/h up to 10 mg/h q2–6 hr. prn or 0.01–0.1 mg/kg/hr. (≤10 mg/hr)								
Midazolam	IV bolus: 0.5–1 mg (0.01–0.08 mg/kg/h) q. 5–30 min; IV infusion: 2–5 mg/h (0.02–0.30mg/kg/h)	0.5–5 min	3–5 min	Short time infusion:5–20 min unpredictable after prolonged infusion: 2–6 h	1–4 h (dependent in infusion duration) 3–11 h		97%	Hepatic CYP3A4 Oxidation	1-Hydroxy-methylmid-azolam
Flumazenil	IV: 0.2–1.0 mg	1–5 min	6–10 min	0.5–3.5 h	60 min	3 mg/h			
Pentobarbital	Induction IV: 5–10 mg/kg								
Dopamine receptor blockers									
Haloperidol	IV: Mild anxiety: 0.5–2.0 mg	10–30 min	30–45 min	4–6 h (single dose)	10–36 h		92%	Hepatic	
	Moderate anxiety: 5–10 mg								
	Severe anxiety: 10–20 mg								
	Maximum 2 doses								
Droperidol	IV: 0.625–2.5 mg	1–3 min	30 min		2–12 h		92%	Hepatic	

Table 15.8 Effects of analgesics and sedative drugs in intracranial pressure (ICP), prevention of ICP increase, cerebral blood flow (CBF), cerebral perfusion pressure (CPP), mean arterial pressure (MAP), jugular venous saturation ($SjvO_2$), and brain tissue oxygen ($PbtO_2$)

Drug class	Drug	ICP	Prevention of PIC increase	CBF	CPP	$CMRO_2$	MAP	$SjvO_2$	$PbtO_2$	Cerebral CO_2 reactivity and autoregulation	Cerebral electric activity
Opioids											
	Tramadol	←→			←→						
	Morphine	↓ (bolus) ←→	+		↓ (bolus)	/←→	↓ (bolus)				←→
	Fentanyl	↓/←→	+	←→	↓	↓	↓				
	Remifentanil	↓/←→	+	←→	↓	↓	↓↓				
	Antagonists										
	Naloxone										
A-2-adrenergic agonists	Clonidine										
	Dexmedetomidine	↓/←→	+		← → ↓	↓ ← →	←→	←→	←→		←→
NMDA antagonists	Ketamine	↓/←→			↓ ← →	↓ ← →		←→		←→	↓
GABA agonists	Propofol	↓↓	+	↓↓	↓	↓↓	↓↓	←→		←→	↓
	Etomidate	↓↓	+		←→	↓↓					←→
Diazepines											
	Lorazepam	↓	+	↓	←→/↓	↓	↓			←→	↓
	Midazolam	↓	+	↓↓	←→/↓	↓	↓			←→	↓
Barbiturates	Pentobarbital	↓↓	+	↓↓	↓	↓↓	↓↓				
Butyrophenones											
	Haloperidol										
	Droperidol										
Curares		←→/↓	+		/←→	←→	←→				←→

treatment of posttraumatic, postoperative superficial tissue injury and myofascial trigger point pains. Cranial scalp block results in better analgesic than local anesthetic infiltration [94].

The addition of low-dose epinephrine to the local anesthetic solution may prolong the duration of the blockade without systemic hemodynamic effects [95]. Scalp and surgical infiltrations with 0.25–0.5% bupivacaine, 0.5% levobupivacaine, or 0.75% ropivacaine associated with 1:200,000 epinephrine before the incision or during or just after wound closure may allow pain alleviation lasting 6–24 h [90], decrease post-craniotomy pain scores up to 8–48 h [90, 93] and opioid consumption for the first postoperative 24 h [95], and reduce nausea and vomiting after supratentorial craniotomy.

Intercostal or thoracic paravertebral nerve blocks with long-acting local anesthetics can be used to control postoperative pain after thoracotomy for spine procedures and for managing pain in patients with lumbar spine injury and multiple rib fractures. Severe axial and appendicular spinal traumatic or post-laminectomy pains may be controlled with epidural or intrathecal short- or long-term infusion of local anesthetics, opioids, and/or adjuvants. Lumbar discectomy and laminectomy may be performed under spinal or epidural anesthesia [96]. The combination of epidural-general anesthesia with postoperative epidural analgesia in spine surgery resulted in better pain control and in lower surgical stress response than general anesthesia followed by postoperative systemic opioid analgesia [97].

15.9 Treatment of Postoperative Neurosurgical Pain

15.9.1 Analgesics and Adjuvants

Pain in NICU patients usually is managed with simple analgesics and regular use or PCA infusion of opioids and/or scalp nerve blockade [76]. Post-craniotomy pain is typically managed with acetaminophen, oxycodone, and intravenous fentanyl on an as-needed (pro re nata (PRN)) schedule. Breakthrough pain usually is short-lived and occurs periodically and usually is controlled with simple analgesics, PCA, or adjustment of the continuous IV infusion of analgesics. The attending physician must be notified when pain remains greater than 4 on a 1–10 pain scale for three consecutive hours. Regular use of paracetamol and ibuprofen results in lower pain scores, less opioid consumption and antiemetic requirement, and shorter hospital lengths of stay than patients on PRN [98].

There is no consensus on postoperative analgesia after craniotomy [99]. Acetaminophen is prescribed in more than 80% of the British neurosurgical units, intramuscular (IM) codeine phosphate primarily in 70%, NSAIDS in about 50%, and morphine in 30% [99]. Tramadol is used as the third- or fourth-line analgesic. In the US NICUs, post-craniotomy pain is usually managed with acetaminophen, small doses of opioids on a PRN, and intraoperative dexamethasone [20].

The most prescribed analgesics in patients with subarachnoid hemorrhage are acetaminophen, dexamethasone, and opioids. Zeiler et al. [100] analyzed the data from 173 patients assisted in French, Canadian, American, Australian, or New Zealand ICUs and concluded that opiates and acetaminophen were the preferred analgesic agents for neurocritically ill patients, with gabapentin ranking as the third choice. Acetaminophen was the most common first-line analgesic (49.1% of patients); opiates were the "second line" (31.5% of patients) and 33% of patients did not receive a second analgesic.

15.9.2 Non-opioid Analgesics

Pain rated as 4 or less can be managed with acetaminophen and/or NSAIDs [56]. Non-opioid analgesics provide pain relief, earlier recovery, patient satisfaction, opioid use reduction, low side effects and healthcare costs, allowance of periodic neurological monitoring, analgesia potentiation, and thereafter less sedation and adverse events [26].

15.9.3 Simple Analgesics

Acetaminophen (N-acetyl-*p*-aminophenol [APAP]) is a non-opioid analgesic without significant anti-inflammatory effect prescribed as oral, rectal, and IV formulations as a unique drug or in association with other medications which compounded the multimodal pain management specially to treat mild to moderate or breakthrough postoperative pains and fever. Weak pain may be alleviated with 650 mg or more of acetaminophen, every 4–6 h. Suggested mechanisms include inhibition of the synthesis of cyclooxygenases (COX) and action on 5-HT pathways that modulate nociceptive DHNs.

The IV formulation allows earlier and higher plasma and cerebrospinal fluid concentrations than oral formulations and is indicated when patients need immediate analgesia, present nausea and vomiting, or do not have accessible gastroenteric route [26]. After the IV administration, APAP is effective in just 5 minutes, which may be beneficial in patients whose pain may cause further neurological abnormalities such as delirium.

Cumulative dosing of acetaminophen is limited because of the risk of liver toxicity, acute hepatic necrosis, nephrotoxicity, and thrombocytopenia, complications more common with elevated multiple doses, but may also occur with a single dose. Patients with impaired liver function or on regular alcohol use should take less than 2.000 mg of acetaminophen daily.

15.10 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are not sedatives with potent analgesic activity [72]. The use of NSAIDs in neurological and neurosurgical patients remains controversial. NSAIDs inhibit the COX enzyme responsible for PGs production. COX-1 is constitutively present in the CNS, kidneys, platelets, gastrointestinal system, skin, and other organs, COX-2 is constitutively found especially in the CNS and kidneys and is induced during the inflammation, and COX-3 is found in the CNS and is related to neuronal sensitization. COX-2 inhibitors, like celecoxib, are safer than nonselective NSAIDs regarding coagulation effect but present risk in patients with cardiovascular thromboembolic disease. Usually, NSAIDs alone are inadequate to treat post-craniotomy pain [98] but may enhance analgesia and potentially reduce the postoperative opioid consumption [69].

Diclofenac 100 mg rectally may be used every 18 h if there is no bleeding problem or renal insufficiency. Ketorolac is 350 times as potent as aspirin and has an opioid-sparing effect [49, 72, 107]. The continuous IV infusion of ketorolac 5 mg/h is more effective than intermittent IV administration[265]. When an NSAID belonging to one class is not effective, other NSAID belonging to another class should be considered. However, there are many controversies about NSAIDs' opioid-sparing effect.

NSAIDs should not be given if there is a known sensitivity to them and avoided in patients with cardiovascular disease or at risk for renal dysfunction and/or gastrointestinal bleeding [23, 67, 98]. Due to platelet function inhibition, except for celecoxib and parecoxib, NSAIDs should be withheld for 4–10 days prior to neurosurgery. Aspirin inhibits irreversibly the platelet function, whereas other NSAIDs inhibit temporarily only while at the therapeutic dosage.

There are many concerns over the antiplatelet effects, e.g., increased risk of bleeding and development of postoperative hematoma, renal toxicity, cardiovascular complication risks, and myocardial ischemia related to the use of NSAIDs in the perioperative period [24].

Palmer et al. (1994) concluded, based on a 5-year retrospective study enrolling around 7000 craniotomies, that 1.1% of the patients required the postoperative surgical evacuation of a hematoma. Risk factors were evidenced in two-thirds of patients, aspirin and NSAIDs being the most associated risk factors. This means that NSAIDs are contraindicated after intracranial or spinal fusion procedures and for patients with neurovascular potentially bleeding diseases as aneurysms and vascular malformations [23].

NSAIDs are the most common cause of postoperative kidney failure because renal blood flow depends on PGs activity. Patients treated with NSAIDs should receive adequate hydration to prevent kidney side effects because renal PGs concentrations may be reduced in patients with hypovolemia or with high concentrations of circulating vasoconstrictors, conditions very common during and after neurosurgical procedures. Proton pump inhibitors reduce the gastrointestinal risks of nonselective NSAIDs.

15.11 Opioid Analgesia

Opioids remain the mainstay of analgesia to treat moderate to severe postoperative pain in neurosurgical patients unresponsive to other analgesics. Opiates also present antitussive effect [83]. Up to 45% of NICU patients do not require opioids for analgesia.

Opioids bind to μ1-, μ2-, κ-, and δ-opioid receptors Activation of μ-opioid receptors induces analgesia, sedation, euphoria, respiratory depression and decreased gastrointestinal motility; κ-opioid receptors induce spinal and supraspinal analgesia, miosis, and dysphoria; δ-opioid receptors induce spinal and supraspinal analgesia.

Opioids are classified as agonists, partial agonists, agonists-antagonists, and antagonists. Opioid agonists bind to receptors with moderate to high affinity, activate G proteins, and produce a maximal response following receptor activation. Partial agonists bind to receptors with higher affinity but activate the receptor and associated G proteins incompletely. The agonists-antagonists act as agonist in one receptor and as antagonist in another receptor. Antagonists bind to all opioid receptor subtypes with high affinity but do not activate the receptor and G proteins.

Codeine, tramadol, morphine, hydromorphone, fentanyl, sufentanil, oxycodone, and remifentanil in association with sedatives are the preferred opioids for analgesia in ICU [60, 99]. The strong opioids most used in NICUs are morphine, fentanyl, and remifentanil. Although most analgesic opioids share many common pharmacodynamical properties, their pharmacokinetic profiles may differ significantly [83]. All have analgesic properties at low dosages and sedative-hypnotic effects at low but especially at high doses, are easy titled, provide comfort, and have side effects and rapid reversibility after drug discontinuation or use of opioid antagonists, as naloxone or naltrexone. Each opioid therapy requires individualized approach because the physiologic responses vary from individual to individual. The IV route is preferred because it allows a faster onset and better tritation [21]. As a rule, opioids are used on as a PRN basis and titrated in accordance with patient needs. After the IV loading, an hourly dose of approximately 1/6 the loading dose is recommended. Most opiates are cleared by renal and hepatic means. IV morphine may result in higher concentrations in patients with renal or liver dysfunction. Fentanyl or sufentanil is less affected and remifentanil is least influenced by hepatic and renal dysfunction.

Codeine, tramadol, and tapentadol are weak opioid analgesics. Codeine produces less analgesia, sedation, and respiratory depression than morphine. In nonventilated patients, satisfactory postoperative period analgesia can be reached with oral, rectal, or IM codeine phosphate [64, 69]. Codeine has a ceiling respiratory depressant effect and does not mask pupillary signs but often causes nausea and constipation. The lack of codeine efficacy observed in some patients may be related to its variable absorption and slow bioactivation. Codeine is metabolized by cytochrome P450 (CYP) 2D6. Up to 15% of codeine undergoes demethylation with a cytochrome P450 enzyme to form morphine. Patients with different CYP2D6 genotypes may respond differently in terms of pain relief and adverse events (poor metabolizers and ultrafast metabolizers). In poor metabolizers, that is, in 10% of

Caucasian population and 2% of Asians (poor metabolizers), there is lack of efficacy of codeine due to its inability to demethylate to morphine [4].

Tramadol has an oral bioavailability of 70%. Over 70% of tramadol is metabolized by O- and N-demethylation to an active metabolite, the O-desmethyltramadol. Tramadol causes less respiratory depression and sedation than morphine but is less effective as an analgesic than codeine, causes more nausea and vomiting than codeine and morphine, may decrease the seizure threshold, and may induce seizures after rapid bolus administration. Tramadol counteracts the development of tolerance in perioperative pain management. In low infusion doses, tramadol is an option for patients with perioperative pain and a history of opioid dependence. Due to the potential risk of seizures and the high incidence of nausea and vomiting, tramadol is avoided in some centers.

Morphine is a strong μ-opioid agonist with neuroprotective activity prescribed for pre-, intra-, and postoperative analgesia, sedation, and dyspnea associated with acute left ventricular failure and pulmonary edema. Due to its high somnolence effect, it potentially is considered as a sleep aid. Majority of morphine molecules do not cross the blood-brain barrier. Morphine has a prolonged duration of action. Due to its low lipid solubility causes slow CNS entry. Morphine provides better analgesia than tramadol and codeine in the neurosurgical population without increasing sedation, vomiting, or respiratory depression [111].

Hydromorphone is six to eight times more potent than morphine. It is prescribed for treatment of moderate to severe pain, especially in patients who require larger than usual doses of opioids to provide adequate relief as often occurring in spinal surgery patients with a previous history of narcotic use. Hydromorphone has a long-acting effect (effects last 4–6 h) that minimizes the time to reach comfort, being a good option as initial bedside titration of IV fentanyl until the pain is relieved. It is metabolized as inactive glucuronide and can be prescribed in patients with renal dysfunction.

Oxycodone is a semisynthetic opioid prescribed for treatment of moderate to severe postoperative pain. Oxycodone is metabolized in the liver to the inactive metabolite noroxycodone and to a lesser extent (less than 10%) to the active metabolite oxymorphone.

Meperidine is not an ideal analgesic at the NICU setting except for treatment of postoperative shivering, because repeated doses cause accumulation of an active metabolite, normeperidine, which is eliminated through the kidneys and induces excitatory neuronal syndrome that may precipitate tremors, myoclonus, delirium, agitation, and seizures.

Whenever rapid wake-up recovery from the sedative effect is required for neurological periodic evaluations without compromising ICP; short half-lives; more lipophilic opioids, rapidly distributed to the brain; and shorter time of effect onset than morphine as sufentanil, alfentanil, and remifentanil are recommended.

Fentanyl is 75–100 times more potent than morphine. Fentanyl has a very rapid onset and short duration of action because it has high lipid solubility and rapid redistribution into peripheral tissues, characteristics that justify the more rapid onset and shorter duration of action than morphine. Fentanyl undergoes extensive hepatic

metabolism resulting in the production of norfentanyl. With continuous infusion, fentanyl accumulates in fat stores, resulting in markedly prolonged duration. Its elimination half-life (5 h) is longer than morphine (4 h). It does not release histamine neither is metabolized to active metabolites and causes less hemodynamic instability than morphine, being suitable for patients in shock. Fentanyl should be used in the lowest tolerated dose to prevent prolonged effects.

Remifentanil is a short-acting μ-receptor agonist, is quickly titrated in continuous infusion, and has a rapid blood-brain equilibrium time (1.0–1.5 min) and ultrashort duration of action (3–5 min) which allows rapid recovery after discontinuation and facilitates frequent awakenings to evaluate periodically the neurologic and other clinical parameters. It is often prescribed for analgesia after craniotomy due to these properties. Remifentanil is less susceptible to accumulation following repeated boluses or continuous infusion due to the very rapid hydrolysis in blood and tissue to remifentanil acid, a compound with little pharmacologic activity eliminated through the kidneys. This means that remifentanil can be prescribed to patients with renal injury or with hepatic dysfunction. The awakening delay with remifentanil is shorter than fentanyl after a short time of sedation [87].

Methadone has a complex pharmacokinetic profile marked by substantial interindividual pharmacokinetic variability and numerous drug interactions. Methadone exhibits a very long terminal elimination half-life (on average from 20 to 35 h, ranging from 5 to 130 h), and in general, steady state is not achieved for approximately 2 weeks after initiation of therapy or dose changes.

Nalbuphine is a kappa agonist and mu antagonist that presents low side effect profile and low abuse potential, possibly because it inhibits midbrain dopamine release. As a μ-antagonist, it should be used with caution in addicted or in individuals on long-term treatment with high doses of μ-opioid agonists because it may cause withdrawal syndrome. It is an option for treatment of itching caused by other opioids.

Naloxone is an opioid antagonist which reverses the opioid effects at μ, κ, and δ receptors, although its affinity is highest at μ receptors. It is the drug of choice for the treatment of opioid-induced respiratory depression. Small doses (0.5–1.0 μg/kg) of naloxone should be administered slowly to avoid reactive pulmonary hypertension with the development of acute pulmonary edema. Adequate titration is also used to reverse other undesirable effects of opioids, for example, itching associated with intrathecal or epidural administration of opioids, without significantly affecting the level of analgesia.

The duration of effective antagonism is limited to around 30 minutes, and therefore longer-acting agonists will outlast this effect and further bolus doses or an infusion (5–10 μg/kg/h) will be required to maintain reversal. Caution is necessary in opioid addicts as naloxone may cause an acute withdrawal state with arterial hypertension, pulmonary edema, and cardiac arrhythmias. Anti-analgesic effects may be observed in subjects who are given naloxone and had never used opioids previously.

Naltrexone has similar mechanism of action, but has few pharmacokinetic advantages compared to naloxone. It has a longer half-life and is effective orally

for up to 24 h. It has been also used to treat opioid addiction and compulsive eating with morbid obesity.

Patients treated with high IV opioid infusion should have the vital signs closely monitored with continuous pulse oximetry and blood pressure and respiration recording. Ketamine and preoperative gabapentin, parecoxib, and lornoxicam may reduce opiate-induced hyperalgesia. Constipation may be relieved with oral naloxone (0.8 mg as an initial dose twice daily, maximum 5 mg a day, titrated up to 12 mg a day) [60]; doses lower than 10% of the daily morphine dosage may be ineffective. Naloxone 0.2 mg is recommended to revert respiratory depression caused by opioid overdose. Naloxone should be repeated as necessary at each 5 minutes till the maximum dose of 10 mg to avoid "overshoot" phenomenon characterized as arterial hypertension, tachycardia, and agitation that may aggravate intracranial hypertension.

In order to reduce the incidence and severity of opioid-induced side effects, the multimodal approach combining opioids with coanalgesics, like paracetamol, NSAIDs, and gabapentinoids or other alternatives, is recommended [21, 85].

15.11.1 α-2-Adrenergic Agonists

Clonidine and dexmedetomidine are the α-2-adrenergic-agonists most prescribed as sedative, analgesic, and sympatholytic in NICU. Both enhance efficacy and decrease the requirements of inhalational anesthetic agents and opioids and are valuable options in the treatment of delirium, as haloperidol may increase the development of seizures and benzodiazepines may obscure the neurologic examination and potentially burden its severity.

Clonidine is prescribed as sedative, analgesic, and antihypertensive drug. It provides sedation, anxiolysis, analgesia, tremor control, and antiemetic effects, enhances opioids and local anesthetics effects, has opioid-sparing effect during the surgery and postoperative period, and blunts substance abuse withdrawal symptoms and postoperative shivering. It is very effective in the treatment of opioid-tolerant patients and alcohol dependence. Clonidine is an adjunct to general, neuraxial, and regional anesthesia. For pain control, clonidine 150 μg is equivalent to morphine 5 mg. It has a longer half-life and lower cost than dexmedetomidine. Clonidine is rapidly distributed to the brain and spinal cord. About 50% of plasma clonidine underdoes hepatic metabolism. Its cardiovascular depressant effects limit its utility.

Clonidine may be administered by oral, IV, transdermal, topical, and intraspinal routes. It is highly lipophilic and has excellent bioavailability and is rapidly distributed to the brain and spinal cord. It decreases CBF, does not alter significantly the ICP in TBI patients, but may impair CPP because it may reduce MAP and does not have a clear effect on $CMRO_2$.

Dexmedetomidine is eight times more specific for α-2-adrenoceptors than clonidine. It provides analgesic, sedative, hypnotic, anxiolytic, sympatholytic, and neuroprotective effects without causing respiratory depression [31] or affecting the

arousal system like propofol and benzodiazepines. It is recommended for short-term sedation (<24 h) and has a potential role in the treatment of withdrawal syndrome from cocaine, alcohol, and opioids [93]. Dexmedetomidine suppresses the spreading depression, reduces the discomfort caused by mechanical ventilation, and allows rapid patient arousal for periodic neurologic examination [17]. It is metabolized in the liver through glucuronide conjugation to inactive metabolites and does not accumulate. Its effect lasts less than 10 minutes, and the elimination half-life is 2 h but may increase in patients with severe liver disease and is less affected by renal disease. IV dexmedetomidine is rapidly distributed to the brain and rapidly eliminated providing easier arousal than propofol and midazolam. It induces sedation without simultaneous loss of attentive behavior and cognition [17], allowing periodic neurologic examination without clinically significant changes in ICP or CPP. Due to lack of amnestic properties, benzodiazepines and narcotics may be required to improve amnesia and analgesia in patients treated with dexmedetomidine.

Dexmedetomidine may exacerbate the effects of other centrally acting depressants. The most common adverse effects of dexmedetomidine include anxiety, dry mouth, light-headedness, bradycardia, and sympathetic rebound (when infused longer than 24 h). The respiratory drive is not compromised at recommended doses. Dexmedetomidine may cause arterial hypotension, bradycardia, and agitation. The high rate and the long duration of dexmedetomidine infusion may result in a not clinically, but a significant statistically, negative impact on hemodynamic parameters, as dose-dependent decrease in systolic and diastolic blood pressure, heart rate, and plasma norepinephrine levels [116]. Often bradycardia and hypotension are observed during the initial loading dose and may be exacerbated by concomitant administration of antihypertensive and antiarrhythmic medications. A transient hypertensive response may occur after IV high-dosage loading boluses due to activation of peripheral vascular α-2-adrenergic receptors preceding its central sympatholytic effect. The high price limits its use in NICU. Infusions longer than 24 h are not approved by the FDA.

15.11.2 Ketamine

Ketamine (2-(o-chlorophenyl) 2-methylaminocyclohexanone) is short-acting nonbarbiturate phencyclidine, non-competitive NMDA receptor antagonist, used as a dissociative general anesthetic, analgesic, and anti-hyperalgesic drug during the postoperative sedation and treatment of pain, usually associated with opioids, local anesthetics, and/or other agents. It can be administered by VO, IV, IM, nasal, rectal, epidural, intrathecal, and topical routes even in non-intubated patients. It is extensively metabolized in the liver to norketamine, a metabolite that exhibits 1/3 of the activity of the parent compound. Ketamine reduces allodynia and hyperalgesia in patients with neuropathic pain, including the post-amputation stump and phantom

organ pains, has opioid-sparing activity, prevents opioid hyperalgesia, reduces opioid tolerance and airway resistance, and spares bowel motility.

As it does not alter the systemic hemodynamics or respiratory drive [2], it is indicated as an anesthetic in patients with hemodynamic instability or hemorrhagic shock because it stimulates the sympathetic activity [99] and may be beneficial in sedated severe TBI patients under controlled, normocapnic ventilation [57]. Ketamine (1–5 mg/kg/h) infusion reinforces the effects of standard sedatives and can be an alternative or adjunct to opioid analgesia. Ketamine can be prescribed alone as analgesic or sedative or in combination with propofol, midazolam, local anesthetics, and opioids [39] especially in patients with a history of bronchospasm. In the multimodal context, it may reduce the risk of opioid-induced hyperalgesia. Intraoperatively, the combination of a bolus of ketamine 0.1–0.5 mg/kg followed by continuous 2–5 μg/kg/min infusion may improve postoperative pain management and allows a decrease of opioid consumption and the need of other analgesics without increasing the risk of the excitatory hallucinogenic activity.

Relative contraindications include mild to severe hypertension, tachyarrhythmia, congestive heart failure, myocardial ischemia, acute alcohol intoxication, alcohol abuse, eyeball lesion, and preexisting respiratory depression. Overall, ketamine does not adversely affect patient outcomes. Ketamine produces analgesia at low doses, sensory distortions at moderate doses, and complete dissociation and anesthesia at higher doses.

In the past, ketamine has been avoided in neuro anesthesia due to the potential detrimental effect on ICP and CBF. However, in recent years, it was shown that it does not increase ICP or CBF in patients under controlled ventilation [39] but, instead, reduces ICP and improves CPP without lowering blood pressure even in pediatric traumatic brain injury patients with high ICP under controlled normocapnic ventilation [20]. The ICP reduction is associated with stable maintenance or increase CPP without significant change in hemodynamic status and does not cause withdrawal symptoms in TBI patients [3, 8].

15.11.3 Other Adjuvant Analgesics

Adjuvant analgesics include antiepileptics, tricyclic antidepressants (TCAs), selective norepinephrine and serotonin and norepinephrine reuptake inhibitors (SNRIs), α- and β-noradrenergic blockers, topical capsaicin, topical and systemic lidocaine, 5-HT antagonists, muscle relaxants, and corticosteroids. These medications are particularly beneficial in the treatment of chronic and neuropathic pains and when environmental, physiologic, or psychological factors influence the pain occurrence.

15.12 Rehabilitation, Physical Medicine, and Psychotherapy

Non-pharmacological interventions, such as physical medicine, acupuncture, trigger-point injections, rehabilitation, music, relaxation, hypnosis, feedback, psychological support, and sleep hygiene, are also components of the multimodal analgesia set. Localized pain and muscle spasms may be treated with ice, heat, or both. Dry needling and local anesthetics trigger-point injections are quite effective in the treatment of cervicogenic headache, low back pain, and myofascial pain syndromes. Sleep is an important physiological phenomenon to recover from illness. Environmental modulation to promote sleep includes minimizing noise, lighting mimicking the 24-hour day cycle, relaxation, music therapy, massage therapy, and the use of earplugs [100].

15.12.1 Sedation

Delirium and agitation can largely complicate the clinical course of NICU patients. After treatment or removal of possible causes of anxiety, agitation, delirium, and pain, sedation should start treating anxiety, facilitating mechanical ventilation and neurological exams, and voiding deleterious changes in ICP and CPP. Opioids, propofol, diazepam, midazolam, dexmedetomidine, ketamine, clonidine, haloperidol, and droperidol are used for sedation [72, 77].

Propofol and midazolam are the first-line sedative agents in NICU. Benzodiazepines reduce agitation but may obscure the neurologic examination and, potentially, may aggravate delirium. Due to their rapid onset of action, midazolam and diazepam should be used for rapid sedation of acutely agitated patients. Diazepam has a long half-life which prolongs its clinical effect. Opioids, like benzodiazepines, have a little hemodynamic effect on euvolemic patients. ICP became lower in TBI patients treated with propofol than morphine sulfate. Propofol is more effective in lowering ICP and causes more hypotension and reduction in CPP than midazolam [72].

Benzodiazepines increase the opening of the GABA-A Cl^- channel and potentiate the GABA effect. IV diazepam, lorazepam, and midazolam are the benzodiazepines more recommended for sedation in NICU. These drugs produce anxiolysis, sedation, hypnosis, muscle relaxation, anterograde amnesia, and antiepileptic effects [101], potentiate the opioid effects of narcotics, decrease CBF and $CMRO_2$, and do not directly change ICP, and their effects may be reversed with IV flumazenil. They have a predominant anxiolytic action but are also recommended for treatment of epilepsy and insomnia and to induce and maintain sedation. Even in small titrated doses, benzodiazepines are effective in relieving the stressful ICU environment without overt compromise of the cognitive functions. The anterograde amnesia caused by benzodiazepines is very useful when uncomfortable procedures are planned or being performed. GABA receptor agonists as benzodiazepines, barbiturates, propofol, and ketamine infusion reduce the risk of secondary seizures [102].

Benzodiazepines are a first-line treatment option for acute management of seizures and status epilepticus. Associated with conventional antiepileptic drugs, benzodiazepines, particularly lorazepam (anti-seizure effect of about 12–24 h), are the preferred initial antiepileptics.

Benzodiazepines are rapidly distributed to the brain, followed by redistribution to muscle and fat. Time to onset and offset of single IV doses are determined by their relative lipophilicity. All benzodiazepines have highly bound on plasma proteins and are bio-transformed in the liver by different cytochrome P450 isoforms. Midazolam elimination half-life is short and diazepam is long, but the clinical recovery is the same due to lipid solubility of midazolam and lorazepam. However, no data are available about their use for sedation in the NICU [3]. Benzodiazepines do not interfere significantly with the blood pressure or heart rate and have little or no effect on ICP but can cause arterial hypotension and increased heart rate especially at high doses in patients with hypovolemia, low cardiac output state, or severe vasodilation. GABA receptor stimulation by diazepines reduces metabolic brain metabolism and $CMRO_2$ and is dose-dependent until the electroencephalogram becomes isoelectric. Benzodiazepines are pure sedative agents and do not have analgesic properties. Thereafter, analgesic drugs should be added to the therapeutic regime when pain is a concern. Rifampicin, carbamazepine, phenytoin, and phenobarbital may enhance benzodiazepines' clearance, and macrolides, azole antifungals, and non-dihydropyridine Ca^{++}-channel blockers may inhibit their clearance [3].

Due to its high lipophilicity, diazepam has the most rapid onset and the most rapid redistribution among the benzodiazepines, followed by midazolam and lorazepam. It should not be given in continuous infusion because it has long half-life. Diazepam is metabolized to its active metabolite, desmethyl-diazepam, a substance with considerable sedative potency and elimination half-life superior to 90 h. The accumulation of both molecules prolongs recovery and oversedation after repeated administration or prolonged infusion [103]. Re-sedation may occur even after flumazenil injection because of the long duration of action.

Midazolam is three to four times more potent than diazepam, has the shortest half-life, and is the most easily titratable of all benzodiazepines. It is water soluble, does not generate significant active metabolites, and is very appropriate for continuous infusion. For short-term use, midazolam is the drug of choice for sedation as an alternative to propofol because it is highly lipophilic; crosses the blood-brain barrier quickly, resulting in a rapid onset of action; and additionally has rapid clearance and duration of action. However, despite the relatively short half-life, midazolam may cause prolonged sedation, unpredictable awakening, and time to extubation when infusions are longer than 48–72 h due to fat absorption (releasing back into the plasma when the infusion is stopped); accumulation in peripheral tissues and in the bloodstream; generation of an active CNS-depressant metabolite (1-hydroxymidazolam glucuronide) that may accumulate, especially in elderly patients or patients with kidney and/or hepatic failure; and P450 inhibition by other drugs.

Midazolam is an independent risk factor for the development of delirium in both surgical and trauma patients [7]. Due to tachyphylaxis, midazolam may require

increasingly high doses [104]. Midazolam, lorazepam, and diazepam do not cause respiratory depression in healthy subjects, unless at high doses. At high dose, they may cause respiratory dysfunction, apnea, and hypercapnia and, as consequence, increase in ICP mainly in children and in patients with chronic pulmonary disease and respiratory and/or hepatic insufficiency or when combined with other sedatives. Caution must be used when combined therapy with an opioid is pursued. Careful attention is needed regarding tachyphylaxis at higher doses and withdrawal symptoms at discontinuation of midazolam [71]. Tolerance develops rapidly and diminishes their efficacy with time. Tachyphylaxis can lead to increasing benzodiazepine doses and may make the ICP control difficult. Withdrawal symptoms can mimic delirium tremens and may occur at drug discontinuation. Switching midazolam to propofol 24 h prior to extubation reduces the risk of withdrawal in intubated patients and the incidence of post-extubation agitation [105]. Flumazenil is a selective benzodiazepine GABA antagonist which reverses the effects of benzodiazepines. It should be used carefully because there is a risk of lowering seizure threshold, rapid ICP increase, and systemic hypertension. Flumazenil decreases tidal volume and blunts response to hypoxia and hypercarbia.

Paradoxical reactions as agitation and delirium may occur in patients with preexisting CNS pathology. Continuous infusion may be required because flumazenil's short duration of action may result in re-sedation. Flumazenil may precipitate withdrawal in benzodiazepine-dependent patients and seizures or status epilepticus. Prolonged use is associated with tachyphylaxis and reversible encephalopathy [71, 104, 105].

15.12.2 Antipsychotics

Haloperidol and droperidol are butyrophenones, the antipsychotic agents of choice for treatment of agitation secondary to psychosis, delirium, anxiety, and agitation in the NICU [106]. Lack of respiratory depression makes butyrophenones a good option to threat delirium in non-intubated patients. However, both do not have analgesic or amnestic properties and are not recommended as a first-line drug for sedation. Increased prolactin secretion; cardiorespiratory depression; orthostatic hypotension, especially in hypovolemic or on beta-blocker patients; neuroleptic malignant syndrome; and jaundice (rare) are their most common side effects.

Parkinsonism, acute and tardive dyskinesias, akathisia, and perioral tremor may also occur, but the frequency of occurrence decreases when benzodiazepines are added. Haloperidol and droperidol should be used with caution in patients with seizure disorders because it may induce slowing, synchronization, and increasing of EEG voltage and reduction of seizure threshold. Both also should be used with caution in patients at risk for cardiac dysrhythmias because even with low doses, they may cause ECG QT prolongation and *torsades de pointes*. The preexisting long QT interval is a contraindication for butyrophenone prescrition [107]. SSRIs may increase circulating levels of both drugs. QTc should be monitored daily in patients treated with high doses of butirophenones [106].

15.12.3 Propofol

Propofol (2,6-diisopropyl phenol) is a pure sedative-hypnotic drug, with little analgesic action. Propofol binds on a different site of GABA-A receptors unlike benzodiazepines, enhances and activates GABA transmission, inhibits Cl^- channels and NMDA receptor, and modulates the neuronal Ca^{++} influx through the slow Ca^{++} channels, resulting in seizure activity suppression, neuroprotection, and anesthetic, sedative, antiemetic, antegrade amnesia, and antipruritic effects [108, 109].

Propofol and remifentanil induce EEG burst suppression associated with CBF reduction, and there are no changes in arteriovenous O_2 saturation difference, suggesting that flow-metabolism coupling is kept intact [110]. Its fast titration and rapid distribution to brain following IV administration provide rapid neuronal uptake and rapid onset of action and large volume of distribution, relatively short half-life due to its redistribution to other less-perfused tissues, and fast elimination rate, and the fast elimination from the CNS results in short duration of action and in rapid recovery of consciousness when the infusion is discontinued after lighter sedation allowing the periodic neurologic examination in sedated patients and the reduction in mechanical ventilation need, ventilator days, and tracheostomy. All these characteristics make propofol the preferable sedative agent in NICU especially in mechanically ventilated patients. Patients treated with propofol need fewer ventilator days than intermittent lorazepam when infused following the daily interruption regime. Propofol is not analgesic and should not be prescribed alone aiming sedation for painful procedures [111].

Propofol potentiates the effects of alcohol, opioids, benzodiazepines, barbiturates, antihypertensives, antiarrhythmics, and other general anesthetics. Monitoring oximetry, respiratory rate, depth of respiration, blood pressure, and serum electrolytes, lactic acid, creatine kinase, and triglycerides is recommended in patients treated with doses higher than 50 μg/kg/min for longer than 48 h [108–111]. Propofol effects can be reversed with IV flumazenil 0.2 mg, repeated, when necessary, at 5-minute interval.

Propofol side effects include respiratory depression, apnea, and urine, hair, and nail beds green discoloration. Abnormal movements during propofol infusion, as myoclonus and seizures, may also occur. Low propofol doses at the beginning of infusion have potential pro-convulsant activity. Tonic-clonic seizures may occur when propofol is abruptly stopped after days of infusion. Propofol may also cause arterial hypotension due to vasodilation, negative inotropic effect, and impairment of cardio-accelerator response to decreased blood pressure, especially when the induction is rapid, and may be more pronounced in elderly, hypovolemic, or reduced cardiac output patients such as occurring with the simultaneous use of other cardio depressors, as alcohol, opioids, benzodiazepines, barbiturates, antihypertensives, and antiarrhythmics [112].

The present formulations contain propofol, soybean oil, glycerol, egg phosphatide, and edetate disodium (EDTA) or metabisulfite, substances that may cause pain at the injection site, which can be lessened with its infusion through a central or large vein or pretreatment with IV lidocaine in the same vein. Anaphylactoid reactions may due to egg and soy products present in emulsion. The high lipid content of propofol solutions may cause hypertriglyceridemia and pancreatitis, and the infusion should be discontinued if triglyceridemia becomes higher than 300 mg/dL. Triglyceride concentrations should be monitored when propofol infusion lasts 2 or more days, and total caloric intake from lipids should be included in the nutrition support prescription [112].

Infusion of doses higher than 4 mg/kg/h of propofol with vasopressors to maintain CPP, prolonged utilization (more than 48 h) in the presence of neurologic diseases, young age, therapeutic hypothermia, catecholamine or glucocorticoid administration, inadequate dietary carbohydrates, and/or subclinical mitochondrial disease may trigger off the propofol infusion syndrome (PRIS), a potentially fatal complication related to propofol-induced mitochondrial fatty oxidation blockade and accumulation of free fatty acids presenting pro-arrhythmic effects, characterized as high anion gap severe metabolic acidosis, rhabdomyolysis, hyperkalemia, acute kidney injury, elevated creatine kinase, rhabdomyolysis, hyperlipidemia, cardiac arrhythmia, bradycardia, progressive renal and myocardial failure, and cardiocirculatory shock [107–112]. Changes in albuminemia levels and alteration of fat altered metabolism, and liver dysfunction may increase the drug concentration and the risk of side effects.

15.12.4 Barbiturates

Barbiturates as thiopental and pentobarbital reduce brain metabolism, cause burst suppression, alter cerebrovascular tone, and improve the regional blood flow to the metabolic demand coupling [111]. High doses of thiopental and pentobarbital should be considered in selected patients with refractory status epilepticus, severe cerebral edema, elevated ICP, and low CPP intracranial hypertension or refractory to other therapeutic methods especially when no surgical lesion is present [113]. Barbiturates should not be prescribed for prophylaxis of intracranial hypertension. According to a meta-analysis, there is no evidence that barbiturate therapy and prophylactic-induced coma improve the outcomes of patients with TBI [113]. Barbiturates should not be used liberally as sedatives in NICU due to their side effects, as hemodynamic instability, hypotension, cardiac depression, immunosuppression, hyper- or hypokalemia, and atelectasis, and unfavorable pharmacological profile due to their accumulation in peripheral tissues after long-term infusions, which can lead to prolonged recovery after sedation withdrawal [111–113].

15.12.5 Volatile Agents

Inhalation anesthetic agents as isoflurane, sevoflurane, and desflurane are emerging as an alternative for ICU sedation. These drugs increase CBF and reduce $CMRO_2$ resulting in favorable uncoupling of CBF and O_2 consumption [114]. Isoflurane decreases cortical spreading depolarization, and isoflurane and sevoflurane induce burst suppression and are potential therapeutic options in patients with refractory status epilepticus. Sevoflurane seems to be an effective sedative in acute ischemic stroke or subarachnoid hemorrhage patients but was associated with a significant increase in ICP and decreased MAP and CPP, and isoflurane improved regional CBF and had a modest effect on ICP when compared with propofol in patients with subarachnoid hemorrhage without intracranial hypertension [114, 115].

15.12.6 Multimodal Analgosedation

The multimodal analgesia approach is recommended postoperatively for neurosurgical patients to lower the side effect profile and decrease toxicity of analgesic and sedative drugs [116]. Potential advantages and disadvantages of each class of drugs and the clinical needs should guide the selection of the analgesic regime. Opioids are frequently necessary in NICU but present many critical side effects [117]. Synergistic co-analgosedation may reduce opiate requirements and the side effects of the analgesics and sedative drugs used in NICU. The association of opioids with non-opioid analgesics and non-pharmacological analgesic procedures may minimize opiate administration. Opioids as morphine, fentanyl, and remifentanil have been associated with sedatives such as propofol, ketamine, dexmedetomidine, and benzodiazepines. Benzodiazepines and haloperidol present synergic activities, and the association of both drugs reduces the risk of impaired respiratory drive and of extrapyramidal symptoms, respectively. The propofol-benzodiazepine combination allows reduction of propofol dose and better hemodynamic stability. The ketamine-propofol combination associated with midazolam may result in potentiation of sedation and antagonization of effects on ICP of both drugs providing the analgesic effects and the possible block of the action of excitatory amino acids of ketamine.

15.13 Conclusion

Pain and delirium are major stressors in NICU patients. Unrelieved pain and delirium cause detrimental effects to the neurological condition and contribute to negative outcomes in critically ill patients. Analgosedation have general (pain, discomfort, anxiety, agitation, delirium, patient-ventilator asynchrony, suffering resulting from painful manipulations, prophylaxis, and control) and neuro-specific (ICP,

hyperthermia and seizure control, and temperature management) effects. To be adequately managed, pain and delirium should be assessed appropriately. The self-report is the best way to evaluate conscious and oriented patients, and the observation of patient behavior is the best way to evaluate nonverbal, non-full conscious, and non-oriented patients. Few studies have addressed the effectiveness of pharmacologic and non-pharmacological interventions aiming at treatment of pain in NICU patients. No single drug can achieve all the requirements for analgesia and sedation. Preservation of the quality of neurologic examination is paramount when considering the choice of analgesics, sedatives, and paralytics.

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Chapter 16
Hemodynamic Management in the Neurocritical Patient

Sâmia Yasin Wayhs and Edwin Koterba

16.1 Introduction

Joseph Priestley discovered oxygen (O_2) in 1774 and Antoine Lavoisier named it from the Greek, "acid producer," as that time it was believed all acids contained oxygen [39]. Its use by cells is the last step in a long chain of cytoplasmic and mitochondrial reactions so that aerobic metabolism enhances energy generation from available substrate. Oxygen is the vital substrate for the maintenance of tissue and cellular homeostasis. Insufficient delivery or reduced cellular utilization of O_2 results into a failure of aerobic metabolism and glycolysis. This has the disadvantage of reduced energy generation and increased production of by-products like hydrogen ions, carbon dioxide, and lactate. These by-products generate adaptive roles that can contribute with integrity and cell function in critical illness; for example, by shifting the oxyhemoglobin dissociation curve to the right.

Cardiac output (CO) is defined by the volume of blood being pumped by heart, by the left or right ventricle, per unit of time, in L/min [22]. It is the product of heart rate (HR—number of heart beats per minute—bpm) and the stroke volume (SV—volume of blood pumped from the ventricle per beat). CO and systolic volume are influenced by preload, afterload, and contractility. Cardiac index (CI) is the relation of the CO to body surface area (BSA), in 1 minute (L/min/m^2). The Frank–Starling law states that SV increases in response to an increase in the volume of blood in the ventricles, before contraction (the end diastolic volume), when all other factors remain constant. It allows the CO to be synchronized with venous return (preload),

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arterial blood supply and maintaining left and right ventricular output equality. The Poiseuille law, from 1840, assumes that the fluid is incompressible and Newtonian; the flow is laminar through a pipe of constant circular cross-section substantially longer than its diameter and there is no acceleration of fluid in the pipe. When velocities and pipe diameters exceed a threshold, fluid flow becomes turbulent, leading to larger pressure drops than calculated by Hagen–Poiseuille equation. Even small variations in vessel radius may result in large variations in vascular resistance. Thus, micro-occlusion in areas with compromised blood flow may cause a large change in perfusion (Fig. 16.1 and Table 16.1).

Shoemaker in 1988 described that survivors of high-risk surgeries presented significantly higher mean CI, oxygen delivery (DO_2), and oxygen consumption (VO_2), than nonsurvivors [35]. Intensive care treatment with pulmonary catheter guided

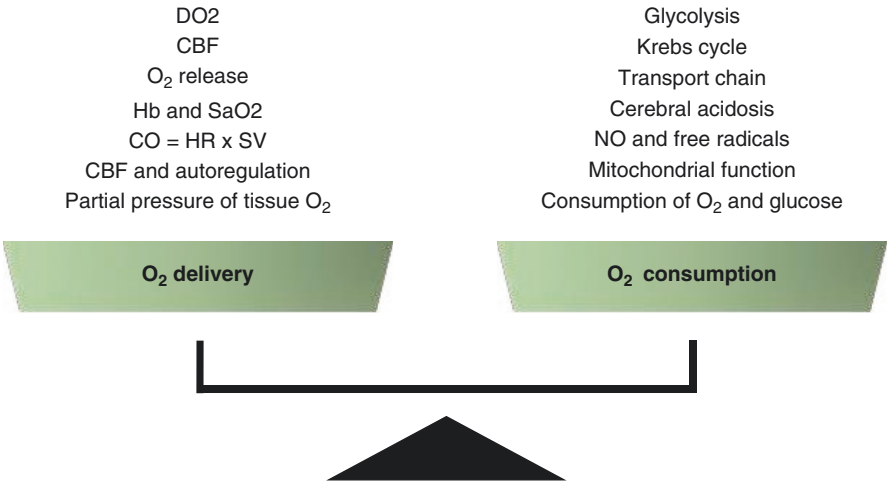

Fig. 16.1 Cerebral metabolism: determinants of oxygen transport. DO_2 oxygen delivery, CBF cerebral blood flow, Hb hemoglobin concentration, SaO_2 arterial oxygen saturation, CO cardiac output—influenced by preload, afterload and contractility, HR heart rate, SV stroke volume, NO nitric oxide, O_2 oxygen

Table 16.1 Causes of secondary brain injury

Systemic	Intracranial
Hypotension	Intracerebral hemorrhage
Hypoxia	Brain swelling and edema
Hypercapnia/hypocapnia	Intracranial hypertension (ICH)
Anemia	Brain herniation
Fever	Vasospasm
Hypoglycemia/hyperglycemia	Hydrocephalus
Hyponatremia	Infections
Sepsis/pneumonia	Convulsions
Coagulopathy	Cerebral vascular lesions
	Brain inflammatory response

protocol showed better results in this classic study. Friedman and colleagues reported in 1998 the concept that VO_2/DO_2 dependency is a marker of septic shock and that interventions to increase DO_2 could be justified in its treatment [15]. The Swan–Ganz catheters were introduced in 1970 and may inform a lot about hemodynamics in critically ill patients. Balloon flotation catheters have advantages compared with conventional catheters, but were over and misused for many, leading to many complications and higher mortality in some prospective randomized trials [6] (Fig. 16.2 and Table 16.2).

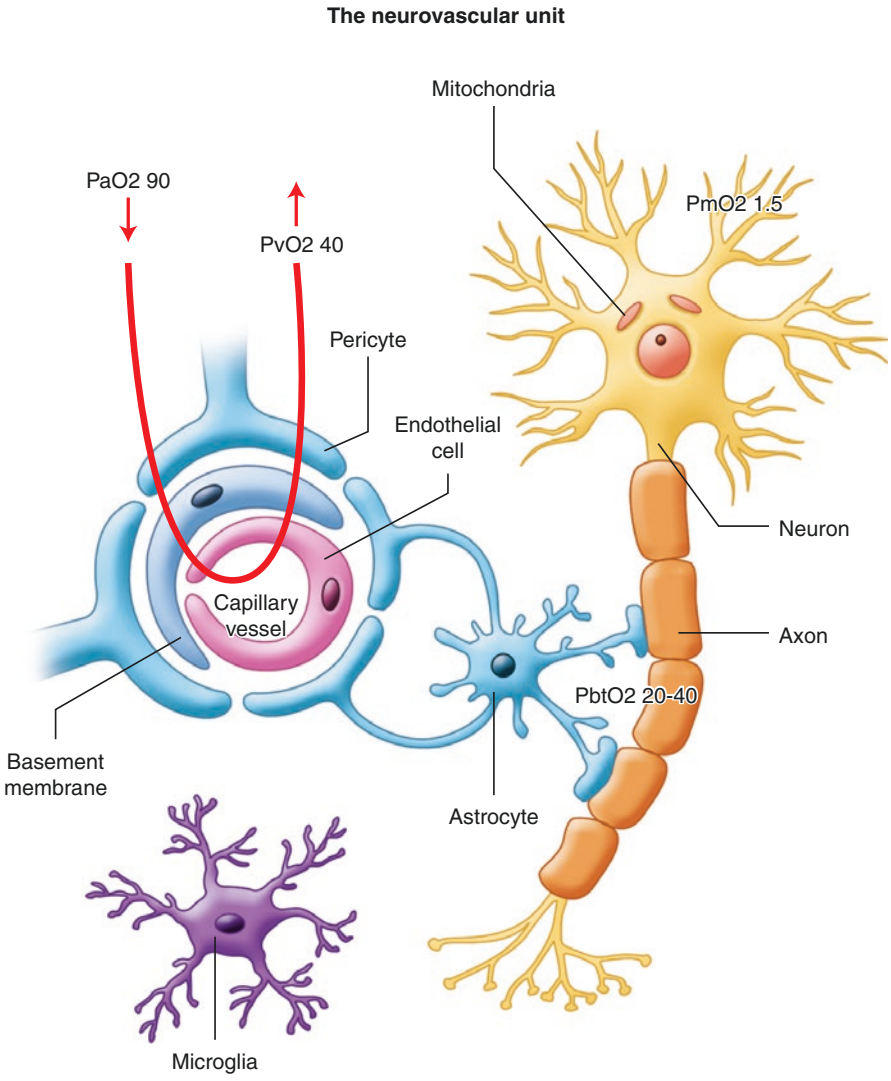

Fig. 16.2 Pressure oxygen gradients in the neurovascular unit. PaO_2 arterial partial pressure of oxygen, PmO_2 mitochondrial pressure of oxygen, $PbtO_2$ brain tissue oxygen tension, PvO_2 venous partial pressure of oxygen

Table 16.2 Important definitions and formulas for hemodynamic evaluation

$CO = HR \times SV$ or $CO = SV/HR$ (Fick Equation)
$CI = CO/BSA$
$SV = EDV - ESV$
$DO_2 = CO \times Hb \times SaO_2 \times C \times 10$
$VO_2 = (CaO_2 - CvO_2) \times CO$
$(O_2ER) = VO_2/DO_2 = (CaO_2 - CvO_2)/CaO_2$ or $(O_2ER) = SaO_2 - SjO_2$
$CaO_2 = (Hb1.34 \times SaO_2) + (PaO_2 \times 0.0031)$
$CBF = CPP/CVR$ or $CBF = MAP - ICP/CVR$
$CPP = MAP - ICP$
$SVV = PPV = PP_{max} - PP_{min}/(PP_{max} - PP_{min})/2$

CO cardiac output, *HR* heart rate, *SV* stroke volume, *CI* cardiac index, *BSA* body surface area, *EDV* end diastolic volume, *ESV* end systolic volume, DO_2 oxygen delivery, *Hb* hemoglobin concentration, SaO_2 arterial oxygen saturation, *C* constant value representing the amount of oxygen bound to 1 g Hb (usually 1.34 or 1.39), VO_2 oxygen consumption, CaO_2 arterial oxygen content, CvO_2 venous oxygen content, (O_2ER) oxygen extraction, SjO_2 jugular venous oxygen saturation, PaO_2 arterial partial pressure of oxygen, *CBF* cerebral blood flow, *CPP* cerebral perfusion pressure, *CVR* cerebral vascular resistance, *MAP* mean arterial pressure, *ICP* intracranial pressure, *SVV* stroke volume variation, *PPV* pulse pressure variation, PP_{max} maximal arterial pulse pressure, PP_{min} minimal arterial pulse pressure. During mechanical ventilation systolic and arterial pulse pressure are maximal during inspiration and declines in expiration (minimal)

16.1.1 Traumatic Brain Injury

The cerebral perfusion pressure (CPP) is defined as the result of the mean arterial pressure (MAP), minus the intracranial pressure (ICP), and determines the pressure gradient for blood flow and O_2 and nutrient delivery to the brain. The maintenance of adequate levels of CPP is basic to improve patient outcome and is proposed to ensure adequate delivery of oxygenated blood throughout the injured brain. Hypotension is associated with secondary ischemic injury and worst outcomes [25], while aggressive maintenance of CPP above 70 mmHg has been associated with increased cardiovascular and respiratory complications. Brain Trauma Foundation guidelines recommend a CPP from 60 to 70 mmHg [5]. Yet, evidence suggests that perfusion requirements may vary across the injured brain and differ depending on the time from the injury. The heterogeneity within and between subjects indicates that individualized therapy may be an appropriate treatment strategy [37].

Cerebral autoregulation is defined as the mechanism responsible for maintaining a relatively constant cerebral blood flow (CBF) over a wide range of arterial blood pressures, brought about by homeostatic change in cerebral vascular resistance. It depends on metabolic, myogenic, and neuronal mechanisms to maintain a suitable CBF based on cerebral metabolic demands. Thus, assuming that CPP provides the stimulus for cerebral autoregulation, no change in flow would be anticipated as long as the CPP remained within the upper and lower limits of autoregulation. Traumatic brain injury (TBI) management includes CPP monitoring in the "bundle" of care. However, the question remains as to whether CPP can, itself, influence outcome,

separate from MAP and ICP monitoring [36]. Advanced cerebral monitoring techniques for blood flow and oxygen include: transcranial Doppler (TCD)/duplex sonography, differences between arterial and arterio-jugular venous oxygen ($AVDO_2$), and measurements of local tissue oxygen. Arterio-jugular $AVDO_2$ globally measures cerebral oxygen extraction. However, the measured $AVDO_2$ can potentially differ from the other unmeasured hemisphere in traumatic brain injury patients. Tissue monitors are placed in the cerebral cortex and directly measure tissue oxygen in the immediate area. Jugular bulb monitoring of arteriovenous oxygen content difference ($AVDO_2$), as a source of information for management decisions, may be considered to reduce mortality and improve outcomes at 3 and 6 months postinjury.

Studies showed impaired perfusion due to an autoregulatory increase in cerebral blood volume (CBV) through a reduction in cerebrovascular resistance (CVR) [3]. This is an attempt to maintain the CBF near the approximate "normal" of 50 mL/100 g/min. However, if perfusion pressure is reduced and maximal CBV is reached, CBF becomes linearly dependent on pressure. Normal metabolic activity can be maintained, with an increase in oxygen extraction fraction (OEF), called "misery perfusion," but at risk of impending cerebral ischemia. The extent and duration of metabolic compromise determine if the ischemia is reversible or not. TCD measurements suggest that blood flow may demonstrate 3 distinct phases following injury: early vasoconstriction and ischemia (minutes–hours postinjury), intermediate hyperemia (higher CPP is probably not required and may even be detrimental), and late phase (days) of reduced blood flow may benefit from an increase in CPP to improve CBF. Brasil and colleagues suggested in 2018 that knowledge of vascular and nonvascular surrogates involved concomitantly in TBI, such as CO_2 reactivity and cerebral autoregulation (CA) impairment, as well as biochemical derangement and mitochondrial dysfunction, require continuous real-time multimodal monitoring and expert handling [2].

16.1.2 Subarachnoid Hemorrhage

The guidelines for the management of aneurysmal subarachnoid hemorrhage (aSAH) from the AHA recommended (evidence Class I) to treat chronic high blood pressure with antihypertensive medication to prevent ischemic stroke, intracerebral hemorrhage, and cardiac, renal, and other end-organ injury. Narrowing (vasospasm) of the angiographically visible cerebral arteries after aSAH is common, occurring most frequently 7–10 days after aneurysm rupture and resolving spontaneously after 21 days. The cascade of events culminating in vasospasm is initiated when oxyhemoglobin comes in contact with the abluminal side of the vessel. The pathways leading to arterial narrowing have been the focus of extensive basic research, but no effective preventive therapy has been developed to date. Part of the reason for this lack of success likely stems from the fact that vasospasm occurs at multiple levels in the arterial and arteriolar circulation. Large artery narrowing seen in

angiographically visible vessels only results in ischemic neurological symptoms in 50% of cases, and although there is a correlation between the severity of large arterial spasm and symptomatic ischemia, there are patients with severe large artery spasm who never become symptomatic and others with quite modest spasm who not only develop symptoms but go on to develop infarction. Probably many factors contribute to the development of ischemia and infarction, including but not limited to distal microcirculatory failure, poor collateral anatomy, and genetic or physiological variations in cellular ischemic tolerance. Delayed cerebral ischemia (DCI), especially that associated with arterial vasospasm, remains a major cause of death and disability in patients with aSAH. Management of arterial pressure is crucial. Induced hypertension may be necessary in case of symptomatic vasospasm if the aneurysm has been secured.

16.1.3 Postoperative Management

All patients who undergo neurosurgical procedures, even a well-performed operation, are in a potentially unstable cardiopulmonary state and at risk for secondary neuronal injury. Also, they can have fresh surgical incisions, delicate vascular anastomoses, friable resection beds, brittle patency of newly open vessels, and/or tenuous hemostasis. All of these factors leave these patients especially vulnerable to postoperative complications.

The need for postoperative hemodynamic support, significant intraoperative blood loss, and substantial intraoperative fluid requirements are criteria for decision to admit a given patient to the neurocritical care unit (NCCU). Increased blood pressure may be associated with pain, emergence from anesthesia, and the underlying disease which can lead to postoperative hemorrhage and exacerbate edema. Acute hypertension is associated with increased mortality in the NCCU. The precise level that represents a risk varies and depends on patient, disease, procedure, lesion size, traumatic disruption of vessels, and premorbid blood pressure. Strategies to limit commons irritants or triggers of hypertension include prevention and timely treatment of bladder distention, pain, and shivering. Fluid loss from the intravascular space (bleeding) and extravascular space (e.g., vomiting, diarrhea, and sweating) can contribute to hypovolemia. This may exacerbate cerebral ischemia. Circulation support to influence CBF is achieved best by increasing blood pressure, as cardiac output appears not to vary with CBF. With active baroreflexes, bradycardia may occur. Careful anticholinergic administration is therefore necessary to augment the sympathomimetic hypertensive action. Patients with low myocardial reserve may require an inotrope. Osmolality is the primary determinant of water movement across the intact blood–brain barrier (BBB). Reduced serum osmolality can increase cerebral edema and ICP.

16.2 Hemodynamic Assessment

New technologies have become helpful in hemodynamic assessment, volume management, and the institution of more specific goal-directed therapy in ICU patients. Arterial pulse contour wave analysis requires invasive arterial lines to obtain data. There are several manufacturers who make analogous equipment taking advantage of arterial pulse pressure (PP) waveform analysis to provide continuous assessments of volume status and cardiac hemodynamics. There is more than one methodological strategy employed to derive such parameters including calibrated PP analysis relying on thermodilution for calibration (PiCCO) and statistical analysis via computer-derived algorithms (Vigileo). One of the more common variables assessed is stroke volume variation (SVV) which is used to optimize volume status in ICU patients such as those with subarachnoid hemorrhage. Noninvasive technologies also exist that assist in fluid management and hemodynamic monitoring. These include impedance cardiography (ICG) and a device that relies on bioreactivity and detecting phase shifts that occur when an alternating current is passed through the thorax (Cheetah NICOM). Lastly, critical care ultrasound techniques such as inferior vena cava (IVC) compressibility are also used to assess volume status. All of these technologies are crucial to the increasingly adopted goal-directed therapy with more restrictive use of crystalloid administration (unless contraindicated) in the perioperative period.

The routine uses of pulmonary artery catheterization in high-risk cardiac and noncardiac patients in not indicated, as evidenced by randomized clinical trials [6]. Nevertheless, some indications still remain: cardiogenic shock, differential diagnosis of pulmonary arterial hypertension, diagnosis and treatment of uncommon causes and complications of heart failure, severe chronic heart failure requiring inotropic, vasopressor or vasodilator therapies and before heart, lung and liver transplantation.

Central venous pressure (CVP) values provide important information about the hemodynamic status of the patient and should not be abandoned, as De Backer and Vincent reported in 2018 [12]. They argued pros and cons of CVP for fluid management, considering easy to measure, cheap and satisfactory predictive value of extreme values (CVP <6–8 mmHg and >12–15 mmHg). It represents the back pressure of all extrathoracic organs, its increase indicates an increase in preload, and an absence of change during fluid administration indicates that insufficient fluids were administered to manipulate preload. In contrast, its limitations are errors in measures, influence of mechanical ventilation, influence of abdominal pressure, and predictive value for fluid responsiveness is lower than dynamic indices. In addition, there is no predefined safety value requiring individual determination.

The state of autoregulation can be predicted through monitoring cerebrovascular pressure reactivity (PRx), measuring CPP, and its effect of changes in ICP [33].

Steiner et al. used a continuous bedside calculated index of pressure reactivity to demonstrate whether blood pressure was within the optimal autoregulatory range. In a retrospective analysis, the authors demonstrated that the head-injured patients who were managed with a mean CPP close to the optimal predicted value were more likely to have a favorable outcome. Continuous assessment of cerebral autoregulation could therefore be used to determine the best CPP for individual patients. Howells et al. compared TBI patients treated with ICP-based and CPP-orientated management protocols [20]. Despite the differences in the management of the patient groups, the authors suggested that optimal CPP management should be determined based on the assessment of cerebral autoregulation. If cerebrovascular pressure reactivity was impaired, CPP should not exceed 60 mmHg, while outcome for patients with intact pressure reactivity may be improved by maintaining CPP above 60 mmHg. Other authors have used bedside daily assessments of changes in TCD ultrasound middle cerebral artery flow velocities and ICP with manipulations in arterial blood pressure to determine optimal CPP [9].

An assessment of CA may provide an alternative means of selecting an appropriate CPP value for an individual patient rather than a blanket prescription for all patients. Indeed, it allows and facilitates rational changes in the required level of CPP over time, which are dependent on the underlying pathophysiological derangements in individual patients. However, impairments in vascular reactivity may not be uniform across the injured brain. Studies demonstrated that although PET imaging derangements in CA are diffuse and not limited to obvious regions of tissue injury, there are differences in autoregulatory capacity between the injured and non-injured sides of the brain, which may be predictive of adverse outcomes. As such, perilesional regions may benefit from a different local perfusion pressure than the rest of the injured but normal appearing brain. When decompressive craniectomy is realized to relief in ICH, usually the CA impairment is not sufficiently solved [13]. Compromised CA leads to diminished tolerance of systemic pressure variations, increasing the risk of brain swelling or hemorrhage in the presence of arterial hypertension and increasing the risk of ischemia when arterial hypotension is found, showing individualized ranges of arterial pressure tolerance for each patient. If impaired cerebral autoregulation is occurring, dynamic CA should be assessed with ICP monitoring, TCD ultrasonography, or laser Doppler, for example.

The guidelines for the management of aSAH from the AHA considered TCD reasonable to monitor the development of arterial vasospasm (Class IIa, Level B of evidence). Studies in traumatic brain injured patients had demonstrated that decompressive craniectomy results in a significant elevation of cerebral blood flow velocity (BFV) in most patients with traumatic brain swelling and transtentorial herniation syndrome. The increase in cerebral BFV may also occur in the side opposite the decompressed hemisphere. BFV increase is significantly greater in the operated hemisphere than contralaterally. Pulsatility index (PI) values decrease significantly postoperatively, mainly in the decompressed cerebral hemisphere, indicating reduction in cerebrovascular resistance. These trauma studies were the starting point for extrapolation to other severe acute brain injuries, with many subsequent studies.

16.3 Differential Diagnosis

Defining volemic status is essential to critical ill patients with hemodynamic instability. Approximately half of acute and critically ill patients have been demonstrated to be effectively resuscitated with intravenous fluid administration. Dynamic measures can be gauged to assess fluid responsiveness, such as variations in stroke volume (SVV) and pulse pressure (PPV). There are risks in obtaining these measures and limitations of interpretation, precluding them from being practical in most of patients. Point-of-care ultrasound is a noninvasive method for clinicians to evaluate the intravascular volume status and fluid responsiveness [27]. It allows to rapidly make critical decisions at bedside, with low cost, regarding appropriate treatment, as volume resuscitation versus the use of vasopressors. The collapsibility index of IVC and the internal jugular vein are related to more traditional predictors of fluid responsiveness like CVP. However, emerging studies demonstrate that large arteries, such as the common carotid artery, can predict fluid responsiveness. Ultrasound is operator dependent, but standardized parameters like corrected flow time may help to eliminate differences in image interpretation. It can also evaluate pulmonary congestion. Ultrasound is more sensitive than plain film imaging or auscultation for pulmonary edema identification.

The passive leg-raising (PLR) is performed by lifting the legs of a patient from a horizontal supine position, inducing a gravitational mobilization of intravascular volume from the lower extremities toward the heart. The maneuver requires an elevation of legs from 0° to 45° while measuring SV and CO before and after it. PLR redistributes 300–500 mL of intravascular volume to the heart, referred to as an "autotransfusion." It is quickly reversible, carries no risk of fluid overload, and can be assessed via the change in SV using point-of-care ultrasound. Prospective cohort studies have demonstrated an increase in SV over 10% induced by PLR, and was predictive of fluid responsiveness, with sensibility of 77–100% and specificity of 88% and 99%. Other study by Monnet et al. demonstrated in 2012 that variation of pulse pressure predicted fluid responsiveness with equivalent accuracy to PLR in patients with greater respiratory compliance. However, this is not applicable to patients with lower respiratory system compliance. Therefore, PLR is an easily noninvasive way to assess volume status.

The early diagnosis of complications in neurocritical patients is essential for better outcomes. One frequent possibility is infection and sepsis. The best practice statements of the 2016 Surviving Sepsis Campaign guide strategies for intensive management dealing with sepsis, frequent complication of neurocritical patients. Sepsis and septic shock are medical emergencies, requiring immediate treatment and resuscitation. The resuscitation from sepsis-induced hypoperfusion may be carried out with the infusion of at least 30 mL/kg of IV crystalloid fluid within the first 3 hours. Following initial fluid resuscitation, additional fluids should be guided by frequent reassessment of hemodynamic status, thorough clinical examination, and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as

available) as well as other noninvasive or invasive monitoring, as available. Further hemodynamic assessment (e.g., cardiac function) to determine the type of shock is necessary if the clinical examination does not lead to a clear diagnosis. Dynamic variables over static should be used to predict fluid responsiveness, when available. A minimal target mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors should be aimed. They suggested guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

The differences of brain oligemia and hyperemia, especially considering the timing from the injury, are important. Prolonged hyperemia may translate into an increased lactate concentration in brain interstitium due to anaerobic metabolism established in the early phase after injury (oligemia phase) combined with hyperglycolysis to restore ion pump homeostasis in the subsequent phase (hyperemia phase) [14].

16.4 Treatment Options

The "Lund Concept," proposed at Lund University Hospital in Sweden and published in 2006, brought interesting warnings and concepts, reporting favorable results [16]. It is an approach based on basic physiological principles to treat severe brain trauma grounded in brain volume and cerebral perfusion regulation. These main goals are to reduce or prevent ICP increase (ICP-targeted goal) and to improve perfusion and oxygenation around contusions (perfusion-targeted goal), reducing hypoxia in areas with compromised perfusion. Also, it considers the consequences of a disrupted blood–brain barrier (BBB) for development of brain edema in a rigid dura/cranium for general cerebral hemodynamics. The disrupted BBB changes the autoregulatory capacity and increases in arterial pressure influences the brain volume. The *Lund therapy* requires normal oxygenation, normovolemia maintenance with normal hematocrit and plasma protein concentrations, antagonizing vasoconstriction through reduction of catecholamine concentration in plasma and sympathetic discharge, minimizing stress and active cooling. It explained that head elevation leads to reduced blood volume by reducing hydrostatic capillary pressure when CPP is reduced. However, it should be weighted with the risk of inducing low CPP, if there is simultaneous reduction in venous return to the heart, especially in deeply sedated patients with impaired motor tone.

Therefore, they hypothesized that positive end-expiratory pressure (PEEP) can be used safely to prevent atelectasis after a head trauma. Stress can be reduced by analgesics and sedatives and they recommend association of drugs with lower doses of each and to avoid high doses of barbiturates, as they have well-known adverse effects (electrolyte, renal, pulmonary and cardiovascular complications, fever) in randomized studies (thiopental only in 2–3 mg/kg bolus +0.5–3 mg/kg/h IV and for at most 2 days). They suggested avoiding hypertension (using up metoprolol, clonidine or angiotensin II inhibitor) and fever, caution usage of crystalloids. Optimal

CPP is individual, in most cases 60–70 mmHg for adults and 40–55 mmHg for children and adolescents. Transient CPP values down to 50 mmHg for adults may be necessary in selected patients to reduce a critically raised ICP. Low CPP may be corrected by correcting latent hypovolemia, no extra head elevation and discontinuing thiopental. The authors had reported mortality of 8% and good neurological outcome of 79% in a series of 53 patients.

Fluid challenge technique should be applied where fluid administration is continued as long as hemodynamic factors continue to improve in patients with sepsis and septic shock. In surviving sepsis campaign international guidelines for management of sepsis and septic shock of 2016 they recommended crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement, using either balanced crystalloids or saline for fluid resuscitation [30]. They do not recommend using hydroxyethyl starches for intravascular volume replacement, neither gelatins when resuscitating patients with sepsis or septic shock.

There is clinical evidence that norepinephrine increases CBF and brain tissue oxygenation in patients with TBI. Lower ICP was reported with norepinephrine when compared with dopamine infusion in a cross-over trial targeting the same MAP in head-injured patients. However, norepinephrine does not appear to have a major impact on ICP in patients with TBI. Norepinephrine is considered the first-line vasopressor in neurointensive care when an increase in CPP is warranted to improve cerebral oxygenation [38]. Coles and colleagues had demonstrated, in TBI patients, the elevation of CPP from 70 to 90 mmHg using norepinephrine [7]. However, probably because of impaired cerebral autoregulation, despite CBF and CBV were increased, cerebral oxygen metabolism ($CMRO_2$) and oxygen extraction fraction (OEF) were reduced. The augmented CBF and the reduced $CMRO_2$ increased oxygen supply and reduced the OEF. Moreover, they reported that CPP elevation clinically significant reduced ischemic brain volume (IBV), in patients with large baseline IBV. Johnston et al. studied the effects of CPP augmentation with norepinephrine in patients with TBI [21]. They demonstrated significant increase in $PtiO_2$ and CBF and significant decrease in OEF using norepinephrine. The authors suggested that CPP augmentation may recruit cerebral capillaries and thereby reduce the oxygen gradients between tissue and vascular compartments.

As increases of CPP could rise ICP, Steiner and colleagues did a randomized cross-over trial in patients with TBI [34]. They performed augmentation of CPP with norepinephrine, estimating increases in CBF by TCD flowmetry, showing no significant increase ICP. Whereas Ract et al. reported lower ICP with norepinephrine compared with dopamine infusion in another cross-over study [28]. They targeted the same MAP and did not demonstrate major impact on ICP in patients with TBI. De Baker and colleagues show that norepinephrine is associated with a smaller number of adverse events compared with dopamine in the treatment of shock [10].

The use of inotropic may be necessary to improve the proper relationship between oxygen supply and consumption, if the initial optimization with fluids is not enough [29]. According to venous oxygen saturation and serum lactate levels, the use of dobutamine may be necessary for resuscitation of the septic patient. Administration

of 5 μg/kg/min dobutamine can improve, but not restore, capillary perfusion in patients with septic shock, beyond systemic hemodynamic variables [11].

Management of severe TBI patients using guidelines-based recommendations for CPP monitoring is recommended to decrease 2-week mortality (Level IIB of evidence) [5]. Maintaining SBP at ≥100 mmHg for patients 50–69 years old or at ≥110 mmHg or above for patients 15–49 or >70 years old may be considered to decrease mortality and improve outcomes (Level III of evidence). The recommended target CPP value for survival and favorable outcomes is between 60 and 70 mmHg. Whether 60 or 70 mmHg is the minimum optimal CPP threshold is unclear and may depend upon the autoregulatory status of the patient (Level IIB of evidence). Avoiding aggressive attempts to maintain CPP >70 mmHg with fluids and pressors may be considered because of the risk of adult respiratory failure (Level III of evidence). The 4th Edition of the Brain Trauma Foundation's guidelines warned caution when using mannitol, barbiturates, and propofol with regard to hemodynamics. Arterial hypotension (systolic blood pressure < 90 mmHg) should be avoided when using mannitol for raised ICP. Mannitol use should be restricted to ICP monitoring to patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes. When high-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment, hemodynamic stability should be guaranteed. Although propofol is a recommended option for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. Caution is required as high-dose propofol can produce significant morbidity (Level IIB of evidence), possibly due to reduced CBF.

Hawryluk and colleagues recently published the Seattle Consensus, suggesting the establishment of tiers of care in the management of TBI [17]. They had not recommended scheduled infusion of hyperosmolar therapy (e.g., every 4–6 hours) and mannitol continuous intravenous infusion, furosemide, and routinely raising CPP above 90 mmHg. They recommended like Tier Zero (Basic Severe TBI Care—Not ICP Dependent), among other basic treatments as fundamental to the care of patients with sTBI with an ICP monitor, regardless of the pressure level: maintain CPP initially ≥60 mmHg and Hb >7 g/dL; optimize venous return (e.g., keeping head midline, ensure cervical collars are no too tight); arterial line continuous blood pressure monitoring, elevation of the head of bed 30°–45°.

In Tier 2, to perform MAP challenge to assess CA and guide MAP and CPP goals in individual patients (Rosenthal G et al. 2011—should be carried out strictly with the physician's supervision, who can assess response and ensure safety; no other therapeutic adjustments (i.e., sedation) should be performed during the MAP challenge; initiate or titrate a vasopressor or inotrope to increase MAP by 10 mmHg for not more than 20 minutes; monitor and record key parameters—MAP, CPP, ICP, and $PbtO_2$—before, during, and after the challenge; adjust vasopressor/inotrope dose based on study findings [32]), raise CPP with fluid boluses, vasopressor, and/or inotropes to lower ICP when autoregulation is intact. They should guide only, as a first attempt at filling the gap in the current clinical literature or as useful tools for

research design subjected to analysis using comparative effectiveness research tools as well as trials.

The 2019 guidelines for the management of pediatric severe TBI recommended a minimum CPP of 40 mmHg to be considered in this setting [23]. A CPP threshold 40–50 mmHg should be considered to ensure that the minimum value of 40 mmHg is not breached. There may be age-specific thresholds with infants at the lower end and adolescents at the upper end of this range. CPP should be determined in a standard fashion with ICP zeroed to the tragus (as an indicator of the foramen of Monro and midventricular level) and MAP zeroed to the right atrium with the head of the bed elevated 30° (Fig. 16.3).

The 2018 *American Heart Association* (AHA) and *American Stroke Association* guidelines for the management of acute ischemic stroke (AIS) recommended correction of hypotension and hypovolemia to maintain systemic perfusion levels necessary to support organ function. Patients who have elevated blood pressure (BP) and are otherwise eligible for treatment with IV alteplase should have their BP carefully lowered so that their systolic BP is <185 mmHg and their diastolic BP is <110 mmHg before IV fibrinolytic therapy is initiated. In patients with AIS, early treatment of hypertension is indicated when required by comorbid conditions (e.g., concomitant acute coronary event, acute heart failure, aortic dissection, postthrombolysis sICH, or preeclampsia/eclampsia). Lowering BP initially by 15% is probably safe. However, it is important to keep in mind that excessive BP lowering can sometimes worsen cerebral ischemia. Ideal management in these situations should be individualized, but in general, initial BP reduction by 15% is a reasonable goal. In patients with BP ≥220/120 mmHg who did not receive IV alteplase or EVT and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours

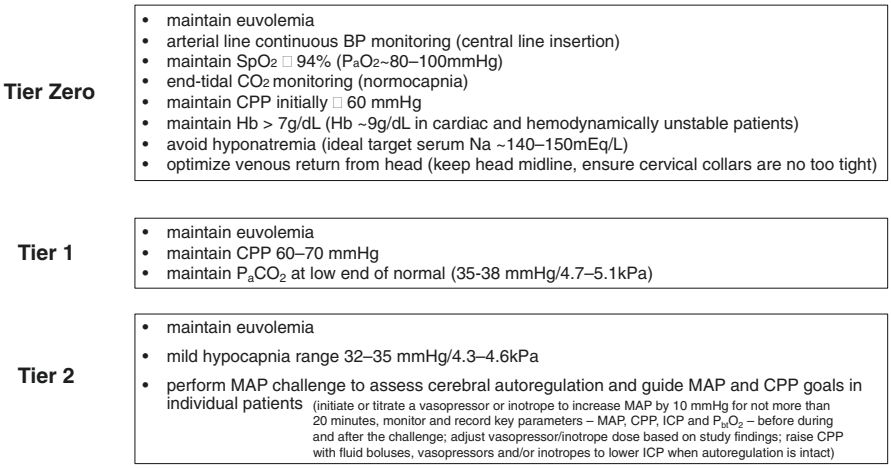

Fig. 16.3 Algorithm for hemodynamic management in acute brain injury

is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mmHg who are neurologically stable is safe and is reasonable to improve long-term BP control unless contraindicated.

The AHA guidelines for the management of spontaneous intracerebral hemorrhage (ICH) recommend that patients presenting with systolic blood pressure (SBP) between 150 and 220 mmHg, and without contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg should be done (Class I; Level of Evidence A). It can be effective for improving functional outcome (Class IIa; Level of Evidence B) [18]. For ICH patients presenting with SBP >220 mmHg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring (Class IIb; Level of Evidence C). High SBP is associated with greater hematoma expansion, neurological deterioration, and death and dependency after ICH. Compared with ischemic stroke, in which consistent U- or J-shaped associations between SBP nadir of 140 and 150 mmHg and poor outcome have been shown, only 1 study of ICH has shown a poor outcome at low SBP levels (<140 mmHg).

Observational studies with advanced neuroimaging have shown no significant ischemic penumbra in ICH, with the perihematomal rim of low attenuation seen on CT being related to extravasated plasma. A randomized clinical trial using CT perfusion in primarily small and medium ICH found no clinically significant reduction in cerebral blood flow within the perihematomal region related to early intensive BP lowering to an SBP target of <140 mmHg within several hours of ICH. In a clinical cohort of 211 patients who received a standard protocol of nicardipine-based BP lowering to reach an SBP target of <160 mmHg at a mean of 30 minutes (range, 15–45 minutes) within 3 hours of the onset of ICH, the best outcomes were seen in the group with the lowest achieved SBP (<135 mmHg). Both the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial, a 4-tier dose-escalation study of intravenous nicardipine-based BP lowering in 80 patients within 3 hours of ICH, and the pilot phase Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT1) trial in 404 mainly Chinese patients within 6 hours of ICH found rapid reduction of SBP to <140 mmHg to be safe.

The main phase INTERACT2 trial has shown no increase in death or serious adverse events from early intensive BP lowering in eligible patients with elevated SBP. Several observational studies have demonstrated that small ischemic lesions identified on diffusion-weighted MRI are common after ICH. However, the impact on outcome and relationships with BP lowering vary across studies. The largest randomized clinical trial evaluating the efficacy of intensive BP lowering is INTERACT2, a phase 3 trial undertaken in 2839 patients with SBP between 150 and 220 mmHg within 6 hours of ICH. Among 2794 participants for whom the primary outcome could be determined, 719 of 1382 participants (52.0%) receiving intensive treatment (to an SBP target of <140 mmHg within 1 hour of randomization and for a duration of 7 days, following protocols that included locally available intravenous agents) compared with 785 of 1412 participants (55.6%) receiving

standard treatment (SBP <180 mmHg) had a primary outcome of death or major disability (modified Rankin scale score ≥3; OR, 0.87; 95% CI, 0.75–1.01; $P = 0.06$).

Analysis of secondary end points indicated significantly better functional recovery on an ordinal analysis of scores on the modified Rankin scale (OR for greater disability, 0.87; 95% CI, 0.77–1.00; $P = 0.04$) and better physical and mental health-related quality of life on the EQ-5D scale (mean health utility scores, intensive group 0.60 ± 0.39 vs standard group 0.55 ± 0.40; $P = 0.002$) from intensive treatment. Although INTERACT2 demonstrated consistency of the treatment effect across several prespecified patient subgroups, there was no clear relationship between outcome and the time from onset of ICH to commencing treatment and no significant effect of intensive BP-lowering treatment on hematoma growth. Moreover, only one-third of patients achieved the target SBP level within 1 hour (half achieved the target by 6 hours), and most (75%) presented with mild to moderate size (<20 mL) hematomas.

Overall, current evidence indicates that early intensive BP lowering is safe and feasible and that surviving patients show modestly better functional recovery, with a favorable trend seen toward a reduction in the conventional clinical end point of death and major disability. It is, therefore, reasonable for ICH patients similar to those enrolled in INTERACT2 to receive early treatment targeted to an SBP level <140 mmHg to improve their chances of achieving better functional recovery should they survive the condition. There are fewer data available pertaining to the safety and effectiveness of such treatment in patients with very high BP (sustained SBP > 220 mmHg) on presentation, large and more severe ICH, and those requiring surgical decompression. Because the speed and degree of BP reduction will vary according to the agent and method of delivery (bolus vs infusion) and clinical features, the choice of agent should consider the practicability, pharmacological profile, potential side effects, and cost. For prevention of recurrent ICH is recommended continued BP controlling in all ICH patients (Class I; Level of Evidence A). Measures to control chronicle BP should begin immediately after ICH onset (Class I; Level of Evidence A) and long-term goal of BP <130 mmHg systolic and 80 mmHg diastolic is reasonable (Class IIa; Level of Evidence B).

The guidelines for the management of aSAH from the AHA recommended oral nimodipine should be administered to all patients with aSAH [8]. Although this agent has not been shown to improve cerebral vasospasm, it does improve neurological outcomes. The value of other calcium antagonists, whether administered orally or intravenously, remains uncertain. Hypertension should be treated, and such treatment may reduce the risk of aSAH. Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (level B of evidence). The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to <160 mmHg is reasonable (Class IIa, Level C), because possibly systolic blood pressure >160 mmHg is associated to aneurysm rebleeding. A variety of titratable medications are available. Nicardipine may give

smoother blood pressure control than labetalol and sodium nitroprusside, although data showing different clinical outcomes are lacking. Although lowering cerebral perfusion pressure may lead to cerebral ischemia, a cohort study of neurologically critically ill patients did not find an association between use of nicardipine and reduced brain oxygen tension. Clevidipine, a very short-acting calcium channel blocker, is another option for acute control of hypertension, but data for aSAH are lacking in that time.

Sodium nitroprusside is relatively contraindicated in neurocritical care patients because of increase of ICP. Maintenance of euvolemia and normal circulating blood volume is recommended to prevent delayed cerebral ischemia (DCI). Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended (Class III, Level B). Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it. For patients with symptomatic cerebral vasospasm who are not rapidly responding to hypertensive therapy, cerebral angioplasty, and/or selective intra-arterial vasodilator therapy is indicated (Class IIa, Level B). The use of packed red blood cell transfusion to treat anemia might be reasonable in patients with aSAH who are at risk of cerebral ischemia, but the optimal hemoglobin goal is still to be determined (Class IIb, Level B). For anesthetic management during surgical or endovascular treatment, minimization of the degree and duration of intraoperative hypotension is suggested (Class IIa; Level of Evidence B). The general goals of anesthetic management involve hemodynamic control to minimize the risk of aneurysm re-rupture and strategies to protect the brain against ischemic injury, as well as during the preoperative time. There are insufficient data on pharmacological strategies and induced hypertension during temporary vessel occlusion to make specific recommendations, but there are instances when their use may be considered reasonable (Class IIb; Level of Evidence C).

The management of aSAH-induced vasospasm is complex. Many significant advances in the understanding of aSAH-induced vasospasm and DCI have been made since publication of the previous version of that guidelines, which focused on prevention with oral nimodipine and maintenance of euvolemia, as well as treatment with triple-H therapy (hemodynamic augmentation therapy) and/or endovascular therapy with vasodilators and angioplasty balloons. First, the case for nimodipine is even stronger, with a comprehensive meta-analysis confirming improved neurological outcomes by preventing processes other than large-vessel narrowing. Although there have been sparse important data on the lack of benefit for prophylactic hypervolemia compared with maintenance of euvolemia, data show that both prophylactic angioplasty of the basal cerebral arteries and antiplatelet prophylaxis are ineffective in reducing morbidity. Robust experimental data indicated a critical role for endothelial dysfunction, particularly at the microcirculatory level.

Several clinical trials have investigated the utility of statins, endothelin-1 antagonists, and magnesium sulfate, but randomized studies and meta-analysis reported no evidence for clinical benefit of them for decreasing the incidence of vasospasm, DCI, or all-cause mortality after aneurysmal SAH. When DCI is diagnosed, the initial treatment is the induction of hemodynamic augmentation to improve cerebral perfusion. Randomized trials of this intervention are missing, but the rapid

improvement of many patients with this therapy and their worsening when it is stopped prematurely are convincing proof of efficacy. The exact mechanism of benefit is unclear. In some patients, increased mean arterial pressures may increase cerebral blood flow in the setting of autoregulatory dysfunction. In others, there may be some direct transluminal pressure effect that leads to arterial dilation. Accumulating literature has shifted the focus from this triple-H therapy to the maintenance of euvolemia and induced hypertension. Endovascular intervention is often used in patients who do not improve with hemodynamic augmentation and those with sudden focal neurological deficits and focal lesions on angiography referable to their symptoms. Interventions generally consist of balloon angioplasty for accessible lesions and vasodilator infusion for more distal vessels.

Both hypernatremia and hyponatremia are frequently observed in the acute phase after aSAH: the reported incidence of hyponatremia ranges from 10% to 30% [31]. Hyponatremia can develop from different mechanisms after aSAH. The syndrome cerebral salt wasting is produced by excessive secretion of natriuretic peptides and causes hyponatremia from excessive natriuresis, which may also provoke volume contraction. The diagnosis of cerebral salt wasting is more common in patients with poor clinical grade, ruptured anterior communicating artery aneurysms, and hydrocephalus, and it may be an independent risk factor for poor outcome. Uncontrolled studies using crystalloid or colloid agents suggest that aggressive volume resuscitation can ameliorate the effect of cerebral salt wasting on the risk of cerebral ischemia after aSAH. One retrospective study has suggested that 3% saline solution is effective in correcting hyponatremia in this setting. In addition, use of hypertonic saline solution appears to increase regional cerebral blood flow, brain tissue oxygen, and pH in patients with high-grade aSAH. Two randomized, controlled trials have been performed to evaluate fludrocortisones to correct hyponatremia and fluid balance. One trial found that it helped to correct the negative sodium balance, and the other reported a reduced need for fluids and improved sodium levels using this mineralocorticoid. A similar randomized, placebo-controlled trial showed reduced natriuresis and a lower rate of hyponatremia in aSAH patients treated with hydrocortisone. The value of albumin as an efficient volume expander during the vasospasm phase in aSAH has been suggested in uncontrolled studies, but there is no clear evidence of its superiority over crystalloids in patients with aSAH.

Studies have shown benefits of using milrinone to improve outcomes in aSAH patients [24]. Naidech and colleagues showed in 2005 that milrinone may be more effective in patients with severely depressed systolic function but who have at least normal vascular resistance and blood pressure and whom raising cardiac output is the primary goal. Dobutamine may be superior when vascular resistance or blood pressure is low. However, as most patients with aSAH do not have significant myocardial dysfunction, milrinone has shown good results in preventing delayed cerebral ischemia (DCI) [26]. A cohort study with 322 patients with aSAH published in 2020 analyzed predictors of refractory vasospasm/DCI despite treatment with IV milrinone, and the outcome of rescue therapy with intraarterial milrinone and/or mechanical angioplasty. Abulhasan et al. concluded that aggressive use of milrinone was safe and effective and is a promising therapy for the treatment of vasospasm/DVI after aSAH [1].

The 2016 Surviving Sepsis Campaign Guidelines recommended norepinephrine as the first-choice vasopressor and adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising mean arterial pressure to target (65 mmHg) or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage [30]. They also suggested using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents. If initiated, dosing should be titrated to an end point reflecting perfusion, and the agent reduced or discontinued in the face of worsening hypotension or arrhythmias. They recommended that all patients requiring vasopressors should have an arterial catheter placed as soon as practical if available resources.

With regard to neurosurgery postoperative care, it is important to resuscitate, stabilize, prevent/minimize secondary neuronal damage, and to optimize functional central nervous system recovery [40]. The basic goals of postoperative neurosurgical care are: provide smooth emergence from anesthesia; optimize postoperative hemodynamic, volume, and electrolyte status; optimize airway and respiratory status; treat coagulopathic states and hemostatic disorders; optimize management of postoperative complications; have reliable and appropriate systemic and neuromonitoring tools; and use subtle and reproducible neurological examination methods. Sympathetic stimulation is responsible for blood pressure increase, so beta-blocker infusions can be used. Esmolol and labetalol are effective agents since they have no significant effect on ICP. Nicardipine is a calcium-channel blocker that is used frequently with good success. Nitroglycerin and sodium nitroprusside are cerebral vasodilators and these agents may increase cerebral blood volume.

The specific agent used will depend on several factors including the perceived integrity of autoregulation and management strategy being employed for a given patient (i.e., Lund vs Rosner theories regarding the relationship between ICP and MAP). In patients with severe postoperative hypertension, the elevated blood pressure also should be considered a sign of intracranial pathology. This is particularly important after posterior fossa surgery. It is important to carefully consider the patient's home medication regimen and be aware of complications from that regimen being altered in the perioperative period (e.g., rebound phenomena from beta blocker withdrawal).

The goals of fluid management after neurosurgery are to maintain intravascular volume, preserve CPP, and minimize cerebral edema. In neurosurgical patients, and often in the postoperative period, intravascular volume is depleted (e.g., diuretic use, osmotherapy, or long spinal surgeries where large volume losses may be encountered). Systemic hypotension (MAP <70 mmHg) and negative fluid balance (<~500 mL) independently aggravate outcome in TBI patients. Basic fluid and electrolyte requirements must be considered in the postoperative period. In clinical practice, fluid management requires circulating blood volume assessment. A patient generally is asymptomatic until the circulating volume has decreased by at least 10%. A persistently low urine output (<0.5 mL/kg/hour) may indicate inadequate fluid replacement and thirst often is the first sign of reduced intravascular volume even though other vital signs are in the normal range. However, when diuretics or mannitol are given, urinary output can be misleading. Thirst is not present if the patient is drowsy or sedated (Table 16.3).

Table 16.3 Drugs used for acute treatment of hypertension

Drugs	Mode of administration and peculiarities	Class of action
Labetalol	5–10 mg i.v. bolus q 10–15 min, infusion begin at 5 mg/h and titrate up	β-adrenergic blockade (both selective α-1 and nonselective β-adrenergic receptor-blocking actions)
Nicardipine	2.5 mg/h and titrate up by 0.5 mg/h increments (central line for prolonged usage suggestion)	L-type calcium channels selective blocker of vascular smooth muscle
Esmolol	1 mg/kg i.v. bolus, then 150–300 μg/kg/min i.v. infusion (maintenance dose titrated to heart rate or goal blood pressure)	β-adrenergic blockade
Hydralazine	5–10 mg i.v. q 10 min (maximum of 50 mg, causes reflex tachycardia, avoid in patients with coronary artery disease)	Direct vascular dilator
Enalaprilat	0.625–1.25 i.v. q 6 h, maximum 5.0 i.v. q 6 h	ACE inhibitor
Nitroprusside	2 μg/kg/min i.v. infusion and titrate – increase ICP and may suddenly reduce CPP	Direct vascular dilator

ACE angiotensin converting enzyme, *i.v.* intravenous

16.5 Complications

The rational use of fluids should seek euvolemia and evaluation of fluid responsiveness. Overuse of crystalloids can cause respiratory complications, such as acute respiratory distress syndrome, as Hirsch had described since 1987 [19]. Furthermore, hypervolemia may cause abdominal compartment syndrome, organ dysfunction, and increased mortality in critically ill patients [4].

Treatment should aim to avoid secondary brain injury and interruption of the inflammatory cascade, treating early as possible neurosurgical lesions [25]. Avoid hypo and hypertension, aiming optimal CPP and oxygenation. The goal is to preserve neurological function, delivering neurocritical patients with better outcomes to society.

16.6 Pearls/Tip

Highlights

- Individualize treatment through multimodal monitoring.
- Measure cerebral perfusion pressure and intracranial pressure.
- Evaluate cerebral autoregulation through transcranial Doppler.
- Assess volume status and cardiac output.
- Maintain euvolemia and normotension, seek physiological parameters.

16.7 Conclusion

Using multimodal monitoring, individualizing neurointensive care to avoid secondary injury and neurological deficit, it is possible to reduce morbidity and mortality in neurocritical patients. It is important that the management of these patients is done by trained teams ideally led by neurointensivists.

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Chapter 17
Blood Transfusion Strategies in Neurocritical Care

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17.1 Historic

Anemia is a common condition in critically ill patients [1]. Two-thirds of the recently admitted patients in the intensive care unit (ICU) have hemoglobin levels lower than 12 g/dL on ICU admission, and 29% had hemoglobin levels lower than 10 g/dL. Overall, 37% of these patients receive at least one red blood cell transfusion during ICU stay with a median of five units of red blood cell packs per patient transfused. Harmful effects of anemia include an increased risk of cardiac morbidity [2] and mortality [2, 3], as well as a generalized decrease in oxygen transport capacity [4]. In patients with traumatic brain injury (TBI), 46% of patients are anemic at some point during their first week of hospital stay, and, among those, 76% receive a blood transfusion [5]. However, the indiscriminate use of blood includes health risks and has significant administrative, logistical, and economic implications. Allogeneic blood transfusion is associated with an increased risk of transfusion reactions, infection, and immunosuppression [1–8]. Besides, blood transfusion does not consistently improve tissue oxygenation [8].

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The pathophysiology of anemia in critical illness is multifactorial and depends on several mechanisms such as systemic inflammatory response syndrome (SIRS), hemodilution, blood loss due to diagnostic phlebotomy or from overt or occult bleeding, impaired erythropoietin metabolism, reduction of red blood cell half-life or hemolysis, nutritional deficiencies, and impaired iron metabolism [9].

The TRICC trial is a hallmark work in critical care studies because it redefined the restrictive strategy as more appropriate and safer for stable critically ill patients. In this study, in the restrictive strategy group, the hospital mortality (22.2% vs. 28.1%, $P = 0.05$) and overall mortality in young people who are less than 55 years old (5.7% vs. 13.0%, $P = 0.02$) and in less sick patients, with an APACHE II score lower than 20 points (8.7% vs.16.1% $P = 0.03$), were significantly lower, but not in those with heart disease. However, the CONSORT diagram showed many exclusions, some of an unusual nature, attracting some criticism if the trial could be genuinely applicable to all those patients admitted to the ICU (838 included in 6451 examined). In the subgroup analysis, no significant differences were observed in 30-day mortality with a restrictive strategy in patients with heart disease (20.5% vs. 22.9%; $P = 0.69$), severe infections and septic shock (22.8% vs. 29.7%; $P = 0.36$), or trauma (10.0% vs. 8.8%; $P = 0.81$). This left questions about the role of the restrictive transfusion strategy unanswered for these patient subgroups.

Anemia is associated with worse outcomes and deleterious consequences on brain function and may impair cerebral oxygenation in brain-injured patients. Moreover, a blood transfusion may increase cerebral oxygen delivery and potentially reduce the risk of tissue hypoxia, but remains a matter of debate [10], although blood transfusion and anemia seem associated with worse outcomes in neurocritical patients [5].

17.2 Pathophysiology of Anemia in the Brain

The oxygen delivery (DO2) to the brain is directly proportional to the cerebral blood flow (CBF) and arterial oxygen content (CaO2), which is highly dependent on hemoglobin (Hb) levels. Therefore, a reduction in hemoglobin levels may lead to cerebral DO2 reduction and potential cerebral hypoxia. There is evidence to suggest that anemia may be injurious to the brain. Various experimental, physiological, and observational data pointed to an increase in partial oxygen pressure in brain tissue (PbtO2) in anemic neurotraumatic patients who received red blood cell transfusion [11].

Anemia during cardiopulmonary bypass has been associated with worsened neurologic status [12]. In this setting, cerebral compensatory mechanisms are activated in others to keep a constant DO2 and avoid cerebral hypoxia.

These mechanisms include activation of aortic and carotid chemoreceptors and hence of the sympathetic tone, which leads to an increase in heart rate and left ventricular stroke volume, resulting in enhanced cardiac output and cerebral blood flow (CBF). Oxygen extraction at tissue level is increased in an attempt of keeping a

constant DO2 [13]. Furthermore, anemia is associated with lower blood viscosity, resulting in lower resistance to blood flow due to reduced endothelial shear stress, which increases venous return and, hence, higher cardiac output and CBF [14]. Moreover, the reduction in DO2 enhances the production of nitric oxide by perivascular neurons and endothelial cells, resulting in cerebral vasodilation and consequently increase in CBF [15].

These reconciling mechanisms to keep a constant DO2 all occur in healthy individuals until a critical hemoglobin threshold, below that cerebral hypoxia, develops. In healthy volunteers submitted to progressive isovolemic anemia, acute reduction of hemoglobin concentration to 7 g/dL does not produce detectable changes in human short- and long-term memory, cognitive function, or fatigue, probably due to activation of compensatory mechanisms. Rather, reduction of hemoglobin level to 6 and 5 g/dl produces a subtle increase in reaction time and impaired immediate and delayed memory. These symptoms could then be reversed by autologous red blood cell transfusion [16]. However, transfusion in critically ill patients has been avoided due to possible infectious risks, complications, mortality, and the risk of ischemia and vasoconstriction mediated by altered nitric oxide metabolism.

In patients undergoing chronic hemodialysis, Pickett et al. [17] showed that normalizing the hematocrit (40–45%) with the use of additional human recombinant erythropoietin results in better neurocognitive function. These findings show that an additional correction of anemia to normal Hct levels can result in continuous improvement of neurocognitive function, improving the ability to maintain attention on easier tasks and improving the ability to recognize, discriminate, and retain stimuli in memory for more tasks. This suggests that a progressive reduction in hemoglobin levels can be compensated by an increase in CBF due to cerebral vasodilation to a critical level of hemoglobin when cerebral DO2 will be progressively reduced, as vasodilation no longer occurs and maximum CBF values are obtained. This critical hemoglobin level appears to be around 5–6 g/dL in healthy individuals. However, these data on healthy volunteers may not directly proportionally translate to brain-injured patients.

17.3 Effects of Anemia on the Injured Brain

Anemia is a common clinical condition in patients suffering from brain injury. Low hemoglobin levels may increase the risk of poor brain oxygen delivery and secondary ischemic injury in brain-injured patients. In these patients, the compensatory mechanisms might be impaired or already been used to keep adequate brain perfusion deflagrated by the brain injury itself and might be limited to compensate for further brain insults such as anemia; i.e., the capability of brain vasculature to vasodilate in response to different stimuli (including changes in mean arterial pressure, arterial carbon dioxide tension (PaCO2), or reduced DO2) is significantly circumscribed when compared with healthy subjects [18]. Besides, brain-injured patients may develop hemodynamic instability or acute heart failure, which would

significantly impair the compensatory increase in cardiac output to provide adequate cerebral oxygenation during anemia. Brain lesions observed after TBI or a stroke may be highly heterogeneous with several presentations, and some territories defined as “penumbra” zones (e.g., moderately ischemic tissue lying between tissue that is normally perfused and an infarcted area) exist, where oxygen supply may become insufficient to meet the required oxygen demand in the case of anemia. Thus, in the injured brain, the compensatory mechanisms are compromised at higher critical hemoglobin levels as compared with healthy volunteers [19].

17.4 Traumatic Brain Injury

Anemia and red blood cell transfusion are associated with worse outcomes in patients with TBI [20, 21]. However, these data come from observational studies that are deeply susceptible to confusion bias, even after statistical analysis of the data, and are particularly influenced by the severity of the patients. Patients with more severe TBI are anemic, and patients with more severe anemia receive more blood transfusions. Thus, patients with TBI who received blood transfusions would always be associated with worse outcomes in this scenario.

Anemia was defined according to different cutoff values, limiting the comparison between different cohorts of patients. Also, a single measure of Hb might be considered inaccurate in the definition of anemia, while exposure of an injured brain to prolonged periods of low Hb levels may be more relevant. Griesdale et al. [22] observed that an Hb time curve above 9 g/dL was associated with better neurological outcomes regardless of red blood cell transfusion administration. The primary outcome, in this case, was mortality and the relationship to the degree of anemia, while other studies have focused on long-term neurological recovery [23].

Oddo et al., in a retrospective analysis of a prospective cohort of patients with severe TBI whose PbtO2 was monitored, showed that Hb levels not exceeding 9 g/dL were associated with PbtO2 impairment. Anemia with simultaneous impaired PbtO2, but not just anemia, was a risk factor for an unfavorable outcome, regardless of the severity of the injury (odds ratio 6.24 (95% CI 1.61; 24.22), $p = 0.008$), as well as the age, GCS, Marshall computer tomography (CT) score, and APACHE II score [24].

17.5 Subarachnoid Hemorrhage

In several studies, including patients suffering from subarachnoid hemorrhage, anemia is associated with an increased risk of cerebral metabolic distress and hypoxia of brain tissue, predicting a poor outcome. Lower Hb levels are associated with worse outcomes, regardless of the severity of subarachnoid hemorrhage (SAH) or the development of vasospasm. These findings may imply that a lower Hb

concentration is largely a marker for a greater degree of systemic disease, rather than necessarily causing direct damage. Nevertheless, the combination is somewhat stronger between patients with more severe SAH. Thus, if there is a benefit in maintaining higher levels of Hb with transfusions or erythropoietin, it may be more pronounced among these patients [25].

In a retrospective study of 580 patients with SAH, anemia was an independent risk factor for mortality and neurological disability in 3 months, even after correction for confounding factors (OR 1.8, 95% CI 1.1–2, 9, $p = 0.02$) [26]. Moreover, in a large cohort of patients with SAH ($n = 611$), higher levels of Hb were found in patients with good neurological recovery compared to those with poor neurological recovery (11.7 ± 1.5 versus 10.9 ± 1.2 g / dl, $p < 0.001$) [27]. Besides, the highest Hb values during ICU stay were independent predictors of good neurological recovery at 3 months.

17.6 Other Forms of Brain Injury

Anemia on admission (identified as a hematocrit value of less than 30%) was found to be among the most significant predictors of poor short- and long-term outcomes in patients with acute ischemic stroke and was associated with poor neurological outcomes in patients with less severe stroke, defined as a score on the National Institutes of Health Stroke Scale lower than 10 [28–30]. In young patients who suffered an acute stroke due to dissection of the cervical artery ($n = 1206$), anemia (defined as Hb levels lower than 12 g/dl) was found in 7% of them on admission and was associated with the injury severity and with worse neurological outcomes [31].

Additionally, anemia can worsen patients' functional status, even when it occurs in the subacute phase of stroke [32]. Lower Hb levels after admission on ICU could predict the increase of the infarction area in stroke patients treated with intravenous thrombolysis [32]. On the other hand, Furlan et al. in 2015 in a retrospective study showed that Hb concentrations above normal limits on hospital admission were associated with poorer functional capacity at discharge and higher mortality within 30 days, even after adjusting for the main confounding factors after an ischemic stroke [33].

In another retrospective study, anemia on admission was identified in 19% of patients with nontraumatic intracranial hemorrhage (ICH) and was considered a predictor of long-term mortality [34]. Besides, lower levels of Hb (<12 g/dL) were found in 23% of 2406 patients with ICH during hospital stay, including 4% with Hb <10 g/dL [26]. In this context, patients with anemia were more likely to have severe neurological deficits on admission, especially when ICH was not associated with the use of anticoagulants. Hb levels below 10 g/dL were also associated with poorer results and increased mortality at 1 year. These results can also be seen in other similar studies [35, 36]. Interestingly, anemia was also a predictor of higher volumes of hematoma in these patients with acute intracerebral hemorrhage [37].

In the group of patients suffering from a brain injury after anoxic hypoxemia, Ameloot et al. [38] found a strong linear relationship between Hb and cerebral oxygen saturation (StO2), assessed by noninvasive near-infrared spectroscopy. Furthermore, Hb levels below 10 g/dL generally result in low StO2 values, while Hb values above 12.3 g/dL have been associated with better results, especially in patients with StO2 values < 62%.

17.7 Transfusion

Various experimental, physiological, and observational data point to an increase in partial oxygen pressure in brain tissue (PbtO2) in anemic neurocritical patients who received red blood cell transfusion.

In Kurtz et al., a prospective observational study, which investigates the effect of blood transfusion on cerebral oxygenation and metabolism in patients with SAH, red blood transfusion was administered on post-bleed day 8. The average Hb concentration levels at baseline were 8.1 g/dL and increased by 2.2 g/dL after transfusion. PbtO2 increased, however, lactate-pyruvate ratio (LPR) did not change during the 12 hours of monitoring, and no relationship between change in LPR and change in Hb was found. These results suggest that blood transfusion resulted in PbtO2 improvement without a clear effect on cerebral metabolism in patients with SAH [39].

Of the 35 consecutive volume-resuscitated patients with subarachnoid hemorrhage or traumatic brain injury requiring PbtO2 monitoring and receiving red blood cell transfusion 26 (74%) of them were observed to have an increase in PbtO2. This PbtO2 increase was associated with a significant mean increase in hemoglobin and hematocrit after red blood cell transfusion (1.4 ± 1.1 g/dL and 4.2% ± 3.3%, respectively; both $p < 0.001$). Cerebral perfusion pressure, SaO2, and FIO2 were similar before and after red blood cell transfusion. Therefore, a red blood cell transfusion was associated with an increase in PbtO2 in most patients with subarachnoid hemorrhage or traumatic brain injury. Additionally, it seems to be independent of cerebral perfusion pressure, SaO2, and FIO2 [40].

In a randomized clinical trial evaluating blood transfusion in neurocritical care patients, patients were randomized to one of three transfusion thresholds: 8, 9, or 10 g/dL. Fifty-seven percent of patients experienced an increase in PbtO2 during the study. Multivariable generalized estimating equation analysis revealed change in hemoglobin concentration to significantly and positively associated with change in PbtO2. Improvement in PbtO2 was not directly related with baseline hemoglobin concentration or low PbtO2. Fifty-six percent of patients experienced an increase in LPR. No significant relationship between change in LPR or transfusion and change in hemoglobin could be demonstrated. The authors concluded that transfusion of packed red blood cells acutely results in improved brain tissue oxygen without appreciable effect on cerebral metabolism [11].

Therefore, red blood cell transfusion is associated with an increase in PbtO2 levels in neurocritical care patients, suggesting that PbtO2 can be used to identify patients who benefit from red blood cell transfusion. If these results translate into better patient-centered results, it remains to be determined. Based on the current evidence, the debate of red blood cell transfusion remains unsettled. Dozens of cohort studies were performed to investigate the association between transfusion and clinical outcomes, such as mortality and long-term neurological function. However, the conclusions were conflicting.

In a retrospective review of all blunt trauma patients with TBI admitted to the ICU, the role of anemia and red blood cell transfusion was investigated. During the study period, 1150 TBI were analyzed. When both anemia and red blood cell transfusion were included in the full model, red blood cell transfusion was significantly associated with higher mortality (adjusted odds ratio [AOR], 2.19 [95% CI, 1.27, 3.75]; $p = 0.0044$) and more complications (AOR, 3.67 [95% CI, 2.18, 6.17]; $p = 0.0001$), but anemia was not. However, when transfusion was not included in the full model, anemia was a significant risk factor for mortality (AOR, 1.59 (95% CI, 1.13, 2.24); $p = 0.007$) and for complications (AOR, 1.95 [95% CI, 1.42, 2.70]; $p = 0.0001$). These results suggest red blood cell transfusion is associated with significantly worse outcomes in traumatic brain-injured patients. Besides, blood transfusion is a major contributing factor to worse outcomes in TBI patients who are anemic [41].

In a retrospective cohort study assessing the association between anemia or transfusion and subsequent adverse outcomes including a total of 245 consecutive patients with aneurysmal SAH, anemia (nadir hemoglobin <10 g/dL) and the use of transfusions were both associated with the combined outcome of death, severe disability, or delayed infarction (odds ratio [OR] for anemia, 2.7; 95% confidence interval [CI], 1.5–5; $p < 0.01$; or for transfusion, 4.8; 95% CI, 2.5–9.1; $p < 0.01$). When both variables were together introduced into a logistic regression model, only the transfusion remained significantly predictive (OR, 4.3; 95% CI, 1.5–9.3; $p < 0.01$). The relationship between anemia and adverse outcomes was stronger among patients diagnosed with vasospasm, whereas for transfusion, it was stronger among patients without vasospasm. Transfusion also was associated with the development of nosocomial infections (OR, 3.2; 95% CI, 1.7–5.5; $p < 0.01$). There was no statistically significant difference in complications based on the duration of blood storage before transfusion [25]. Therefore, anemia is predictive of adverse outcomes in patients with SAH; however, red blood cell transfusion has an even stronger association with worse outcomes on these patients.

Therefore, anemia, as well as red blood cell transfusion, is associated with worse outcomes in neurocritical care patients. However, these data come from observational trials that are deeply susceptible to confusion bias, even after careful statistical analysis of the data, and are particularly influenced by the patients' severity. The most severe neurocritical patients are anemic, and the most severe anemic patients receive red blood cell transfusion. Thus, neurocritical patients receiving red blood cell transfusion would be always associated with worse outcomes in this setting. Therefore, only adequately powered randomized clinical trials could answer the question if a strategy aimed at correcting anemia by red blood cell transfusion could benefit severe neurocritical patients. However, only a few clinical trials have

compared the effects of red blood cell transfusion on the outcomes of patients with acute brain injury. All of them are small, did not include patients with anemia, or are just a subgroup analysis of larger trials.

In the TRICC trial, a subgroup analysis of the large 838 patient cohort, included the 67 critically ill patients with a closed head injury. Median hemoglobin concentrations and red blood cell units transfused per patient were expressively lower in the restrictive when compared to the liberal group. The 30-day all-cause mortality rate in the restrictive group were was 17% as compared to 13% in the liberal group (risk difference 4.1 with 95% confidence interval [CI], 13.4–21.5, $p = 0.64$). Presence of multiple organ dysfunction (12.1 ± 6.4 vs. 10.6 ± 6.3, $p = 0.35$) and changes in multiple organ dysfunction from baseline scores adjusted for death (4.5 ± 6.2 vs. 3.4 ± 6.2, $p = 0.49$) were similar between the restrictive and liberal transfusion groups, respectively. Average length of stay in ICU (10 days, interquartile range 5–21 days vs. 8 days, interquartile range 5–11 days, $p = 0.26$) and hospital (27 days, interquartile range 14–39 days vs. 30.5 days, interquartile range 17 to 47 days, $p = 0.72$) were very similar among the restrictive and liberal transfusion groups. Therefore, no significant improvements in mortality or clinica outcomes with a liberal strategy as compared to restrictive transfusion strategy in trauma victims with moderate to severe head injury were reported [10].

The trial by Robertson et al. compared the effects of erythropoietin and two different hemoglobin transfusion thresholds (7 and 10 g/dL) on neurological recovery after traumatic brain injury. They conducted a randomized clinical trial of 200 patients with a closed head injury who were inefficient to follow simple commands and were enrolled within 6 hours of injury. Compared with placebo, both erythropoietin groups were futile. Favorable outcome rates were 37/87 (42.5%) for the hemoglobin transfusion threshold of 7 g/dL and 31/94 (33.0%) for 10 g/dL (95% CI for the difference, −0.06 to 0.25, $P = 0.28$). There was a higher incidence of thromboembolic events for the transfusion threshold of 10 g/dL (22/101 [21.8%] vs. 8/99 [8.1%] for the threshold of 7 g/dL, odds ratio, 0.32 [95% CI, 0.12 to 0.79], $P = 0.009$) [42].

The TRAHT study, a randomized clinical trial comparing a restrictive transfusion strategy (hemoglobin threshold of 7 g/dL; n = 23) with a liberal transfusion strategy (hemoglobin threshold of 9 g/dL; n = 21) for ICU patients with severe traumatic brain injury (TBI), points to the superiority of the liberal transfusion strategy. Fewer red blood cell units were administered in the restrictive than in the liberal group (35 vs. 66, $p = 0.02$). Hospital mortality was higher in restrictive than in the liberal group (7/23 vs. 1/21; $p = 0.048$), and the liberal group showed a tendency to have a better neurological status at 6 months ($p = 0.06$). However, the restrictive group showed more changes in the pupil and more deviation from the midline ≥5 mm at brain CT, and more patients received blood transfusions before randomization compared to the liberal groups 9 (43%) and 15 (65%), respectively. Additionally, the TRAHT was a pilot study, with a small sample size, which may have led to unbalanced groups, and even after statistical analysis of the data, they may be influenced by the severity of the patients [43].

Although the results may be conflicting, the three randomized clinical trials (RCTs) have different populations, and important limitations should be noticed. The trials by McIntyre et al. [44] and Robertson et al. [45] found no significant difference in overall mortality, while in TRAHT a significant reduction of mortality was found (7/23 vs. 1/21, $p = 0.048$). Part of these results might be explained by a different design, inclusion criteria, and patient populations. The trial by McIntyre et al. is a sub-analysis of the TRICC trial, evaluating 67 TBI patients from the main 838 patient cohorts, randomized to a liberal (Hb > 7.0 g/dL) or conservative (Hb > 10 g/dL) transfusion strategy. The trial included stable condition and resuscitated patients in the intensive care unit (ICU) and was not designed to study TBI patients. Furthermore, in the trial by Robertson et al., anemia was not an inclusion criteria, and the patients in both groups had baseline hemoglobin concentrations higher than 9 g/dL at all reported time points (e.g., Hb 9.7 vs. 11.4 g/dL at day 9, in restrictive and liberal groups, respectively), which may have prevented adequate assessment of the effects of the restrictive transfusion strategy. The TRAHT trial, still, is a pilot randomized clinical trial, and, although the mortality and neurological functional results are noteworthy, the trial did not have adequate statistical power nor was designed to evaluate for these variables.

17.8 Treatment

17.8.1 Transfusion Strategies

An optimal transfusion strategy should be based on a critical appraisal of the available medical literature associated with careful patient evaluation. The optimal Hb level to trigger red blood cell transfusion in brain-injured patients has not yet been defined. There is no evidence enough to base targeting an Hb concentration greater than 7 g/dl or a liberal transfusion strategy in this patient population. The European guideline on management of major bleeding and coagulopathy following trauma [37] recommends targeting an Hb level of 7 g/dL to 9 g/dL. This is a broad and superficial recommendation including a very wide range, which does not take into account the severity or singularity of patient evaluation.

Several surveys, including intensivists, general surgeons, and neurosurgeons, show that transfusion practices are variable and transfusion triggers may lie between 7 g/dL and 10 g/dL depending on clinical expertise, patient diagnosis, and severity, with higher triggers in more severe patients [25, 46]. It reflects the conflicting nature of evidence and broad recommendations of the guidelines, suggesting that different transfusion triggers might be used depending on the diagnosis and severity of the patient.

In general, a restrictive transfusion strategy should be considered safe for brain-injured patients who are awake and can undergo repeated clinical examination. In these patients, red blood cell transfusion to keep Hb levels higher than 7 g/dL should be considered [47]. In the case of neurological deterioration or poor-grade patients, the

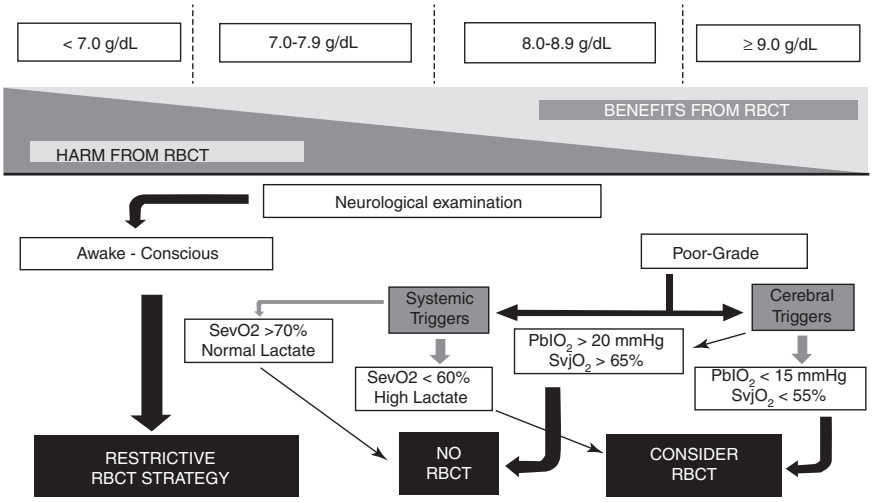

Fig. 17.1 The decision to administer transfuse red blood cells should take into account the potential benefits and harms of the intervention, according to the severity of the patient at different hemoglobin (Hb) levels. A restrictive transfusion strategy should be considered safe for brain-injured patients who are awake and can undergo repeated clinical examination. In these patients, red blood cell transfusion to keep Hb levels higher than 7 g/dL should be considered. In the case of neurological deterioration or in poor-grade patients, the decision to transfuse should then be individualized to some specific triggers suggesting a poor tolerance to anemia (e.g., ischemic heart disease, low superior vena cava oxygen saturation (ScvO2), or high lactate levels) or diffuse cerebral tissue hypoxia (jugular vein oxygen saturation (SvjO2), brain tissue oxygen pressure (PbtO2)), to guide red blood cell administration. (Adapted from Lelubre et al. [19])

decision to transfuse should then be individualized to some specific triggers suggesting a poor tolerance to anemia (e.g., ischemic heart disease) or diffuse cerebral tissue hypoxia, which may be secondary or at least highlighted by reduced Hb levels (Fig. 17.1).

Cerebral triggers may be helpful and should include the invasive or noninvasive assessment of cerebral oxygenation (e.g., venous saturation in the jugular vein (SvjO2), PbtO2, or StO2) to individualize transfusion requirements, even though they may suffer technical limitations and do not necessarily mean that, once abnormal, blood transfusion would correct them or directly translate into clinical benefits. Moreover, only patients with anemia (e.g., Hb < 9–10 g/dL) and concomitant cerebral hypoxia (e.g., PbtO2 < 15–20 mmHg, SvjO2 < 55%) should be considered as potential candidates for red blood cell transfusion. The main limitations of such an approach are that these oxygenation-monitoring devices are not available in all centers and some of them are costly and give information only for a very limited area of the brain [48]. Thus, it would be difficult to recommend the wide use of such tools in all poor-grade brain- injured patients. Importantly, red blood cell transfusion is not the only therapeutic intervention that may improve cerebral oxygenation in such patients. Clinicians should rule out other possible causes for

cerebral hypoperfusion (e.g., increased intracranial hypertension, severe hypocapnia, systemic hypotension) or hypoxia (e.g., seizures, hyperthermia, arterial hypoxemia) before considering red blood cell transfusion in the management of these patients.

In the absence of tools to evaluate cerebral oxygenation, systemic triggers such as mixed (SvO2) or superior vena cava (ScvO2) oxygen saturation, lactate, or capillary refill time might be used. However, the correlation between systemic markers of tissue perfusion and brain oxygenation may not be optimal. Moreover, patients may present with signs of low systemic oxygen delivery (e.g., low ScvO2) and normal cerebral oxygenation (e.g., PbtO2 > 20 mmHg). In this case, if the aim is to improve cerebral oxygen delivery, cerebral triggers should be preferred to target Hb levels in acute brain-injured patients, although this strategy may result in systemic hypoperfusion and non-cerebral organ dysfunction. Thus, the decision to initiate red blood cell transfusion in brain-injured patients remains a critical challenge for clinicians in the absence of specific monitoring tools.

Pearls/Tips

- Anemia is a common condition in critically ill patients, and its pathophysiology is multifactorial and depends on several mechanisms such as systemic inflammatory response syndrome (SIRS), hemodilution, blood loss due to diagnostic phlebotomy or from overt or occult bleeding, impaired erythropoietin metabolism, reduction of red blood cell half-life or hemolysis, nutritional deficiencies, and impaired iron metabolism.
- Anemia is associated with worse outcomes and may impair cerebral oxygenation in brain-injured patients. Moreover, a blood transfusion may increase cerebral oxygen delivery and potentially reduce the risk of tissue hypoxia. Nevertheless, blood transfusion and anemia are associated with worse outcomes in neurocritical patients.
- An optimal transfusion strategy should be based on a critical appraisal of the available medical literature associated with careful patient evaluation. Different transfusion triggers might be used depending on the diagnosis and severity of the patient.

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Chapter 18
Ventilatory Strategies in the Neurocritical Care

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18.1 Introduction

Patients with severe respiratory failure or imminent cardiac arrest must be submitted to immediate endotracheal intubation (EI). This procedure is also indicated when airway protection becomes necessary, such as consciousness impairment or vomiting in order to avoid bronchial aspiration.

EI presents potential complications since it could significantly alter patient hemodynamics. Therefore, it must always be carefully evaluated for each patient, weighing the possible benefits and harms. The decision to perform EI is influenced

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by specific parameters of the patient's physiology, clinical environment, and predicted clinical course. However, despite the procedure risks, it must be readily performed when adequately indicated.

In patients admitted to a neurointensive care unit (NICU) because of acute conditions such as traumatic brain injury (TBI), ischemic stroke, intracranial hemorrhage (ICH), and subarachnoid hemorrhage (SAH), EI rationale includes the evaluation of interactions between cerebral and pulmonary dynamics. One must consider the effects of mechanical ventilation (MV) on the cerebral perfusion and secondary injuries that could occur [1, 2].

The objective of invasive MV in neurocritical care is to guarantee airway patency when consciousness is impaired and protective reflexes are lost, adequate ventilation and tissue oxygenation, and control of CO2 levels in patients with intracranial hypertension. Therefore, airway and breathing management is paramount in acute cerebral injury. MV parameters seek to maintain arterial pressure of oxygen (PaO_2) above 90 mmHg and arterial pressure of carbon dioxide (PaCO2) between 35 and 40 mmHg [2]. The general indications for EI are summarized in Table 18.1, and the AHA/ASA evidences for respiratory management recommendations are demonstrated in Table 18.2**.**

Cerebral vascular resistance (CVR) reflects vascular tonus, which is sensitive to $PaCO_2$. When $PaCO_2$ is too low, there is vasoconstriction, whereas high values lead to vasodilation. Chances in carbon dioxide alter the cerebral blood flow (CBF), and an increase in 1 mmHg in the $PaCO_2$ could lead to a 2–3% elevation in CBF. Values in the range of 25 mmHg reduce CBF by 40%, and electroencephalogram shows a

Table 18.1 General indications for endotracheal intubation in NICU patients

Impaired consciousness, Glasgow Coma Scale <9
Hypoxemia despite supplementary oxygen
Physiological tracheal clearance impairment
Difficult airways
Transport safety
ICP monitoring
The necessity of drugs for seizures that depress the respiratory center

Table 18.2 The 2018 guidelines by AHA/ASA for respiratory management (recommendations)

Recommendation	Evidence level
EI and MV in patients with impaired consciousness, incapable of protecting their airways because of brainstem dysfunction or intracranial hypertension	I
Maintaining normal levels of oxygen and carbon dioxide	NA
Continuous oxygen monitoring in stroke patients in the ICU Supplementary oxygen must be offered when $SpO_2 < 94\%$	I
Supplementary oxygen is not recommended in patients who do not present hypoxemia	III
Hyperbaric oxygen is not recommended, except in cases of air embolism	III

50% reduction when $PaCO_2$ reaches 20 mmHg. When those values reach 80–100 mmHg, CBF may be increased by 100%. Prostaglandins have a regulating effect over CBF, especially E2 and prostacyclin, which increases in arterial hypotension scenarios [2].

The raised ICP is one of the most frequent complications in the NICU, which has increased associated mortality – both overall and within the NICU [2]. Moderate positive end-expiratory pressure (PEEP) levels could effectively prevent secondary airway injury, and increases in PEEP lead to mean arterial pressure (MAP) and CBF reduction [3].

18.2 The Positive End-Expiratory Pressure (PEEP) and the Effects of O_2 and CO_2

Hyperventilation in patients with TBI reduces the CBF and is related to higher oxygen consumption, therefore causing more substantial ischemic injuries [4]. However, moderate hyperventilation is capable of reducing ICP, as seen in patients with TBI, and this technique is used to treat intracranial hypertension [5, 6].

Hyperoxia in SAH is associated with a more considerable risk of late cerebral ischemia, and studies suggest that oxygen excess must be avoided in those patients [7].

PEEP and alveolar recruitment are necessary to optimize lung expansion and oxygenation [8, 9]. PEEP values up to 12 cmH_2O showed oxygenation benefits while keeping a stable MAP and ICP [10]. Nonetheless, elevated PEEP levels could increase jugular venous pressure, ICP, and intrathoracic pressure with subsequent venous return impairment. In many cases, this could have negative impacts on the patients [11]. Due to PEEP effects on cerebral hemodynamics, ICP, and cerebral perfusion pressure (CPP), there is no consensus regarding MV tuning, and this must be done carefully [10].

A comparative study among stroke patients did not show the superiority of continuous oxygen use in low doses (2–3 L/min) compared to oxygen when necessary [13]. Current guidelines for TBI management recommend lowering PaO2 considering jugular bulb saturation of partial pressure of oxygen in the brain to maintain saturation levels within normality and avoid hyperoxia [14].

When dealing with MV, one must avoid secondary lesions due to hypoxia, hypocapnia, and hypercapnia, for they may affect cerebral metabolism [14]. Furthermore, hyperoxia must also be avoided, for it impairs CBF by altering cerebral complacency, which may lead to ischemia [16].

There is no current consensus about the tidal volume and respiratory rate in these patients. However, higher tidal volumes associated with hypertension are related to more extensive pulmonary lesions and intracranial hypertension [17]. In patients under neurocritical care requiring MV, it is recommended to use low tidal volumes, around 6 mL/kg, with adequate PEEP in order to maintain pressure under 30 cmH_2O. Those measures resulted in lower mortality rates [18, 19].

A multicentric study demonstrated that PEEPs from 6 to 8 cmH_2O and tidal volume ≤ to 7 mL/kg could shorten the MV period and decrease mortality [20]. PEEP in patients with intracranial hypertension must be cautious for the ICP levels could increase further. Some authors suggest that PEEP could worsen ICP levels when $PaCO_2$ is elevated, whereas alveolar recruitment without $PaCO_2$ increases has no repercussion in ICP [21].

Experimental studies in swine demonstrated that elevated PEEP (25 cmH_2O) does not increase ICP. According to the same author, patients with acute strokes submitted to elevated PEEPs present a lowering of the MAP and CBF. Subsequent studies showed that lowering of CBF depends on changes in the MAP as a result of impaired cerebral self-regulation [22, 23].

Accurate ICP monitoring is efficient when using ideal PEEP to control MAP and maintaining adequate CPP [24]. In selected patients, prone positioning could be employed to improve oxygenation, but one must observe that this position could increase ICP and subsequently decrease CPP [12]. Among maneuvers of alveolar recruitment, prone positioning is one of the most efficient but must be employed carefully in the patients with strokes due to possible intrathoracic pressure increase, causing lower venous return and subsequent ICP increase [25]. One study exists analyzing prone positioning in the NICU setting, but its results are controversial [26]. Prone positioning should be considered in severe hypoxemic scenarios, and the patient must be under rigorous neuromonitoring for ICP evaluation.

There are other strategies to improve cerebral oxygenation. However, such strategies may also produce harmful effects on ICP. Ventilation with high frequency and low tidal volume are among them, but ICP, MAP, and $PaCO_2$ must be diligently monitored [27]. Certain severe respiratory impairments present with hypoxemia refractory to all ventilation strategies, requiring circulatory support [28].

In conclusion, patients in neurocritical care using MV must be monitored with multimodal, neurologic, ICP, MAP, and $PaCO_2$ assessments. Noninvasive multimodal monitoring is a valuable resource to individualize each patient's ventilatory parameters [29].

18.3 Weaning from Mechanical Ventilation

Weaning from MV to extubate a patient involves multiple factors such as consciousness, sedation characteristics, vomiting reflex, and risk factors for reintubation [30].

Patients in the NICU need gradual weaning of the ventilatory support, avoiding muscular fatigue and loss of alveolar stability. This process must start when the base condition that leads to MV is almost or entirely solved. Through clinical evaluation, even when patients have a ventilatory capacity that enables spontaneous ventilation, one needs to evaluate whether or not to wean under a broader perspective. Individuals with severe cerebral injuries often remain with consciousness impairment for long periods, with Glasgow Coma Scale ≤8. This impairment alone can cause an

impossibility or reduction of the capacity to protect and maintain airway patency. However, one must also observe the chronic condition that requires complementary evaluations.

Furthermore, in the presence of the endotracheal tube, it becomes hard to thoroughly assess airway patency and protection capacity after extubation. Therefore, some factors must be taken into account when deciding to extubate a patient whose airway protection capacity is doubtful:

- Indication of cuff-leak test
- Direct association between intubation time and incidence of mechanical ventilation-associated pneumonia, which determines greater morbimortality and higher healthcare costs
- Need for nasotracheal aspiration in individuals with the low or absent capability of airway protection, demanding more intensive care and technical abilities of the multidisciplinary team [2]

18.4 Spontaneous Breathing Test (SBT)

It is performed in patients under spontaneous modality keeping support pressure ≤ 8 cmH_2O. Allowing the evaluation of muscular effort and neural respiratory drive, pulmonary expansion, and oxygenation under minimal ventilatory assistance is essential to the safe weaning of ventilatory support.

18.5 Sedation Weaning Protocols

This should be initiated 24 hours after starting invasive MV, except for hemodynamic or neurological instability, envisioning easier ventilatory support weaning. This is essential to avoid MV-associated complications. As important as sedation is adequate analgesia since decompensations due to pain are associated with ventilatory weaning failure.

18.6 Cuff-Leak Test

It is used in individual cases when laryngeal edema is suspected, and extubation might fail. It is important to notice that if glottic edema is evidenced during the test, medications (i.e., corticosteroids) can be used to reduce this edema. Therefore, 24 hours after the medications, the test may be repeated [2]. Patients in the NICU who are likely to have successful extubation are young patients, with upper airway reflexes present, negative hydric balance, and presence of cough [2, 31].

18.7 Tracheostomy

Up to 45% of patients admitted to NICUs require tracheostomy, whereas in regular ICUs, this rate ranges from 10% to 15% [31]. Tracheostomy provides a drop-in airway resistance and less orolabial ulcers, improves oral and bronchial hygiene, reduces the number of lung infections and the need for sedation, provides more patient comfort, and reduces the muscular effort considerably by reducing the dead space. Those benefits ease ventilatory weaning and, therefore, lower the ICU stay.

Generally, tracheostomy is considered when the expected NICU stay is extended in patients who present dysphagia, difficult ventilatory weaning, or extubation failure due to the inability to keep a patent airway. Postponing tracheostomy in these patients might result in avoidable damage to the vocal cords, larynx, and recurrent laryngeal nerves due to positioning or local pressure of the endotracheal tube [2].

The development of an assistance plan that respects the clinical conditions presented by the patient during the weaning process has shown to be efficient for patients in the NICU, thereby producing a homogeneous and detailed process. Other systemic factors must be observed when initiating the weaning process, such as heart rate, mean arterial pressure, oxygen saturation, tidal volume, respiratory rate, and Tobin's index. Indirect manifestations of failure should also be observed, such as sweating, agitation, or impaired consciousness [2].

Individualized planning should guide the weaning process. Possible subjectivity in the clinical and physiotherapeutic evaluations, alongside the variability and unpredictability of the clinical manifestation, could delay the process. Respecting individual limits, tolerance during weaning, and not exposing the patient to a considerable period on the nebulizer are critical aspects to a successful ventilatory weaning protocol [2].

18.8 Final Considerations for Ventilatory Support Weaning in Patients Under Neurocritical Care

As important as choosing the adequate ventilation strategy, weaning from MV and sedation requires the precise evaluation of consciousness levels, respiratory pattern, blood gas analysis, outcome, and ability to maintain airway patency. Sedatives' weaning affects the extubation process directly. Furthermore, one must consider the presence of infectious and inflammatory lung conditions, such as aspiration or MV-associated pneumonia, as well as the need for noninvasive ventilatory support in the post-extubation period, making sure there are no traumatic facial and airway injuries that exclude the viability of noninvasive support [2].

Table 18.3 Summary of ventilatory strategies in NICU

Indications/situations	Parameters
Endotracheal intubation	Consciousness impairment Intracranial pressure monitoring Airway protection and swallowing difficulties Airway protection for safe transport
Supplementary oxygen	Oxygen saturation < 94% Maintaining $PaCO_2$ in physiological levels
Mechanical ventilation	Tidal volume 6–8 mL per kg Driving pressure < 15 cmH_2O Plateau pressure < 25 cmH_2O
Positive end-expiratory pressure (PEEP)	5–8 cmH_2O

18.9 Conclusion

Patients in neurocritical care have particularities that should be considered when defining the adequate ventilation strategy. The general principles are summarized in Table 18.3. However, each case should be individualized, and multimodal monitoring, including parameters such as intracranial pressure, is key to correct management.

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Chapter 19
Endotracheal Intubation, Extubation, and Tracheostomy: How, When, and Why?

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19.1 Introduction

The timing of endotracheal intubation (EI), extubation, or tracheostomy in neurocritical patients is a great challenge. Airway management and mechanical ventilation in these patients vary with baseline neurological disease [1–3]. The polio epidemic that occurred in Europe in the 1950s was one of the milestones of the association of mechanical ventilation with neurological diseases. Since then, the technological development of mechanical ventilation has been significant, especially concerning the management of patients with neurological and neurosurgical diseases [4].

It is estimated that about 200,000 patients per year require mechanical ventilation secondary to neurological injuries. Approximately 10% of stroke victims require mechanical ventilation. Mortality for this population varies from 20% to 50%, and in those who need EI on admission, mortality is even higher [5]. In parallel, the costs related to mechanical ventilation of these patients are very high, and the reduction of time-dependent artificial respiration has significant economic implications [2, 3, 6].

Approximately 20% of all patients who require mechanical ventilation suffer from neurological dysfunction [2]. Besides, there is a current trend for neurocritical patients to be managed in a more specific way than critically ill patients in general for other pathologies [7]. When we include the term "neurocritical patient," it is known that there are neurosurgical patients, represented mainly by traumatic brain injuries, aneurysmatic subarachnoid hemorrhage, hypertensive intracranial hemorrhage, and cervical spine fractures. Among the neurological diseases that have the

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most significant relationship with mechanical ventilation are Guillain–Barre syndrome (GBS) and myasthenia gravis (MG) [2].

From the anatomical point of view, the interruption of the respiratory control centers originating in the brainstem as a result of an injury to the central nervous system is one of the causes of the need for mechanical ventilation. The observed breathing patterns, such as the presence of apnea, "ataxic" breathing, and Biot's breathing, are markers of an imminent respiratory collapse. In order for changes in breathing patterns to occur, animal models demonstrate that bilateral lesions are necessary. However, in humans, unilateral pontine lesions and lateral bulbar syndrome are sufficient to compromise the rhythm and breathing pattern. Unfortunately, for the proper functioning of the respiratory system, it is not only the respiratory centers in the pons and medulla that must be intact. The effector mechanisms in the spinal cord, the respiratory muscles, and the baroreceptors and chemoreceptors in the aortic arch and carotid bodies must also be intact. Benign breathing patterns also serve as clues for possible injuries in other systems, such as Cheyne–Stokes breathing in heart failure, central hyperventilation in pulmonary embolism and sepsis, and Kussmaul breathing in situations of severe metabolic acidosis such as diabetic ketoacidosis [3, 6].

The injuries that generate ventilatory dysfunction are observed in traumatic situations, tumoral lesions, subarachnoid hemorrhage, cerebral ischemia, among others. Also, the respiratory impairment may be secondary to opioid and sedative analgesic drugs, commonly used in neurocritical care units. Pulmonary impairment itself is also seen in situations of neurogenic pulmonary edema, bronchoaspiration pneumonia, and post-traumatic pneumothorax. These are essential indications for mechanical ventilation in the neurological and neurosurgical population [2, 7].

In parallel with the knowledge of the pathophysiology of neurological diseases that require mechanical ventilation, it is important to note that ventilatory disorders also generate secondary neurological injuries. Hypercapnia and hypoxia, as a subsequent event of ventilatory dysfunction, increase the cerebral blood volume. In situations with increased intracranial pressure and less cerebral compliance, such gasometric changes further compromise the clinical neurological situation [2, 3]. In typical situations, $PaCO_2$ is the main determinant of cerebral blood flow in the range between 20 and 80 mmHg. In patients with suspected or documented neurological lesions, the increase in PCO_2 and the reduction in PO_2 must always be investigated as a possible cause of the lowering of the level of consciousness [2, 3, 6]. On the other hand, there are also situations of pathological central hyperventilation caused by impaired regulatory input in hemispheric lesions. This context can further compromise neurological damage as there is excessive cerebral vasoconstriction.

19.2 Endotracheal Intubation: When to Perform?

In neurologically ill patients, airway management must be performed quickly and effectively to prevent possible secondary neurological injuries. The main indications for EI can be divided into four broad groups, which can occur in isolation or

Table 19.1 Principal indications for endotracheal intubation

Loss of ventilatory drive
Brainstem infarct
Hemorrhagic stroke
Opioids or benzodiazepines intoxication
Reduced pulmonary compliance
Pneumonia
Pneumothorax
Pulmonary hypertension
Pulmonary thromboembolism
Atelectasia
Chronic obstructive pulmonary disease
Low Glasgow coma score
Traumatic brain injury
Ischemic or hemorrhagic stroke
Acute hydrocephalus
Metabolic disturbances
Infection
Exogenous intoxication (includes opioids and benzodiazepines)
Ventilatory fatigue
Neuromuscular junction disorders (Guillain–Barre syndrome; myasthenia gravis)
Cervical spine injury (below C4 – intercostal muscle weakness)
Cervical spine injury (above C4 – diaphragmatic and intercostal muscle weakness)

combination: loss of ventilatory drive, impaired pulmonary compliance, a low score on the Glasgow Coma Scale (compromising gas exchange), or ventilatory fatigue secondary to neuromuscular junction disease (Table 19.1).

The lowering of consciousness in comatose patients creates airway obstruction due to the fall of the tongue in the posterior pharyngeal wall. This obstruction is one of the main indications for EI in neurological patients. Although there is no study with a high level of evidence to indicate which score on the Glasgow Coma Scale justifies EI, most authors recommend scores below or equal to eight [8].

Many steps are necessary in preparation for EI. Neurological examination before sedation, identification of factors associated with difficulty in laryngoscopy, selection of induction agents, as well as fluids and vasopressors to maintain hemodynamic stability, are essential. Unlike the surgical room environment, in emergency and intensive care, patients are more unstable, and the conditions for EI are much worse [1]. It is observed that traumatic situations in which cervical injury is suspected, immobilization care must be taken before intubation [1, 3]. Obese patients should have their heads raised in a “ramping up” system so that the external auditory meatus is aligned with the sternum and there is an alignment between the mouth, pharynx, and larynx [9].

Ventilating the patient with a mask may be more harmful than difficult intubation. Sedated and paralyzed patients may evolve with cardiorespiratory arrest if they are not adequately oxygenated. The MOANS mnemonic can be used to predict difficult ventilation with a bag-and-mask system [2, 3, 6].

- *M* = mask seal (beard, unusual anatomy)
- *O* = obesity/obstruction
- *A* = age > 55y
- *N* = no teeth
- *S* = stiff lungs

While MOANS classically predict difficulty in ventilating the patient, the mnemonic LEMON help to identify patients with possible difficulty in laryngoscopy.

- *L* = look (at the face, mouth, and neck)
- *E* = evaluate the mouth opening and airway position
- *M* = Mallampati score
- *O* = obstruction
- *N* = neck mobility

It is essential to have a trained team in which each member knows their roles. A minimum of four people is ideal. The leader will guide the actions and monitor the execution of tasks by each member. It is necessary to have the hands free to make the best decisions, especially the change in technique between EI attempts and the decision to have a cricothyroidotomy if necessary. A leader who is responsible for EI can suffer a "cognitive overload" and impair his decision-making ability. The "runner" is a nursing assistant who brings the necessary medications and materials. The doctor is responsible for EI and the nurse who is in charge of handling the equipment, emergency/intubation cart, and medications. Ideally, it should know the technique and help with maneuvers, such as "chin lift" and "BURP" back, up and right position, as well as how to prepare and assist in the use of cricothyroidotomy, if necessary [1].

19.3 Endotracheal Intubation: How to Perform?

Preoxygenation often does not reach safe levels, but despite this, when performing the washout of nitrogen in the lungs, it increases the time of desaturation of oxyhemoglobin. It is estimated that the failure rate in the first attempt reaches 30% of the cases, with 25% suffering severe hypoxemia (oxygen saturation less than 80%). Recently, intensive care and anesthesia societies have developed recommendations. Among them, the main one is to maintain the patent airway without hypoxemia [1–3]. In urgent situations or in those where the functional reserve is reduced, the risks of hypotension, arrhythmia, cardiac arrest, and death are not negligible [1].

At least two advanced airway access techniques must be available. The most common is the laryngoscope with a curved blade and as an alternative an extra glottic device (e.g., laryngeal mask) or video-laryngoscopy. A percutaneous cricothyroidotomy kit should always be available. In this stage, difficult airway prediction is also performed. About 6% of patients admitted to the intensive care unit have an

Table 19.2 Macocha score calculation worksheet

Factors	Points
Factors related to patient	
Mallampati score III or IV	5
Obstructive sleep apnea syndrome	2
Reduced mobility of cervical spine	1
Limited mouth opening <3 cm	1
Factors related to pathology	
Coma	1
Sever hypoxemia (<80%)	1
Factor related to operator	
Nonanesthesiologist	1
Total	12

Definition of abbreviation: MACOCHA = Mallampati score III or IV, Apnea syndrome (obstructive), Cervical spine limitation, Opening mouth <3 cm, Coma, Hypoxia, Anesthesiologist non-trained. Coded from 0 to 12: 0 = easy; 12 = very difficult [11]

airway that is considered "difficult". When complications related to EI occur in the ICU, mortality is 60 times higher than complications from EI performed in the surgical room environment [1]. There are several possible pre-EI evaluations [10], but the Macocha Score is currently the most recommended (Table 19.2). The score ranges from 0 (easy) to 12 (very difficult). A Macocha Score >3 indicates a difficult airway, in which case the ideal is to call a second doctor to help [11]. An important recommendation is that in patients with difficult airways, the cricothyroidotomy site should be marked before the first attempt at EI, either by palpation or using ultrasound. This measure will save time if a cricothyroidotomy is necessary [1].

For positioning, the "sniff position" is recommended as the initial position, with tilting the head back (chin lift) and angulation/occipital pad in order to level the external meatus to the sternal manubrium. If tolerated, the head of the bed must be raised. Proper positioning facilitates access, improves airway patency, increases functional residual capacity, and reduces the chances of aspiration. Ideally, use a 10–15 liter per minute face mask for 3 minutes, but many critical patients can benefit from CPAP before EI. Inspiratory pressures >20 cmH2O are avoided to minimize gastric distention. Maintaining a nasal oxygen catheter in the context of eventual apnea may be helpful. If the patient is agitated, a low dose of hypnotic sedative such as ketamine can help, as long as it does not cause respiratory depression. Still, in pre-treatment (pre-intubation), an essential point in anticipation of hemodynamic instability. In general, crystalloid solution, 10–20 mL/kg is used. In patients with hypotension before EI, the use of vasoactive amines may be necessary, and the norepinephrine infusion must already be prepared for use. Ketamine and etomidate are the most suitable hypnotic agents in situations where hypotension should be avoided [6]. Gastric emptying by nasogastric tube in patients on a full stomach and the use of cricoid pressure are optional.

Table 19.3 Induction agents – Sedatives

Drug	Usual doses (mean)	Comments
Propofol	2 mg/kg	Hypotension, short duration
Etomidate	0.3 mg/kg	Adrenal suppression
Midazolam	0.3 mg/kg	Longer duration of action
Ketamine	1 mg/kg	Hallucinations, sympathomimetics
Thiopental	3 mg/kg	Extravasation necrosis

Table 19.4 Induction agents – Paralytics

Drug	Usual doses (mean)	Comments
Succinyl coline	1 mg/kg	Rapid onset and offset; hyperkalemia
Rocuronium	0.6 mg/kg	Variable pharmacokinetics
Cisatracurium	0.2 mg/kg	Safe to use in hepatic and renal failure
Vecuronium	0.1 mg/kg	Hepatic metabolism/unaffected by renal failure

Table 19.5 Induction agents – analgesics

Drug	Usual doses (mean)	Comments
Fentanyl	2–5 μg/kg	Muscle rigidity in high doses
Alfentanil	20–50 μg/kg	Muscle rigidity in high doses
Sulfentanil	0.5–5 μg/kg	Muscle rigidity in high doses
Remifentanil	1 μg/kg	Postoperative hyperalgesia
Morphine	100–200 μg/kg	Histamine release, nausea, vomiting

The use of ketamine that until recently was banned in neurocritical patients with the assumption of increasing intracranial pressure has been resurging. Due to its sedative power without hemodynamic instability, which can be associated with a low dose of fentanyl, it becomes a good option for inducing EI. The main contraindication is the coronary insufficiency.

Although ketamine and etomidate are the most indicated hypnotic agents today, the others such as midazolam and propofol are also useful. It is emphasized that it is essential to know the mechanism of action of the hypnotic, as well as the analgesic and muscle relaxant that will be used (Tables 19.3, 19.4, and 19.5).

19.4 Endotracheal Intubation in Raised Intracranial Pressure

Patients with cerebral edema are susceptible to increased intracranial pressure or decreased cerebral perfusion pressure at the time of EI. Particular attention should be given to adequate sedation and analgesia during laryngoscopy. The act of placing the laryngoscope blade in the pharynx causes sympathetic stimulation, with tachycardia, hypertension, bronchospasm, and increased intracranial pressure [9, 12].

In the moments before EI, keeping the head of the bed high is essential. If necessary, the reverse Trendelenburg position can also be useful. Blocking the pharyngeal reflex with lidocaine, analgesia with fentanyl, and blocking beta receptors with esmolol minimize the impacts of sympathetic discharge on intracranial pressure. Although the evidence for the use of these medications is not robust, there are no harmful effects at first [9, 12, 13].

Just as in situations of intracranial hypertension, in the EI of patients with low cerebral perfusion pressure (stroke patients), episodes of hypotension should be avoided. This hypotension avoidance is especially crucial in areas of ischemic penumbra, in which vasodilation is maximal in an attempt to maintain local tissue oxygenation. Any episode of a drop in cerebral perfusion pressure will primarily affect these potentially reversible sites for tissue damage. In this context, hypertension and tachycardia can be maintained, a safeguard for the ischemic penumbra area. The use of post-intubation capnography is important since unintentional hyperventilation causes cerebral arterial vasospasm, and this, in turn, worsens cerebral ischemia, whether in post-traumatic situations, after subarachnoid hemorrhage, or ischemic events [3].

19.5 Endotracheal Intubation in Cervical Spine Injuries

Cervical spine injuries occur in up to 3% of significant accident victims and are associated with increased morbidity and mortality. In the clinical suspicion of bone or ligament injury in the cervical spine, measures to protect movement have to be taken, since the cervical musculature does little to help immobilization. The patient must immediately be fitted with cervical immobilization equipment. At the time of laryngoscopy and EI, an assistant must maintain the alignment of the cervical spine. The cervical subluxation can occur in chin lift, bag-and-mask ventilation, cricoid pressure, and tracheal intubation. According to Hauswald et al., mask ventilation is the most susceptible moment for cervical dislocation than any other. In a study on cadavers with fluoroscopy, it was observed that the displacement of the cervical bodies was 2.93 mm for mask ventilation, 1.51 mm for oral intubation, 1.65 mm for guided oral intubation, and 1.20 mm for nasal intubation [14].

The improvement of intubation techniques in patients with cervical injury was carried out by the *American College of Surgeons in its Advanced Trauma Life Support* (ATLS) course. In emergencies, at the scene of the accident, EI maintaining cervical alignment is preferable to mask ventilation. Cricoid pressure should also not be routinely used due to the risk of cervical dislocation [15, 16]. Also, if flexible fiberoptic intubation is available, it is the method with the least cervical displacement [17]. If intubation can be done via the nasal route, the chances of displacement of the cervical spine are minimal, but assuming that patients with cervical injury have intracranial injuries until evidence to the contrary, the use of nasal intubation is restricted to a few situations in which the intracranial injury has already been excluded [17].

19.6 Extubation

The outcome of patients with neurological injury undergoing mechanical ventilation has improved dramatically in recent years. Ventilatory dysfunction is directly related to the severity of the intracranial injury, and high mortality is associated with it. Some observations must be made before the patient's extubation process.

For example, if there is a compromised respiratory rhythm secondary to a brainstem injury? A small percentage of patients have central lesions, whether in the Kölliker-fuse nucleus and medial parabrachial nucleus in the pons or in the ventral and dorsal respiratory group in the medulla, which justify changes in the respiratory rhythm and eventually apnea [18]. In brainstem injured patients, strict surveillance should be performed, as well as the suspension of opioid drugs that may interfere. If a lesion is confirmed in these topographies, the patient may need a tracheostomy and a diaphragmatic pacemaker.

In patients with difficulty in mobilizing secretion or in those where the patency of the upper airway is compromised (e.g., in cases of severe obstructive sleep apnea), there may be a need for tracheostomy, but this will be for a limited time.

The ventilatory weaning process should start as early as possible as soon as clinical and ventilatory stability is achieved. Although the ventilatory effort is not ideal in the acute stages of neurological injury, a certain degree of respiratory muscle effort is necessary to avoid atrophy and a longer ventilatory weaning process. It is known that prolonged mechanical ventilation is directly related to nosocomial pneumonia and other clinical complications. Spontaneous breathing trials (SBTs) in neurological patients should not be performed in cases of severe ARDS, risk of lung de-recruitment, $FiO_2 > 60\%$, PEEP >10 cm H_2O, deep sedation to control seizures, intracranial hypertension or shivering. Other situations, such as symptomatic vasospasm, atrophy of the respiratory muscles that do not tolerate ventilatory modes of support pressure, and central apnea, are also contraindications to SBTs [3].

Initially, ventilatory weaning occurs with a slow and progressive reduction in FiO_2, and the PEEP is kept below 8 cm H_2O. The respiratory rate is reduced using synchronized mandatory ventilation or pressure support triggered by each respiratory incursion. If spontaneous breathing occurs at this time, the patient can be placed in CPAP mode (continuous positive airway pressure) with small support pressure to overcome the resistance caused by the orotracheal tube. There is the possibility of placing the patient in a T-piece, where the patient breathes spontaneously for some time. If it tolerates for more than 60 minutes, with an adequate respiratory rate and a tidal volume of fewer than 105 liters, there is a good chance of success in extubation. It is observed that these parameters were applied in a general ICU, and not in an exclusively neurological ICU environment [19].

When evaluating exclusively neurological patients, we observed that up to 15% of patients are reintubated within 48 hours. Extubation failure is related to more extended hospital stays and poor functional outcomes. The leading causes of failure in extubation include weakness of the accessory respiratory musculature, reduction of protective airway reflexes, lowering of the sensorium, water overload, and

impairment of the brainstem [20, 21]. Neurological patients are the most difficult to predict whether extubation will succeed. According to Wang et al., in addition to the factors already known as pneumonia, atelectasis, prolonged mechanical ventilation, other variables such as gag reflex, GCS, following commands are related to extubation failure [22].

19.7 Tracheostomy: Should Be Earlier?

Tracheostomy is traditionally done for comfort, better secretion aspiration, oral hygiene, and weaning from mechanical ventilation when this period exceeds 14 days. Also, by reducing the dead space, less ventilatory effort is necessary. It can be done surgically or percutaneously. However, the procedure is not without complications, such as pneumothorax, bleeding, infection, and injuries to the trachea [23].

In comatose patients or in those with severe neuromuscular weakness in which it is anticipated that the ventilator time will be prolonged, an early tracheostomy can be performed, usually between the third and fifth days after EI [15, 16, 19, 24]. Bosel et al., in a pilot study, demonstrated lower mortality in patients with early tracheostomy [23]. In another retrospective study, Villwock et al. found lower mortality rates when early tracheostomies were performed [25].

Schönenberger et al. recently validated SETscore to define which patients would benefit from early tracheostomy (Table 19.6). According to these authors, a SETscore >10 predicts the need for tracheostomy in patients with stroke and ventilatory dysfunction with a sensitivity of 64% and specificity of 86% [26]. Although promising, professionals involved in performing early tracheostomy should be

Table 19.6 SET score to predict tracheostomy

Area of assessment	Situation	Points
Neurological function	Dysphagia	4
	Observed aspiration	3
	GCS on admission <10	3
Neurological lesion	Brainstem	4
	Space-occupying cerebellar	3
	Ischemic infarct >2/3MCS territory	4
	ICH volume > 25 mL	4
	Diffuse lesion	3
	Hydrocephalus	4
General organ function/procedure	Neurosurgical intervention	2
	Additional respiratory disease	3
	$PaO_2/FiO_2 < 150$	2
	Apache II > 20	4
	Lung injury score > 1	2
	Sepsis	3

aware that at the time of tracheostomy, elevations in ICP may occur and worsen CPP, and they must take the necessary measures to minimize such complications.

Alsherbini et al., adding new variables (body mass index, African-American race, intracerebral hemorrhage, and culture of positive tracheal secretion) to SETscore, improved its accuracy. The AUC improved from 0.74 to 0.89, with the new included variables [24].

The advantages of early intervention are not evident, when analyzed in a general context. Studies are controversial for specific populations. According to the meta-analysis by de Franca et al., which analyzed severe head trauma victims, early tracheostomy was related to shorter mechanical ventilation time, ICU stays, and hospital stay. There was also a lower incidence of mechanical ventilation-related pneumonia. There was no difference in mortality between groups. It is observed that this work evaluated more than 4000 studies and included only seven for analysis [27]. In this context, it is evident that more studies are needed to define whether early tracheostomy influences mortality. Despite this, its results are promising, and soon, in the personal opinion of the authors, these benefits will be demonstrated.

19.8 Conclusions

Knowledge of the indications for intubation, extubation, and tracheostomy is essential for professionals involved in the care of neurocritical patients. Despite the existing controversies and countless options, the individualized decision making for each patient is essential to improve the functional outcome and reduce mortality. The economic and social impacts of the moment and the ideal method to guarantee access to the patients' airway are immeasurable.

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Chapter 20
Infections in Neurocritical Care Units

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20.1 Introduction

The patient population in neurocritical care units is unique and poses special challenges in management. Patients frequently have some degree of dysphagia, increasing the risk of developing aspiration pneumonia and pneumonitis. Often, they have urinary retention necessitating the use of Foley catheters and increasing the risk of catheter-associated urinary tract infections (CAUTI). Underlying neurological illness that necessitated admission in the neurocritical care unit (NSICU) may increase the risk of developing healthcare-associated ventriculitis and meningitis. These infections are especially difficult to diagnose and treat, particularly when dealing with multidrug resistant organisms (MDRO). To complicate matters further, the blood-brain barrier makes it harder to achieve an adequate concentration of antimicrobials to combat complicated infections. Antimicrobials themselves pose toxicity to the central nervous system, including risk of prolonged encephalopathy and in severe cases seizures or nonconvulsive status epilepticus. Brain injury itself increases the risk of infection due to immunosuppression, formally termed as CNS injury-induced immunodepression syndrome (CIDS) [1].

This chapter will go over key points of the most commonly encountered infections in NSICU, their risk factors, diagnosis, and treatment. Where applicable, there will be a short discussion on the prevention of infections. Summary of the treatment options for commonly encountered infections in NSICU is listed out in Table 20.1.

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Table 20.1 Commonly encountered NSICU infections, their causative organisms, and treatment options

Infection source	Common infectious organisms	Empiric treatment suggestions
Ventilator-associated pneumonia	*Streptococcus pneumonia, Hemophilus influenza,* methicillin-sensitive *Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia, Enterobacter* species, *Proteus* species, and *Serratia marcescens*	Vancomycin + piperacillin/ tazobactam
		vancomycin + cefepime
		Vancomycin + meropenem
Ventriculitis	*Staphylococcus epidermis, Staphylococcus aureus, Streptococcus* sp., *Propionibacterium acnes, Pseudomonas* sp., *Acinetobacter, Escherichia coli, and Klebsiella* species	Vancomycin + cefepime
		Vancomycin + meropenem
Meningoencephalitis	Presence of foreign object: *Staphylococcus epidermidis, Staphylococcus aureus, Propionibacterium acnes*, and gram-negative bacilli	Vancomycin + cefepime +/− ampicillin
		Vancomycin + meropenem
	Community acquired: *Neisseria meningitidis, Streptococcus pneumoniae, and Listeria monocytogenes*	Vancomycin + ceftriaxone
Urinary tract infections	*Escherichia coli, Klebsiella* Sp., *Proteus* Sp., *Pseudomonas* Sp., *Enterococcus* Sp., *and Candida* species	Ceftriaxone
		Ciprofloxacin
Bacteremia	Coagulase-negative *Staphylococcus* species, *Staphylococcus aureus, Enterococcus* species, gram-negative bacilli such as *Klebsiella pneumoniae* and *Escherichia coli, and Candida* species	Vancomycin + ceftazidime +/− fluconazole

20.2 Key Definitions

The literature on infection in neurocritical care population has inconsistent data reporting and lack adherence to uniform definitions of infection. In this section, we present key definitions to assist in further understanding of specific infections.

Ventilator-associated pneumonia (VAP) is defined as pneumonia that develops after 48-hours of endotracheal intubation [2]. VAP is associated with high mortality [3]. It is of major concern in NSICU because of the increasing incidence of MDRO.

Meningitis is defined as inflammation affecting the meninges. Typically, it leads to headaches, fevers, and meningismus. Encephalitis leads to focal neurologic deficits and altered mentation [4]. Altered mentation may be secondary to direct injury to the brain or secondary to seizures, or in severe cases nonconvulsive status epilepticus. Often, meningitis and encephalitis coexist, coining the term meningoencephalitis. Ventriculitis is inflammation of the ependymal cells lining the ventricular

system. Albeit rare, meningoencephalitis and ventriculitis are commonly encountered in NSICU as postneurosurgical complication.

Urinary tract infections are fairly common in NSICU. In this chapter, the focus will mainly be on catheter-associated urinary tract infections (CAUTI). According to the National Healthcare Safety Network, a section within the Centers for Disease Control and Prevention, CAUTI is diagnosed when a patient has an indwelling catheter for at least 48-hours, a positive urine culture, and at least one of the signs and symptoms of an infection—including fevers, flank pain, and suprapubic tenderness [5]. Diagnosis based on clinical signs and symptoms is often challenging in NSICU patients due to underlying severe neurological injuries leading to decreased consciousness, altered cognition, or language deficits. Overall morbidity and mortality are low for CAUTI when compared to other healthcare-associated infections. However, given its high prevalence, the cumulative burden on the healthcare system remains high. Approximately 13,000 deaths annually are attributed to CAUTI [6]. It also increases the length of stay and overall cost burden to the system.

Catheter-related blood stream infection (CRBSI) is defined as bacteremia where the causative agent for bacterial infection was the catheter. A central line-associated bloodstream infection (CLABSI) is defined as bloodstream infection in a patient with a central line within the 48-hour period of its diagnosis. CLABSI is a term utilized by CDC for surveillance purposes [7]. Patients with CRBSI will be included under the umbrella term of CLABSI; however, the converse is not true. An example of CLABSI, which is not a CRBSI, is when a patient with endocarditis and bloodstream infection requires a central line, where the central line itself is not specifically the cause of infection. It is worth mentioning that CLABSI and CRBSI are used interchangeably in published literature.

Healthcare *Clostridium difficile* (*C. diff*) infection is divided into three categories. Healthcare facility onset is defined as a positive test in a patient who has been hospitalized for more than 72-hours prior to the onset of infection. Community-onset healthcare facility-associated cases of *C. diff* is diagnosed in patients posthospitalization but within 28 days of discharge. Lastly, a patient who presents from the community with *C. diff* is diagnosed with community-associated infection [8].

20.3 Epidemiology

The highest prevalence of healthcare-associated infections is pneumonia. Magill et al. studied 199 hospitals between 2011 and 2015, where approximately 15% of the patients were from intensive care units, and found over time an overall reduction in the surgical site (SSI) and urinary tract infections (UTI). However, there was no change in the overall prevalence of pneumonia, gastrointestinal infection (particularly *C. diff*), and blood stream infection [9]. Recent data suggest that the incidence of ventilator-associated pneumonia ranges from 9% to 27% [10, 11]. In a study from Kourbeti et al., approximately 22.5% of the postcraniotomy patients developed pneumonia [10]. Similarly, Frontera et al. demonstrated an incidence of

pneumonia at 20% in a subarachnoid hemorrhage (SAH) cohort [3]. Abulhasan et al. predominantly looked at postneurosurgical and patients with CNS malignancies, and found an incidence rate of 18.4 VAP per 1000 ventilator days [12].

Other commonly encountered infections include CAUTI with an incidence rate of 4.9 per 1000 catheter days, ventriculostomy associated infection (VAI) with an incidence rate of 4 per 1000 catheter days [12]. Overall incidence of VAI has ranged from 2% to 27% [3, 13].

Interestingly, while the overall prevalence for catheter-related bloodstream infection has remained constant between 2011 and 2015, the overall incidence rate remains fairly low at 0.6 per 1000 central line days [9, 12]. Despite its low incidence, the crude mortality associated with bacteremia is estimated to be around 27% [11]. CLABSI accounts for approximately 25,000 preventable deaths and adds approximately $21 billion to healthcare costs [14]. As such, it is important to make an early diagnosis and initiate early treatment whenever possible.

Of major importance in NSICU are surgical site infections (SSI) and *Clostridium difficile* infections. Kourbeti et al. reported an incidence of SSI at 9% in postcraniotomy patients from an academic center [10]. Overall, *Clostridium difficile* infection rates remain low, specifically in the NSICU population. One study, specifically looked at NSICU population, had identified an incidence rate of 8.3 per 10,000 ICU days [15].

It is worth noting that the incidence rates in literature are highly variable when discussing infections in NSICU. The most likely explanation for this is related to variability in definition of infection in a cohort with poor mentation. Additionally, some older studies show high prevalence and incidence rates when compared to newer data. This variability is in part related to the implementation of better prevention strategies.

20.4 Ventilator-Associated Pneumonia (VAP)

Nosocomial pneumonia is very common in neurocritically ill patients. Poor mentation, bulbar weakness, and immunocompromised state contribute to higher prevalence of nosocomial pneumonia in the NSICU patient population [1]. The physiology is related to the translocation of gastrointestinal flora into the respiratory tract [4]. A specific subset of nosocomial pneumonia is ventilator-associated pneumonia (VAP). The pathophysiology of VAP is complex and multifaceted. In brief, presence of endotracheal tube requires sedation and leads to suppressed cough and gag response. This in turn results in a higher risk for microaspiration. Additionally, collection of the microaspirate around the cuff of an endotracheal tube allows for biofilm formation. In intubated patients, there is impairment of mucociliary clearance, and when combined with positive pressure from ventilators, it further propagates bacterial pathogen into the lower respiratory tracts [16]. Extubation followed by reintubation also increases the risk of VAP.

Diagnosis of VAP can be challenging in ICU population. Radiographic changes often lag behind the clinical changes. In order to assist with the diagnosis of VAP, Pugin et al. introduced the clinical pulmonary infection score (CPIS) in 1991. His study revealed a sensitivity of 93% and specificity of 100% at diagnosis of VAP [17]. Since then, several additional studies have been performed, which show an overall sensitivity of 65% and specificity of 64% [18]. Additionally, CPIS has not yet been validated in the NSICU population. It is possible that certain components of CPIS may not be valid in NSICU cohort. For instance, patients with subarachnoid hemorrhage or traumatic brain injury may have leukocytosis and fevers from noninfectious etiologies. Often, patients may have aspiration pneumonitis and neurogenic pulmonary edema, which can make interpreting chest radiographs more challenging. These factors may also contribute to higher oxygenation requirements in severe cases, invalidating CPIS for the NSICU population.

Typically, early-onset VAP is less likely to be associated with multidrug resistant organism. Common pathogens in early VAP include *Streptococcus pneumonia, Hemophilus influenza, methicillin-sensitive Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia, Enterobacter species, Proteus species,* and *Serratia marcescens*. Late onset, longer than 4-days postintubation, VAP is more likely to be caused by MDRO. Common causative agents for late VAP include methicillin-resistant *Staphylococcus aureus* (MRSA)*, Acinetobacter, Pseudomonas aeruginosa,* and extended-spectrum beta-lactamase-producing bacteria (ESBL) [16]. Additional risk factors for MDRO-associated VAP include intravenous antibiotic use in the past 90 days, septic shock at the time of VAP diagnosis, 5 days of hospitalization prior to diagnosis, renal replacement therapy, and ARDS prior to VAP diagnosis [19]. In general, treatment with broad-spectrum antimicrobials should be initiated early when there is high clinical suspicion. In patients with a high risk of MDRO, broad-spectrum coverage should target MRSA and *Pseudomonas*. When there is high suspicion for ESBL, or local antibiogram is suggestive of high rates of ESBL, antimicrobials should be adjusted to cover for ESBL. Table 20.1 provides few combinations of antibiotics, which may be used as initial therapy until susceptibility is obtained from culture. The 2016 IDSA guidelines recommend a total duration of 7 days [19]. In clinical practice, the duration of therapy ranges between 5 and 14 days, depending on patient's clinical course and severity of illness.

There are several ways to reduce the risk of VAP. First, whenever possible, the use of noninvasive positive pressure ventilation is preferred over invasive positive pressure ventilation. In patients with neuromuscular diseases, use of noninvasive modes of ventilation has decreased work of breathing and reduce the need for invasive ventilation needs. Sedation holidays and daily weaning trials have shown to decrease the amount of time patient remains intubated. Shorter duration of mechanical ventilation assists in lowering the risk of developing VAP. Intermittent subglottic suctioning assists with removal of aspirate just above the endotracheal tube cuff. Additionally, avoidance of the head of bed at zero degrees is preferred. With current literature, it is unclear if 30-degrees is sufficient in prevention of VAP; however, it

is clear that being in supine position for prolonged periods increases the risk of infection. Studies that have evaluated using ICU bundled order sets to achieve the above goals have shown to be beneficial in lowering rates of VAP [20].

20.5 Ventriculitis

There are several risk factors for the development of ventriculitis in patients admitted to NSICU. Often, NSICU patients have presenting illness, which require cerebrospinal fluid diversion with use of external ventricular catheters (EVD). Risk factors for the development of EVD-associated ventriculitis are listed in Table 20.2 [13, 21]. It has become increasingly more common to have patients from community presenting with ventriculomeningitis as well. Partly, this is due to increased use of intrathecal infusion pumps. There is also an increase in use of deep brain stimulators (DBS) for the treatment of various neurological disorders including Parkinson's disease, essential tremors, and dystonia. Additional research is ongoing for use of DBS in major depression, obsessive-compulsive disorder, epilepsy, and chronic pain [22].

The diagnosis of ventriculitis is often challenging in the NSICU patient population. Presenting symptoms vary and may have a protracted course before presentation. Diagnosis is typically made when there are high clinical suspicion and appropriate risk factors. CSF analysis with white blood cell (WBC) count, red blood cell (RBC) count, glucose, protein, lactic acid, India ink stain, and bacterial cultures should always be performed when there is high suspicion for ventriculitis. CSF WBC count can be normal in up to 20% of the cases. Additionally, it is worth noting, that a negative gram stain does not exclude the presence of ventriculitis [21]. Pfausler et al. first looked at using CSF cell index as a tool for early diagnosis of ventriculitis. By using cell index, their group was able to diagnose ventriculitis 3 days earlier in culture-confirmed cases [23]. Lunardi et al. looked at a larger sample size and used cell-index as potential means of diagnosing ventriculitis. They suggest that a higher cutoff value for the index may be helpful. More importantly, their study also suggested that trending cell index was of no value in following treatment with antimicrobials [24]. Few small studies have looked at using CSF procalcitonin in

Table 20.2 Risk factors for developing EVD related ventriculitis

EVD related infectious risk factors
Frequent CSF sampling through EVD
Long duration (greater than 11 days)
Presence of intraventricular hemorrhage
Surgical technique (tunneled vs. nontunneled)
Absence of antimicrobial impregnated catheters
Prolonged use of prophylactic systemic antibiotics

the diagnosis of bacterial infection [21]. Cutoff value for serum procalcitonin is not yet well understood at this time. As such, in clinical practice, procalcitonin is not routinely tested. Given the challenges in the diagnosis of ventriculitis, it is important to follow patients clinically. In practice, cultures should be held for longer than usual 3-day period to monitor for growth of slow-growing organisms such as *Propionibacterium acnes*. Additionally, presence of CSF glucose less than 10 mg/dL, multiple positive cultures, and fever higher than 40 °C are suggestive of ongoing infection [21].

Causative organisms for ventriculitis vary depending on the underlying risk factor. For infectious cases related to intrathecal pumps, the most common agent is *Staphylococcus aureus*. For patients with EVD, the most common causes of infection tend to be gram-positive organisms including *Staphylococcus epidermis, Staphylococcus aureus, Streptococcus sp., and Propionibacterium acnes* [11]. Approximately 25% of the EVD-related infections are caused by gram-negative organisms which include *Pseudomonas sp., Acinetobacter, Escherichia coli, and Klebsiella* species [11]. When starting empiric coverage, it is prudent to cover for local high resistance. Typically, coverage with vancomycin and cefepime is recommended to cover for MRSA and *Pseudomonas* species. Alternative combination includes vancomycin and meropenem, vancomycin and ceftazidime, and vancomycin and aztreonam (when meropenem or cephalosporins are contraindicated). When vancomycin is contraindicated or there is concern for vancomycin resistance, an alternative agent of choice is linezolid. For infections caused by carbapenem-resistant *Acinetobacter*, the recommended treatment is colistimethate sodium. When targeting treatment with vancomycin, it is important to monitor serum vancomycin trough levels, and maintaining levels between 15 and 20 μg/mL [4, 11, 21]. The evidence of intraventricular antibiotics remains controversial. Expert opinions suggest its use in limited cases when systemic treatment is ineffective [11, 21]. If needed, there is limited safety data on use of polymyxin B, colistimethate sodium, gentamicin, and vancomycin. Agents that are neurotoxic, such as carbapenems or penicillin/cephalosporins, should be avoided [21]. Of note, when an infection develops in the setting of foreign objects, such as EVD or DBS, it is imperative to replace the infected hardware.

Prevention of procedural related ventriculitis is achieved with proper handwashing and sterile insertion technique, use of periprocedural prophylactic antibiotics, and use of antimicrobial impregnated catheters. Prolonged systemic antimicrobials are not recommended due to higher rates of multidrug-resistant organism related infections. Prophylactic catheter exchanges are also not recommended due to increased risk of infection when compared to single catheter placement [21].

20.6 Meningitis/Encephalitis

Risk factors for developing bacterial meningitis in the community include young children or elderly adults. Pregnancy increases the risk of meningitis from listeria. Acquired or inherent immunocompromised states HIV, functional asplenia, or

complement deficiency are also risk factors for community-acquired meningitis [25]. Other risk factors include traumatic brain injury, postcraniotomy CSF leak, perioperative steroid use, and presence of foreign objects such as DBS and intrathecal pumps [21].

The diagnosis of meningitis and encephalitis is made with the appropriate clinical presentation in conjunction with CSF studies. Classic presentation of meningismus, fever, photophobia, emesis, headaches, with or without encephalopathy, and abnormal CSF studies is typically seen in community-acquired cases of meningoencephalitis. For cases caused by a bacterial infection, CSF studies will show elevated WBC count, elevated protein, and low glucose. CSF gram stain may be positive or negative. CSF culture may be negative if broad-spectrum antibiotics are started prior to obtaining the CSF sample. There may be some value in using cell index for diagnosis of infection. It is worth noting that larger, randomized studies are lacking to suggest the benefit of using cell index for diagnosis of meningitis. Several studies have looked at the utilization of CSF lactate in the diagnosis of meningitis. CSF lactate may be of some value when using to diagnose postoperative meningitis when using a high cutoff value of 4 mmol/L. Using a higher lactate cutoff value yields a sensitive of 88–93% and specificity of 98–99% [26, 27].

Most common causative infections in patients with foreign objects are *Staphylococcus epidermidis, Staphylococcus aureus, Propionibacterium acnes,* and gram-negative bacilli [21]. Common causative infection in community-acquired meningitis is *Neisseria meningitidis, Streptococcus pneumoniae,* and *Listeria monocytogenes* in immunocompromised and pregnant patients, or age greater than 50 years [4]. When meningitis or meningoencephalitis is suspected, empiric treatment should be started as soon as possible. A lumbar puncture should be performed and sent for gram stain, cultures, and appropriate cell count testing. For regions with high MRSA strains, vancomycin plus addition of third-generation cephalosporin is recommended. In the setting of foreign objects, third-generation cephalosporin should be replaced with fourth-generation cephalosporin such as cefepime. Additionally, if patient is immunocompromised, pregnant, or is older than age 50 years, ampicillin should be added to include coverage for *Listeria* [4]. Patients who have contraindication to ampicillin, but have risk factors for Listeria, the recommended agent is IV sulfamethoxazole/trimethoprim plus IV gentamycin or meropenem. Meropenem can also be an alternative agent in patients with an allergic reaction to cephalosporins. Lastly, if there is concern for by carbapenem resistance, meropenem can be switched for aztreonam [21].

With the advent of vaccines, rates of meningitis have reduced drastically. Since the introduction of *Haemophilus influenzae* type B vaccine, the infection rate declined by 92.5% in Greece and 99% in the United States [28, 29]. Similar findings are seen with the use of a pneumococcal vaccine in England and Whales [30]. Currently, the Center of Disease Control and Prevention recommends vaccination with pneumococcal, meningococcal, and *Haemophilus influenzae* type B for prevention of meningitis. Postexposure prophylaxis is also recommended when exposed to meningococcal infection (caused by *N. meningitidis*). Chemical prophylaxis is achieved with use of rifampin, ciprofloxacin, or ceftriaxone [31].

20.7 Urinary Tract Infections

Risk factors for the development of urinary tract infection can be broken down into two categories: modifiable or intrinsic. Intrinsic risk factors for developing UTI include benign prostate hypertrophy, older age, presence of renal calculi, and female gender. Modifiable risk factors for developing UTI include uncontrolled diabetes mellitus, hospital stay greater than 7 days, and catheterization [32].

Urinary tract infection diagnosis is made when a patient has clinical signs and symptoms and has positive cultures. A subcategory of UTI is CAUTI where the diagnosis requires the presence of a catheter in addition to positive cultures and symptoms. Clinical signs and symptoms of UTI include the presence of fever, suprapubic tenderness, costovertebral tenderness, dysuria, increased urinary frequency, or increase urinary urgency [4, 6]. A positive urine culture requires growth of at least 10^5 culture colonies of no more than two known pathologic organisms. When obtaining a culture, a mid-stream urine specimen should be analyzed to minimize false positives. As stated earlier, a CAUTI is diagnosed when a urinary catheter is placed within 48-hours or removed within 24-hours of the inciting event.

Most common causative agents for UTI are gram-negative organisms (*Escherichia coli, Klebsiella* Sp., *Proteus* Sp., *Pseudomonas* Sp.), *Enterococcus* Sp., and *Candida* Species [6, 11]. A CAUTI should be treated as complicated urinary tract infection. For complicated UTI, empiric treatment should be initiated with third-generation cephalosporins such as ceftriaxone. Duration of treatment for CAUTI varies between 5 and 7 days. For patients who are septic, have upper urinary tract infections, or critically ill, longer duration (10–14 days) of therapy is preferred. Alternative to cephalosporins includes fluoroquinolones (ciprofloxacin or levofloxacin) for the treatment of complicated UTI. For uncomplicated UTI, the agent of choice is sulfamethoxazole/trimethoprim for 3 days. Alternatively, nitrofurantoin for 7 days or fluoroquinolone for 3 days can be considered in patients who have contraindication to sulfamethoxazole/trimethoprim [33].

The NISCU patient population is unique in that the neurologic injury may necessitate the use of urinary catheter. Thus, it is paramount for care providers to be aware of infection prevention strategies. A 2014 Cochrane review looked at using antibiotic or antiseptic impregnated catheters for prevention of catheter-associated urinary tract infection. In the review, antibiotic-coated catheters were found to be superior in the prevention of CAUTI and lowered rates of bacteriuria. Antibiotic impregnated catheters were also superior at prevention than antiseptic catheters. It is worth noting that while antibiotic-impregnated catheters prevented infections, they were also associated with higher patient discomfort [34]. Impregnated catheters are also expensive and may not be suitable for broad usage. Other strategies for prevention of CAUTI involve creating a bundle set where the daily need for catheter is monitored, standardized technique for aseptic catheter insertion is followed, creating system-based criterion for catheter utilization, providing continuing education for proper catheter maintenance, and promoting good perineal care practices [32, 35].

20.8 Bacteremia

Main risk factor for bacteremia in an NSICU is the presence of central venous catheters. These may be used for infusions of vasoactive agents, assist with the understanding of patient's intravascular volume status, and administration of high concentrated saline, to name a few. Host factors play an important role when it comes to identifying potential risk factors. Older age, use of parental nutrition, malnutrition, and immunosuppression are some of the common host risk factors for developing bacteremia [11]. Historically there had been controversy regarding the ideal location for placement of the central venous catheter and associated risk of infection. A large multicenter, randomized, French trial (3SITES) looking at academic and nonacademic hospitals showed a high risk of infection with femoral access when compared with subclavian or internal jugular access [36]. Similar results were seen in a prospective observational study by Deshpande et al. [37].

Diagnosis of bacteremia is made with positive blood cultures. For the infection to be classified as catheter-related bloodstream infection, one of two criteria has to be met. First, the causative organism should grow at least 10^3 colonies from the tip of the catheter and a different peripheral site. Second, a positive culture from a catheter drawn blood sample should yield the same organism as the peripherally drawn blood sample. The two samples have to be collected within 2 hours apart [11, 14, 38].

Most frequent organisms associated with catheter-related bloodstream infections are coagulase-negative *Staphylococcus* species, *Staphylococcus aureus, Enterococcus* species, gram-negative bacilli such as *Klebsiella pneumoniae* and *Escherichia coli, and Candida* species [11, 38]. The incidence of MRSA and multidrug-resistant gram-negative bacilli associated bacteremia has been increasing over the past several years. Initial empiric treatment focuses on the patient's risk factors and targeting common causative organisms. Vancomycin is the initial treatment of choice. Addition of third- or fourth-generation cephalosporins is recommended in patients who are critically ill and septic, neutropenic, have femoral central venous access, or received recent treatment for gram-negative organism [38]. Ceftazidime is the preferred third-generation cephalosporin due to its activity against *Pseudomonas* species. For Enterococcus species that are susceptible to ampicillin, the preferred agent is ampicillin. Often third-generation cephalosporins will provide some degree of coverage against *Enterococcus* species. Combination therapy with daptomycin and ampicillin or ceftriaxone has some additional benefit in treatment for VRE strains [38]. For patients who have femoral access, received parental nutrition, or have underlying active malignancy, the risk for fungemia is also higher. When *Candida* fungemia is suspected, patients should also be started on fluconazole. Alternative treatment regimens for *Candida* infection include the use of liposomal amphotericin B or micafungin [38]. Optimal duration of antimicrobial treatment varies based on the causative agent. For VRE, typically 6 weeks of therapy is recommended. Similarly, for *S. aureus* related infection, treatment is generally longer due to increased risk of development of endocarditis, particularly if

blood cultures remain positive for more than 3 days [38]. For uncomplicated or less virulent infections, the treatment duration can be as short as 2 weeks short course of antibiotics.

There are several ways to mitigate the risk of catheter-related bloodstream infections. As with every procedure, prevention starts with proper hand hygiene. Maintaining sterile field and using sterile insertion technique help lower the risk of infection. Skin should be prepared with use of 2% chlorhexidine. Patients should be evaluated at least daily for early removal of invasive lines [14]. For multilumen catheters, unused ports should be secured using disinfecting caps. Additionally, ports should be sterilized prior to initiating infusion. A 2016 Cochrane review evaluated the benefit of using impregnated catheters for the prevention of catheter-related bloodstream infection. The review highlighted that while impregnated catheters prevented CRBSI, it did not reduce the all-cause mortality or clinically diagnosed sepsis [39]. Given the high cost of these catheters and lack of reduction in all-cause mortality, impregnated catheters are less often utilized in clinical practice.

20.9 Other Infections

Several other infections are encountered in NSICU. These include surgical site infections (SSI) and *Clostridium difficile* colitis. While uncommon, their presence often increases the overall cost to the healthcare system and affects the hospital length of stay.

There are several risk factors for developing SSI. These risk factors include diabetes, smoking, hypertension, obesity, and higher ASA class to name a few. When possible, patient optimization should be performed in elective cases to help minimize risk of SSI. These interventions include adequate control of underlying chronic illness, smoking cessation educations, and weight loss planning [40]. While many providers continue to use antiseptic showers preoperatively, a Cochrane review article suggested no benefit in the prevention of SSI with its use [41]. Perioperative prophylaxis is recommended for the prevention of SSI. Use of perioperative antibiotics has been well studied since the 1980s and has been shown to reduce the incidence of SSI in the neurosurgical patient population [42]. Should an infection develop despite the use of appropriate preventive strategies, systemic treatment should be initiated to cover for aerobic and anaerobic organisms, including gram-positive and gram-negative bacteria. If purulent drainage is visualized, an incision and drainage should be performed along with systemic antibiotics [43].

Patients with new and unexplained liquid stools, more than three episodes in a 24-hour period, should be tested for *Clostridium difficile* colitis. Testing should be performed using a nucleic acid amplification test when possible due to its high sensitivity [8]. Risk factors for the development of *C. difficile* colitis include recent antibiotic exposure (particularly third-/fourth-generation cephalosporin, fluoroquinolones, carbapenems, and clindamycin), age greater than 60 years, prolonged

hospitalization, severe underlying disease process, and gastric acid suppression, particularly with the use of proton pump inhibitors [8, 44]. Once *C. difficile* is confirmed, treatment should be initiated with oral vancomycin or fidaxomicin for a total of 10-days [8]. Repeat testing is not recommended while undergoing treatment. In cases of *C. difficile* infection and associated ileus, shock, or megacolon, treatment with oral or rectal vancomycin plus intravenous metronidazole should be initiated. Preventive strategies for *C. difficile* include proper hand hygiene when entering or leaving a patient's room, isolating the patient in a private room, and using gowns and gloves when engaging with an infected patient [8].

Finally, the choice of the antibiotic regimen in the NSICU (regardless of the source of infection) should also take into consideration specific adverse events frequently observed in this special population. Ciprofloxacin can lower the seizure threshold in neurological patients, and cefepime can lead to severe encephalopathy, or in more severe cases, nonconvulsive status epilepticus in patients with decreased renal function. Metronidazole can cause acute peripheral and central neurotoxicity with characteristic involvement of the corpus callosum. Linezolid can cause serotonin syndrome, and patients with myasthenia gravis should have their drug regimen carefully selected, as several antibiotics can disturb neuroconduction in these patients.

20.10 Conclusion

In this chapter, we reviewed commonly encountered infections in neurocritical care units. By far the most common infectious illness in neurocritical care includes pneumonia. The neurocritical care population is susceptible to infections from many causes. The diagnosis of infection remains a challenge given the high prevalence of noninfectious fever. When there is high clinical suspicion, treatment should be started early and with broad-spectrum agents. Once the culture results are available, antimicrobials should be tapered to mitigate the risk of antibiotic resistance. It is worth mentioning that much of the literature that is currently available relates to medical and surgical ICU. Additional research specifically relating to neurocritical care units is warranted.

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Chapter 21
Acid-Base and Electrolyte Disorders in Neurocritical Care

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21.1 Introduction

Acid-base and electrolyte disturbances in neurologic ICU are common, but severe in terms of prognostic. Many mechanisms of fluid and electrolyte homeostasis are mediated by the central nervous system (CNS) and are suddenly lost in head-injured patients. Additionally, these patients may have fluid restriction due to altered conscious level, administration of chloride-rich fluids, diuretic therapy causing sodium (Na) and potassium (K) disorders, use of hypertonic solutions for fluid resuscitation or control of intracranial pressure, and neuroendocrine disturbances with central diabetes insipidus (DI), syndrome of inappropriate antidiuretic hormone secretion (SIADH) or salt wasting syndrome (CWS) [1].

In this chapter, we address the main acid-base and electrolyte disorders in neurocritical care, addressing particular issues in neurocritical patients.

21.2 Fluid Management in Neurologic Disorders

There are several challenges in fluid management of neurosurgical critically ill patients. After CNS injury, most patients experience loss of consciousness with limited water intake, disturbances in central control of electrolyte balance, excessive blood loss in cases of multiple trauma with inadequate volume resuscitation, hyperosmolar therapy, and drug-induced dysnatremias which are the greatest challenges for fluid management in neurocritical care [2].

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Negative fluid balance has been associated with secondary injuries in traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH). Patients with negative fluid balance are at highest risk for delayed ischemic injury in SAH and poor outcomes in TBI [3, 4]. Clifton et al. [5] published a critical threshold for fluid balance for acute brain injury and found that a fluid balance <594 ml has negative effects on outcomes. The "dehydration hypothesis" for improvement of brain edema and neurologic outcomes was inferred by the use of mannitol in TBI to reduce brain edema [6]. However, concomitantly to the osmolar effect for reduction of intracranial pressure (ICP), dehydrated patients experience hypotension (mean arterial pressure (MAP) <90) in addition to increased ICP with insufficient cerebral perfusion pressure (CPP) [7].

Therefore, an optimized fluid management with adequate resuscitation is mandatory for neurocritical patients. The ideal resuscitation fluid is a matter of controversy; the universal use of crystalloids has encouraged its standard use in neurologic ICU [1].

21.2.1 Volume Resuscitation: Types of Fluids

21.2.1.1 Crystalloids

Ionic (Na, Cl) and nonionic (mannitol, dextrose) crystalloid solutions are used for fluid replacement in critically ill patients. Hypotonic (NaCl 0.45% or dextrose 5%) or dextrose containing solutions is not recommended for TBI [8]. Hypotonic solutions should be avoided due to large volume distribution with limited volume expansion. Additionally, reduction in osmolarity results in increased ICP. Glycemic control is an individual outcome predictor for TBI and SAH. Hyperglycemia has negative immune and metabolic implications in brain-injured patients and has been associated with unfavorable outcomes [9].

Isotonic solutions (NaCl 0.9% or lactated Ringer's solution) are the most commonly used in critically ill patients in general for fluid resuscitation. The sodium chloride solution is widely available and provides similar osmolarity compared to plasma and Ringer's solution. The effects of crystalloid composition have been studied in randomized clinical trials with positive findings with the use of balanced solutions (lactated Ringer's solution or Plasma-Lyte A) compared to saline in the reduction of hyperchloremic metabolic acidosis and major adverse kidney events in ICU patients. However, it is stated that these results may not be inferred for neurocritical patients with high ICP that might be jeopardized with relative hypotonicity of balanced solutions. It is important to mention that delayed fluid resuscitation with low MAP and CPP has been implicated with secondary injuries and even worse outcomes [8, 10].

Hypertonic solutions (20% mannitol or hypertonic saline) are widely used as osmotherapy for neurologic patients with increased ICP. Other benefits are optimal plasma expansion and increased oxygen delivery to the CNS. The primary effect in

reducing ICP is regarding a compensatory cerebral vasoconstriction and reduction in cerebral blood volume. The osmotic gradient occurs as an effect with removal of water from brain interstitium [11, 12].

Mannitol vs Hypertonic Saline in Neurocritical Care

Since the 1960s, mannitol has emerged as an optimal osmotherapy in neurologic patients. A preserved blood-brain barrier (BBB) limits passage of mannitol causing a loss of free water from the brain parenchyma and consequent brain relaxation. However, the large osmotic load produces a diuretic effect with development of acute tubular necrosis and acute kidney injury. The recommendation is to keep blood osmolarity <320 mOsm/L and to not use in patients at high risk of kidney disorders. In addition, in patients with loss of BBB, mannitol might accumulate in the brain interstitium and shift water into the brain with worsening of brain edema [7]. It is recommended that mannitol 20% is 0.25–1 g/kg over 20 minutes for patients with signs of raised ICP [4].

The hypertonic saline emerged as an alternative hyperosmolar therapy in the 1980s. Its osmotic benefits also depend on the integrity of semipermeable BBB with additional benefits of increasing cardiac output, arterial vasodilation with improvement in peripheral perfusion, and attenuation of secretion of inflammatory mediators after TBI. Risks of kidney injury are less likely compared to mannitol. However, important changes in serum sodium provide risk of seizures and coma and theoretical risk of central pontine myelinolysis [8, 13]. In addition, the fast volume expansion might aggravate pulmonary congestion and, as a saline solution, the increased risk of hyperchloremic metabolic acidosis. The lack of consistency in the use of hypertonic saline is regarding different methods of administration. The concentration varies from 3% to 23.4% and is used either as bolus or in continuous infusion. It is recommended a continuous infusion of NaCl 2–3% aiming a serum sodium within 145–155 mEq/L in 4–6 hours [1].

21.2.2 Fluid Management in Traumatic Brain Injury

The prevention of hypotension remains a priority in the management of patients with intracranial trauma. The guidelines recommend maintaining systolic BP ≥100 mmHg for patients aged 50–69 years and ≥110 mmHg for patients aged 15–49 or >70 years of age [4].

The objective is to maintain euvolemia with preferential use of isotonic fluids. Saline is the fluid of choice because the use of albumin is associated with increased mortality. While balanced crystalloid solutions are used to decrease the risk of acute kidney injury in other critically ill patients, normal saline is preferred in TBI, since balanced solutions are relatively hypotonic and may worsen cerebral edema [10, 14].

Mannitol and hypertonic saline are widely used to treat patients with TBI and increased intracranial pressure. Meta-analysis included 12 randomized controlled trials that analyzed data from 464 patients to compare treatment with mannitol or hypertonic saline. It was observed that there were no significant differences in mortality between the two treatments (relative risk [RR], 0.69; 95% confidence interval [CI], 0.45, 1.04; $P = 0.08$). There were also no significant differences in the favorable neurological outcome between hypertonic saline solution (HS) and mannitol (RR, 1.28; 95% CI, 0.86, 1.90; $P = 0.23$). The *Guidelines for Management of Severe Traumatic Brain Injury* [4] recommends use of mannitol for raised ICP because of lack of evidence in the use of hypertonic saline [7, 15].

21.2.3 Fluid Management in Subarachnoid Hemorrhage

The main recommendations for acute SAH are regarding MAP control to prevent hypertension-related rebleeding with an adequate cerebral perfusion to avoid secondary injuries [3]. In terms of fluid management, the current recommendation is maintenance of euvolemia to avoid delayed ischemic injury (DCI). If DCI is suspected, some authors suggest immediate resuscitation with sodium chloride 0.9% (15 ml/kg) infused over 1 hour, induced hypertension, and early treatment of aneurysms [16].

Fluid restriction to correct hyponatremia appears to be potentially dangerous in patients with aneurysmal SAH. Fluid restriction is a standard component of therapy in syndrome of inappropriate secretion of antidiuretic hormone (SIADH), but may promote cerebral vasospasm in patients with SAH who are usually treated with volume expansion. Hyponatremic patients with SAH and SIADH might be treated with hypertonic saline (3%) to both preserve cerebral perfusion and prevent complications from hyponatremia-induced brain swelling [8]. One proposed regimen is an initial infusion rate of 20 mL/h with subsequent dosing being dependent upon serial measurements of serum sodium at 6-hour intervals [17].

21.3 Sodium Disorders in Neurocritical Care

Sodium disturbances are independent predictors of poor outcomes in neurocritical care. Sodium disturbances are the result of a combination of clinical variables of CNS injury, kidney failure, or iatrogenic therapies implemented in intensive care [18]. Intensive care studies suggest that the majority of sodium disturbances are preventable [19, 20]. Patients' osmolarity and volume status should be monitored closely, and blood tests should be taken frequently for early detection of dysnatremias in neurocritically ill patients. Standardized sodium protocol should be implemented in neurologic ICU. Spatenkova et al. [21] suggested a sodium protocol

measuring serum levels and urine osmolarity, complete fluid balance every 6 hours, and limited fluid intake to 40 ml/kg/weight/day without use of hypotonic saline, thiazide, and desmopressin (DDAVP) for normonatremic patients. Although it did not show functional benefit, incidence of dysnatremias was lowered over the 5 years of prospective follow-up. The main implication of sodium control protocols is that physicians should always be aware of sodium disturbances in neurologic ICU.

21.3.1 ICU-Acquired Sodium Disorders

The ICU stay is a risk factor for hypo- or hypernatremia. Stelfox et al. [2] determined predictors of sodium disturbances from a multicenter epidemiological study including over 8000 patients with serum sodium levels at admission in ICU. Younger age, neurological trauma, level of consciousness, and hyperglycemia were predictors of acquired hyponatremia, while worse baseline creatinine and mechanical ventilation were risk factors for hypernatremia in multivariate analysis. Of note, acquired hypernatremia in ICU is independently responsible for 40% increase in risk for hospital mortality and 28% in ICU length of stay [22].

21.3.2 Hyponatremia

Hyponatremia, defined as a serum sodium concentration below 135 mEq/L, is the most common and important electrolyte disorder affecting patients with neurological diseases. Mechanisms underlying hyponatremia are related to sodium loss (e.g., hyperaldosteronism, vomiting, diarrhea, thiazides) or free water retention (e.g., SIADH) [21]. The prevalence of hyponatremia in neurosurgical patients is nearly 50% [23, 24]. Hyponatremia is a predictor of mortality in hospitalized patients. A serum sodium <130 mmol/L was related to 60-fold increase in mortality. Another prospective study showed that hyponatremic patients were seven times more likely to die in the hospital and two times more likely to die after discharge compared to normonatremic patients [25].

Neurological dysfunction is the principal manifestation of hyponatremia and can be associated with a worsening in the patient's neurological condition. Severe hyponatremia, or a rapidly falling serum sodium level, can lead to confusion, lethargy, seizures, and coma [26, 27]. Seizures are usually triggered at low sodium levels (<115 mEq/L). Patients with TBI may already have cerebral edema, and concomitant hyponatremia can lead to further increases in ICP and death from herniation [1]. Hyponatremia in SAH patients is associated with increased morbidity.

Acute hyponatremia is considered once it is developed within less than 48 hours. Arieff et al. reported that patients with acute onset of hyponatremia are all

symptomatic, with greater risk of complications and necessity for more aggressive therapy. Another classification considers the serum osmolality. Hyperosmotic hyponatremia is usually secondary to hyperglycemia in patients who received large doses of mannitol with a degree of kidney injury. The osmolar effect of glucose shifts free water into the extracellular fluids and decreases sodium concentration. Hypoosmotic hyponatremia might occur by different mechanisms. The main differential might be inferred by the volemic status of the patient. Spatenkova et al. reported a 3.5% incidence of hypo-osmolar hyponatremia by measuring daily serum sodium and osmolality and concluded that this is a common dysnatremia in neurocritical care [21, 28].

Hypoosmotic hyponatremia with hypovolemia is caused by renal sodium loss (diuretics; e.g., thiazides) and extrarenal sodium loss through vomiting or diarrhea, secondary to hypokalemia, or due to the cerebral salt-wasting syndrome (CSWS).

21.3.2.1 Cerebral Salt-Wasting Syndrome (CSWS)

The cerebral salt-wasting syndrome (CSWS) is a potential cause of hyponatremia in those with a central nervous disease. It is characterized by hyponatremia and extracellular fluid depletion due to inappropriate renal loss of sodium. Cerebral salt wasting is due to elevated levels of circulating natriuretic factors, possibly including atrial natriuretic factor [3, 4].

CSW is diagnosed in the patient with clinical evidence of hypovolemia who has the following characteristics: hyponatremia (less than 135 mEq/L) with a low plasma osmolality, an inappropriately elevated urine osmolality (>200 mmol/kg), a urine sodium concentration usually above 40 mEq/L, and a low serum uric acid concentration due to urate wasting in the urine. The clinical determination of hypovolemia should follow a combination of physical examination – dry skin, tachycardia, orthostatic hypotension, negative daily fluid balance, central venous pressure < 6 mmHg – and laboratory exams with increased hematocrit and blood urea nitrogen (BUN).

The objectives of the treatment of CSW are volume replacement and maintenance of a positive salt balance [3]. Initially, normal saline is used and then hypertonic solutions. Excessive urinary sodium excretion should be managed with mineralocorticoid administration [1, 29, 30]

Hypoosmotic hyponatremia with normovolemia is primarily related to SIADH in neurocritical care which is more frequent than CSWs in brain-injured patients. Prevalence of 5–25% is estimated in TBI patients. Hypothyroidism and glucocorticoid deficiency are differentials for refractory hyponatremia in neurologic ICU. Euvolemic hyponatremia might also be induced by some medications widely used intensive care; particularly carbamazepine and proton pump inhibitors [31].

21.3.2.2 Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH)

The SIADH is a disorder of impaired water excretion caused by enhanced secretion of antidiuretic hormone (ADH). If intake exceeds reduced urine production, the resulting water retention will lead to the development of an even hypervolemic hyponatremia. The most common neurological causes of SIADH are SAH, TBI, brain tumor, and meningitis/encephalitis.

The diagnosis of SIADH requires the following: hyponatremia (serum sodium <135 mEq/L), hypo-osmolarity (serum osmolarity <285 mOsm/L), urine osmolarity greater than serum osmolarity, and inappropriately high urine sodium (>40 mEq/L) [29]. In addition, the patient generally has no changes in serum potassium levels, there is no acid-base disorder, and the serum uric acid concentration is often low. The choice of therapy of SIADH is dependent upon a number of factors, and the main guideline for the treatment is fluid restriction of 800–1000 ml per day [8] (Table 21.1).

Hypo-osmolar hyponatremia with excess interstitial fluids occurs in conditions such as cirrhosis, cardiac failure, and renal failure [32].

The appropriate diagnostic work-up for hyponatremia is necessary for adequate management. In neurocritical patients, a detailed physical examination is required to determine patient's volemic status and laboratory work-up – electrolytes, BUN, creatinine, bicarbonate, hematocrit, and urinary sodium – to determine serum and urinary osmolality. Dosage of cortisol and TSH/T4 is important for differentials in euvolemic hypo-osmolar hyponatremia to rule out adrenal insufficiency and hypothyroidism [25].

The treatment of hyponatremia in neurointensive care should be avoiding further declines in the serum sodium concentration, decreasing intracranial pressure, relieving the symptoms of hyponatremia, and avoiding excessive correction. The purpose of the correction rate in cases of severe hyponatremia is to increase the serum sodium concentration by 4–6 mEq/L over a 24-hour period. In patients with acute hyponatremia or with severe symptoms, this correction should take place in 6 hours

Table 21.1 Clinical differences between CSW and SIADH (Rhaman)

	CSW	SIADH
Weight	Weight loss	Weight gain
Volume depletion	Present	Absent
Hematocrit and BUN[a]	High	Normal or low
Postural hypotension	Present	Absent
Plasma albumin concentration	Increased	Normal
Fluid balance	Negative	Positive
Central venous pressure	<6 cmH2O	>6 cmH2O

[a]BUN – blood urea nitrogen

or less; afterward, serum sodium can be maintained at a constant level for the remainder of the 24-hour period. The maximum rate of correction should be 8 mEq/L in any 24-hour period. In case of rapid correction, patients are at risk of osmotic demyelination syndrome (ODM) which may lead to quadriparesis. In acute hyponatremia (<48 hours), the risk of ODM is low. However, particular attention should be taken for alcoholism, malnutrition, hypokalemia, and liver disease that are at higher risk for ODM [29].

Management of CSWs and SIADH has divergent treatment directions; while the CSWs should be treated with sodium reposition and controlled fluid resuscitation, the SIADH should be managed with fluid restriction.

The CSW's initial fluid restoration is with isotonic solutions (0.5–1 ml/kg/h) with additional oral sodium intake or intravenous reposition with NaCl 3%. Mineralocorticoids reduce urinary sodium excretion with normalization of sodium balance. Hydrocortisone and fludrocortisone showed promising results in reducing natriuresis in TBI and SAH.

SIADH treatment is based on limited fluid intake to 800–1000 ml/day. In patients with SAH, water restriction is not recommended due to increased risk of DCI. High-protein diet is recommended or even urea administration (gastric tube or IV), as second-line treatment, for inducing osmotic diuresis that limits sodium excretion. The use of vaptans – blockers of vasopressin – is also considered as an alternative with promising results in reposition of serum sodium after a single dose. However, the incidence of overcorrection and side effects of hypokalemia, hypotension, and liver injury are relatively common which limits its use in critical care [1, 8, 29].

21.3.3 Hypernatremia

Hypernatremia is defined as a serum sodium level greater than 145 mEq/L. It occurs less commonly than hyponatremia; the incidence is approximately 1% in the general inpatient hospital population and 9% in the intensive care setting. It is usually caused by inadequate free water intake or excess water loss and rarely with excessive salt intake [2]. In neurointensive care, hypernatremia is multifactorial and may be associated with the use of osmotic therapy using mannitol or hypertonic saline solution or diuretic therapy with furosemide. ICU-acquired hypernatremia is an independent predictor of mortality for critically ill patients. Hypokalemia, hypoalbuminemia, and renal dysfunction are independent predictors of ICU-acquired hypernatremia [33].

The clinical signs of acute hypernatremia begin with lethargy, weakness, and irritability and can progress to twitching, seizures, and coma. Severe symptoms usually require an acute elevation in the serum sodium concentration to above 158 mEq/L. Values above 180 mEq/L are associated with a high mortality.

Hypervolemic hypernatremia is usually caused by the administration of hypertonic saline or other fluids that contain excess solute in relation to free water. *Hypovolemic hypernatremia* is the result of conditions that cause excessive amounts

of free water loss by the kidneys – diabetes insipidus, loop diuretics, and mannitol – or by conditions in which there are nonrenal free water losses, diarrhea and vomiting, burns, open wounds, drains, and patients under mechanical ventilation [2, 22].

21.3.3.1 Central Diabetes Insipidus (DI)

Central diabetes insipidus is characterized by decreased release of antidiuretic hormone (ADH), resulting in a variable degree of polyuria. The change in ADH release can be caused by hypothalamic disorders or those in the upper portion of the supraoptic-pituitary tract. The most common causes of central diabetes insipidus are idiopathic diabetes insipidus, primary or secondary brain tumors, infiltrative diseases, neurosurgery, and trauma. The incidence of DI in severe TBI is 15–28%. The central DI in diffuse lesions such as TBI and SAH might be transient with complete recovery within 5 days [29, 34].

The diagnosis of DI requires presence of polyuria (>2 ml/kg/h or >300 ml/h over two consecutive hours), urinary hypo-osmolality (< 300 mOsm/kg), and low natriuresis (<15 mmol/L) [35]. Most patients with central DI have a slightly elevated plasma sodium concentration because stimulation of thirst minimizes the degree of water loss. However, hypernatremia is severe in neurocritical patients since thirst may be impaired or there is limited access to water.

21.3.3.2 Induced Hypernatremia (Non-DI)

Hypernatremia usually occurs due to the loss of unsubstituted water, but it can also be induced by administration of hypertonic saline or by the excessive intake of sodium chloride. When the patient has an increased potassium intake without the corresponding water, there is also an increase in the serum sodium concentration, since most of the administered potassium will enter the cells, which will cause the osmotic movement of the water from the extracellular fluid to the cells, resulting in a small increase in serum sodium. The use of hypertonic saline solution (3%) in patients with intracranial trauma is a classic example of iatrogenic hypernatremia [33].

Other causes that can lead to hypernatremia are osmotic diarrhea induced by lactulose or by specific pathogens which are associated with an isosmotic diarrheal fluid that has more sodium and potassium concentration between 40 and 100 mEq/L, leading to an excessive loss of water. The loss of free water in the urine can lead to hypernatremia if it is not replaced, which usually occurs in patients with nephrogenic diabetes insipidus or osmotic diuresis that occurs due to the presence of unabsorbed solutes, such as glucose, mannitol, or urea.

The treatment of hypernatremia includes identifying and correcting any reversible factors, correcting volume depletion if present, and replacing the calculated free water deficit. The goal of water repletion in patients with chronic hypernatremia is to lower the serum sodium by approximately 10 mEq/L in 24 hours. Hypernatremia

is acute if it has been present for 48 hours or less, is uncommon, and occurs in patients with diabetes insipidus. In patients with TBI and intracranial hypertension, prophylactic hypernatremia (ranging from 145 to 155 mmol/L) is recommended for better control of ICP [36].

The DI management is based on correction of free water deficit with hypotonic solutions, preferentially through oral ingestion or enteral tube. For the treatment of polyuria in ID patients, the most used drug is desmopressin, which is an analogue of ADH. Water retention leading to the development of hyponatremia is a potential risk in patients with central DI who are treated with desmopressin or other therapies that increase the response to or secretion of ADH and could lead to brain injury and increased intracranial pressure if the plasma sodium is not carefully monitored [29].

21.4 Potassium Disorders in Neurocritical Care

Potassium is the main intracellular cation, with cells containing approximately 98% of body potassium, while sodium is the main extracellular cation, and the difference in the distribution of the two cations is maintained by the Na-K-ATPase pump in the cell membrane. The intracellular potassium concentration is approximately 140 mEq/L compared to 4–5 mEq/L in the extracellular fluid. Under physiological conditions, potassium is absorbed in the intestine and largely excreted in the urine.

Alterations in the serum potassium level have a multifactorial origin. Hypokalemia and hyperkalemia are especially dangerous in critically ill patients, in whom simultaneous disorders can exacerbate the adverse effects of potassium disorders. In intensive care patients with potassium disorders, pharmacological agents, acid-base disorders, hypomagnesemia, and renal failure should always be investigated [37].

21.4.1 Hyperkalemia

Hyperkalemia contributes to expressive morbimortality rates in critical illness. In hospitalized populations, it is reported to occur in 1.3–10% of patients. It is precipitated by excessive potassium intake, impaired renal excretion, or altered cellular uptake. Iatrogenic potassium supplementation, renal failure, chronic use of medications, increased tissue catabolism, insulin deficiency, hyperglycemia, and hyperosmolarity are the main causes of hyperkalemia. Medications classically related to drug-induced hyperkalemia are diuretics (e.g., spironolactone), angiotensin-converting enzyme inhibitor, nonselective β-blockers, heparin, and succinylcholine [33].

The most serious manifestations of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias. Hyperkalemia can be associated with a variety of electrocardiographic changes: high peak T waves with reduced QT interval are usually the first manifestations. As hyperkalemia

becomes more severe, there is a progressive increase in the PR interval and QRS duration, the *P* wave can disappear, and, finally, the QRS increases further to a sine wave pattern, until the absence of electrical activity [38].

The urgency of treatment of hyperkalemia varies with the presence or absence of the symptoms and signs associated with hyperkalemia, the severity of the potassium elevation, and the cause of hyperkalemia [38].

21.4.2 Hypokalemia

Hypokalemia is one of the most common electrolyte changes in clinical practice. When defined as less than 3.6 mmol/L, hypokalemia is found in more than 20% of hospitalized patients. Hypokalemia increases the risk of morbidity and mortality in patients with cardiovascular complications.

There are many causes that can lead to hypokalemia, such as decreased intake, increased translocation into the cells, or, most often, increased losses in urine, the gastrointestinal tract, or sweat and can also be the result of hypomagnesemia due to magnesium's role in activating the sodium/potassium pump. Hypokalemia appears to be common in TBI patients due to increased adrenergic stimulation and subsequent intracellular shift of potassium. The clinical presentation is proportional to the degree and duration of the reduction in serum potassium. Symptoms generally do not manifest until serum potassium is below 3.0 mEq / L and unless serum potassium drops rapidly. Signs and symptoms of hypokalemia include nausea, vomiting, muscle weakness, rhabdomyolysis, cardiac arrhythmias, and renal abnormalities [33, 39].

21.5 Calcium Disorders in Neurocritical Care

Calcium circulates in the blood in three ways: (1) ionized (50%); (2) linked to protein, mainly to albumin (40%); and (3) chelated with other ions (10%). Thus, serum calcium concentrations in patients with low or high levels of albumin do not accurately reflect the actual ionized calcium concentration. In malnourished patients with chronic diseases that present hypoalbuminemia, the total serum calcium concentration may be low when the serum-ionized calcium is normal, a phenomenon called pseudo-hypocalcemia.

Hypocalcemia is an extremely common electrolyte disturbance in patients with critical illness. It results from a variety of causes, including sepsis, hypomagnesemia, vitamin D deficiency, hypoparathyroidism, administration of chelating substances (i.e., citrate from red blood cell transfusions, albumin, bicarbonate), and alkalosis. Medications of particular importance for development of hypocalcemia in ICU are propofol and contrast dye which perform chelation of potassium through calcium binding with edetate.

Hypocalcemia is associated with a variety of clinical manifestations (paresthesias, carpopedal spasm, tetany, seizures, Chvostek's or Trousseau's signs, bradycardia, impaired cardiac contractility, and prolongation of the QT interval). In patients with asymptomatic hypocalcemia, it is important to verify with repeat measurement of ionized calcium or total serum calcium corrected for albumin that there is a true decrease in the calcium concentration. In cases of acute symptomatic hypocalcemia, intravenous calcium gluconate (IV) is the preferred therapy, while in chronic cases, it is treated with oral calcium and vitamin D supplements.

Hypercalcemia is a common clinical problem in chronic renal disease with secondary hyperparathyroidism and malignancies. It is reported an occurrence in 15% of critically ill patients [1, 8, 29, 33].

21.6 Magnesium Disorders in Neurocritical Care

Magnesium is an essential element in normal physiological functioning, and plays a critical role in modulating vascular smooth muscle tone, which dominates peripheral vascular resistance and blood flow dynamics. The plasma magnesium concentration is not usually measured as part of routine blood tests. Thus, the identification of patients with hypomagnesemia often requires clinical suspicion in patients with risk factors (mainly caused by gastrointestinal and/or renal disorder) or with clinical manifestations of hypomagnesemia. Other causes that can lead to a reduction in the serum magnesium level in the context of intensive care are increase in circulating catecholamines, adrenergic activity, acid-base imbalances, increased levels of free fatty acids, hyperglycemia, and use of corticosteroids.

Hypomagnesemia is common in all hospitalized patients, reported in 50% of critically ill patients with coexisting electrolyte abnormalities and may lead to secondary hypokalemia and hypocalcemia, seizures, and severe neuromuscular and cardiovascular clinical manifestations (ventricular arrhythmias). Hypomagnesemia at admission has been found in up to 38% of patients with subarachnoid hemorrhage (SAH) and is associated with higher World Federation of Neurosurgical Societies severity scores. Hypomagnesemia may cause severe and potentially fatal complications if not timely diagnosed and properly treated, and associated with increased mortality [33, 40].

21.7 Hyperchloremia in Neurocritical Patient

Chloride is the most abundant anion in the extracellular environment and an important constituent of plasma tonicity, playing an essential role in various body functions, such as regulation of body fluids, electrolyte balance, acid-base status, muscle activity, and osmosis. In neurocritical care, it is common administration of hypertonic saline solution or normal saline solution (0.9% saline solution). However, both

solutions can cause hyperchloremia, an independent predictor of mortality in critically ill patients.

Another important entity associated with serum changes in chloride is hyperchloremic acidosis in which there is an acidosis state (pH less than 7.35) with an increased ionic chloride concentration. Hyperchloremic metabolic acidosis is a condition resulting mainly from the loss of bicarbonate that leads to acidosis, and it can also be caused by gastrointestinal changes (losses of bicarbonate due to severe diarrhea, pancreatic fistula), kidney diseases (renal tubular acidosis, chronic use of inhibitors of carbonic anhydrase), and exogenous causes (ingestion of acids such as ammonium chloride and hydrochloric acid and volume resuscitation with saline).

Patients with hyperchloremic acidosis have no symptoms attributed to hyperchloremia necessarily. However, acidosis can have many side effects. Headache, lack of energy, nausea, and vomiting are common complaints. Additionally, severe acidosis might cause stupor, coma, myocardial instability, or even cardiac arrest. It is expected to see an increase in respiratory rate as the body attempts to decrease CO_2 in compensation; however, in long-standing disease, this may lead to muscle fatigue and respiratory failure [41].

21.8 Acid-Base Balance in Neurocritical Care

Acid-base metabolic and respiratory disorders occur as single and mixed entities. Acid-base balance is maintained by normal pulmonary excretion of carbon dioxide, metabolic utilization of organic acids, and renal excretion of nonvolatile acids.

A patient is considered to have acidemia when arterial pH is less than 7.35 and alkalemia when arterial pH is above 7.45. In acidosis, a process occurs that tends to lower the pH of the extracellular fluid, which can be caused by a drop in the concentration of serum bicarbonate (HCO_3) and/or an increase in PCO_2. In the case of alkalosis, we have a process that tends to increase the pH of the extracellular fluid, which can be caused by an increase in the serum concentration of HCO_3 and/or a decrease in PCO_2.

There are four primary acid-base disorders: metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. It is essential to always remember that there are mixed acid-base disorders, when there is the simultaneous presence of more than one acid-base disorder.

21.8.1 Acidosis in Neurocritical Care

21.8.1.1 Metabolic Acidosis

Metabolic acidosis commonly aggravates critical illness. It is a pathologic process that increases the concentration of hydrogen ions in the body and reduces the serum concentration of HCO_3 and pH. It can occur by three main mechanisms: increased acid

generation (lactic acidosis, ketoacidosis, ingestions, or infusions), loss of bicarbonate (severe diarrhea), or diminished renal acid excretion (proximal renal tubular acidosis).

Several factors contribute to the regulation of brain tissue pH: PCO_2 of brain tissue, physiological buffer systems, and metabolic production of acidic substances (mainly lactate, the most important acid generated by brain metabolism). Patients with intracranial trauma may present states of lactic acidosis that occur with tissue hypoperfusion that may be secondary to systemic hypotension. Brain tissue acidosis is associated with damage after traumatic and ischemic injuries, as the low pH of the tissue contributes to the formation of edema [42, 43].

21.8.1.2 Respiratory Acidosis

Respiratory acidosis is a disorder that increases arterial PCO_2 and lowers pH, usually associated with hypoventilation. Hypercapnia should always be suspected in neurocritical patients due to the risk of hypoventilation associated with changes in the state of consciousness. Other common etiologies are the use of sedatives, deficits in the functioning of the respiratory muscles, or thoracic cage disorders.

At the time of diagnosis, primary care should be focused in airways, breathing, and circulation; stabilize the airways by analyzing the need for oxygen therapy and mechanical ventilation. Respiratory acidosis can have several effects on CNS, including changes in cerebral blood flow, changes in neuronal function, and changes in consciousness and seizures. On the other hand, hypocapnia promotes cerebral vasoconstriction and decreases intracranial pressure. Severe hypercapnia can cause loss of consciousness (hypercapnic narcosis) triggered from a $PaCO_2$ greater than 90–120 mm Hg.

In patients with severe head trauma, tissue acidosis occurs during the first hours, due to an increase in PCO_2 brain tissue. This change occurs as a result of insufficient CO_2 clearance due to impaired cerebral micro or macrocirculation, an increase in arterial CO_2, an increase in cerebral CO_2 production, and profound tissue acidosis with an increase in CO_2 generation via carbonic anhydrase reaction; there is also an increase in lactate concentrations. Patients with aneurysmal SAH vasospasm are significantly related to lower pH and increased PCO_2 in brain tissue [42, 43].

21.8.2 Alkalosis in Neurocritical Care

21.8.2.1 Metabolic Alkalosis

Metabolic alkalosis is a disorder that increases the serum concentration of HCO_3 and pH, usually accompanied by hypokalemia, and can be the result of several mechanisms such as gastrointestinal loss of hydrogen ions, excessive loss of renal hydrogen ions, diuretics administration, and retention of bicarbonate ions. In neurocritical patients, clinical presentation with severe vomiting commonly develops metabolic alkalosis due to loss of acidic gastric fluid.

Patients with metabolic alkalosis usually develop respiratory compensation characterized by hypoventilation and an elevation in arterial PCO_2. Symptoms can be lassitude, easy fatigability, muscle cramps, and postural dizziness, and the clinical consequences of severe metabolic alkalosis are neurologic manifestations, hypoventilation, and decreased systemic oxygenation [42].

21.8.2.2 Respiratory Alkalosis: Early Ventilation

Respiratory alkalosis is a disorder that reduces arterial PCO_2 and raises pH. Hypocapnia and acute alkalosis decrease cerebral blood volume and the oxygen supply leading to decreased perfusion in organs and tissues which increases risk of secondary brain injury. Hypocapnia also causes a severe inflammatory response to brain tissue, and a tissue lactic acidosis appears to occur almost immediately. For TBI, hyperventilation is recommended as temporizing strategy to reduce raised ICP. Prolonged prophylactic hyperventilation with $PaCO_2 \leq 25$ mmHg is discouraged.

An optimized ventilation for TBI starts with lower $ETCO_2$ and pCO_2 since manual ventilation in the primary care is necessary avoiding desaturation episodes. Additionally, continuous capnometry ventilation avoids hyperventilation and formation of oxygen free radicals [44].

21.9 General Recommendations

(a) Avoid secondary injury through adequate fluid and electrolyte management, and control of acid-base disorders is the main goal of neurocritical care.
(b) Hyponatremia is the most common electrolyte imbalance in patients with neurological disease. SIADH and CSW syndromes are rare in clinical practice. However, ICU physicians should be familiar with those conditions.
(c) Electrolyte disturbances are often caused by over-administration and are preventable in the majority of cases.
(d) The care of the neurocritical patient is provided by a multidisciplinary team trained and specialized to recognize and deal with patients, often in situations of risk for irreversible neurological injury.

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Chapter 22
Basic Aspects of Nutrition in Neurocritical Care

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22.1 Introduction

The main challenge of neurocritical care is to avoid secondary insults to an injured brain. After acute neurologic insult, critically ill patients develop a hypermetabolic and hypercatabolic state with demanding nutritional needs [1, 2]. It is estimated a 200% increase in energy expenditure, negative nitrogen balance for up to 4 weeks, water and salt retention, poor glycemic control, and immune dysfunction immediately after a traumatic brain injury [3]. Therefore, early nutritional therapeutic support is mandatory to relieve exacerbated catabolism and inflammatory cascade in those severe conditions to reduce morbidity and mortality [4, 5]. Approximately 30–50% of patients in neurologic intensive care units (ICU) are malnourished [2]. There is no consensus in determining nutritional needs for those patients. Individual therapy should be aimed for satisfactory clinical outcomes [6, 7].

The main acute neurologic diseases that require intensive care are traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), acute ischemic, and hemorrhagic stroke. However, nutrition issues were addressed only in TBI guidelines [1, 3, 8]. The American Heart Association/American Stroke Association did not address nutritional aspects for patients with acute stroke [9, 10].

In this chapter, we have reviewed aspects of nutritional support in neurocritical care addressing benefits, challenges, route of access, types of nutritional therapy, and assert recommendations for a systematic approach for nutritional planning in neurologic ICU.

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22.2 Hypermetabolism and Hypercatabolic State in Critical Care

The metabolic response after neurologic injury starts immediately after its onset and reaches an inflammatory peak on days 2–4. In the phase of persistent hypermetabolism, lasting for at least 10 days, there are high oxygen consumption, increased lactate production, and exacerbated loss of nitrogen—main energy source to support the inflammatory demand. Thus, amino acids are released in the circulation as a consequence of hormonal control from increased glucagon, adrenergic tone, hypercortisolism, downregulation of thyroid hormones, and increased insulin resistance to maintain continued moderate gluconeogenesis. Additionally, there are compensatory hemodynamic changes after amino acids secretion with augmented cardiac output and low vascular resistance. There is a preferential use of glucose in the central nervous system (CNS) and immune cells, while liver and heart cells can be supplied by fatty acids, pyruvate, or even lactate. This condition was named as hypermetabolism-multiple organ failure (HOF) which is a condition with an urgent and high demand for the exogenous supply of amino acids [2, 11].

22.3 Benefits of Optimized Nutrition in Critically Ill Patients

22.3.1 Immune-Modulation and Infection Prevention

Several patients under neurocritical care have infectious complications during their stay in ICU. Nearly 20% of late death in these patients are attributed to sepsis, which are attributed to disturbances in cell-mediated immunity. The hypermetabolic state triggered by the acute brain injury promotes the secretion of catabolic hormones (e.g., corticosteroids and catecholamines) and inflammatory cytokines (e.g., IL-1, IL-6, and tumor necrosis factor-α). This mechanism results in increased CD8 cytotoxic cells (T suppressor) and reduction in CD4 (T-helper/inducer) surface antigens. It was hypothesized that early nutrition therapy would prevent infection through increasing CD4 cells (C4–C8 ratio) with improvement in cellular response to infectious agents [12]. However, this hypothesis was not confirmed in the latter randomized clinical trials [13]. The exact mechanism has not been determined thus far. However, it is common sense that early enteral nutrition triggers the secretion of anabolic agents, anti-inflammatory cytokines (IL-8) prevents starvation-induced immune depletion and reduces colonization in the digestive tract preventing bacterial translocation [13].

New strategies of nutrition therapy have been suggested with immune-enhancing formulas for enteral nutrition with modulatory function against systemic inflammatory response. Immune enhancing nutrition consists in enteral diets with additives of probiotics, nucleotides, Omega-3 fatty acids, and arginine. Omega-3 fatty acids

(docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) are essential for cell repair after inflammatory damage, improve lymphocytes function, and less immunosuppressant prostanoids production [14]. Glutamine and arginine are essential amino acids for protein synthesis with additional specific properties—glutamine enhancing neutrophil phagocytic activity and arginine involved in the production of nitric oxide in the inflammation process [4, 13, 15]. Clinical trials and a recent meta-analysis have confirmed the benefits of an immune-modulating diet compared to a standard formula with regard to reduction of infection rate, morbidity, and mortality of neurocritical patients [4, 15, 16].

22.3.2 Benefits on Ventilatory Support

The length of mechanical ventilation in ICU is an important variable to assess outcomes in intensive care. To evaluate the effectiveness of nutrition therapy in clinical trials is mandatory to consider this variable. Malnutrition in critically ill patients has marked protein loss in the first day after injury reaching up to 16 g per day [15, 17]. Therefore, the weakened respiratory muscles in addition to the blunted respiratory response to hypercarbia and hypoxia, increased risk for developing pulmonary complications (e.g., atelectasis and pulmonary congestion), hypoperfusion and anemia result in impaired respiratory drive, prolonged time under mechanical ventilation, and higher risks of ventilator-associated pneumonia [6, 16, 18]. Furthermore, head-injured patients are at high risk of broncho aspiration after the loss of consciousness in a setting of altered immune function, which is favorable to the development of aspiration pneumonia.

There is strong evidence of reduction in days spent under ventilatory support in patients who underwent early enteral nutrition in ICU [4, 19].

22.3.3 Optimized Gastrointestinal Function

The hypermetabolic state combined with prolonged fasting in neurologic critical ill patients is a harmful combination for gastrointestinal functioning. Head-injured patients present gastrointestinal dysmotility, delayed gastric emptying [3], mucosal atrophy with decreased absorption of macronutrients, and impaired expression of gut-lymphoid tissue (GALT) [8]. Although, there is a high incidence of intolerance to enteral nutrition in neurologically ill patients, an early nutrition therapy, started within at least 48 hours, enhances mucosal blood flow and preserves its structural integrity, improves GALT expression with a better absorption of nutrients, and reduces the risk of bacterial translocation [8, 15, 20]. Additionally, glutamine is the primary source for the regeneration and function of small intestinal epithelial cells and for immune cells [21].

22.3.4 Benefits on Wound Healing

Patients in neurologic ICU who underwent surgical intervention (e.g., decompressive craniectomy and intracranial pressure monitoring) or with associated burn or abrasive wounds in high-energy multiple trauma require adequate nutritional status for satisfactory wound healing. When analyzing infection in critically ill patients, wound infection rate varies from 5% to 13% in most clinical trials addressing the benefits of nutrition therapy to prevent infectious complications [19]. It is noteworthy that unhealed wounds are an important entry point for bacteria and other microorganisms.

22.3.5 Brain Regeneration and Neurological Outcomes

Neurologic outcomes on diffuse neurological injuries (e.g., diffuse axonal injury and diffuse cisternal subarachnoid hemorrhage) are uncertain and depend on a combination of multifactorial variables from medical intensive care to cognitive and motor rehabilitation. Adequate nutrition therapy is necessary to prevent catabolic metabolism in the neurological environment preserving healthy cells and neurological function. The Cochrane meta-analysis addressing nutrition for head-injured patients suggests a tendency for a decreased mortality and less disability in the follow-up in patients who underwent early initiation of enteral nutrition. Several basic science research works have investigated the regeneration pathways of the injured brain. Protective strategies should target inflammatory cascades in the CNS, control cell death, and prevent oxidative stress. Micronutrients such as vitamin C and E, and some amino acids (e.g., taurine and arginine) attenuate oxidative stress markers in neuronal tissue and inflammatory cytokines (TNF-α, IL-6, caspase-3) preserving more neuronal tissue for better functional outcomes [12, 16, 22].

22.4 Clinical Assessment of Neurocritical Patients for Nutritional Planning

Clinical comprehension of different phases of illness is necessary for the nutritional plan. Pamplin et al. [23] have suggested a phases-of-illness diagram to facilitate communication in the interdisciplinary healthcare team to improve patient care and outcomes. Each phase has different severities of illness, goals of care, and treatment objectives. During ICU stay, patients might be stratified in four different phases [16]:

1. Acute/active resuscitation (1–2 days)
2. Stabilization/persistent inflammation phase (3–7 days)

3. Stable/weaning/chronic disease
4. Recovery/rehabilitation

In phase 1, active resuscitation is at highest priority. Fasting is recommended at this stage. For patients at high nutritional risk, lipid-free total parenteral nutrition might be considered. Early enteral nutrition is a disease-modifying therapy in phases 2 and 3. At this stage, continuous body mass consumption monitoring is necessary for adequate brain metabolism and homeostasis. In the recovery phase, the transition to oral diet is the main goal with adequate support of a multidisciplinary team [16, 23, 24].

Once patients are grouped in a framework of severity of illness, they should be evaluated individually. An adequate clinical examination of the gastrointestinal tract is a prerequisite to determine a feeding regimen. Presence of abdominal distension and absence of bowel sounds limit early initiation of enteral diet. Diarrhea should be interpreted as possible intolerance to the diet composition or route of access. However, *Clostridium difficile* colitis should always be suspected. In critically ill patients with prolonged acute phase and persistent hypercatabolism, associated septic shock, pancreatitis, and paralytic ileus should be considered [25].

The clinical history of the neurologic injury is determinant for nutrition therapy. The main neurologic conditions—TBI, stroke, subarachnoid hemorrhage—have divergent energetic demands [5, 6]. Patients with TBI should be comprehended as victims of multiple traumas. The Glasgow coma scale score at admission, presence of intracranial hypertension, associated facial/skull base fractures, and urgent neurosurgical procedures should also be considered for implementation of nutrition support.

22.5 Challenges in Nutrition of Neurocritical Ill

22.5.1 Timing of Initiation

The European Society for Clinical Nutrition and Metabolism (ESPEN) [16] recommends early enteral nutrition for critically ill patients with a cutoff of 48 hours. However, there is no consensus in the definition of “early” initiation of nutrition therapy. Some authors suggest the first 24 hours as early acute phase or even as late as 7 days after admission. The Brain Trauma Foundation (BTF) suggests that the basal caloric replacement should be reached at least by the fifth day and at most by the seventh day based on limited evidence. In this study, it was considered patients who underwent to early initiation of enteral nutrition within the first 48 hours, but also those patients who received more than 2.5 L of formula within 72 hours [26]. Efforts have been made toward early enteral nutrition. However, established contraindications should be respected. In this case, TPN should be implemented within 3–7 days [16].

22.5.2 Medications

Medications should be taken into consideration for nutritional planning in neurologic ICU. Main medications with potential complications are listed below.

(a) *Sedatives*

Hypermetabolism and catabolism rate in critical care are compensated by several medical treatments. Sedation is an important strategy for attenuation of exacerbated inflammation and brain injury. However, the daily energy expenditure and protein need should be adjusted to this induced "resting state" [3].

Benefits of propofol in neurologic injury were attributed to intracranial pressure control. However, it did not show improvements in mortality or neurologic outcomes at 6 months follow-up. Additionally, this medication is an important source of fatty acids. The lipid concentration of propofol is 1.1 kcal/mL which should be considered as a large calorie source in the nutritional planning [16, 27].

(b) *Hyperosmolar therapy*

The BTF suggests the use of mannitol as hyperosmolar therapy to control raised ICP (0,25–1 g/kg). Although this strategy has several hemodynamic benefits in critically ill patients, it has dehydrating properties that should be avoided. Therefore, keeping an adequate mean arterial pressure (MAP) is necessary and a multidisciplinary team should be aware about the estimated amount of amino acids and sodium administered [1, 8, 28]. The tube feeding syndrome characterized by hypernatremia, azotemia, and dehydration might be the consequence of large amounts of protein administered in relatively dehydrated patients and moderate intake of sodium [29].

(c) *Medications and glycemic control*

In the acute phase, adrenergic agents and catecholamines are often used for active resuscitation. However, those medications are usually related to glucose release which influences intensive glycemic control required for neurocritical care [12].

(d) *Medications causing acute diarrhea*

Acute diarrhea is a marked symptom of enteral nutrition intolerance. Different clinical factors should be considered, including medications that have osmotic properties or with inflammatory reactions in the gastrointestinal tract, such as: antibiotics, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, prokinetics, laxatives, and sorbitol-containing preparations [12].

22.5.3 Gastrointestinal Intolerance to Enteral Nutrition

Gastrointestinal (GI) tolerance is clinically detected by the absence or abnormal bowel sounds, vomiting, abdominal distension, diarrhea, GI bleeding, reduced passage of flatus and stool, or abnormal abdominal radiographs. This might also be inferred based on high nasogastric tube output or high gastric residual volumes [12].

The European Society of Intensive Care Medicine (ESICM) [30] suggests some strategies to reduce GI intolerance rate. It is recommended that EN starts at a slow rate (10–20 mL/h) while carefully monitoring for intolerance symptoms. If well tolerated, it should be increased slowly. However, depending on the magnitude of abdominal symptoms in case of intolerance, EN should be ceased and imaging diagnosis should be performed for investigation of severe diseases (e.g., mesenteric ischemia) [30].

Increased GI intolerance is expected for deeply sedated patients with or without concomitant use of neuromuscular blocking agents, and is expected to occur in up to 50% of patients on mechanical ventilation. In patients with high doses of vasoactive drugs, the mesenteric ischemic injury should be included as a differential diagnosis [31].

Strategies have been employed to optimize the delivery of EN. Starting at a minimal rate based on feeding protocols, use of motility agents, the discrete elevation of the head of the bed, and preference for small bowel feeding through postpyloric tube [18].

22.5.4 Interruptions of Enteral Nutrition

Nutritional support in ICU is accurately estimated to supply adequate energetic requirements after neurologic injury. The main cause of interruptions to feeding is related to fasting for medical interventions. Other reasons for EN interruptions are related to severe symptoms of GI intolerance and mechanical failure of feeding tubes—misplacement, tube occlusion, inadvertent removal. For those patients with suboptimal EN due to frequent interruptions, protein supplementation is recommended. Clinical trials have suggested that continuous infusion of EN provides greater volume with less GI intolerance and interruptions when compared to bolus EN delivery [3, 12, 25, 26].

In large clinical series, Chapple et al. [3] registered interruptions to feed in 66% of patients. From these, 34% had four or more days where feeding was interrupted. The mean duration of interruptions was 25 hours per patient. Lambert et al. [32], suggest that EN can be safely delivered up to the time of transport to the operating room with a low risk of aspiration event.

22.5.5 Refeeding Syndrome

Refeeding syndrome[12, 33] is a series of metabolic events caused by the provision of nutrients, primarily carbohydrates, to a nutritionally compromised patient. It has been described in intensive care settings due to a large caloric load in parenteral and enteral nutrition in critically ill patients. Patients at higher risk to develop refeeding syndrome, are those with prolonged period of NPO, low body mass index (BMI) or obese patients and those with chronic ingestion of alchool. For those patients,

feeding progression should be slower in permissive underfeeding strategy to reach the energy intake goal in 3–4 days.

Clinical manifestations of RFS are secondary to hypophosphatemia, hypokalemia, and hypomagnesemia. The main manifestation is related to muscle weakness, which leads to respiratory depression. Neurologic manifestations include sensorium changes, encephalopathy, and paralysis [12, 33].

22.6 Determination of Energy Requirements

Determination of energy requirements in neurocritical care is a challenge in ICU. Energy expenditures might be estimated by general formulas (e.g., 25–30 kcal/kg/d) or based on indirect calorimetry (IC)—the gold standard method to determine energy needs in clinical nutrition. The main bias in determining nutritional support based on fixed formulas is the dynamic progression of neurologic diseases in ICU.

Variables in neurologic intensive care that should be considered to estimate metabolic rate of critically ill patients include phases-of-illness, ventilator settings, sedation, presence of intracranial hypertension, muscle activity and tone, body temperature, uncontrolled seizures in addition to individual variables of body weight, body mean index (BMI) and age [5, 8, 16]. The poor predictive value of these equations to determine energy needs have been reported in several studies. Clifton et al. [2] reported a measured resting energy expenditure (mREE) of 100–125% of expected values in patients in barbiturate coma after TBI. Following stimulation, sweating, or fever, these values reach up to 250%. The main standardized equations are listed in Table 22.1.

Indirect calorimetry is the most accurate method to measure resting energy expenditure to target nutritional requirements and monitor nutritional support. It consists of a dynamic, day-to-day clinical assessment of energy needs. Recent meta-analysis showed a reduction of short-term mortality when using IC. Other

Table 22.1 Equations for estimation of energy expenditure [7]

Testing normal volunteers	Harris Benedict	Men: 13.75(wt) + 5(ht) – 6.8(age) + 66 Women: 9.6(wt) + 1.8(ht) – 4.7(age) + 655
	Mifflin St. Jeor	Men: 10(wt) + 6.25(ht) – 5(age) + 5 Women: 10(wt) + 6.25(ht) – 5(age) – 161
Testing hospital patients	Penn State	PSU(HBE) = HBE(0.85) + Tmax(175)d + Ve(33)d – 6344 PSU(HBEa) = HBEa(1.1) + Tmax(140)d + Ve(32)d – 5340 PSU(m) = Mifflin(0.96) + Tmax(167)d + Ve(31)d – 6212
	Swinamer	BSA(941) – Age(6.3) + T(104)c + RR(24)c + Vt(804) c – 4243
	Ireton-Jones	Wt (5) – Age (10) + Male(281) + Trauma(292) + Burn(851)

Wt weight, *ht* height, *PSU* penn state equation, *HBE* Harris Benedict equation, *T* body temperature, *Ve* expired minute ventilation, *BSA* body surface area in meters squared, *RR* respiratory rate in breaths/min, *Vt* tidal volume in L/breath

clinical trials showed, reduction in 60-day survival and reduction in the infection rate [16].

For the ESPEN guideline, the definition of underfeeding in critical care is an energy administration below 70% of the defined target, while overfeeding is 110% above the defined energy expenditure [16].

22.6.1 Permissive Underfeeding Strategy

Clinical trials have supported a short programmed permissive underfeeding with energy restriction of nonprotein calories. The energy-restricted diets could reduce adaptive or maladaptive responses to systemic inflammatory response, in addition to benefits on longevity biomarkers, insulin sensitivity and metabolic inflammation, and oxidative stress. However, Arabi et al. [34] in a multicenter randomized clinical trial did not demonstrate a significant effect on mortality in patients that received moderate amounts of nonprotein calories (40–60% of estimated caloric requirements) as compared to patients that received standard 70–100% of caloric requirements. The Committee on Nutrition, Trauma, and the Brain Food and Nutrition Board of the Institute of Medicine suggest an early initial permissive underfeeding for TBI with the administration of 50% of mREE increasing to 25–30 kcal/kg/day within a period of 2 weeks [16, 30].

22.6.2 Energy Requirements in Different Neurologic Diseases

(a) *Traumatic Brain Injury*

TBI is the most severe neurologic disorder in terms of energetic demands [2, 5]. The hypermetabolic state is the result of the release of several cytokines and counter-regulatory hormones. Increased nitrogen excretion keeps elevated for up to 4 weeks [2]. Even though adequate caloric support is delivered with 2.3 g of protein/kg/day for patients with severe TBI (GCS < 8), they maintain negative nitrogen balance, with weight loss and hypoalbuminemia [35].

Early enteral nutrition is encouraged within 24–48 hours. The Brain Trauma Foundation recommends that mREE should be measured by indirect calorimetry. However, if it is not available, it should be administered 25 kcal/kg/day, or 70% of the estimated mREE in 7–10 days [1]. The ASPEN [12] and ESPEN [16] also suggest early initiation of EN, as soon as the patient is hemodynamically stable, with immune-modulating formulations or supplemented with eicosapentaenoic acid or docosahexaenoic acid.

(b) *Subarachnoid Hemorrhage*

Subarachnoid hemorrhage (SAH) creates a significant catabolic state with elevated mREE and nitrogen deficits. There was an evidenced correlation of elevated mREE and poor-grade SAH in Hunt-Hess and Fisher grading scales [5, 36]. Additionally, surgical clipping of ruptured aneurysms might contribute to

the catabolic state due to surgical-related trauma and prolonged fasting before and during the procedure. It is noteworthy that the most recent guidelines for acute management of SAH do not discuss nutritional support in this disease.

(c) *Stroke*

Patients with acute neurologic disorders present an elevated need for calories and protein. In ischemic stroke, patients are at high risk of aspiration. Those patients are often malnourished with swallowing difficulties which increases the risk of infection and poor outcomes at 6 months. In addition, more than 40% of acute stroke patients present with negative nitrogen balance before the ictus [37].

22.7 Macronutrients

22.7.1 Proteins

The nitrogen balance is the most challenging condition to be compensated with nutritional support. Critical illness is associated with marked proteolysis and muscle loss (approximately 1 kg/day). A high protein intake is necessary as anabolic resistance to hypermetabolism. However, the amount of protein provided is frequently less than nitrogen loss due to technical difficulty with commercial product composition not adequately enriched with protein. The clinical guidelines recommend an amount of 1.5–2.0 g/kg/day of protein in enteral nutrition formulas, more than 50% of mREE [1, 12, 16]. Several observational studies confirmed the benefits of high protein delivery on improvement of body protein balance, on reducing the duration of mechanical ventilatory support, and better survival rates. Zusman et al. [38] showed significant improvement in survival of patients receiving >1.3 g/kg/day with a gain of 1% survival of each 1 g of protein administered.

The beneficial effects of high amino acid concentration formulas on the improvement of creatinine clearance and in the nitrogen balance did not show any benefit in survival or clinical endpoints in clinical trials [39]. In patients under permissive underfeeding by a limited amount of nonprotein calories, renal replacement therapy was less required compared with patients receiving a standard caloric diet [34].

The optimal timing for increment in protein intake is also controversial. In recent studies, the overall recommendation is an early protein administration reaching 1.2 g/kg/day up until the fourth day after admission monitoring signs of overfeeding and refeeding syndromes [12, 16].

22.7.2 Lipids

Lipids oxidation provides more than half of the energy utilized by the liver, heart, and skeletal muscles. Essential fatty acids (FA) are recommended at a dose of 8 g/day. However, a pure fish oil lipid emulsion might contain necessary composition of

other FA as an optimal source for pediatric patients. Of note, fat absorption is impaired in critically ill patients and lipid overload might impair lung and liver function in addition to relative immune suppression [16].

Hasadsri et al. [40] suggest that polyunsaturated fatty acids (PUFFA) may represent a critical function of neuronal repair and regeneration through control of glutamate-triggered excitotoxicity, injury-induced oxidative stress, and regulation in apoptotic cell death.

22.7.3 Carbohydrates

Glucose is the main energy source for the brain, immune cells, red blood cells, and renal medulla. Therefore, it should be widely available in a clinical setting that the brain is the main organ affected. However, glycemic control in neurocritical care is challenging with important deleterious effects of hyper- and hypoglycemia. Hypoglycemia is an important predictor of mortality in critically ill patients. Microdialysis studies showed that hypoglycemia produces significant neuroglycopenia that contributes to neurological distress and secondary brain injury. Hyperglycemia promotes important effects on the immune system with increased vulnerability to nosocomial infections. Meta-analysis addressing glycemic control clinical series suggested that intensive glycemic control with insulin therapy leads to higher mortality with increased risk of hypoglycemia compared to an intermediate strategy targeting glucose levels not higher than 200 mg/dL [41, 42].

22.8 Micronutrients

Supplementation of micronutrients with important antioxidant properties against hypermetabolism and systemic inflammation is necessary in nutrition therapy. Several randomized clinical trials have shown a reduction of infectious complications and of mortality with administration of micronutrients in safe doses (5–10 times dietary reference intakes).

The main micronutrients investigated were some minerals—selenium and zinc—and vitamins such as vitamin C, E, and beta-carotene. Low serum levels of zinc and selenium have been associated with intense systemic inflammation, severe infectious complications, and poor outcomes. Vitamin C and E are essential antioxidants against systemic inflammation. In addition, vitamin C has properties to induce the production of nitric oxide synthase and also prevents thrombin-induced platelet aggregation restoring microcirculatory flow [12, 38].

22.9 Route of Access—*Enteral* vs. *Parenteral*

The early enteral nutrition is the most recommended nutrition support in clinical guidelines of TBI. The beneficial effects of EN include the decrease on infection rates, provide better glycemic control, maintain integrity of the GI mucosa, stimulate expression of gut-associated lymphoid tissue are well documented. Previous meta-analysis showed significant reductions in morbidity, period under mechanical ventilation, and ICU length-of-stay. Furthermore, high caloric administration through TPN has been associated with cases of refeeding syndrome [33].

EN should be delayed in case of hemodynamically unstable shock, uncontrolled life-threatening hypoxemia, hypercapnia or acidosis, active upper GI bleeding, bowel ischemia, abdominal compartment syndrome, and gastric aspirate volume >500 mL/6 h [16].

22.10 Recommendations in Nutrition Support in Neurocritical Care

(a) Early enteral nutrition—within 48 hours.
(b) Indirect calorimetry (IC) to measure energy expenditure.
(c) If IC is not available, an estimate by general formulas with continuous clinical assessment.
(d) Start EN at slow rates with prokinetic agents to avoid intolerance.
(e) Avoid EN interruptions.
(f) Preference for immune-enhancing formulas with supplementation of micronutrients and essential fatty acids.
(g) Understand energetic demands of different neurologic conditions and of intensive care strategies such as the use of deep sedation, vasoactive drugs, hyperosmolar therapy, and hypothermia.

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Chapter 23
General Principles of Neurosurgical Postoperative Care

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23.1 Introduction

The goal of postoperative neurosurgical care is to prevent or minimize complications related to anesthesia and the surgical procedure [1, 2]. Careful, frequent neurological assessments by neurology-trained staff are the cornerstone of postoperative neurosurgical care. However, management of systemic complications is an essential task that can help minimize serious neurological consequences [3].

The most commonly observed postoperative neurological complications of elective cranial surgery include decreased level of consciousness, cerebral vasospasm, refractory seizures, reoperation, hemiparesis, and intraparenchymal hematoma [3]. In non-elective surgery, intracranial hypertension (ICH), motor deficits, recurrent subdural hematoma, intraparenchymal hemorrhage, vasospasm, and seizures are also reported [4–6].

Postoperative systemic complications of elective neurosurgery include nausea and vomiting, hypotension, respiratory distress, and surgical site infection. In non-elective surgery, pain and nosocomial infections are also present [7, 8].

The overall mortality rate is only 1% after elective neurosurgery, compared with 29% after emergency neurosurgery, with postoperative complications increasing the risk of death in both groups. Early recognition and the management of complications are crucial for improve outcome of these patients [9, 10].

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23.2 Postoperative Monitoring of Neurosurgical Patients

The patient's neurological assessment score in the intensive care unit should be a simple assessment, developed and validated specifically to assess the postoperative neurosurgical neurological status [11, 12].

Although simpler in application, it should be sufficient for patients undergoing brain surgery, allowing the use by the multidisciplinary team, which facilitates communication between the different individuals involved in patient care [12]. In our institution, we usually perform pupil size and reactivity assessment and use the Glasgow Coma Scale (GCS) for summary evaluation.

There are several validated clinical and neurological assessment scales, such as the National Institute of Health Stroke Scale (NIHSS), the Mini Mental State Examination (MMS), and the Diagnostic and Statistical Manual of Mental Disorders (DSM). The main disadvantage of these assessment scales is that they are long and complex and therefore not easily applicable in the immediate postoperative period. Other neurological assessment scales, such as the Ramsay scale, Canadian Neurological Scale (CNS), and Nursing Delirium Screening Scale (Nu-DESC), are more suitable for the evaluation of postoperative and extubated neurosurgical patients [13, 14].

The main limitations of periodic assessments with clinical assessment scales include subjectivity and high interobserver variability, discontinuous records, observer difficulty in differentiating between deep sedation levels, and work burnout of nurses resulting from systematic application of the scales [15].

In general, postoperative patients will require only 12–24 hours of ICU-level monitoring and can then be discharged to the general floor. However, when complications occur, the time to detect and intervene on the problem will directly affect the recovery and the level of function the patient achieves in recovery. Planning of postoperative care begins at the preoperative assessment. A detailed assessment of risk factors for postoperative morbidity should be made including surgical and anesthesia related as well as of postoperative needs such as nutrition and analgesia. A comprehensive baseline neurological assessment must be completed.

Intracranial surgery is associated with significant morbidity (23.6%). The most frequent complications following neurosurgery are bleeding requiring transfusion, reoperation within 30 days of the initial operation, and failure to wean from mechanical ventilation. Significant predictors of complications include preoperative stroke, sepsis, blood transfusion, and chronic steroid use. The intensity of monitoring depends on the complexity of the operative procedure and any underlying premorbid condition. A high degree of clinical vigilance is required for the earliest identification of surgical complications [16].

Invasive neuromonitoring measures may be required in critically unwell patients admitted to intensive care unit following neurosurgery. Several techniques are now available for global and regional brain monitoring that provide early warning of impending brain ischemia and allow optimization of cerebral hemodynamics and oxygenation. Modern neurointensive care utilizes a combination of these

monitoring techniques (multimodal monitoring – like ICP monitoring, PtO2, microdialysis) to identify or predict secondary cerebral insults and guide therapeutic interventions. Developments in multimodal monitoring have allowed a movement away from rigid physiological target-setting toward an individually tailored, patient-specific approach [17].

The GCS, originally developed as a prognostic tool for head-injured patients, is now widely used to estimate the level of consciousness in critically ill patients and has also been shown to be a predictor of successful extubation in neurosurgical patients [18]. There are several shortcomings of the GCS: it may not detect subtle neurologic changes, it does not consider brainstem reflexes, and in intubated patients the verbal response cannot be examined, making the assessment of deeply comatose patients difficult.

Wijdicks et al. recently introduced a new coma scale, the FOUR Score [5]. In contrast to the GCS, it consists of four components: eye response, motor response, brainstem reflexes, and respiration. Though more time-consuming and more difficult to perform than the GCS, this new score offers important additional information [19].

Hypoxia and hypotension have been shown to be the two most important systemic secondary insults in neurosurgical patients. Therefore, oxygen saturation by pulse oximetry and blood pressure are continuously monitored. Continuous ECG is also routinely used as severe arrhythmias may occur in neurosurgical patients [20].

The most important monitor for postoperative neurosurgical patients is the repeated clinical examination. Imaging procedures should be used only when the result of the examination could lead to a change in treatment. The incidence of elevated ICP in the postoperative phase of patients with subarachnoid hemorrhage (SAH) or cerebral tumors is most likely underestimated. However, in this setting the impact of increased ICP on outcome has not been studied. For most patients the extent of specialized neuro-monitoring must be based on the clinical presentation and the experience of the responsible physician.

23.3 Prophylaxis for Venous Thromboembolism After Neurosurgery

The optimal prophylaxis against deep venous thrombosis (DVT) and pulmonary embolism (PE) for patients undergoing neurosurgical cranial or spinal procedures remains controversial. Neurosurgeons are performing more procedures on a wide variety of patients, many of whom are advanced in age and have multiple medical comorbidities. These multifactorial medical issues may necessitate the use of prophylaxis against DVT.

The incidence of DVT in neurosurgical practice is astonishingly high, with DVT reaching up to 25% in some reports, and PE up to 3%. Noteworthy, an analysis of the most recent trials so far published on this subject indicates that PE is one of the

major causes of death in neurosurgical patients, with a mortality rate ranging between 9% and 50% [21, 22].

However, not all neurosurgical patients are equal as they do not carry the same risk for DVT: those that pose particular concerns in terms of their perioperative management and prevention of postoperative DVT are traumatic brain injured patients, or those undergoing elective or emergent surgical procedures for vascular or neoplastic pathologies [23].

Although the use of low-molecular-weight heparin remains controversial in the setting of elective neurosurgical procedures, few investigators have assessed the efficacy and safety of this therapy in the setting of traumatic closed head injury. Norwood et al. reported on the safety of administering enoxaparin for PE prevention in patients with injuries resulting in ICH. Enoxaparin was given 24 hours after the time of admission or after the conclusion of surgery. The results of the study demonstrated progression of ICH in six (4%) of 150 patients after initiation of enoxaparin therapy [24].

For patients undergoing major neurosurgical procedures, the American Society of Hematology 2019 guidelines suggest against using pharmacological prophylaxis (conditional recommendation based on very low certainty in the evidence of effects). Patients undergoing major neurosurgical procedures are expected to receive prophylaxis with mechanical methods. Pharmacological prophylaxis may be warranted in a higher-risk subgroup of patients, such as those experiencing prolonged immobility following surgery. In addition, pharmacological prophylaxis could be considered for patients undergoing major neurosurgical procedures that carried a lower risk for major bleeding and in those patients with persistent mobility restrictions after the bleeding risk declines following surgery [25].

The methods that can be used in these scenarios include:

1. Sequential compression stockings/boots should be applied to all neurosurgical patients unless anatomic or functional barriers exist.
2. Low-molecular-weight heparin (i.e., enoxaparin 40 mg SC once per day or 30 mg twice per day).
3. Unfractionated heparin 5000 units 2 or 3 times per day.

23.4 Postoperative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) is one of the most common causes of patient dissatisfaction after anesthesia, with reported incidences of 30% in all postsurgical patients and up to 80% in high-risk patients [26]. The pathophysiology of PONV is complex and it involves various pathways and receptors. There are five primary afferent pathways involved in stimulating vomiting, as follows: the chemoreceptor trigger zone (CTZ), the vagal mucosal pathway in the gastrointestinal system, neuronal pathways from vestibular system, reflex afferent pathways from the cerebral cortex, and midbrain afferents. The etiology of emesis is multifactorial.

Table 23.1 Risk factors for post-operative nausea and vomiting

Patient	Intraoperative	Anesthesia	Postoperative
Female gender (the strongest patient-specific predictor) Previous PONV after surgery Nonsmokers (smokers: gradual desensitization of CTZ occurs) Age < 50 years Body mass index (recent data suggest no association)	Longer surgeries	Nitrous oxide use (stimulation of sympathetic nervous system with catecholamine release; increased abdominal distension resulting from exchange of nitrous oxide and nitrogen in gas introduced into gastrointestinal tract during mask ventilation) Continuous etomidate infusion as a part of balanced anesthetic technique Opioids (stimulation of receptors located in CTZ; weak predictor; no difference among different opioids)	Ambulation, sudden position changes, transport from the postanesthetic recovery unit (particularly after opioids) Postoperative opioids (dose-dependent; irrespective of route of administration; Nonsteroidal anti-inflammatory agents suggested to reduce opioid requirements)

The factors influencing the PONV depend on individual factors, intraoperative events, anesthesia, and postoperative factors (Table 23.1).

The following medications may be useful for treating PONV:

1. Ondansetron 4–8 mg

   Several studies have been performed with 5-HT3 receptor antagonists. Ondansetron is effective in the treatment of PONV, having a better effect against vomiting than nausea. It was shown that 8 mg of ondansetron at the end of surgery did not offer better efficacy than 4 mg [27].
2. Promethazine 6.25–25 mg

   Phenothiazines have antiemetic effects by blocking D2 dopaminergic receptors from the chemoreceptor trigger zone and central nervous system cortical centers. Promethazine still exhibits antihistamine and anticholinergic activities [28].
3. Antihistamine agents

   Antihistamines have antiemetic properties because of their ability to suppress vestibular stimuli and their anticholinergic and sedative effects. Dimenhydrinate is effective in PONV prophylaxis especially in patients at moderate or high risk, although no benefit has been shown compared to ondansetron. Its most common side effects are headache, drowsiness, and dizziness. However, sedation is a prominent side effect of treatment with promethazine in a dose-dependent manner.
4. Butyrophenones

   Butyrophenones have antiemetic effects by blocking D2 dopaminergic receptors from the chemoreceptor trigger zone of the posterior area. They have better effects against nausea than vomiting. Studies show that there are no statistical differences in PONV prophylaxis and occurrence of paraffects with droperidol (0.625 mg or 1.25 mg) or ondansetron (4 mg) [29]. Monitoring of the QTc interval is often required with repeated administration of droperidol.

5. Anticholinergic agents

   Anticholinergic agents are antagonists of M1 receptors in the cerebral cortex and H1 receptors in the hypothalamus and center of vomiting. They also suppress the noradrenergic system, improving adaptation to vestibular stimulation and are widely used in the management of kinetosis. Scopolamine transdermal therapy is effective in PONV prophylaxis, bringing better results in patients with past kinetic disease and opioid-induced nausea [30].

6. Corticosteroids

   Dexamethasone is a common medicine used in neurosurgical patients to treat brain edema. It blocks the synthesis of prostaglandins, which sensitizes nerves to other commonly involved neurotransmitters in emesis control. It also may have central effect by antagonizing 5-HT3 receptors or corticosteroid receptors in the nucleus tractus solitarius. Its side effects are gastrointestinal disorders and insomnia. Preoperative dexamethasone 8 mg enhances the postdischarge quality of recovery in addition to reducing nausea, pain, and fatigue. It is administered at the time of induction due to relatively slow onset of action [31]. Dexamethasone can also be used to control PONV in addition to use for post-operative edema

The rescue therapy should be initiated after the onset of PONV, and simultaneously, clinical evaluation should be performed to exclude inciting medications, e.g., opioids, or mechanical factors for nausea and/or vomiting. For treatment in ICU after surgery, the most widely studied rescue drug types are 5-HT3 receptor blockers. This class has better results in the treatment of vomiting episodes than nausea [32]. There is little information available on the use of other pharmacological classes in the treatment of PONV. Rescue PONV treatment should be started with a drug of a different class from prophylaxis.

23.5 Glucose Control

In the general inpatient population, both high blood glucose levels and low glucose levels are associated with unfavorable outcomes [33]. This is also true for neurosurgical patients. Both prospective and retrospective studies showed that hyperglycemia is a risk factor for poor outcomes in traumatic brain injury, and increases both short and long-term mortality in patients with primary intracerebral hemorrhage and wound infections following spinal procedures [34].

Surgical procedures themselves are known to induce intraoperative hyperglycemia [35]. On the other hand, anesthetics moderate glucose and glucose metabolism. For example, volatile anesthetics inhibit secretion of insulin in response to glucose and thus inhibit the stress induced hyperglycemia. Clinical and animal studies suggest that hyperglycemia exacerbates neurological damage due to brain ischemia [36, 37]. These results, in addition to those outlined above, emphasize the deleterious effects of poor glycemic control. Figure 23.1 presents the contributing factors to the development of hyperglycemia and its detrimental effect on clinical outcome.

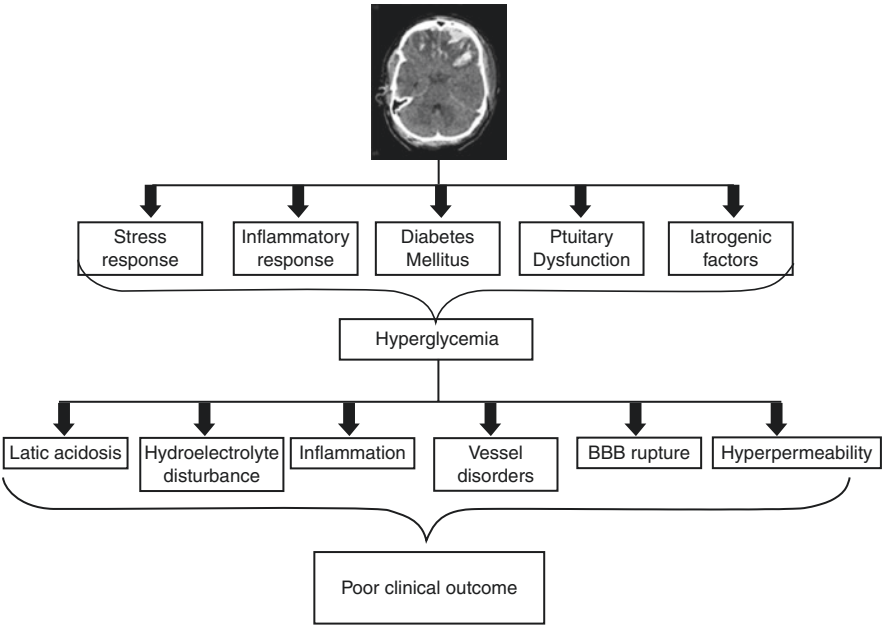

Fig. 23.1 Hyperglycemia in patients with brain injury and explaining a detrimental effect of hyperglycemia on clinical outcome

Finally, another factor that often induces hyperglycemia is the use of glucocorticoids. Risk factors for steroid induced hyperglycemia include traditional risk factors for type 2 diabetes mellitus, along with dose and duration of steroid usage. Glucocorticoids can induce hyperglycemia in patients without diabetes and worsen glucose control in established diabetic patients, with negative consequences outlined above [38].

Postoperative hyperglycemia is common due to surgical stress mainly in pediatric patients. Several studies recognize the importance of hyperglycemia in pediatric intensive therapy, increasing the patients' morbidity and mortality during hospitalization. In a neurosurgical setting, hyperglycemia is poorly studied. In a retrospective cohort study, Mekitarian Filho et al. found a hyperglycemia incidence of 62.6% in 198 children undergoing several neurosurgical procedures. However, multiple analysis did not show an association between hyperglycemia and longer length of hospitalization or stay in intensive care units, or mechanical pulmonary ventilation [39]. Oliveira Filho studied children who underwent elective neurosurgery and identified an association between hyperglycemia on ICU admission and an increased length of stay in the ICU and hospital [40]. Hirshberg et al. assessed children who were hospitalized in the ICU for over 24 hours and also found an association between the occurrence of hyperglycemia (blood glucose $\geq$150 mg/dl) during hospitalization in the ICU and a longer hospital stay [41].

Insulin increases glucose utilization and reduces the damage of hyperglycemia to brain cells. Owing to insulin resistance after traumatic brain injury, most studies use exogenous insulin and dynamically monitor blood glucose to fight against hyperglycemia after traumatic brain injury. In 2001, intensive insulin therapy (IIT) was implemented in intensive care units (ICUs) worldwide after a landmark clinical trial, which demonstrated clinical benefits of IIT in a surgical ICU. However, several trials could not confirm the findings of this study. One study demonstrated that maintaining low blood glucose with IIT (a blood glucose target of 81–108 mg/dL (4.5–6 mmol/L)) was in fact associated with an increased risk of mortality and even hypoglycemia (glucose < 40 mg/dL (2.2 mmol/L)), which may be due to the effects of IIT on cerebral glucose homeostasis after severe TBI [79, 80]. Another study also showed that IIT results in a net decrease in microdialysis glucose but an increase in microdialysis glutamate and lactate/pyruvate, with an adverse effect on the long-term recovery of neurological function. Therefore, in patients with severe TBI, decreased glucose levels with insulin can induce and aggravate secondary brain injury [42].

There are no specific studies for elective surgery. However, the studies analyzing traumatic brain injury and SAH showed that tight glucose control improved the neurological outcomes and reduced rates of infection. Mortality was not affected by the tight glucose control, but it did result in more hypoglycemic events. These results did not enable the authors to determine the optimal glucose targets, which means the question of appropriate glycemic targets remains, to a certain degree open [42]. Nevertheless, the available evidence suggest that the glycemic goal between 140 and 180 mg/dL appears to be appropriate for critically ill neurosurgical patients [43].

23.6 Approaches to Optimal Postoperative Hemoglobin

Patients with traumatic brain injury, SAH, intracranial hemorrhage (ICH), and acute ischemic stroke admitted to the Neurosurgical Intensive Care Unit (NICU) commonly develop anemia and require red blood cells (RBC) transfusion. A large-scale study examined 38,000 neurosurgical cases from the National Surgical Quality Improvement Program database and reported that the need for preoperative transfusion with more than 4 units of RBCs is significantly associated with complications in neurosurgery. It remains unclear whether anemia is a marker of disease severity, or an independent predictor of worsened outcomes. What is clear, however, is that RBC transfusion in neurosurgical patients deserves special attention and considerations [16].

Despite the potential worsening of outcomes observed in the literature, especially for critically ill cardiac patients, there is a pathophysiological concept of improving oxygen transport, which is of great importance for patients with neurocritical condition [44]. Decreased tissue perfusion becomes particularly important in neurosurgical patients due to the possibility of secondary cerebral injury. Oxygen

is so important to the stressed brain that oxygen carrying capacity should be normalized by optimizing circulating oxygen carrying hemoglobin. Low hematocrit has been associated with cognitive dysfunction, impaired vascular regulation, neurological injury, and increased mortality. Low hematocrit may lead to anaerobic cerebral metabolism, tissue acidosis, and promotion of cerebral inflammation.

The first major evidence of hemoglobin threshold in critically ill patients was published in 1999 by the Canadian group in the Transfusion Requirements in Critical Care Trial (TRICC), in which the transfusion strategy was segmented into a restrictive hemoglobin-defined regimen. Serum levels were below 7 g/dL and in a liberal regimen, defined as a 10 g/dL hemoglobin target value. The study of 838 critically ill patients showed that in both groups there was no significant difference in mortality at 30 days, but lower mortality was observed in patients with prognostic score <20 and patients under 55 years of age in patients who belonged to the restrictive transfusion strategy group.

Lelubre et al. described that the pathophysiology of anemia in these patients remains multifactorial, and "... whether anemia is merely a reflection of the high severity of the underlying disease or a significant determinant of neurological recovery in such patients remains undefined." The authors further state that "... there is insufficient evidence to provide strong recommendations for the optimal hemoglobin value to be achieved and which transfusion strategy should be chosen in this patient population" [45].

In anemia situations in patients considered normovolemic, there is activation of compensatory response mechanisms in the macro and microcirculation, aiming to keep the oxygen supply to the tissue constant. The main compensatory mechanism activated in anemic situations is the activation of so-called chemoreceptors, located in the aortic and carotid artery vascular wall and modulated by the sympathetic autonomic nervous system, which results in increased cardiac output and heart rate. Other important macrocirculatory parameters in patients with acute neurological injury are CSF and jugular venous oxygen saturation (SvjO2) [46].

Cerebral vasodilation is the most important event that occurs in response to tissue hypoxemia after brain injury in neuronal microcirculation, mediated by increased nitric oxide (NO) production through neuronal perivascular tissue and endothelial cells. Importantly, the regulation of brain microcirculation and the effect of NO on it are extremely complex and regulated by other components and systems. These systems include chemoregulation, self-regulation, and neurovascular coupling, in order to meet local cerebral metabolic demand and, probably, a direct autonomic neurovascular influence [47]. The interaction of these components has not yet been completely clarified and is part of a complex mechanism called cerebral self-regulation (RA), as described initially by Strandgaard and Paulson as the brain's ability to maintain CSF constant in the presence of changes in mean arterial pressure (MAP), between 50 mmHg and 150 mmHg [48]. This mechanism protects the brain parenchyma from damage caused by tissue hypo- or hyperperfusion. Schramm et al. demonstrated in a study of 16 patients with severe TBI that impaired nadir brain self-regulation mechanisms on the fourth day after trauma, followed by incomplete recovery until the seventh day [49]. Panerai et al. published in 2004 a

study of 32 patients with severe traumatic brain injury and found a significant correlation between loss of regulatory mechanisms of brain self-regulation and worse clinical outcome [50].

Blood transfusions have been found to increase brain tissue oxygenation (PTio2) in patients with head injury irrespective of their cerebral perfusion pressures, especially in those who were anemic with a low baseline PTio2 [51]. PTio2 of 15 mmHg is associated with increased risk of stroke and mortality. However, the extent of brain injury cannot be quantified based on PTio2. Microdialysis has made it possible to assess brain injury and changes in brain metabolism by monitoring neurotransmitters and other neurochemical markers present in the extracellular space [52]. The benefits of these novel methods of monitoring have yet to be fully elucidated.

The first randomized study involving traumatic brain injury patients was conducted by Robertson et al. including 200 patients, but the primary objective of this study was to evaluate the effect of erythropoietin (EPO) use on patients with 7 g/dL and 10 g/dL Hb and subsequent neurofunctional correlation according to Glasgow Coma Scale (GCS). No benefit was observed in the intervention group (EPO), and there was a greater number of thrombotic complications in the liberal group (i.e., patients with a hemoglobin threshold of 10 g/dL) [53].

About this issue our group performed a phase 2 trial. Our results differ from those of Robertson et al. in which maintaining a hemoglobin concentration of at least 10 g/dL did not result in improved neurological outcome at 6 months. However, these authors included a different TBI population and did not use hemoglobin concentration as an inclusion criterion. As a result, both groups had hemoglobin average concentrations greater than 9 g/dL at all reported time points. This hemoglobin concentration is higher than the value that has been associated with cerebral hypoxia in experimental studies [54]. In our study, by including only patients with traumatic brain injury, with a hemoglobin concentration less than 9 g/dL, we created a difference between the groups, using a real restrictive transfusion strategy in the control group. The restrictive group had higher mean flow velocities in all studied cerebral arteries. Hospital mortality was significantly lower in the liberal group than in the restrictive group, and neurological outcome at 6 months also tended to favor the liberal group. These observations may be related to impaired cerebral oxygenation in patients in the restrictive group. However, cerebral oxygenation was not measured in our study, so we were unable to confirm this mechanism. Another hypothesis is that the worse outcomes in the restrictive group may have been related to the higher incidence of cerebral post-traumatic vasospasm as detected by serial transcranial Doppler [55].

There are all these important pathophysiological principles for avoiding the condition of anemia in the postoperative period of neurosurgery and in neurocritical patients. Still, controversy exists regarding thresholds for transfusion and what types of transfusions will benefit the most these patients. Evidence-based guidelines concerning blood transfusion in neurosurgery are also relatively scarce. Thus, transfusion medicine within neurosurgical practices are highly variable and often based on institutional preferences.

There have been no RCTs to date that have examined whether patients undergoing elective craniotomy benefit from either aggressive or restrictive perioperative RBC transfusion criteria. Alan et al. recently published the first large scale study examining the effect of perioperative anemia on outcomes in patients undergoing elective cranial surgery. Using the National Surgical Quality Improvement Program database, they identified more than 6500 patients who underwent elective craniotomy for brain tumor, developed perioperative anemia, but were not transfused. Anemia was defined as mild (hematocrit 30–38%), moderate (26–30%), and severe (<26%). The study found that perioperative anemia, irrespective of severity, was associated with increased hospital length of stay but not increased 30-day morbidity or mortality [56].

Complex brain tumor resections are often associated with significant amounts of blood loss due to increased vascularity and inherent hemostatic challenges. Moreover, skull base surgery can be complicated by cerebral vasospasm. Wei et al. reported that post-operative fibrinogen deficiency was closely associated with poorer clinical outcomes and increased need for blood transfusions [57]. The literature describing blood transfusions in brain tumor surgeries is particularly scarce.

Neurosurgical procedures can be complicated by significant blood losses requiring RBCTs. However, evidence-based practices concerning transfusion thresholds and indications among the variety of neurosurgical diseases are limited. The complications of blood transfusions should be considered along with the cerebral outcomes of each disease state. Although blood transfusions are a safe and effective method of increasing Hb concentration, few studies have investigated RBCTs with other blood components such as platelets, fresh frozen plasma, or cryoprecipitate in neurosurgical patients. In addition, the outcomes of most large studies are not controlled for the disease of individual patients. Therefore, further research is needed to better understand the optimal utilization of RBCTs to improve neurosurgical outcomes and to standardize patient care.

23.7 Postoperative Cerebrospinal Fluid Leak

The diagnosis and management of the patient with a cerebrospinal fluid (CSF) leak depend on the location of the leak, its etiology, and symptoms. CSF leaks can result from diverse etiologies, including trauma, hydrocephalus, tumor, infection, and iatrogenic and idiopathic causes [58]. Clinical manifestations range from frank drainage of CSF that is easily recognized to slow, intermittent leakage that can be difficult to diagnose. Localization of a CSF leak can also prove challenging. The pertinent anatomy and mechanisms of formation of cranial and spinal CSF leaks must be understood to diagnose and treat these lesions properly. A clear understanding of their natural history is also mandatory for making sound management decisions [59].

Leaks may be identified during the early posttraumatic period, or leak presentation may be delayed. An active surgical approach to closing CSF leaks from defects at the skull base may provide better long-term outcomes compared to more

conservative management, particularly in patients who have a prior history of ascending bacterial meningitis [6]. Delay in leak presentation may be attributed to resolution of associated brain edema, devascularization of tissue, formation of the fistula tract, and resolution of blood products, all of which can result in increased ICP [58].

A postoperative CSF leak occurs when CSF is able to travel from the intracranial space through an osseous defect in the skull base, due to disruption of the intervening dura mater [60]. Skull base surgeries, such as transsphenoidal surgery, suboccipital craniectomy, and functional endoscopic sinus surgery, increase the relative risk of CSF leak [61]. Moreover, resection of skull base tumors, including the anterior and middle cranial fossae and clivus, also increase the risk of CSF leak. CSF leak can result in intracranial hypotension, meningitis (both aseptic and bacterial), and cerebral abscess [62]. Sites of CSF leak tend to occur in regions of thin bone, including the cribriform plate and sphenoid sinus.

Postoperative infections after endonasal approaches for intra-sellar lesions, including bacterial meningitis, tend to have a low incidence of 1–10% [63]. This has been attributed to the use of perioperative antibiotics, frequent intraoperative irrigation, careful reconstruction with vascularized flaps, and no need for non-biodegradable materials left at the completion of the surgery. Risk factors for infection have been described as associated with complex tumors, presence of an external ventricular drain or shunt, and postoperative CSF leak.

23.7.1 When to Suspect of CSF Fistula in ICU

Patients in postoperative presenting with unilateral clear nasal discharge associated with nonspecific headache symptoms raise suspicions for rhinorrhea of cerebrospinal origin. Patients can also present with mental status changes, seizure, and meningitis, thereby requiring a high level of suspicion for accurate diagnosis [63, 64]. Rhinorrhea secondary to a CSF fistula can be provoked by placing the patient's face in a downward position and observing for leakage for several minutes. Patients with a CSF leak and benign intracranial hypertension may also display bilateral papilledema.

Beta-2 transferrin immunofixation is currently the gold standard for diagnosing CSF rhinorrhea. Beta-2 transferrin is found in CSF, perilymph, and the vitreous fluid of the eye. Perilymph is produced in small amounts, and contamination of other fluid with vitreous eye fluid is highly unlikely, allowing beta-2 transferrin to serve as a highly specific assay for the presence of CSF. This assay has been noted to have a sensitivity of 100% and a specificity of 71% for detection of CSF leaks [65].

Localization of the leak may be accomplished by direct visualization with diagnostic nasal endoscopy, although this technique is typically insufficient, particularly in patients without a history of sinonasal surgery. Radiologic studies can aid diagnosis with plain films, coronal computed tomography (CT) images, or magnetic resonance imaging (MRI) [66].

Cisternography with intrathecal radioactive isotope is a well-established method of confirming and localizing CSF fistulas when clinical suspicion of CSF rhinorrhea is present, but the leak has not been localized on CT or MRI [66].

Once a CSF fistula has been identified, management is dictated by the etiology of the leak, its location, and its flow volume. High-flow CSF leaks rarely close spontaneously and often require surgical intervention, mainly to nose. For low volume leaks, conservative measures may be employed like suture reinforcement, head positioning, and resting [67].

23.8 Postoperative Head CT

Neurosurgical services vary greatly on the elective cranial surgery management regarding postoperative head CT. Routine postoperative CT imaging is usually ordered in this scenario to avoid or detect any early postoperative complications such as intracranial bleeding, ischemia, or brain swelling. Furthermore, some surgeons may order it to assess the surgical technique (e.g., confirm the correct placement of electrodes and catheters after deep brain stimulation or ventricular shunting) and to obtain a benchmark of the postoperative anatomy for future comparisons.

This common practice within the first hours after neurological surgeries has been advocated since the introduction of CT in the 1970s [68]. Postoperative head CT studies are commonly ordered indiscriminately to rule out complications, and, in many neurological surgery units, patients must be "cleared" by CT scanning before being transferred for the ICU or ward settings. However, significant concerns over radiation exposure, costs, and hospital logistics involving excessive CT scans have arisen specially in the past decade [69].

At around 70 million head CT are performed each year in the United States [70]. Over the last 20 years, imaging services and associated costs have grown at about twice the rate of other technologies in health care [71]. Equally or even more important, the largest man-made source of radiation exposure to the general population is medical imaging. Since the 1980s, the average radiation dose received annually by the American population increased more than 7 times [72]. For example, a victim of SAH is expected to receive a mean cumulative radiation dose of 2.8 Gy during the index hospitalization [73]. Studies have estimated that each additional head CT is associated with a 0.07% increased lifetime risk of cancer as a result of radiation exposure [74].

While there are some conditions (e.g., postoperative neurological deterioration) that demand urgent head CT scanning, growing evidence suggests that routine, indiscriminate head CT may not be necessary. This universal postoperative head CT "strategy" lacks an evidence basis and has been maintained partly due to the tradition and dogma on the neurosurgical training.

Garret et al. prospectively evaluated a cohort of consecutive 801 head CT studies ordered for 462 patients admitted to a single neurosurgical service (University of California, Los Angeles) over a 4-month period. Among the total 126 postoperative

head CT images, only 6 scans presented positive findings and 1 scan (<1%) changed the patient management [72].

Fontes et al. retrospectively analyzed 892 intracranial procedures followed by an early postoperative CT scan performed over a 1-year period at Rush University Medical Center. These cases were classified according to postoperative neurological status: baseline, predicted neurological change, unexpected neurological change, and sedated or comatose. In the subgroup of comatose patients or those with neurological examination changes postoperatively, postoperative head CT yielded positive findings that led to nonsurgical or surgical interventions in 10–22% of cases. On the other side, in patients with postoperative neurological stability, head CT led to nonsurgical interventions in only 2.2–2.4% of cases, and no emergency surgical intervention was required due to the postoperative head CT finding [69].

On a retrospective review, Zygourakis et al. evaluated a database of 304 patients who underwent elective, nonruptured aneurysm clipping from 2010 to 2014 at the University of California, San Francisco. The number of postoperative head CT scans and its findings and effects on patient management were determined, as well as the associated hospital and imaging costs. Neurologically intact patients required 99 head CT scans, at a cost of $28,908, to obtain 1 head CT scan that influenced medical management. In contrast, patients with a focal neurological deficit required only 11 head CT scans, at a cost of $3212, to obtain 1 head CT scan that changed clinical management [75].

A common elective or semi-elective is chronic subdural hematoma evacuation. Chronic subdural hematoma recurs in 3–39% of patients after evacuation by means of neurosurgery [76–78]. The influence of routine follow-up head CT on the outcomes after surgical evacuation of chronic subdural hematoma was evaluated on a recent, randomized, controlled clinical trial – the only of its kind until now. At a single center, Schucht et al. randomized a total of 361 patients within 48 hours after surgery to undergo either follow-up CT at 2 days and 30 days after surgery or CT only if there was clinical deterioration or persisting neurologic deficit. The primary endpoint was survival at 6 months without severe disability, as determined by a score of 0–3 on the modified Rankin Scale (ranging from 0 to 6, with 0 indicating no neurologic impairment and 6 indicating death). They found no benefit for routine follow-up CT after surgery for chronic subdural hematoma over CT performed only in patients with clinical deterioration or persisting neurologic deficits. The CT group had more repeat surgeries and a mean overall medical costs per patient 18% higher than the costs in the no-CT group [79].

On a prospective, single center, cohort study, Schär et al. evaluated whether a regime of early extubation and close neurological monitoring without routine CT was safe. For a period of 3 and a half years, all cranial neurosurgical procedures performed at their service were followed up for the primary endpoint of return to the OR ventriculostomy outside the OR due to intracranial hemorrhage, edema, or acute obstructive hydrocephalus within 48 hours. Secondary endpoints were time to extubation after surgery, the rate of ordered emergency head CT scans within 48 hours, timing of CT imaging after surgery, duration of surgery, and 30-day mortality. Early extubation combined with close neurological monitoring was safe and

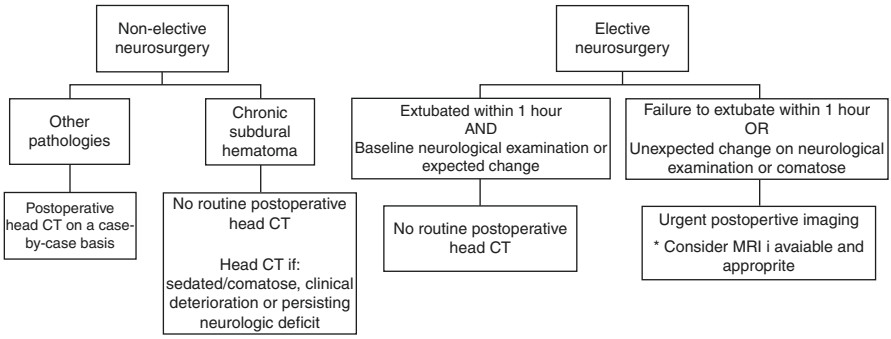

Fig. 23.2 Algorithm for a rational and efficient ordering of postoperative imaging

omitted the need for routine postoperative CT. Of note, failure to extubate within 1 hour was associated with a significantly higher risk of surgical intervention within 48 hours (rate 13.0%, $p = 0.004$, odds ratio 13.9, 95% confidence interval 3.1–62.4). Patients not extubated within 1 hour do need early CT, since they had a significantly increased risk of requiring emergency neurosurgical intervention [80]. The authors stressed that a dedicated, well-trained multidisciplinary team (neurosurgeon, neuroanesthesiologist, and neurointensivist) is required for the success of such approach of early extubation combined with close neurological surveillance.

One should also not forget that the advent of MRI and its increased availability supplanted CT imaging in specific situations, such as intrinsic and pituitary tumors, for the early, or even intraoperative, evaluation of the extent of resection adjuvant therapy planning. In these cases, a strategy of early MRI contributes to the reduction of CT burden.

The following algorithm (Fig. 23.2) is proposed for the rational and efficient use of the postoperative head CT resource:

There are always exceptions for individual cases and local scenarios, and attending teams should use their clinical judgment for the final decision on the appropriateness of postoperative imaging. The potential devastating consequences of postsurgical complications in neurosurgical patients should not be underestimated, and concerns about particular patients may demand early investigation.

23.9 Postoperative ICU Admission

A US database analysis including 38,058 neurosurgical patients reported an overall complication rate of 14.3%, including pulmonary complications in 5%, cardiovascular complications in 4%, and neurological complications in 3% of them [16]. Early detection and management of these and other complications require a multidisciplinary team for targeted neuromonitoring and constitute the rationale for postoperative ICU admission. Protocols for admission of postoperative neurosurgical

patients in the ICU are largely variable among countries, centers, and even within the same hospital, depending not only on local tradition but also on available resources.

Although ICU beds comprise less than 10% of US hospital beds, they respond for more than 20% of the total hospital costs, which equates at around 1% of the US gross domestic product [81, 82]. In effect, the daily ICU bed cost is three to five times greater than that of general ward bed [83–85]. Thus, to balance ICU bed capacity and its rising costs with the fear of postoperative complications is a daily struggle and expresses the need to create more specific selection criteria for ICU admission.

Accordingly, alternative perioperative management strategies have been studied with a special focus on the last decade, but almost 40 years ago it had already been addressed by Knaus et al. in the neurosurgical setting [86]. Most patients submitted to elective craniotomies did not require ICU-specific interventions before being discharged to the ward. They suggested that an increase in personnel on general wards might allow a more frequent monitoring of the postoperative neurological status, thus decreasing the ICU admission rate. Of note, two decades ago, a study including more than 17,000 ICU patients clearly demonstrated that more than 95% of them would rather receive "intensive monitoring" than "intensive care" [87]. There is emerging opinion that many neurosurgical patients do not require ICU care postoperatively to be provided safe and appropriate care [88]. Some studies have sought to identify factors associated with ICU admission and the need for ICU-level interventions.

In 2003, Ziai et al. performed a retrospective chart review of 158 patients submitted to brain tumor resection at a neurocritical care unit of a university teaching hospital. Only 15% of patients required prolonged (>1 day) ICU stay, which was associated with higher tumor severity score, higher fluid scores (a composite of estimated blood loss and intraoperative fluid administration), and postoperative intubation. Of those with prolonged ICU stay, few required ICU resources beyond the first 4 hours after surgery [89].

Another retrospective study by Bui et al. analyzed 394 patients who underwent elective craniotomy over almost 5 years to assess the need for ICU admission. Long operation times, extensive blood loss, and high anesthetic risk were predictive of ICU admission [3].

Rhondali et al. performed a cohort study including 358 patients admitted to a neurological ICU after elective intracranial procedures. Postoperative complications were defined as unexpected events occurring within 24 hours of surgery that required imaging or treatment for neurologic deterioration. Fifty-two patients were transferred while still sedated. Of the remaining 306 patients subjected to an attempt to awake and extubate in the operating room, 26 (8%) developed 1 postoperative complication, primarily a new motor deficit, unexpected awakening delay, or subsequent deterioration in consciousness. Intracerebral hematomas that required surgical evacuation occurred in four patients, and each of these was detected within 2 hours after surgery. Predictors of postoperative complications were the failure to extubate in the operating room, duration of surgery of >4 hours, and lateral positioning during surgery [90].

On a prospective study published in 2014, Hanak et al. evaluated a consecutive cohort of adult patients undergoing elective craniotomy at the Massachusetts General Hospital between 2010 and 2011 to identify which patients require ICU-level interventions or experience significant complications during the postoperative period. Multivariable analysis found older age and diabetes to be predictive of a patient's need for ICU-level intervention and, thus, ICU admission [91].

The well-known, simple, and objective Surgical Apgar Score (SAS) may be used to assess the risk of postoperative complications, despite the lack of specific validation for neurosurgery. A small recent study retrospectively explored whether the application of SAS in 99 patients undergoing elective craniotomy for meningioma resection could predict major postoperative complications. Indeed, that was the main finding on the multivariable analysis, and each one-unit increase in the mean SAS decreased the rate of major complications by 43% [92].

The team by Florman et al. took a step further and developed and implemented a protocol for transfer of patients to the neurosurgical floor after a 4-hour recovery period in the post anesthesia care unit (PACU) following elective craniotomy for supratentorial tumor. Their protocol and initial experience was published in 2017. Criteria included hemodynamically stable adults without significant new postoperative neurological impairment, and the outcomes of postoperative complications and events leading to transfer to a higher level of care were registered. Of the first 200 consecutive patients admitted to the floor, 5 underwent escalation of care in the first 48 hours due to agitation (3), seizure (1), and neurological change (1). Ninety-eight percent of patients meeting criteria for transfer to the floor were managed without incident. No patient experienced a major complication or any permanent morbidity or mortality following this care pathway [93].

Whether the local strategy is ICU or PACU admission, level and specialist training of staff is essential in the management of the postoperative neurosurgical patient. Quimby et al. reported on a before-after observational study that the availability of a PACU neurocritical care specialist led to a significant reduction in discharge time from PACU to the ward, as well as reduction in the mean LOS [94].

Even a day surgery strategy has been explored for select patients undergoing craniotomies for tumor resection. Aggregate results from a more than 10-year experience in Canada and the United Kingdom showed that out of 177 patients scheduled for outpatient craniotomy for supratentorial tumor resection (163 awake procedures), only 9 required direct postoperative admission, and 2 required readmission following discharge. Inclusion criteria included living with a responsible adult, no comorbidity requiring hospitalization, and surgery completion prior to 1:00 PM, allowing for a 6-hour observation [95].

These data support the notion that ICU admission should not necessarily be a routine for patients undergoing elective craniotomy unless preoperative conditions, type of lesion, or intraoperative data suggest so in order to benefit the enhanced recovery after surgery to facilitate uncomplicated hospital stay – assuming adequate neuromonitoring could be delivered in another non-ICU setting [96]. Selective

rather than routine postoperative ICU-level care should be our goal, with evidence-based risk factor assessment for identification of patients for whom an alternative to ICU-level care may be appropriate [88].

In summary, some studies have identified factors associated with higher risk of a complicated postoperative course, such as patient characteristics (older age, diabetes, high anesthetic risk), pathology features (tumor severity score, infratentorial location), surgical data (blood loss, intraoperative fluid administration, surgery duration, surgical apgar score, or similar ones), and very early clinical course (failure to extubate in the operating room and worse neurological status, specially reduced consciousness or lower cranial nerve deficits). Moreover, the most common "ICU-level interventions" were intravenous blood pressure medication and intravenous analgesics, which can clearly be safely performed in non-ICU observational units prepared for such – intermediate care units, post anesthesia care units, or other step-down units [96].

Efforts are needed to prospectively develop and validate comprehensive clinical scoring systems and cost-benefit analyses so that the best outcomes are achieved on an efficient manner guided by evidence-based decision-making regarding selective patient allocation to postoperative ICU-level observation [88].

Table 23.2 summarizes the proposed inclusion and exclusion criteria for non-ICU management after elective craniotomy based on the authors' experience and adapted from Refs. [15, 18]. It should be emphasized that there is a scarcity of high-quality evidence in this specific field literature. The proposed criteria below represent experts' suggestions, and a case-to-case evaluation is highly recommended.

Table 23.2 Proposed inclusion and exclusion criteria for non-ICU management after elective craniotomy

Moment	Preoperative	Pathology	Intraoperative	Early postoperative
Inclusion criteria	Age ≥ 18[a] ASA 1 or 2	–	Duration <4–6 hour Consider: Surgical Apgar Score[a] Intraoperative fluid administration[a]	Extubation ≤1 hour Neurological examination stable or expected change Observation on post anesthesia care unit ≥4–6 hour Hemodynamic and respiratory stability
Exclusion criteria	Diabetes KPS < 70	Infratentorial Extensive cerebral edema Hypothalamic (primary location or manipulation)	Transfusion Prolonged temporary or definite artery clipping Seizure	Electrolytic disturbance Continuous intravenous medication infusion Seizure

[a]There is no quality evidence to propose additional cut-off values

23.10 Conclusion

Despite the lack of high-grade evidence for most interventions in the care of emergency neurosurgical patients, there is a broad consensus on how to monitor and treat intensive care patients after neurosurgical emergencies. Careful, frequent neurological assessments by neurology-trained staff are the cornerstone of postoperative neurosurgical care. However, management of systemic complications is an essential task that can help minimize serious neurological consequences. The most important monitor for postoperative neurosurgical patients is the repeated clinical examination. Imaging procedures should be used only when the result of the examination could lead to a change in treatment.

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Chapter 24
Head Injury

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24.1 Introduction

While the term head injury technically refers to a traumatic insult to the scalp, skull, or brain, it often is used to describe brain injury. The term traumatic brain injury—TBI—is more precise. The US Department of Defense defines TBI as a traumatically induced structural or physiological disruption of brain function (decreased or complete loss of consciousness, amnesia, neurological deficits or alterations in mental state, intracranial lesion) as a result of an external force. The severity of brain injury is stratified into mild, moderate, or severe based on the patient's clinical presentation.

24.2 Epidemiology

Head injuries and TBIs are significant public health problems globally and continue to be a cause of thousands of deaths and disabilities worldwide. TBI is one of the leading causes of overall mortality in trauma patients and is particularly implicated in early and late deaths [1]. Accurately comparing the incidence of TBI in

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different studies is challenging because of the lack of a standardized definition in the literature [2]. According to a report released by the Centers for Disease Control (CDC) in 2014, there were 2.87 million (837,000 in children) TBI-related ED visits, hospitalizations, and deaths in the USA and TBI contributed to 56,800 deaths (2529 in children) [2]. Between 2006 and 2014, TBI-related ED visits increased 54%, hospitalization rates decreased by 8%, and death rates decreased by 6% [2]. A cross-sectional study from Europe found that in 2012 there were 1.38 million TBI-related hospital discharges and 33,415 TBI related-deaths across 25 counties in Europe [3].

In the same report published in 2014, the CDC found falls to account for roughly half of all TBI related emergency department visits. Overall, falls and motor vehicle crashes respectively were the leading causes of all TBI-related hospitalizations (52 and 20%), while motor vehicle crashes were the leading cause of TBI-related hospitalizations among adolescents and adults. Intentional self-harm was the leading cause of TBI-related deaths (33%) [2].

24.3 Emergency Room Presentation

Regardless of the anatomic location of injury, all trauma patient should be evaluated in a systematic fashion. The primary survey consisting of airway maintenance with cervical spine precautions, breathing and ventilation, and circulation with control of hemorrhage. At the end of the primary survey, a quick neurological evaluation should be performed. The most common and widely validated method includes the Glasgow Coma Scale (GCS) (Table 24.1) [4]. The scale consists of three

Table 24.1 The Glasgow Comas Scale [4]

Glasgow Coma Scale		
Eye opening	Spontaneous	4
	To voice	3
	To pain	2
	No response	1
Verbal	Alert and oriented	5
	Disoriented/confused	4
	Non-sensical speech	3
	Moaning/incomprehensible speech	2
	No response	1
Motor	Follows commands	6
	Localizes to pain	5
	Withdraws to pain	4
	Decorticate (flexor) posturing	3
	Decerebrate (extensor) posturing	2
	No response	1

components: eye response, verbal response, and motor response, and has been shown to be predictive of in-hospital mortality [5]. The addition of pupillary size and light reactivity to this quick assessment has been shown to have significant prognostic value [6].

After the initial primary survey and stabilization of patient's vital functions, a more thorough secondary survey is undertaken. Any external signs of head trauma (suspected open or depressed skull fractures, signs of basilar skull fractures), GCS < 15, multiple episodes of vomiting, any period of amnesia or loss of consciousness or dangerous mechanism of trauma should be followed up with a computed tomography (CT) scan of the head [7].

24.3.1 Principles of Early Management

- Blood pressure: Stabilization of blood pressure is crucial in early management. A single episode of systolic blood pressure < 90 mm Hg has been shown to double the rate of mortality, with current ATLS guidelines focusing on avoidance of hypotension [8]. Hypotension impairs cerebral blood flow and could exacerbate brain injury. Hypertension, on the other hand, can propagate and exacerbate hemorrhage.
- Oxygenation: O_2 saturation is crucial to maintain the increased demands in acute TBI. Hypoxia (O_2 Saturation < 90% or PaO_2 < 60 mm Hg) has been shown to increase mortality rates [9]. Early efforts to improve oxygenation, including intubation, are paramount.
- Temperature: Currently, data from randomized control trials have failed to demonstrate the benefit of hypothermia in prevention of secondary injury in TBI patients, but mild hypothermia can still be utilized for secondary benefit in lowering Intracranial pressure [10, 11]. However, it should be used judiciously owing to increased susceptibility to infections (mainly pneumonia and sepsis) and can result in coagulopathy [12, 13]. Normothermia maintenance is preferred as initial treatment in severe TBI [11].
- Hematocrit: Patients with TBI may often have concomitant injuries that lead to acute blood loss. Transfusions should be reserved for those patients who have acute blood loss or show signs of decreased tissue perfusion. However, no current research demonstrates a benefit in maintaining hemoglobin >10 g/dL or hematocrit >30% [14]. Advances in monitoring of coagulopathies using thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have enabled optimization of blood product therapy [15]. However, studies demonstrating the accuracy of these technologies and correlation of their use in improving outcomes are still lacking [16, 17].
- The goal of early resuscitative measures is not so much as to reverse the initial traumatic insult, but is rather targeted at the prevention of secondary brain injury.
- Other considerations:

- Hyperventilation: While there is a role for hyperventilation in quickly reducing intracranial hypertension (by reducing the intracranial pressure, ICP), prophylactic or extended use should be avoided to prevent reduction in cerebral blood flow (CBF) that can lead to cerebral ischemia. Hyperventilation should be strictly used as a temporizing measure when patients exhibit dangerous signs of increased ICP until more sustainable efforts, such as hyperosmolar solutions or surgical decompression are possible.
- Hyperosmolar solutions: Mannitol and more recently hypertonic saline have been used as a therapeutic measure to reduce intracranial hypertension. These solutions initially increase intravascular volume causing hemodilution that leads to decreased blood viscosity and improved cerebral blood flow, although increasing osmotic gradient and reducing brain water content may also be a factor [18, 19]. Mannitol is usually given as a bolus of 0.25–1 g/kg over 20–30 minutes with peak effect in 20 minutes. However, because of mannitol's diuretic properties, failure to replace urine output with normal saline or isotonic solutions can lead to systemic hypotension and resultant cerebral ischemia. More recently, hypertonic salines (in this case referring to solutions containing at least 3% sodium chloride) have gained favor as a hyperosmolar solution as they can reduce ICP in patients without the adverse effects of nephrotoxicity and hypovolemia [20]. More recent studies have also shown hypertonic solutions to be superior to mannitol and have championed their use as a first-line medical therapy for reducing ICP [21]. The dose varies considerably, but commonly includes 30 mL boluses of 23.4% sodium chloride or 150 mL boluses of 3% sodium chloride. About 3% sodium chloride solutions may also be run as infusions with serum sodium goals of 145–150 mEq/L or higher, but not to exceed 155. It is generally felt that serum osmolality should not exceed 320 mEq/L [11].
- Antiepileptic drugs (AEDs): About 5–7% of patients with TBI experience early or late posttraumatic seizures [22]. Phenytoin is one of the most studied agents for posttraumatic seizure prophylaxis [23]. Levetiracetam has been gaining popularity as an alternative due to its ease of use without requiring drug level monitoring. In some studies, levetiracetam has been shown to be better at prophylaxis for posttraumatic seizures [24]. Prophylaxis against early posttraumatic seizures is usually administered for no greater than 7 days post-TBI, unless clinically warranted [25]. However, no AEDs to date have been shown to reduce the incidence of epilepsy following TBI [26].
- Steroids: Currently, high-dose steroids are contraindicated acutely (within 72 hours) in TBI and have shown to increase mortality rates in the CRASH trial [27].

24.4 Classification of Head Injuries

- Scalp laceration: Can be found during the secondary survey or may need to be addressed during the primary survey if they continue to be a source of major bleeding. Patients arriving in hemorrhagic shock with scalp lacerations may ini-

Table 24.2 Types of skull fractures

Skull fractures		
Location	*Considerations*	
Vault	Linear or stellate	
	Depressed or non-depressed	
	Open (compound) or closed (simple)	
Basilar	*Temporal fractures*	Longitudinal: parallel to eternal auditory canal, VII/VIII nerve sparing
		Transverse: perpendicular to external auditory canal, with potential VII/VIII nerve involvement
	Clival fractures	Longitudinal, transverse, or oblique
	Occipital condyle fractures: Anderson and Montesano classification types	Type I: Communition of the condyle following impact. *Stable*, as there is minimal fragment displacement into foramen magnum
		Type II: Results from a basilar skull fracture extending into one or both condyles. *Stable*, provided the tectorial membrane and alar ligament remain intact
		Type III: Avulsion fracture due to lateral bending and rotation. *Rule out occipitocervical dislocation*. May be *unstable*

tially have small amount of active bleeding. After resuscitative measures are completed and blood pressure normalized, the laceration may continue to bleed actively. Bleeding can be controlled with direct pressure, cauterization, or application of Raney clips in emergent situations. Prior to wound closure, a laceration should be thoroughly inspected for underlying fractures and CSF leaks.

- Skull fractures: Classification of skull fractures in Table 24.2.
  - Cranial vault fractures: Linear fractures are usually self-limiting and rarely require any surgical intervention by themselves. Figure 24.1 shows a displaced left occipital fracture with an associated subdural hematoma, as well as a fracture near the torcula causing an epidural hematoma. This patient sustained multiple injuries after being struck by a car. Depressed skull fractures generally require surgery if there are any signs of CSF leakage, underlying hematoma, neurological deficit corresponding to underlying brain parenchyma, and/or depression >1 cm. Special considerations should be made when fractures are overlying dural sinuses. The sinus may require repair, and there is a risk of significant intraoperative blood loss and air embolism. Prophylactic antibiotics and early surgical management are crucial in reducing risk of infection [28].
  - Basal skull fractures: The fractures may be associated with CSF leaks and cranial nerve palsies. Clinical signs that raise concern for basilar fractures include periorbital ecchymosis (raccoon eyes) and retroauricular ecchymosis (Battle's sign). Currently, there is no data to support the use of prophylactic antibiotics in patients with basilar fractures, with or without CSF leak, with no difference in frequency of meningitis, all-cause mortality, or meningitis-related mortality [29].

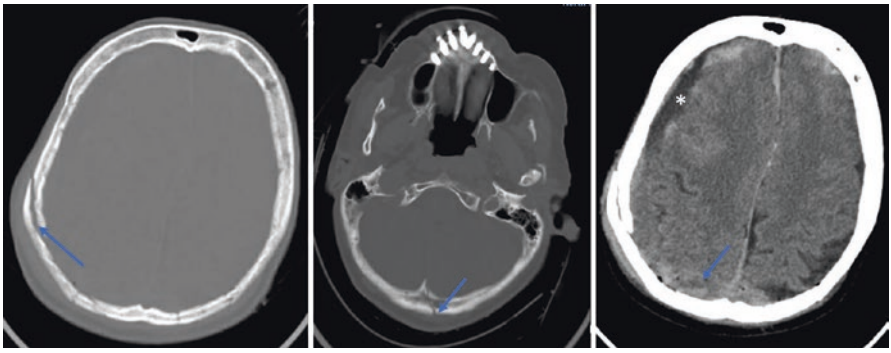

Fig. 24.1 CT scan demonstrating multiple skull fractures—a displaced right occipital fracture (left), a nondisplaced fracture near the torcula (middle), a subdural hematoma (right, *) associated with the occipital fracture, and an epidural hematoma and intracranial air associated with the sinus injury (arrow)

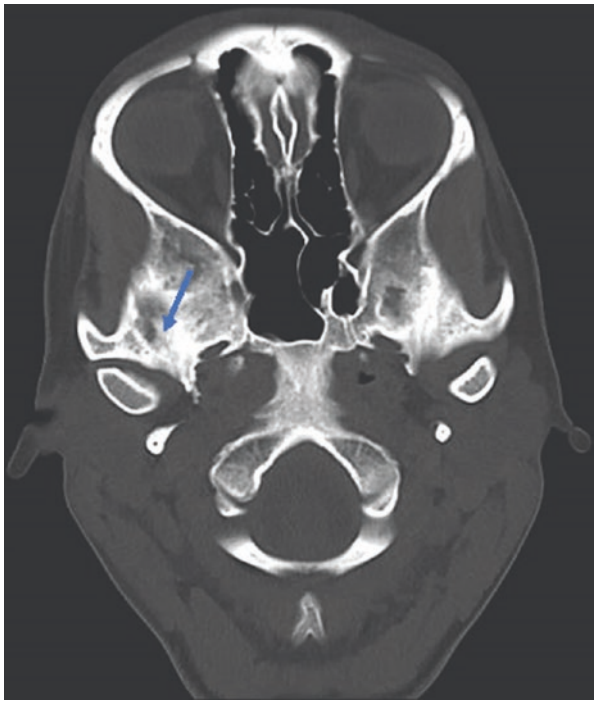

Fig. 24.2 CT scan demonstrating a nondisplaced right temporal bone fracture

– Temporal bone fractures: These may be detected with otoscopic examination of the external auditory canal (EAC). They may result in unilateral VII or VIII nerve palsies. An ear/nose/throat (ENT) consult is warranted in these patients, and steroids can be started for any new onset cranial nerve palsy. If symptoms do not improve with steroids, surgical decompression may be considered, usually in a delayed fashion. Figure 24.2 demonstrates a nondisplaced right

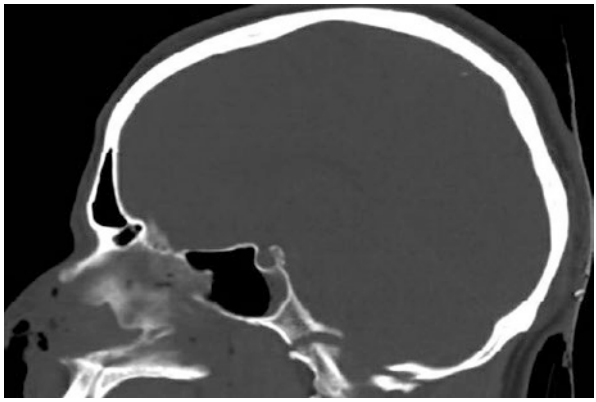

Fig. 24.3 CT scan demonstrating a transected clivus in a pedestrian struck. The patient sustained multiple skull fractures and a significant closed head injury

temporal bone fracture in a patient presenting with retroauricular ecchymosis after a fall.

- Clival fractures: These should raise high suspicion for injury to CN III-VIII, vascular dissections, or occlusions of the vertebrobasilar system and/or anterior circulation, and delayed development of traumatic aneurysms. When there is high suspicion of vascular injury, standard noncontrast CT can be followed with a CT angiogram. Figure 24.3 shows a displaced fracture of the clivus in a patient struck by a fast-moving vehicle.
- Occipital condyle fractures: These types of fractures have a very rare incidence of about 0.4–0.7% patients with major trauma [30]. Diagnosed initially on a CT scan, these should be followed up with a magnetic resonance imaging (MRI) to assess integrity of the craniocervical complex. A type III fracture that involves avulsion of the condylar fragment is usually treated with external immobilization for 6–8 weeks. Surgical fixation is usually indicated in those patients with compression of neural elements or craniocervical misalignment (occiput to cervical interval > 2 mm). Figure 24.4 shows an occipital condylar fracture in the same patient who sustained the clival transection.
- Pneumocephalus and tension pneumocephalus: These injuries results from air build up within the cranial cavity following damage to the skull and/or meninges. Persistent build up in the case of tension pneumocephalus can result in significant mass effect on the brain followed by neurological deterioration. Treatments include positioning the patient with the head down (i.e., in Trendelenburg), use of a non-rebreather mask with 100% oxygen, and in cases of tension pneumocephalus, surgery to repair the skull, dural lacerations, and close any areas where air may be pulled into the brain. Figure 24.5 shows a small amount of pneumocephalus and a small subdural hematoma adjacent to a traumatic right frontal bone fracture. This patient did not develop tension pneumocephalus and did not require any intervention.

- Intracranial hemorrhage:

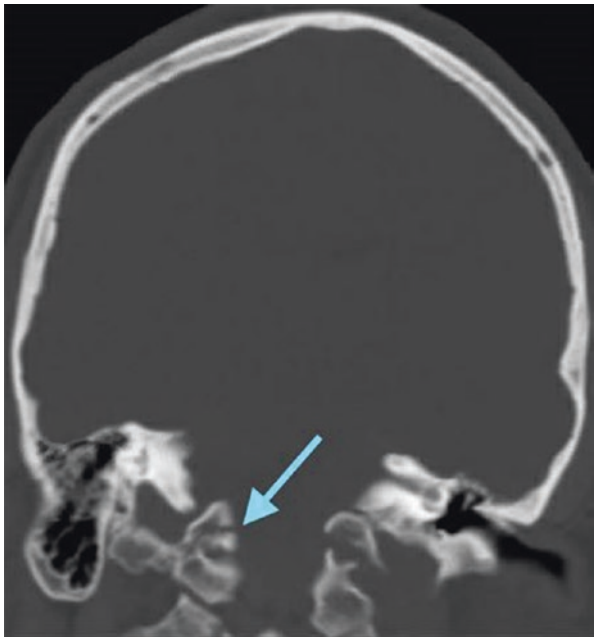

Fig. 24.4 Occipital condylar fracture (arrow). This patient also sustained a transection of the clivus, indicative of craniocervical dislocation

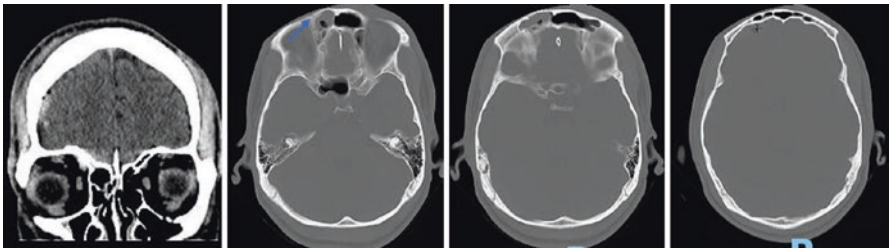

Fig. 24.5 CT scan demonstrating a small subdural hematoma and pneumocephalus resulting from a right frontal bone fracture (arrow)

– Epidural hematomas (EDH): These are relatively uncommon, especially in patients aged 2 years and younger or 60 years and older. EDHs are caused by the disruption of an arterial source of bleeding, often by temporal bone fractures disrupting the middle meningeal artery. In the case of arterial bleeding, these lesions usually become symptomatic due to mass effect causing localized pressure on brain parenchyma. As the EDH grows, it puts continued pressure on the brain and can cause uncal herniation. Patients typically can present with lucid interval (which can last hours) followed by rapid deterioration. Symptoms include contralateral hemiparesis, ipsilateral hemiparesis (Kernohan notch phenomenon [31]), ipsilateral pupillary dilation, and obtundation. EDHs are diagnosed with CT scans showing classical biconvex shape, usually with uniform density. Small, nonsymptomatic stable hematomas

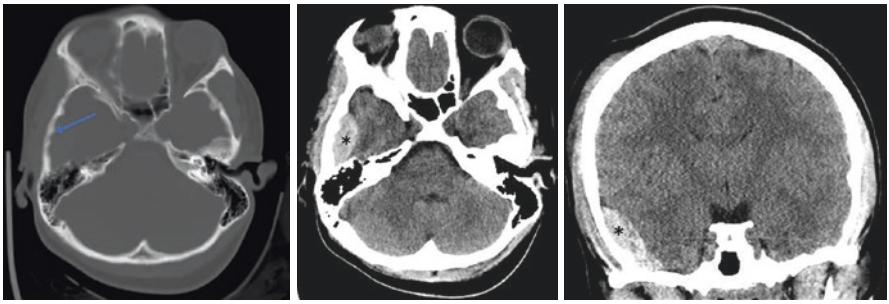

Fig. 24.6 CT scan demonstrating a temporal skull fracture (arrow) with middle meningeal artery tear causing an acute epidural hematoma (*)

(often resulting from venous bleeding) may be managed medically with serial imaging and observation. Volume > 30 cm^3, altered or decreasing GCS, and/or neurological symptoms are all indications for emergent surgical evacuation of the clot, with an emphasis on surgical hemostasis and tenting of the dura in the region to prevent reaccumulation. Figure 24.6 demonstrates an EDH in a young woman who fell and sustained a right temporal bone fracture.

– Subdural hematomas (SDH): Subdural hematomas result from disruption of bridging vessels along the surface of the brain, and are often associated with underlying damage to brain parenchyma. Use of anticoagulation and antiplatelet agents has been shown to increase the risk of developing subdural hematomas [32]. Based on timing of presentation, SDH are usually divided into acute (1–3 days), subacute (4 days–2–3 weeks), and chronic (>3 weeks). Age of the hematoma and appearance on CT scan significantly alters the management. These lesions are usually diagnosed with a CT scan and are typically divided into convexity, interhemispheric, tentorial, or posterior fossa locations.

  Acute subdural hematomas (aSDH): These can be managed medically or observed with serial imaging and clinical assessment if there is no abnormal neurological exam, the GCS score remains stable, and there is no significant midline shift. Surgical evacuation is warranted if thickness is >10 mm or midline shift >5 mm regardless of clinical presentation [33]. If possible, use of anticoagulation or anti platelet agents and their adequate reversal (Table 24.3) should be noted prior to surgery. Surgical evacuation entails craniotomy or craniectomy for adequate evacuation of acute blood clot and adequate exposure to control any active bleeding. The bone flap can be left off (craniectomy) if there is concern for significant swelling at the time of surgery. Figure 24.7 shows a thick, acute subdural hematoma with midline shift.

  Chronic subdural hematomas (cSDH): These are usually seen in elderly patients, with or without history of trauma. The fluid collection is generally motor oil in appearance and consistency. If the fluid collection is clear

Table 24.3 Anticoagulation and anti-platelet drugs and their reversal agents

Drug	Reversal agent
Antiplatelet agents	
1. Glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban, abciximab)	Platelet transfusion (partially effective for abciximab) [49]
2. Platelet aggregation inhibitors (acetylsalicylic acid/aspirin, clopidogrel, cangrelor, integrilin, ticagrelor)	1. Desmopressin 2. Platelet transfusion (only indicated when planned surgical intervention. To be given at the time of maximal desired benefit) [50] 3. Cryoprecipitate
3. Protease-activated receptor-1 antagonist (vorapaxar)	Platelet transfusion (limited efficacy) [51]
Anticoagulation agents	
1. Vitamin K antagonist (warfarin)	1. Vitamin K (non-emergent reversal) 2. Fresh frozen plasma (FFP) 3. Prothrombin complex concentrate (PCC, 3 or 4-factor)
2. Indirect Factor Xa inhibitors (antithrombin activation) (unfractionated heparin, low molecular weight and ultra-low molecular weight heparin, enoxaparin, fondaparinux)	1. Protamine sulphate (not effective for fondaparinux) 2. Recombinant factor VII (for reversal of fondaparinux)
3. Direct thrombin inhibitors (dabigatran and argatroban)	Idarucizumab (antibody fragments against dabigatran) [52]
4. Direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)	1. Tranexamic acid 2. Prothrombin complex concentrate [52] 3. Andexanet alfa (not indicated for reversal of edoxaban) [53]

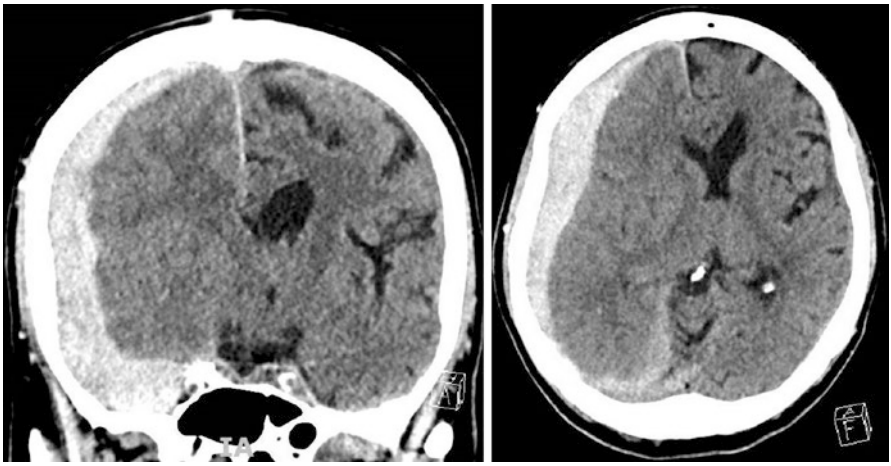

Fig. 24.7 CT scan demonstrating a large, acute right sided subdural hematoma causing sulcal and cisternal effacement with significant midline shift in a patient who fell

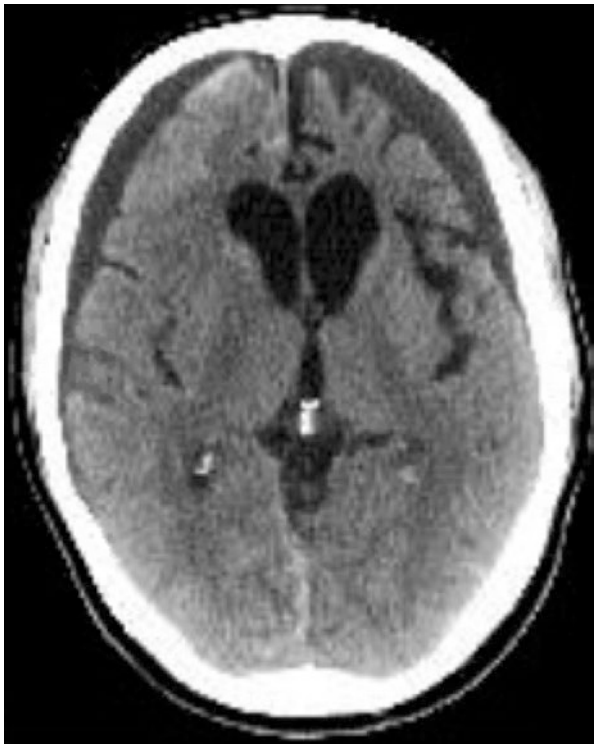

Fig. 24.8 CT scan demonstrating bilateral chronic subdural hematomas in an elderly patient

CSF, it is termed a subdural hygroma. cSDH usually are a sequalae of acute bleeds and form as a result of degradation of the blood clot and formation of neomembranes. Indications for treatment include patients who present with neurological symptoms and large or increasing size. Chronic SDH may be treated with burr holes, with or without the use of subdural drains. Complications include reaccumulation as a result of failure of re-expansion of the brain, seizures, and in some instances subdural empyemas [34]. Figure 24.8 shows the CT scan of a patient with bilateral chronic subdural hematomas.

Special considerations in treatment of cSDH

- Steroids: Dexamethasone has been used in the treatment of cSDH, either pre or postoperatively, especially in the event of recurrence. Results are mixed. The goal of steroid treatment is to reduce inflammatory mediators and inhibit the formation of neomembranes and neocapillaries, thus reducing recurrence or propagation [35]. However, one meta-analysis found an increased morbidity without any significant improvement in recurrence and cure rate with adjuvant use of corticosteroids [36]. A lack of randomized trials leaves its use reserved for the symptomatic patient until surgical drainage is possible, in those in whom surgery is associated with high risk, or at the surgeon's discretion.

- Tranexamic acid (TXA): An antifibrinolytic agent has been proposed as a stand-alone or adjuvant to surgery in treating cSDH. A recently published randomized trial showed that, while steroids used postoperatively reduced cSDH recurrence, the complication rate was higher that those patients receiving placebo [37]. One study from Japan found a significant decrease to complete cure in patients taking TXA, regardless of surgical drainage [38]. However, its role in patients taking anticoagulation has not been investigated. Currently, the use of tranexamic acid in chronic subdural hematomas (TRACS), a placebo-controlled phase IIb trial, is underway to review the safety and feasibility of its use in these patients [39].
- Other: Some studies have also investigated the use of atorvastatin and angiotensin converting enzyme (ACE) inhibitors with mixed results [35].
- Middle meningeal artery (MMA) embolization: Recently centers have investigated angiographic embolization of MMA in treatment of refractory or recurrent cSDH showing resolution, decreased rates of recurrence, and similar complication rates to surgical drainage [40–42].

– Traumatic intracerebral hemorrhage (tICH): Traumatic ICH lesions usually present in a coup-contrecoup pattern within parenchyma near bony prominences (frontal, temporal, and occipital poles) in patients suffering from head trauma. CT scan usually makes the diagnosis. Some patients present in a delayed fashion with tICH not present on the initial scan. Most can be treated nonsurgically, with interval imaging to demonstrate stability. Careful monitoring for enlargement, mass effect with increasing midline shift, with or without signs of impending transtentorial herniation may warrant surgical evacuation. Nonsurgical management includes strict blood pressure control,

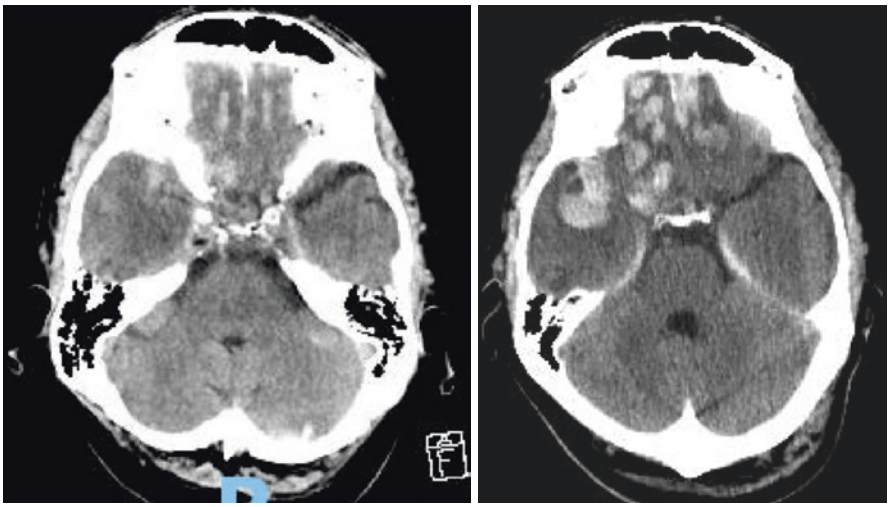

Fig. 24.9 CT head demonstrating bifrontal and a right temporal contusion (left) with blossoming of the contusions on a scan obtained 6 hours later (right)

correction of any systemic coagulopathy, serial imaging, and ICP monitoring for patients with GCS less than 8 [25]. Figure 24.9 shows a tICH that blossomed on an interval follow-up scan.

– Diffuse axonal injury (DAI): DAI results from acceleration/deceleration motions that shear axons at gray-white matter junctions. High-speed motor vehicle crashes are the most common cause. Adam's classification is used to describe the severity of DAI:

  Grade I—Mild DAI involving corpus callosum, brainstem, and cerebral cortex
  Grade II—Moderate DAI with focal lesions in the corpus callosum
  Grade III—Severe DAI with additional focal lesions in the brainstem

  DAI is suspected in patients with a persistently low GCS after resuscitative measures and/or surgical treatment of other traumatic brain injuries. Patients with mild DAI may have mild headaches and dizziness. Severe injuries may present with persistent vegetative state. These patients may present with central autonomic dysfunction such as tachycardia, tachypnea, vasoplegia, hyperthermia, and posturing [43]. CT scans are usually not helpful; diagnosis is usually made with MRI. Diffusion tensor imaging showing drop in fractional anisotropy in white matter tracts is diagnostic; microhemorrhages are often seen on other sequences, including susceptibility weighted imaging (SWI). Treatment remains primarily nonsurgical and is aimed at preventing secondary injury. Early resuscitation and maintaining cerebral perfusion by preventing hypotension, reducing ICP, and improving oxygenation are mainstays of management. Invasive neuromonitoring for ICP and monitoring of brain oxygenation is indicated in patients with GCS < 8. Prognosis in severe diffuse axonal injury remains poor. Figure 24.10 demonstrates MRI findings in a patient with DAI.

- Penetrating head injuries: These can be caused by missile (i.e., gunshot wounds) or nonmissile injuries. Primary injury occurs by damage to the scalp and surrounding facial structures (e.g., orbits). The tract formed by the bullet or object

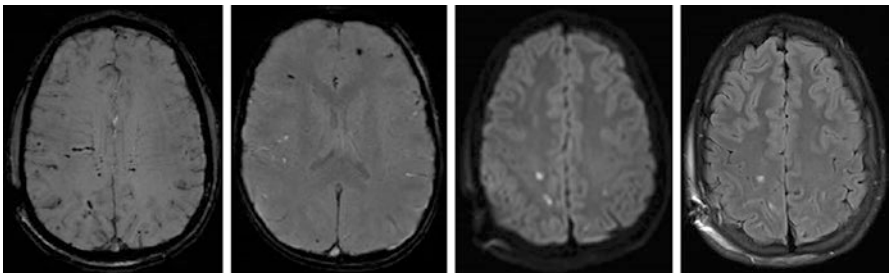

Fig. 24.10 MRI findings in diffuse axonal injury (DAI). The two left images demonstrate microhemorrhages on susceptibility weighted imaging (SWI) in two different patients. The third image demonstrates high signal on diffusion weighted imaging (DWI), and the rightmost image demonstrates the corresponding FLAIR changes

seeds bacteria into the inner parenchymal structures. Comminuted fractures of the skull damage underlying blood vessels, which can cause hematomas and direct damage to brain parenchyma. Fragmentation, richochetting, and deformation of the missile, as well as pressure waves if the weapon is at close range, can cause significant additional injuries and trauma. Secondary injury follows, with fulminant cerebral edema, sudden increase in ICP, and decrease in cerebral perfusion. Delayed complications include abscess, traumatic aneurysm, arteriovenous fistulas (AVFs), seizures, and complications associated with fragment migration (like hematomas).

- The work up begins with the identification of the entry and exit sites and x-rays and CT scans to identify the missile and extent of injury to inner structures. Angiographic imaging is indicated in patients with suspected vascular injuries. For patients with low GCS scores, surgical management is not indicated. If surgery is pursued, goals include debridement, evacuation of hematomas, removal of missile and bone fragments, and hemostasis.
- Neuromonitoring devices:
  - Electroencephalogram (EEG): EEG can detect subclinical or non-convulsive seizures. Consider EEG in patients who have a clinical picture does not match the imaging findings, and when in patients have symptoms that wax and wane. Noninvasive scalp electrodes are usually used. Besides the detection of seizure activity, cortical surface electrodes may be useful in diagnosing cortical spreading depression (CSD), or peri-infarct depolarization (when located in peri-ischemic brain tissue). Recently, use of ketamine has shown to be beneficial in inhibiting CSD in acute brain injury [44].
  - ICP monitors: ICP is recommended to be monitored in patients with a GCS 8 or less or in other patients whom a concern that intracranial hypertension may develop in the post injury period. ICP can be measured with an external ventricular drain (EVD) or a parenchymal pressure monitor, sometimes called a "bolt." EVDs allow CSF drainage; however, draining CSF requires intermittently clamping the drain in order to view the ICP. Parenchymal monitors allow continuous ICP monitoring. Since they are useful in measuring more regional cerebral pressure they should be placed in areas at greatest risk of injury. Unfortunately, values tend to drift with time and probes cannot be recalibrated. Regardless of the device, post insertion CT scan is needed to confirm placement and identify any complications (e.g., hemorrhage, incorrect position). Figure 24.11 shows an intraparenchymal pressure monitor (bolt).
  - Brain oxygenation monitors: The monitoring of brain tissue oxygen tension ($PbtO_2$) has been rapidly gaining popularity. In conjunction with ICP, the clinician may monitor and manage cerebral perfusion pressure. The probe is inserted into white matter and provides information on regional oxygen tension. Brain tissue oxygenation <20 mm Hg should trigger an algorithm to address tissue hypoxia [45].

    Global cerebral oxygenation can be assessed with $SJVO_2$ monitors that involve placement of a fiberoptic probe in the internal jugular vein. Values below 50% indicate global ischemia. They can also be used to measure oxygen content from jugular venous blood, from which arterial jugular venous

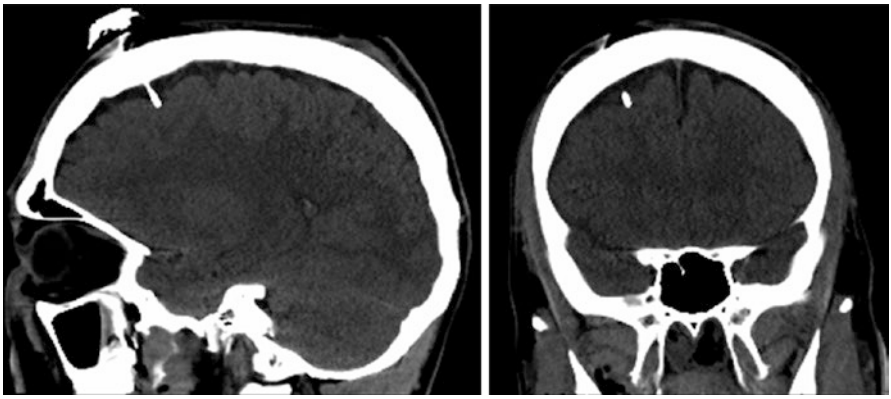

Fig. 24.11 CT scan demonstrating an intraparenchymal pressure monitor (bolt)

content difference can be calculated. Values above 9 mL/dL indicated presence of global ischemia and less than 4 mL/dL indicates hyperemia [46].

– Cerebral metabolism monitors: Microdialysis catheters allow frequent monitoring of substrates and neurotransmitters, giving insights into cerebral metabolism and informing of need for additional and/or response to therapies. The catheter has a semi-permeable membrane, and is inserted into the subcortical white matter. While current guidelines have not yet found sufficient evidence to recommend its routine use in TBI patients, it has been shown to strongly correlate with outcomes [47, 48]. Common substrates monitored include glucose, pyruvate and lactate levels. Additionally, glutamate and glycerol, markers of vasospasm and underlying ischemia, can be monitored. Placement in perilesional areas, or areas at greatest risk of injury, provides most valuable information to guide treatment.
– Other: Non-invasive imaging modalities like positron emission tomography (PET) and MR spectroscopy (MRS) may also play a role in monitoring cerebral metabolism. These technologies are not widely used in TBI management.

24.5 Conclusions

TBI remains a significant global health problem and is directly related to early and late mortality in trauma patients. Management is targeted toward early resuscitation and prevention of secondary injury.

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Chapter 25
Spontaneous Subarachnoid Hemorrhage and the First Week After Aneurysmal Subarachnoid Hemorrhage

Brenna Kathleen McElenney, Craig Schreiber, Joseph Georges, and Peter Nakaji

25.1 Introduction

Nontraumatic subarachnoid hemorrhage (SAH) is an emergency diagnosis that often results from the rupture of an intracerebral aneurysm [109]. SAH is associated with high morbidity and mortality and requires a multidisciplinary treatment plan that focuses on treating the aneurysm, its precipitating cause, and numerous possible resulting complications [93]. Consequently, the critical care management of an SAH patient requires not only extensive neurological knowledge but also an appreciation of general critical care to address the systemic multi-organ sequelae that SAH can initiate. While this chapter focuses on the first week of management for aneurysmal SAH, the disease process is a continuum that often extends out for 3 weeks or more. Therefore, some recommendations are for immediate short-term concerns and interventions, and others carry on into long-term management. Throughout this discussion, emphasis will be placed on interventions for aneurysmal SAH, though many of these interventions are applicable to SAH caused by other sources.

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25.2 Early Critical Care Management

25.2.1 Initial Management and Stabilization

Initial management of a patient with a SAH should address life-threatening conditions such as securing the airway, hemodynamic stability, and recognition of intracranial hypertension due to either hemorrhage or hydrocephalus. Though few patients present with a compromised airway, neurological conditions that may jeopardize respiratory function can develop rapidly secondary to the effects of SAH including, but not limited to, hydrocephalus, seizures, and sedation [87, 137, 167]. Therefore, airway surveillance is crucial since up to 37% of patients with SAH will require intubation during their hospitalization [125]. Intubation is indicated for patients with Glasgow Coma Score (GCS) of 8 or less, with an elevated ICP, with poor oxygenation or hypoventilation, or that require sedation. Elective intubation is possible; this ensures the security of the airway in agitated patients, especially those who require transportation, and prepares patients for expedited cerebral angiography [140]. In this stage of management, arterial line placement is crucial for constant and accurate blood pressure monitoring, which is important in care both prior to securing the aneurysm and afterward. Good IV access is also paramount at this stage and the use of a central line is common. The placement of a subclavian central line is often preferred over an internal jugular line, which has been documented to disturb jugular venous outflow and precipitate increased ICP [190]. The use of a femoral line is less common in the ICU setting secondary to increased risk of arterial injury, thrombosis, and infection and therefore only used in emergency situations [82].

25.2.2 Evaluating Consciousness and Severity

After patient stabilization, the severity of the SAH is evaluated. Though literature reflects that no consensus has been reached as to a single SAH grading scale due to few validation studies, and conflicting and limited data, the Hunt and Hess grading system is nearly universally used among the neurovascular community and will be discussed in more detail below [25, 167].

In addition to evaluating the severity of the SAH utilizing a SAH grading scale, it is essential that each SAH patient be evaluated using the GCS. This should be completed at the time of initial management and stabilization. The GCS score is a standardized tool for measuring levels of consciousness in trauma patients and has been effective in predicting outcome after SAH [55, 171]. Additionally, it is a valuable tool that is simple to implement and conveys a universal message across all fields of medicine for nurses, doctors, and advanced practitioners alike. After establishing the patient's GCS score, the severity of a patient's SAH can be evaluated using one of several SAH scales.

As noted above, though no single SAH grading scale has been adopted, nearly every SAH patient is presented with their Hunt and Hess score, which allows all medical professionals working with SAH patients to immediately assess the severity of the patient. The Hunt and Hess grading scale was originally intended to determine surgical risk in patients requiring repair of intracranial aneurysms; however, it has widely evolved to include its use to assess SAH severity [64]. Although it is easily administered, its utility is limited by vague terminology that leaves assessment to a subjective determination by the physician [148]. The development of additional scales was prompted by this constraint, and therefore it is most common for the Hunt and Hess grading scale to be reported along with a grade from an additional scale that is determined by each institution.

An additional scale that was proposed 20 years after the Hunt and Hess scale is the World Federation of Neurological Surgeons (WFNS) grading scale that incorporates the GCS and motor deficits into its grading [142]. Unlike the Hunt and Hess grading scale, it employs more objective terminology but is more complex to administer [148].

The Fisher scale is an index of the risk for vasospasm, in contrast to the two previously mentioned scales that are largely prognostic. The Fisher scale employs the evaluation of hemorrhagic patterns observed in the initial CT scan and has also been integrated in other grading scales, including the VASOGRADE and the Ogilvy and Carter grading system [44, 79]. However, the Fisher scale has demonstrated limitations as it does not take into account the presence of thick cisternal blood and concomitant intraventricular or intraparenchymal blood. In two studies, these limitations resulted in the Fisher scale lacking a correlation with the development of clinical vasospasm [141, 158]. A subsequent scale called the modified Fisher scale was then developed that calculates a grade based on the presence of cisternal blood or intraventricular hemorrhage. This scale was found to be superior to the original Fisher scale and predicted clinical vasospasm in patients after SAH more accurately [49]. Another scale that utilizes CT imaging and does not address clinical outcome is the Claassen CT rating scale that serves as an index of delayed cerebral ischemia (DCI) after vasospasm. However, the Claassen CT rating scale has not received prospective validation [21].

The previously mentioned VASOGRADE scale is a classification of the risk for DCI after SAH and is based on the WFNS score and the Fisher scale at the time of admission [29]. Lastly, the Ogilvy and Carter grading system distinguishes patients by age, Hunt and Hess scale, the Fisher grade, and the size of the aneurysm. It stratifies patients into grades ranging from 1 to 5 and has demonstrated statistically different outcomes for patients with grades 2, 3, and 4 when compared to the adjacent lower grade [122].

Wilson et al. [184] described another grading scale that attempts to quantify the amount of subarachnoid hemorrhage from 1 to 5, with increasing values correlating with more likelihood of vasospasm and cerebral infarction. This scale has been validated by some additional studies [31, 120].

Although CT grading scales are useful for classifying patients and creating risk stratification for complications such as vasospasm, for the most part, they do not

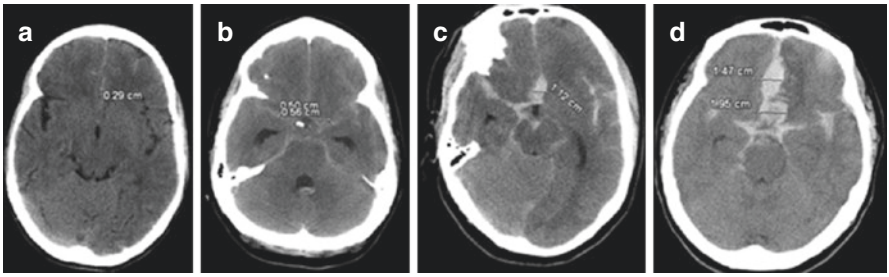

Fig. 25.1 These four axial CT images of patients show different amounts of subarachnoid hemorrhage. In the Fisher scale, all four are grade 3, whereas in the Wilson scale (**a**) would be 2, (**b**) would be 3, (**c**) would be 4, and (**d**) would be 5

change management. It is likely for this reason, and because the grading systems that are available are sometimes in conflict, no single scale is in universal use (Fig. 25.1).However, it is sensible to use one or more of them in a consistent fashion, to be able to follow and compare patients.

25.2.3 ICU Observation

Following stabilization and initial evaluation, patients should be transferred and admitted to intensive care units of high-volume centers with a dedicated, specialized, and multidisciplinary neurovascular team [25, 33, 137, 167, 169]. Superior outcomes and decreased mortality have been demonstrated through observational data at centers which meet these criteria [6, 26, 71, 103, 179].

25.2.4 Surgical Intervention to Prevent Rebleed

Once patient care and observation are transferred to a neurocritical care setting, the primary focus of treatment turns to the prevention of rebleed and the management of immediate neurological or medical complications. Long-term prevention of a rebleed is accomplished by repairing an unsecured aneurysm via surgical clipping or endovascular interventions. Prior to surgical intervention, the risk of a rebleed is managed through control of blood pressure, fluid maintenance, the administration of antifibrinolytics, pain management, treatment for acute hydrocephalus, and the assessment of the aneurysm with computed tomography angiography (CTA) or digital subtraction angiography (DSA) [25, 87, 128, 137, 167].

Risk of rebleeding after aneurysmal SAH can only be fully mitigated by surgical clipping or endovascular interventions [136, 137]. Use of one approach versus the other is determined on a case-by-case basis. A team of specialists will determine the

ideal method depending upon assessment of the individual patient and the particular attributes of the subject aneurysm. This team should include cerebrovascular neurosurgeons, endovascular practitioners, and neurointensivists endeavoring to reach a consensus while considering the patient's age, aneurysm location, morphology, and the impact of adjacent vessels [167]. Regardless of the approach taken, the necessity of early intervention remains the same. Guidelines from the American Heart Association and the American Stroke Association, as well as European Guidelines, implore the securing of a ruptured aneurysm as early as possible [25, 166].

How expeditiously endovascular or surgical repairs are attempted varies with the patient's condition and the predicted stability of the aneurysm. In general, this is carried out as soon as is feasible, given the known risks of rebleeding, which average 4% over the first 24 hours and 25% over the first 2 weeks [11, 32, 42, 92, 123].

Since the introduction of endovascular coiling in 1991, the choice between endovascular interventions and clipping has become controversial [25]. The most exhaustive study to have assessed the efficacy of each was the International Subarachnoid Aneurysm Trial (ISAT). Its comparison of the two techniques involved the random assignment of clipping or coiling to 2143 patients with ruptured aneurysms where clinical equipoise was determined. The study's most prominent conclusion was that the risk of death or dependency at 1 year was lower in those who underwent endovascular coiling rather than microsurgical clipping, with an absolute risk reduction of 7.4% and relative risk reduction of 23.9%. This survival benefit was, also, demonstrated at 7 years [108]. Similarly, seizures are twice as common in patients undergoing clipping rather than endovascular treatment [87, 108]. As is discussed below, the differences observed are particularly notable in patients 65 years and older [152]. Despite increased survival rates, the risk of rebleeding was higher in patients where endovascular coiling was employed rather than clipping. Furthermore, retreatment was four to six times more frequent where endovascular coiling was employed rather than clipping; similar results have been confirmed by additional investigations in the United States [65, 108]. Overall, the neurovascular community has been moving toward an endovascular approach as the default treatment in cases of clinical equipoise, presumably because in general it is perceived as safer and preferred by patients; however, these factors are dependent on the expertise and experience of available surgeons and interventionalists [101, 107, 108].

There are certain aneurysm characteristics, however, that do dictate a preference for endovascular interventions or microsurgical clipping. Aneurysms with necks greater than 4.0 mm, with small dome to neck ratios, that have arterial branches or vessels originating from their body, that are associated with a parenchymal hematoma >50 mL, and that are arising from the middle cerebral artery are all indicated for a surgical clipping [25, 137, 152]. Meanwhile, many remaining indications, specifically basilar tip or other posterior circulation aneurysms, advanced age, poor clinical grade, and underlying systemic conditions, call for endovascular interventions [137, 167]. Independent of the previously mentioned parameters, age presents its own controversy, as some contend that the advantage associated with endovascular interventions shown within ISAT cannot be applied to patients under the age of

40. That contention is based upon the assumption that the conclusion from ISAT, that endovascular interventions should be elected in the case of clinical equipoise, cannot be attributed to a younger population because younger patients better withstand surgical intervention compared to the elderly and the increased likelihood that younger patients gain a greater benefit from the augmented long-term prospects provided by surgical clipping [15, 106].

The controversy in this area has not been resolved even by subsequent studies. The Barrow Ruptured Aneurysm Trial (BRAT) attempted to distinguish between clipping and coiling by randomizing all patients with nontraumatic subarachnoid hemorrhage. Five hundred patients were entered into the study and analyzed in an intent-to-treat fashion. At 1 year, there was a significantly better outcome for patients who underwent coiling. However, this difference became statistically insignificant at 3 years [159]. When patients with only saccular aneurysms were analyzed out to 10 years, there was no statistically significant difference between clipping and coiling at any point in time [160, 162]. However, these results reflect the experience of a single center and have not been generalized to current care. These results are also restricted from generalization because BRAT lacked statistical power. Despite its lack of statistical power, BRAT's raw data evidences that coiling results in notably lower rates of complete obliteration of aneurysms and significantly increased retreatment rates, while clipping demonstrates the opposite results in both values [159]. Although patients who underwent coiling generally experienced inferior results, among those who were followed for 6 years, none of them experienced recurrent hemorrhages [161]. On the other hand, one statistical difference BRAT revealed relates to the location of the aneurysm. Coiling proved to be advantageous for posterior circulation aneurysms. By comparison, results for anterior circulation aneurysms demonstrated an inconsequential difference between coiling and clipping. These results suggest that the location of the aneurysm may play a significant role in deciding among possible surgical interventions. However, despite the improved results for coiling in posterior circulation aneurysms described above, those results were significant for only 1 year [160, 161].

25.2.5 Acute Care Prior to Securing the Aneurysm

While surgical intervention aimed at long-term prevention of a rebleed is the primary objective, interim/short-term strategies to prevent rebleeding also are of importance.

The presence of acute symptomatic hydrocephalus should be addressed prior to the management of blood pressure to avoid over-reduction of cerebral perfusion pressure [140]. Acute hydrocephalus occurs in approximately 20% of patients and most commonly occurs within the first few days [167]. In addition to initial diagnostic imaging, patients presenting with a decreased level of consciousness and other signs of an increased ICP should be imaged until radiographic stability of hemorrhage and hydrocephalus is demonstrated, imaging that is especially crucial in

patients who show signs of good recovery in early stages followed by a decline or plateau in their progress [87, 167]. An external ventricular drain (EVD) should be placed if hydrocephalus is identified. Rapid clinical responses and improvement have been well demonstrated after the insertion of EVDs. Nevertheless, complications can be seen with the use of an EVD, most prominently an increased rebleeding rate. Studies that have identified this association have established that hydrocephalus may serve as a neuroprotective mechanism to oppose the rebleed, and therefore the use of an EVD would remove this benefit. The specific effects of EVD placement on the instigation of rebleeding could be due to a sudden change in ICP and transmural pressure or ventricular shift that displaces aneurysmal clots that may have been tamponading the aneurysm, or it could be secondary to the sensitivity aneurysms exhibit to stress and pressure changes. Lastly, EVD placement may trigger the fibrinolytic pathway that would lyse the aneurysmal clot and result in rebleed. The management paradigm for an EVD changes once the aneurysm has been secured. The focus changes from preventing rerupture to treating hydrocephalus and removing any intraventricular clots that are present. There are various ways EVDs can be managed, and for the most part, it is based on clinicians' experience and the patient's clinical status. A literature review recommended the maintenance of an ICP of 15–20 mm Hg to mitigate the risk of rebleed for patients with unsecured ruptured aneurysms; however, due to the variability in patients, this management primarily depends on the physician's judgment [45]. An additional literature review looking at prospective studies on continuous versus intermittent draining strategies found that the early clamping and intermittent drainage strategy was most compelling after the ruptured aneurysm was secured [20]. Nevertheless, a randomized control study at the Barrow Neurological Institute suggested that a rapid weaning strategy, after securing the ruptured aneurysm, reduced EVD, ICU, and hospital days with no consequential adverse effects on safety, or change in the frequency of DCI, or clinical outcome [80]. A similar result was demonstrated in a 2019 review that concluded the use of intermittent CSF drainage, and a rapid wean was associated with fewer VP shunt placements, fewer complications, and shorter length of stay when compared to a continuous CSF drainage [138]. Thus, a definitive treatment strategy and removal protocol for EVDs require further investigation to determine the superior method. Approximately one-third of patients who present with acute hydrocephalus develop chronic hydrocephalus requiring CSF diversion, typically with placement of a ventriculoperitoneal shunt. The remaining two-thirds of patients who present with acute hydrocephalus are successfully weaned from EVDs [167].

Hypertension portends an increased risk of rebleed and demands consideration in the initial evaluation and interim management before surgical intervention. The goals for treatment of hypertension in this setting are elusive with little trial data to provide evidence-based support for exact blood pressure parameters. Nevertheless, from retrospective investigations, there is indirect evidence that a systolic blood pressure greater than 160 mm Hg appears to be associated with an increased risk of rebleeding [25, 33, 137]. Recommendations regarding the maintenance of MAP targets, however, are varied. Frequently reported parameters target a MAP of

70–90 mm Hg. This is the common range in clinical practice that is implemented at many institutions [89]. Additional recommendations, however, advise maintaining a mean arterial blood pressure of 110 mm Hg when the patient's baseline levels are unknown. Antihypertensive agents such as labetalol, hydralazine, and most commonly nicardipine are used once indications for treatment are met. After administration of any antihypertensive treatment, it is imperative to avoid sudden decreases in perfusion pressure as it can result in cerebral ischemia, with additional susceptibility in patients with an elevated ICP [137, 140, 169].

In 2015, the Neurocritical Care Society (NCS) and Society of Critical Care Medicine (SCCM) together published guidelines that recommend the reversal of all anticoagulation agents in the setting of acute SAH prior to securing the aneurysm. The study provided the following specifications for each antithrombotic agent:

- Reversal of antiplatelets with a 0.4 mcg/kg intravenous dose of desmopressin and platelet transfusions in the setting of neurosurgical interventions.
- Intravenous vitamin K and 4-factor prothrombin complex concentrate (PCC) should be utilized in the reversal of any vitamin K antagonist. Fresh frozen plasma (FFP) or thawed plasma can serve as alternative if PCC is unavailable.
- For the reversal of direct oral anticoagulants, a specific reversal agent or antidote is preferred, such as idarucizumab for dabigatran or andexanet alfa for direct factor Xa inhibitors. In the absence of these specific treatments PCC, antifibrinolytics, and desmopressin should be considered.

These interventions may be discontinued after the aneurysm is definitively secured [52].

The administration of antifibrinolytics, most commonly aminocaproic acid and tranexamic acid, is also among the initial therapies considered, particularly when there is a delay in surgical clipping or endovascular interventions of a ruptured aneurysm (including during patient transfer). Antifibrinolytics may help stabilize the thrombus formed at the bleeding site and have demonstrated a reduced risk of rebleed with a risk ratio of 0.65 (95% CI 0.44–0.97) [5, 52]. The use of an antifibrinolytic agent is based on the understanding that rebleeding is a result of the stimulation of fibrinolysis and reduced clot stability during the first 6 hours post-bleed [86]. Use of aminocaproic acid and tranexamic acid is strongly advised to be limited to short-term use, less than 72 hours, as its later use has been associated with an increased risk of thrombotic events, including cerebral infarcts and deep venous thrombosis. Despite the reduction seen in rebleeds with antifibrinolytics, long-term clinical outcomes are not improved, most likely secondary to the increase in ischemic events [137, 146, 167, 169].

Neuroprotection to decrease the risk of DCI and poor functional outcomes is recommended. Specifically, the calcium channel blocker, nimodipine, improves the odds of a good outcome after SAH. Administration of nimodipine is recommended upon admission into the ICU as a method of neuroprotection that results in a decreased risk of DCI and poor functional outcomes [7, 36]. The recommended dose is 60 mg either orally or via nasogastric tube every 4 hours. The therapy is continued for 21 days [131]. It is important to meticulously observe any changes in

blood pressure; if hypotension is induced, the nimodipine dose should be halved and given every 2 hours [137]. Interestingly, nimodipine first was used in studies to reduce the risk of vasospasm in patients due to its vasodilatory properties [39, 129]. While those studies produced no evidence that nimodipine decreased angiographic or clinical vasospasm, patients receiving nimodipine showed a consistent benefit in clinical outcomes, and it is universally recommended for treating SAH patients.

Pain management has also shown to have therapeutic value and typically is achieved with the administration of short-acting intravenous opiates, such as morphine, specifically to avoid oversedation; the sedative implications of long-acting opiates could make differentiation from the development of hydrocephalus or clinical vasospasm challenging. Fentanyl has largely replaced the use of morphine due to its more rapid onset of action and decreased risk of hypotension in patients [127, 150]. The respiratory depression associated with fentanyl and other opioids can be advantageous in SAH patients to keep CO_2 levels normal and thus avoid vasoconstriction. Consequently, administration of fentanyl is dosed based on maintenance of respiratory status, pCO2 levels, and patient's comfort. Acetaminophen, a milder analgesic, is also potentially effective and can be useful as an antipyretic agent as well though opiates such as morphine are usually required for severe pain [140, 146]. Sedation of neurosurgical and neurocritical patients is influenced by the need to complete regular neurological examinations, and this requires arousal of the patient to complete an accurate exam. Propofol, a GABAergic drug, is a potent sedative that is often used in ICU patients because discontinuation of the drug results in rapid arousal of the patient within 10–15 minutes after the infusion is stopped; this provides conditions in which a proper neuro examination can be achieved [48, 97]. Propofol is useful in hemodynamically stable patients and has an advantage in neurosurgical patients as it can decrease intracranial pressure. Propofol is also preferred in patients with status epilepticus due to its anticonvulsant effects [48, 91]. However, propofol can produce hypotension and respiratory depression [102, 145]. Another sedation considered in this setting, dexmedetomidine, may be superior to propofol as arousal of the patient does not require the discontinuation of this agent. Dexmedetomidine is an alpha-2 agonist that allows for cooperative sedation, in which arousal can be achieved and patients can respond and follow commands. Upon completion of the exam, patients are able to return to a sedative state without holding infusion of the agent. Dexmedetomidine is well-suited for patients on mechanical ventilation as well as neurocritical patients [126, 163, 170]. Adverse effects of dexmedetomidine include a higher risk of bradycardia and other risks associated with traditional sedatives including hypotension which are not statistically different in dexmedetomidine [170].

Historically, the strategy of establishing prophylactic hypervolemia in SAH patients was a part of a treatment method known as "Triple-H" therapy, which encompassed the induction of hypertension and hemodilution as well. This therapeutic approach, however, has not exhibited a clinical improvement in cerebral blood flow or a decrease in the development of DCI or vasospasm, but has shown to intensify the frequency of cardiogenic complications when administered prophylactically. Consequently, current recommendations aim to maintain euvolemic

conditions for patients, by administration of isotonic saline and the avoidance of hypotonic solutions [137, 146, 167]. Notably, while no longer implemented prophylactically, triple-H therapy, particularly the induced hypertensive component, remains a reasonable treatment of clinically determined vasospasm.

25.2.6 Anticonvulsants

Abnormal or seizure-like movements frequently occur at the onset of SAH, but it is difficult to know whether such movements are true seizures or may be a consequence of increased intracranial pressure. The initial seizure-like movements typically are witnessed by family or friends lacking medical training, and therefore the circumstances described by them are difficult to attribute clinical meaning [18, 85, 143]. A 2013 study found that seizures during hospitalization occurred in 2.3% of SAH patients. Overall, clinical seizures not caused by the initial rupture are rare (1–7%), and when they occur prior to surgical intervention, such seizures typically indicate a rebleed [33, 139]. Prophylactic treatment with anticonvulsants in SAH patients without seizures has previously been commonplace. While no known trials have addressed this specific issue, currently the use of prophylactic anticonvulsant is no longer recommended because of worse long-term clinical outcomes. This may be particularly a consequence of SAH patients being administered phenytoin and possibly was observed when SAH patients were treated with nimodipine because of a potential pharmacokinetic interaction, in that phenytoin lowers levels of nimodipine and thereby inhibits nimodipine's ability to improve outcomes for SAH patients [81, 116]. However, it appears that short-term anticonvulsant may not increase risk and may be reasonable for patients with a clinical diagnosis of seizures or the evidence of seizure activity on EEG [19, 136, 167], or patients with parenchymal hematomas (with disruption of cortex), or patients whose SAH was treated with clipping. Levetiracetam has become the standard because, among other reasons, of its ease of administration and dosing and its minimal side effects or drug interactions; phenytoin has been most closely associated with negative long-term outcomes. The recommended treatment is 3–7 days. However, it appears that short-term anticonvulsant (other than phenytoin) treatment (3–7 days) may not increase risk and may be reasonable for patients with a clinical diagnosis of seizures or the evidence of seizure activity on EEG [19, 136, 167].

25.2.7 Summary of Initial Management Recommendations

Thus far, this chapter has focused on the management of SAH patients beginning with immediate assessment and care through the securing of a ruptured aneurysm (open surgery and/or endovascular treatment). This focus emphasized stabilization of the airway, circulation, and respiration, typical of most emergent cases. Key

recommendations unique to SAH patients contemplate transferring to high-volume centers with experienced neurovascular teams and assessing severity of SAH (most commonly through a Hunt and Hess grade, accompanied by a GCS report, and an additional grade using a scale of the institution's preference). Prompt treatment of the aneurysm by microsurgical clipping or endovascular intervention is critical. Interim precautions preceding these interventions include addressing hydrocephalus with an EVD and strict management of blood pressure, with administration of antihypertensive agents when systolic pressure exceeds 160 mm Hg. Also, if patients are on anticoagulative therapy, temporary discontinuation and reversal agents are indicated. Administration of fluids to maintain euvolemia should be considered, while prophylactic "Triple-H" therapy of hypervolemia is not recommended. Nimodipine is started as a neuroprotective agent in an effort to improve outcomes. Antifibrinolytics can be considered because there is some evidence that it reduces the risk of rebleed. Sedation can be achieved with dexmedetomidine, and pain can be mitigated by administration of fentanyl. Finally, confirmed seizure activity, the presence of parenchymal hematomas, or surgical clipping suggests the use of anticonvulsants. All of these interventions help stabilize and prepare patients for clipping or endovascular interventions. Discussion of recommended treatment and care after these interventions follows in the remainder of this chapter.

After a patient undergoes definitive management of the aneurysm through either endovascular intervention or surgical clipping, the concentration of care in the ICU focuses on preventing any further deterioration of the patient. Within the first week of management, much of what was discussed previously is maintained. For example, the maintenance of euvolemia with isotonic saline is still recommended throughout the first week as is the administration of nimodipine (to complete the 21-day course). The treatment of hydrocephalus is continued as well with the removal of an EVD to be considered as soon as possible and placement of a permanent shunt as soon as persistent hydrocephalus is recognized. Pain management also echoes what was previously discussed, with care to avoid oversedation of the patient which might disguise symptoms of deterioration. Contrarily, any antithrombotic reversal therapy should be discontinued. Additional interventions to be considered implementing within the first week of care are discussed below with the primary objective of preventing late and systemic complications caused by SAH.

25.3 DCI, Cerebral Infarct, Vasospasm, and Monitoring

25.3.1 Diagnosis and Monitoring

Delayed cerebral ischemia (DCI) can occur anytime within the first week, but can also occur up to 2 weeks after the initial hemorrhage and is descriptive of any neurological or cognitive deterioration when all other possible causes of neurological decline have been excluded [28, 94, 109, 151]. DCI occurs in approximately 30% of

patients and is considered a major cause of mortality and morbidity in patients after SAH [109]. It is most often associated with cerebral vasospasm, which refers to the narrowing and vasoconstriction of cerebral arteries. There are two distinct categories of relevant vasospasm: (1) angiographic vasospasm and (2) clinical vasospasm. The former occurs in up to 70% of patients and is defined as vasospasm seen on digital subtraction angiography (DSA). The latter occurs in 20–30% of patients and is defined as a clinical decline attributed to vasospasm by virtue of elimination of all other causes; it is this category that is associated with poor outcome and DCI [51]. The existence of other etiologies of DCI was elucidated by the CONSCIOUS-1 trial that investigated the endothelin receptor antagonist, clazosentan. The endothelin receptor is believed to be behind the mechanism of vasospasm; accordingly, it was presumed that an antagonist could alleviate the incidence of vasospasm. The trial, however, demonstrated that clazosentan was able to decrease vasospasm radiographically but failed to show an improved outcome in patients compared to a placebo group. This prompted research into other possible causes and additionally prompted the concept and study of early brain injury (EBI) [95]. Other causes of DCI include microemboli, cortical spreading ischemia, and microcirculatory spasm [94].

Due to the importance of diagnosing DCI, there exist an extensive number of modalities used for monitoring patients after SAH. This includes frequent neurological exams (every 1 to 2 hours) that are intended to identify any changes in neurological status as well as numerous physiological and imaging studies. For instance, 24 to 48 hours after securing an aneurysm, a follow-up head CT is recommended to evaluate for hypodensities that, if not attributable to EVD insertion or intraparenchymal hematomas, are usually indicative of cerebral infarct from DCI [180].

Transcranial Doppler sonography (TCD) is a noninvasive aid for detecting and assessing vasospasm, a key mechanism of DCI. By detecting changes in velocity, TCD can anticipate the occurrence of vasospasm in patients and provide a window of opportunity for treatment prior to clinical decline. TCD has a higher sensitivity for the middle cerebral and internal carotid artery distributions than it does for anterior cerebral artery distribution [168]. TCD vasospasm has been found to predict CT-confirmed cerebral infarction and the outcome of SAH [88, 164]. The Lindegaard ratio, the mean cerebral blood flow velocity of the middle cerebral artery to the mean cerebral blood flow velocity of the internal carotid artery, can predict cerebral vasospasm. The Lindegaard ratio is diagnostic of mild middle cerebral artery vasospasm when it is >3 and severe when >6 [54, 77, 134]. When interpreting data from TCD, practitioners should be aware that despite its adequate sensitivity and specificity for detection, it is not only an operator-dependent modality but also dependent on the cranial bone window [109] (30,516,599). Additionally, false positives can occur in patients with elevated blood pressure, and false negatives can occur in patients with extreme artery narrowing due to low blood flow; therefore, it is crucial to correlate TCD findings to clinical exam findings [94].

Because of the limitations of TCD, they are not singularly diagnostic. Instead, DSA remains the gold standard for detection of large or middle-sized arterial vasospasm and confirmation of the aneurysmal rupture [9]. DSA incorporates

three-dimensional reconstructions that facilitate superior characterization not only of the morphology, orientation, and neck size of the aneurysm but also of adjacent vessels [56]. Concerns surrounding the use of DSA include complication rates compared to less invasive diagnostic modalities. However, several studies have demonstrated low complication rates for DSA [68, 74]. One meta-analysis specifically reported a risk of neurological complications of 0.5–1.8% with permanent deficit in 0.09–0.5% with the use of DSA. It is notable that this same study did recommend the use of CTA first, but also emphasized the frequent need to follow up with DSA. To monitor vasospasm, cerebrovascular surgeons will recommend a routine surveillance angiogram on post-bleed days 5–7. If radiographic spasm is present, the neurovascular team is able to monitor and manage the findings accordingly [109]. Since DSA is an invasive modality with inherent risk, many institutions are now using CTA as the initial imaging modality [78, 94, 109]. CTA has demonstrated, in a prospective study, accurate detection of large vessel vasospasm with a very high negative predictive value, but is less accurate when assessing medium and small vessels and distal aneurysms [17, 73].

One retrospective investigation has uncovered the importance of including CT perfusion (CTP) imaging. The study revealed that CTA combined with the mean transit time (MTT; the mean time it takes for blood to perfuse a region of tissue) derived from CTP was the most accurate diagnostic tool for angiographic vasospasm. Specifically, predicting DCI with CTA was augmented in this study by CTP findings of a MTT of greater than 6.4 seconds [185]. Additional studies have also confirmed the amplification of CTA with CTP in predicting the occurrence of DCI in acute SAH patients [38, 130, 177, 178]. It is of note that CTA may overestimate the presence of vasospasm and the use of CTA may be limited due to repeated dye loads and radiation exposure [25, 94, 109]. CTA has also been considered as redundant as DSA is often still required for therapeutic treatment, and the rate of false negatives with CTA will subsequently demand the use of DSA as follow-up [68, 73]. Overall, the use of DSA remains the gold standard and a class I recommendation, and while the use of CTA is possibly a highly accurate alternative, it still requires further investigation. Other techniques to consider in the assessment of cerebral perfusion include perfusion and diffusion-weighted MRIs and older methods like positron emission tomography (PET), xenon-enhanced CT (Xe-CT), and single-photon emission computed tomography (SPECT); however, these techniques are rarely implemented in modern practice [84].

Continuous EEG (cEEG) monitoring also effectively detects cerebral ischemia as well as subclinical or nonconvulsive seizures in SAH patients. Detection of ischemia can be achieved by applying quantitative analysis encompassing relative alpha variability and poststimulation alpha/delta ratio to cEEG. cEEG detection can identify ischemia at a reversible stage and prior to clinical changes and prior to changes detectable by noncontinuous modalities [22]. However, cEEG has a lower specificity because it does not convincingly differentiate ischemia caused by vasospasm from ischemia caused by increased ICP [182]. Additional limitations that impede widespread implementation of cEEG include the time to apply, remove, and reapply electrodes for CT or MRI, the difficulty of interpreting data in the absence of an

electroencephalographer, and the considerable expense of cEEG monitoring compared to other options [78, 109]. Nevertheless, due to a low-risk profile, there is low threshold for the use of cEEG. If any patient presents with a neuro exam that is inconsistent or unexplained by imaging they should have at least 24 hours of EEG monitoring to rule out subclinical seizures. Findings on cEEG can lead to therapeutic interventions including, but not limited to, antiepileptic medication, hypertensive therapy, or additional diagnostic testing such as CTA or DSA [22].

Near-infrared spectroscopy (NIRS), the newest advancement in monitoring SAH-related deterioration, evaluates cerebral blood flow dynamics. NIRS is a continuous modality that offers a quantitative measurement of hemoglobin concentration and cortical oxygen saturation (CoSO2) in the underlying cortex [78]. The promise of this approach was shown in a small study where it was able to demonstrate greater accuracy than TCD; specifically, by way of daily measurements, a 3.9–6.4% decrease in CoSO2 in the MCA was found to be 100% sensitive and 85.7% specific for CTA-confirmed vasospasm [189]. Nevertheless, validation via prospective studies is necessary prior to inclusion of NIRS into the standard of care [78].

Lastly, invasive monitoring methods include brain tissue oxygen ($PtiO_2$) monitoring, microdialysis, thermal diffusion, and jugular bulb oximetry. These invasive methods require the insertion of a probe into a targeted brain region and subsequently provide useful data on changes in the microenvironment. $PtiO_2$ monitoring detects lower cerebral tissue pH and higher pCO2 in SAH patients who have developed vasospasm and can serve as an indicator of ischemia during vasospasm [16]. Additional studies also show that $PtiO_2$ monitoring reliably detects impaired autoregulation in patients who developed cerebral infarcts [66]. Microdialysis detects significant changes in concentrations of lactate, glucose, and glutamate levels prior to the development of symptoms in patients who developed ischemia [175] (11,354,405). Furthermore, microdialysis reveals that elevated levels of lactate, nitrite, and taurine are potential predictors of poor neurological outcome after SAH and may be relevant in the development of brain damage after SAH [165]. Similarly, a thermal diffusion probe can be inserted to collect continuous data regarding variations in cerebral blood flow (CBF). This is noteworthy because CBF may decrease post-hemorrhage in patients with vasospasm, despite concurrent increases in CPP [176]. Jugular bulb oximetry is an additional modality that can assess CBF globally. Its use involves the insertion of an oxygen saturation probe into the jugular vein superior to the facial vein, to provide samples from intracranial circulation, from which the cerebral oxygen extraction can be determined [78]. One particular study demonstrated that the cerebral oxygen extraction value rises significantly up to 24 hours before the arrival of clinical vasospasm and normalizes after the institution of the triple-H therapy [60] (15,038,475). While all of these techniques have exhibited utility in the detection of DCI, their use is largely diminished due to their invasive and therefore inherently riskier nature, and due to the fact that each samples only the region of insertion or is global, and therefore may miss changes.

25.3.2 Treatment

Vasospasm prevention and monitoring includes the maintenance of euvolemia with concurrent implementation of meticulous monitoring to detect any clinical changes. Though nimodipine has not been shown to decrease vasospasm, it has shown efficacy for improving outcomes for SAH patients. Vasospasm treatment is implemented upon the diagnosis of clinical vasospasm, as the risks that accompany DCI treatment do not justify treatment of radiographic vasospasm. Instead, angiographic or TCD vasospasm should be closely monitored and managed [25, 33, 109].

As noted above, the triple-H therapy (induced hypertension, hypervolemia, and hemodilution) is no longer recommended as a prophylactic intervention but is reserved for confirmed vasospasm and DCI treatment [1, 90, 110]. Given that the need usually arises at the end of the first week, interventions to raise the blood pressure are reserved until there are clinical or radiographic signs of vasospasm. Hypervolemia is achieved with an IV crystalloid, colloid, or albumin boluses and increased maintenance fluids to achieve euvolemia or mild hypervolemia [90]. The administration of alpha-1 receptor agonists, like norepinephrine or phenylephrine, is preferred to induce hypertension by continuous infusion [104, 109]. Dopamine is used minimally [33]. This process should progress in a stepwise fashion with the maintenance of frequent neurological exams. The first of these steps often targets a mean arterial pressure (MAP) of approximately 20 mm Hg above baseline MAP, and this commonly results in a MAP greater than 90 mm Hg. At institutions using systolic blood pressure targets, the first goal is approximately 20 mm Hg to 40 mm Hg above baseline systolic blood pressure, the outcome of which is often a systolic blood pressure of greater than 180 mm Hg or greater than 200 mm Hg [109]. Stepwise increases should be continued if examinations and imaging fail to improve [33]. The potential cardiac and pulmonary side effects of induced hypertension on each particular patient should be weighed in the clinical decision-making process. Furthermore, if physical examinations and imaging return to baseline levels and remain unchanged, additional blood pressure augmentation should not be necessary [109].

Additionally, in the context of cerebral ischemia, cardiac output can affect cerebral blood flow. Therefore, inotropes such as milrinone and dobutamine should be considered to address poor cardiac output, especially in patients with acute or chronic cardiomyopathy [47, 70, 113]. Indication of clinical vasospasm, including new or worsened neurological deficit, especially in the setting of hypertensive therapies, calls for expeditious DSA; if vasospasm is confirmed, then endovascular therapy follows. Utilizing CT prior to DSA can be beneficial for identifying hydrocephalus and antecedent strokes prior to endovascular intervention. In the event TCDs indicate vasospasm, and all other etiologies for neurological decline have been excluded, the CTA should be bypassed to expedite initiation of DSA and subsequent endovascular therapy.

The two endovascular therapies currently supported by observational data include intra-arterial vasodilators and transluminal angioplasty. The following intra-arterial vasodilators have demonstrated effectiveness: nicardipine, milrinone, nimodipine, verapamil, and intra-arterial and intrathecal nitroprusside [4, 47, 61, 63, 72, 172]. Their administration is typically reserved for diffuse and small vessel vasospasm because balloon angioplasty in small peripheral arteries is not feasible and presents an unacceptable risk [156]. Papaverine may also be administered to dilate vessels; however, significant disadvantages such as recurrent vasospasm, the required multiple treatments, and the risk of increased ICP have been identified and resulted in its limited use and promoted its replacement by other vasodilatory agents [156]. Transluminal angioplasty has been successful in extenuating angiographically confirmed severe vasospasm and has demonstrated sustained clinical improvement and reversal of DCI deficits [25, 43, 133]. These favorable outcomes are more likely when angioplasty is initiated early following the onset of severe vasospasm and may be restricted to short-term benefits [111, 149]. Furthermore, vessels treated with balloon angioplasty showed compression and stretching of arterial walls without long-term damage or disruption of cellular or connective tissue elements [156].

25.3.3 Medical Complications

25.3.3.1 Fever

Fever is the most common sequelae of SAH, occurring in 59–70% of the population [76, 109, 167]. It is associated with poor clinical outcomes including cognitive impairment and loss of independence, as well as vasospasm, longer hospital stays, and a higher mortality rate [35, 109, 124, 167]. Patients with high-grade SAH or a poor neurological status are more likely to contract a fever; additional strong predictors include the presence of intraventricular hemorrhage and a poor Hunt and Hess grade [40, 109]. Fevers of all types are increased after SAH, and therefore, regular temperature checks and assessment for infectious etiologies should be performed [24] (12,629,243). Nevertheless, fever is more often secondary to noninfectious causes likely associated with SIRS and chemical meningitis [109]. Treatment for fevers includes maintenance of normothermia with antipyretics, most commonly acetaminophen, and treatment of infectious causes if present [28, 40]. Use of cooling blankets and intravascular devices may be considered if medications lack sufficiency, but the avoidance of shivering is critical [34, 99, 109, 167].

25.3.3.2 Hyperglycemia

Hyperglycemia is frequently diagnosed in patients after SAH. Increased stress and inflammatory responses are likely contributory factors. Hyperglycemia has been associated with poor clinical outcomes and serious complications including DCI,

congestive heart failure, respiratory failure, pneumonia, and brain stem compression from herniation, though a causal relationship has not been identified [50, 83]. Target ranges for glycemic control remain undetermined, but avoidance of hypoglycemia is indicated because it can lead to metabolic crisis in the brain. However, tight glycemic control (80–110 mg/dL) has also been demonstrated to produce worse outcomes when compared to a looser approach (120–150 mg/dL) [181] (22,610,193). Overall, it is suggested that blood sugar be maintained between 80 and 200 mg/dL to avoid the consequences of either extreme [28, 109].

25.3.3.3 Hyponatremia

Hyponatremia is common after SAH. There are several possible mechanisms underlying the development of hyponatremia including (1) cerebral salt wasting (CSW), (2) the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), (3) acute cortisol insufficiency, and (4) improper fluid management [98, 135].

CSW and SIADH laboratory findings appear similar: low serum sodium, low serum osmolality, a higher urine osmolality than serum osmolality, and an elevated urinary sodium concentration [57]. Although similar, these findings can be distinguished by determining intravascular volume status. CSW provokes a volume contraction that can increase the risk of DCI and poor outcomes [2], while patients with SIADH are euvolemic or hypervolemic. The differentiation of the etiology is important for safe, effective, and prompt treatment [144].

CSW is caused by an uncontrolled release of natriuretic peptides that precipitate hyponatremia by extreme natriuresis. Therefore, treatment calls for fluid resuscitation with isotonic solution if serum sodium levels are normal accompanied by oral salt tablets if patient is conscious [57, 155]. The use hypertonic solution can be used if followed by consideration of the use of fludrocortisones [2, 105].

SIADH is caused by the inability to suppress the secretion of ADH. Excess ADH increases the free water absorption in the principal cells of the kidney, resulting in hyponatremia. Typical treatment of SIADH includes fluid restriction in order to reduce the expansion of extracellular volume; however, this may not be desirable for patients after SAH [46]. Fluid restriction in the setting of impaired cerebral blood flow, as seen in SAH, may increase the possibility of hypovolemia-associated cerebral infarction and vasospasm [9, 183]. Alternatives have been investigated, though the efficacy and superiority of any one are not yet determined. The use of 3% hypertonic saline has been shown to increase the plasma sodium concentration sufficiently but presents the potential complication of volume overload such as cerebral edema, pulmonary edema, and heart failure [98]. The use of albumin has demonstrated benefits in curtailing natriuresis, though its use remains controversial because of limited randomized trials [100]. Fludrocortisone has been implemented, but its use also is limited because of the heightened risk of fluid overload, making it more appropriate in the setting of CSW. Additionally, conivaptan, a vasopressin receptor antagonist, has been studied on a small scale but still remains outside of the scope of routine care secondary to issues with increased risk caused by rapid correction

(thereby reducing its safety profile) and its high cost [37, 112, 186]. The last intervention that has been minimally investigated is the use of urea, which induces sodium resorption in the ascending loop of Henle in the nephron and thereby indirectly promotes osmotic diuresis. By this mechanism, it has been demonstrated to be useful in the treatment of SIADH [30, 132].

During treatment, scrupulous monitoring of serum sodium levels is essential and should be checked every 6 hours, and target correction rate should be a maximum of 0.5 mEq/L/h to avoid central pontine myelinolysis [46, 98].

25.3.3.4 Cardiac and Pulmonary Complications

Cardiac and pulmonary complications are also well documented after SAH. Common electrocardiographic abnormalities include ST segment elevations and depressions and peaked T waves and T wave inversions, indicating myocardial ischemia as well as QT prolongation and U waves [10, 27, 140]. Furthermore, SAH patients may develop supraventricular and ventricular arrhythmias, elevated troponin levels, and myocardial dysfunction [10, 27]. The level of troponin elevation is shown to be associated with an increased risk for cardiovascular problems, DCI induced by vasospasm, and worse neurological outcomes [69, 117]. Left ventricular dysfunction in the first week after SAH has an incidence rate from 9% to 30%, which can comprise of wall motion abnormalities unrelated to corresponding coronary artery territories and severe systolic left ventricular impairment with ejection fractions less than 30% [109]. The severity of SAH determined by the Hunt-Hess grade has been shown to independently correlate with the occurrence of cardiac complications, particularly myocardial necrosis, and therefore suggests a neural etiology for these complications [174]. Data suggest cardiac damage is facilitated by the catecholamine surge that occurs after SAH. Patients are shown to have a threefold elevation of norepinephrine that persist throughout 7- to 10-days post ictus [119]. This sympathetic activation after aneurysmal rupture results in myocardial injury, decreased inotropy, increased preload (secondary to venous constriction), and increased afterload (due to peripheral arterial constriction). Stroke volume is subsequently reduced, triggering reflex tachycardia that is ineffective and decreases cardiac output, resulting in neurocardiogenic shock. Takotsubo cardiomyopathy may also be induced, in which apical ballooning is commonly detected on echocardiograms and like neurocardiogenic injury results in contraction band necrosis [10, 140, 188]. Neurogenic cardiomyopathy in SAH is correlated to higher mortality and worsened outcomes [109, 188].

In the setting of SAH, it is crucial to differentiate neurocardiogenic injury from acute myocardial infarction, which would show evidence of coronary artery disease on coronary angiography [188]. The Neurocritical Care Society recommends serial assessment of enzymes, ECG, and echocardiography, specifically in patients with confirmed myocardial damage and dysfunction [33]. In the setting of an acute MI and CAD, beta-blocking agents are administered to patients, while nitroglycerin and nitroprusside are contradicted because of their venovasodilatory effects that

could significantly elevate ICP. On the other hand, treatment of neurocardiogenic shock remains empirical secondary to a lack of randomized trials. Nevertheless, clinically, the treatment of the underlying neurological condition is essential [140]. Inotropic agents such as milrinone and dobutamine are administered for patients with neurocardiogenic shock; these agents are suitable for neurocardiogenic shock due to their ability to increase cardiac output without lowering the blood pressure, whereas beta-blockers are contraindicated as they reduce both cardiac output and blood pressure [75, 109]. A retrospective study at Columbia University determined that milrinone and dobutamine may be superior in different clinical situations. In SAH patients with markedly depressed systolic function but normal vascular resistance and blood pressure, where cardiac output is the principle target, milrinone may be more effective. Conversely, dobutamine may be preferred when vascular resistance or blood pressure is low [113]. With that said, it must be emphasized that the most critical step in treatment of cardiac complications after SAH is deciphering the correct etiology as the treatments are discordant and can affect the efficacy of triple-H therapy in the setting of clinical vasospasm [67, 75].

Pulmonary edema is associated with neurocardiogenic shock in 8% of patients within 12–24 hours of aneurysm rupture [154]. This can be caused by left ventricular dysfunction and independently from neurogenic-mediated injury; neurogenic pulmonary edema (NPE) is secondary to the increased sympathetic tone when the catecholamine surge substantially increases pulmonary capillary pressure. Hypoxia and decreased cerebral perfusion pressure are the main concerns resulting from NPE, and therefore the patient must be diligently managed [109]. Supplemental oxygenation may be sufficient, but often mechanical ventilation is required. Recommendations for tidal volumes are less than 7 cc/kg of ideal body weight without permissive hypercarbia. Mechanical ventilation for NPE is similar to that of patients with other causes of respiratory failure; nevertheless, there are some crucial distinctions for NPE. The first is to note that high levels of positive end-expiratory pressure (PEEP) can impair cerebral venous outflow and return and consequently elevate intracranial hypertension (increased ICP) [23]. The second is that hypercapnia can cause cerebral vasodilation, thereby also increasing cerebral blood flow and potentially increasing ICP [8]. Overall, NPE reflects the severity of an SAH bleed and is additionally a critical predictor of poor outcomes [27, 154].

25.4 DVT Prophylaxis

Patients with poor-grade SAH and those who are immobilized due to poor mental status are also at risk for the development of a deep venous thrombosis (DVT). Therefore, it is appropriate to begin mechanical prophylaxis with pneumatic compression stockings prior to aneurysmal treatment [28, 169]. Initiating pharmacological thromboprophylaxis (PTP) appears to be safe within 24 hours after successful endovascular treatment of the aneurysm. If the patient undergoes surgical clipping, PTP initiation depends on the judgment of the surgeon, but often begins within

48 hours [96]. Heparin and its derivative enoxaparin, a low molecular weight heparin, have been demonstrated to be useful for PTP and possibly reduce the incidence of clinical vasospasm [13, 58, 187].

25.5 Anemia

Anemia commonly develops during the course of SAH including at presentation, after securing the aneurysm, and through the peak period of DCI (days 5–9) [3]. The fall in hemoglobin levels may be due to the hemorrhagic blood loss as well as the suppression of erythropoiesis through inflammatory mechanisms [153]. The negative consequence of anemia is diminished oxygen delivery and subsequent compromised cerebral oxygenation. The compromised oxygen-carrying capacity in these patients causes cellular hypoxia, cell energy dysfunction, and neurological deficits [3, 25, 53, 121, 153]. Additionally, anemia becomes more prominent in SAH patients who are being treated for DCI via hypervolemic therapy; administration of fluids to mitigate vasospasm further decreases hemoglobin concentration [118]. Data from several studies suggest that higher hemoglobin levels are associated with improved outcomes as well as decreased rates of cerebral infarction and improved functional outcomes at 14 days and upon discharge and lastly improved functional outcomes at 3 months [3, 25, 114, 115, 118]. Anemia can be ameliorated with blood transfusions; however, its potential benefit is tempered by evidence that transfusions can be an independent risk factor for vasospasm, poor outcomes, and increased mortality [3, 12, 25, 41]. Consequently, it is not clear that a liberal transfusion strategy is an appropriate method to increase hemoglobin levels in anemic SAH patients because in a randomized trial, data demonstrated that in the restrictive transfusion group (7 g/dL), there was a lower mortality and less ill patients compared to the liberal group (10 g/dL) [59]. Additional studies that did not include patients with neurological conditions have shown similar evidence that restrictive transfusions are beneficial in critically ill patients [62, 147]. The Neurocritical Care Society's Multidisciplinary Consensus Conference in 2011 recommends that patients receive packed red blood cells to maintain a hemoglobin between 8 and 10 g/dL, and the conference consensus suggests that in patients at risk for DCI and vasospasm, it may be appropriate to maintain even higher hemoglobin concentrations [33].

Nutrition is also a routine part of ICU management in order to prevent malnutrition and nutrient deficiencies in critically ill patients. The enteral route is universally preferred as it has demonstrated preservation of gut integrity, barrier and immune functions, and reductions in infectious complications [14, 97]. Tube feeding should commence within 24–48 hours of admission to ensure the protective factors of tube feeding [97]. Stool softeners should also be considered for patients with acute SAH. Stool softeners help eliminate straining and prevent hypertension during bowel movement and thereby decrease the risk of rebleeding prior to surgical intervention [128, 137]. The use of GI prophylaxis is also essential. As previously discussed, there is often an increased sympathetic tone in SAH patients resulting in a

stress response that can weaken gastric defenses and result in stress ulcers [173]. These erosions and ulcers are common among all critically ill patients, and hypoperfusion of the gut also results in disrupted gastric mucosa. Therefore, GI prophylaxis is often implemented when patients are admitted and is especially important for patients who are dependent on mechanical ventilation for more than 48 hours. The most common prophylactic measure is the use of H_2-receptor antagonists to block the production of gastric acid. The most common of these agents are ranitidine and famotidine given as IV bolus; 50 mg every 8 hours and 20 mg every 12 hours, respectively. Risks of this regimen include an increased risk of infection, specifically *Clostridium difficile* enterocolitis, and an increased risk of aspiration pneumonia. Proton pump inhibitors can also serve to block gastric acid production, and they are considered more potent in reducing gastric acidity than H_2-receptor antagonists; however, they have not been shown to be superior in prevention of stress ulcers and are associated with a higher risk of infection [97, 157].

25.6 Summary

Subarachnoid hemorrhage (SAH) is a complex, multisystem, life-threatening neurocritical emergency that requires diligent management provided by a specialized neurovascular team. Prompt recognition of SAH is critical for improving long-term prognosis; therefore, the threshold for investigational studies remains low. Upon recognition, improved outcomes are dependent upon treatment by qualified high-volume centers with adequate neurovascular teams. Expeditiously determining the precipitating factor and subsequent mitigation of the cause(s) are the initial primary focus. Treatment involves early securing of a ruptured aneurysm. Prior to securing the aneurysm, securing the airway, maintaining proper circulation, treating hydrocephalus, and managing blood pressure remain top priorities. After intervention, ICU observation and routine exams are compulsory. The objective during treatment in the ICU includes prevention and rapid treatment of neurological or systematic sequelae. These include, but are not limited to, hydrocephalus, seizures, fever, hyperglycemia, hyponatremia, DVTs, anemia, DCI, and cerebral infarcts. Standardized neurocritical care should be provided for at least the first 2 weeks. While scales exist to determine a clinical grade at admission in order to provide prognostic information, outcomes are influenced by many additional factors, including a patient's values and preferences, comorbidities, social support, resilience, and time for recovery. Central to all these issues is proper and attentive management by a multidisciplinary neurovascular team.

Highlights

1. Once patients presenting with aneurysmal SAH are acutely stabilized, they are evaluated for pathology-specific complications such as development of hydrocephalus and re-hemorrhage. Various grading scales are employed early in management to communicate the severity and prognosis of the pathology.

2. Following stabilization and initial evaluation, patients should be transferred and admitted to intensive care units of high-volume centers with a dedicated, specialized, and multidisciplinary neurovascular team
3. Interim/short-term acute care strategies are employed to prevent rebleeding, assess hydrocephalus, maintain normotension, and reverse anticoagulant/antiplatelet agents.
4. The risk of acute rebleed and long-term prevention of rebleed is not completely attenuated until the unsecured aneurysm is repaired using microsurgical clipping or endovascular interventions; therefore, these interventions should be pursued as soon as possible.
5. Treatment then turns to prevention of delayed cerebral ischemia and management of neurological and medical complications including, but not limited to, fever, hyperglycemia, hyponatremia, vasospasm, cardiac and pulmonary complications, deep venous thrombosis prophylaxis, and anemia.

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Chapter 26
Hemorrhagic Stroke

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26.1 History

Intracerebral hemorrhage (ICH) consists of the rupture of an intracranial vessel with a subsequent overflow of blood directly to the brain parenchyma. It was first recognized as a cause of stroke by Morgagni in 1761. Gower and Osler were the firsts to describe the usual locations of ICH, with their respective clinical signs and symptoms. Aring and Merritt [1] published the clinical and pathological findings of 245 patients who presented with stroke and were submitted to necropsy at the Boston City Hospital [1]. ICH was seen as an invariably lethal disease in the era precomputed tomography (CT).

Microscopic pseudoaneurysms with subclinical leaks are a hallmark of ICH. They can be detected by observing multifocal hemosiderin deposition on magnetic resonance imaging (MRI). The prevalence of these microbleeds ranges from 5 percent in healthy adults to 60 percent on patients with ICH [2]. Their location varies with etiology, with hypertensive microbleeds being more common in deep subcortical and infratentorial regions, whereas amyloid pathology occurs in more superficial lobar regions. There is also a genetic correlation, with APOE alleles ε2/ε4 being more related to microbleeds in lobar regions, especially when associated with cognitive impairment and regional amyloid deposition.

After the initial rupture and deposition of blood on the brain parenchyma, there is a direct injury due to the expanding cloth and cytotoxic perilesional edema. This

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causes mass effect and, if significant, increased intracranial pressure (ICP). Reduced cerebral perfusion may then succeed. Dramatic cases can culminate in cerebral herniation.

There is commonly a significant growth of the hemorrhage in the following few hours after symptoms onset. A follow-up of 103 ICH patients showed that the hemorrhage increases in 38 of them over the next 24 h after symptoms onset [3]. Independent predictors of hemorrhage expansion include time from symptom onset to CT, ICH volume, use of anticoagulants and antiplatelets, and the presence of contrast extravasation on neuroimaging. There is a strong correlation between hemorrhage growth and worse outcome, which gives the health-care team a window of opportunity to minimize secondary deficits following the onset of the bleeding [4].

26.2 Epidemiology

Nontraumatic ICH is a major cause of morbimortality burden worldwide, being greater than ischemic stroke in terms of death and disability. It is the cause of 9–27% of all strokes. There is a higher frequency of ICH in Asians and African-Americans. A higher percentage of strokes in patients under 40 years old are hemorrhages, though ICH is also common during the later years of life. There is no gender association [5]. Overall risk factors for ICH in men and women are similar. In a Brazilian series [6], men had a higher frequency of alcohol abuse and smoking. Women were older, had an increased time length from symptoms onset to hospital admission, and had worse prognosis at discharge [6].

26.3 Etiology

Hypertension is the most common cause of ICH. The chronic action of hypertension over the walls of the cerebral vessels promotes hyperplasia of the smooth muscle cells, posteriorly replaced by collagen. The collagen weakens the vessel walls and induces the formation of microscopic pseudoaneurysms. This phenomenon, known as lipohyalinosis, occurs mainly on deep small vessels, which explains why hypertensive ICH is twice as common on the basal ganglia, brainstem, and cerebellum rather than lobar territories [7]. Hypertension is one of the most important modifiable risk factors as the crude prevalence among adults in the USA has been estimated to be 45.6% [8].

The second most common cause of ICH is cerebral amyloid angiopathy. The deposit of amyloid material on small arteries of the cortex and leptomeninges may cause lobar bleedings. It can cause recurrent hemorrhages in different brain areas simultaneously. The histopathological analysis of cerebral brain autopsied shows

deposition of Congo red-stained amyloid material, responsible for the weakening of brain vessels [7].

Hematomas may also be caused by arteriovenous malformations (AVM), dural fistulae, or cavernous angiomas. The presence of subarachnoid hemorrhage alongside ICH suggests aneurysm or AVM rupture as the cause of bleeding. Cavernous venous malformations, commonly known as cavernous hemangioma, may be identified as the source of bleeding on specific MRI sequences, demonstrating a characteristic "popcorn" or "berry" appearance with a rim of signal loss due to hemosiderin.

ICH due to bleeding of an intracranial neoplasm is uncommon, accounting for 10% of cases [9]. Glioblastoma, melanoma metastasis, bronchogenic carcinoma, choriocarcinoma, and renal cell carcinoma are the most common etiologies. Blood dyscrasias, such as hemophilia, immune-mediated thrombocytopenia, and some forms of leukemia are associated with ICH.

The use of antithrombotic therapy, especially anticoagulants, is a major risk factor for ICH. Warfarin increases the risk of ICH two- to fivefold, depending upon the intensity of anticoagulation. The risk is more prominent on elderly patients, on diabetics, on hypertensives, or with antecedents of stroke or recent traumatic brain injury. Direct oral anticoagulants (DOACs) have a lower risk of intracranial bleeding compared with warfarin. The overall relative risk of intracranial bleeding with DOACs when compared to warfarin was 0.5 on a meta-analysis of the major randomized trials [10]. An observational cohort study, CROMIS-2, found that the presence of cerebral microbleeds and diabetes mellitus were the only two variables associated with ICH due to anticoagulation post-stroke and transient ischemic attack (TIA) [11]. Regarding antiplatelets, there is a small increase in the risk of ICH associated with monotherapy. A reasonable estimate of the risk of hemorrhagic stroke associated with the use of aspirin is 0.2 events per 1000 patient-years [10]. However, adding a second antiplatelet increases the risk of ICH twofold compared with aspirin alone. In a retrospective study of 82,576 patients, in-hospital mortality was higher among patients with ICH on dual antiplatelet therapy compared with no antiplatelet therapy [12]. Resuming antiplatelet in a patient post-ICH was studied on a randomized clinical trial. After 2 years of follow-up, those patients who resumed antiplatelet medication actually had a lower rate of recurrent symptomatic ICH (4 versus 9 percent, 95% CI 0.25–1.03) [13].

A pivotal trial of secondary stroke prevention with the use of statins suggested that atorvastatin could increase the risk of ICH among patients with previous stroke [14]. However, observational studies had not confirmed this association, and some even suggested a protective effect [15]. Autoimmune vasculitis can cause either ischemic or hemorrhagic strokes. Non-inflammatory vasculopathy, such as reversible cerebral vasoconstriction syndrome (RCVS), can also present with ICH. Sympathomimetic drugs are major triggers of RCVS, including cocaine, amphetamines, and serotonin receptor inhibitors. An algorithm has been proposed to classify ICH into six most common etiologies (Fig. 26.1).

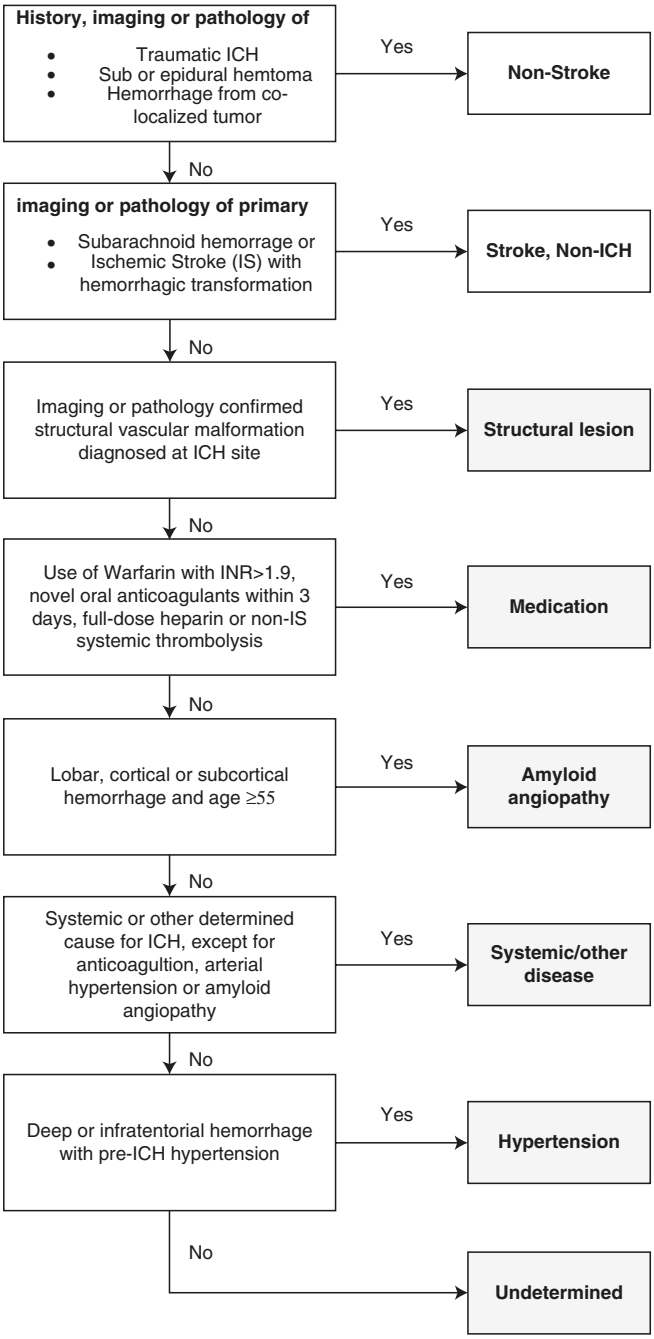

Fig. 26.1 Algorithm for etiology classification according to SMASH-U. ICH intracerebral hemorrhage, SMASH-U Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined. (Adapted from Meretoja et al. [26])

26.4 Clinical Features

The usual clinical presentation of an ICH is a focal neurological deficit. The precise symptoms depend upon the location of the hemorrhage. The most common locations of bleeding are the putamen (35%), subcortex (30%), cerebellum (16%), thalamus (15%), and pons (5%) [16]. The clinical presentation according to the specific topographies is described in Table 26.1.

Of note, most cases of ICH take place during routine activity. The symptoms usually progress over minutes or a few hours. Headache, drowsiness, and vomiting occur as hemorrhage enlargers, due to intracranial hypertension. A major hemorrhage may provoke stupor or coma, which usually implicates a poor prognosis.

Several factors affect the timing of hospital arrival. Systolic blood pressure, mean arterial pressure, and pulse pressure are significantly higher in patients arriving within 3 h of the onset of symptoms. Patients who arrive early also have a higher National Institutes of Health (NIHSS) score, a lower Glasgow Coma Score, and presence of intraventricular hemorrhage [17].

26.5 Diagnosis

As a medical emergency, an acute evaluation of a suspected ICH is of paramount importance. Neuroimaging, either brain CT or MRI, confirms the diagnosis and excludes other causes. Brain CT is usually the imaging of choice due to its high accuracy to detect intracranial bleeding, wide availability, speed, and low cost. Once the diagnosis is confirmed, the etiology is sought after by clinical, laboratory, and imaging features. The recommended laboratory tests are listed in Table 26.2 [18].

On imaging, the blood on brain CT appears hyperdense almost immediately. Over several weeks, it will become isodense and eventually hypodense. Brain MRI can detect blood using T2-sensitive pulse sequences such as gradient echo (GRE). The sensitivity of the MRI to detect blood is close to 100% [19]. The signal intensity states by being hyperintense on T2 on the hyperacute phase. Acutely, it becomes

Table 26.1 Clinical features associated with hematoma localization

Localization of hematoma	Clinical features
Putamen	Contralateral motor deficit, aphasia, extinction, gaze palsy
Cerebellum	Drowsiness, ataxia, dizziness, nausea, and vomit
Pons	Drowsiness, tetraplegia, pinpoint pupils, dysautonomia, and neurogenic shock
Thalamus	Drowsiness, contralateral sensitive-motor deficit
Intraventricular	Headache, drowsiness, meningeal irritation
Lobar	Contralateral sensitive-motor deficit, headache, seizures, extinction, gaze palsy

Table 26.2 The recommended laboratory tests for patients with ICH

The recommended laboratory tests for patients with ICH include:
Complete blood count, electrolytes, blood urea nitrogen, creatinine, and glucose
Prothrombin time (with INR) and activated partial thromboplastin time for all patients; thrombin clotting time for patients taking direct oral anticoagulants
Cardiac-specific troponin
Toxicology screen to detect cocaine and other sympathomimetic drugs
Urinalysis and urine culture

ICH Intracerebral hemorrhage, *INR* International normalized ratio

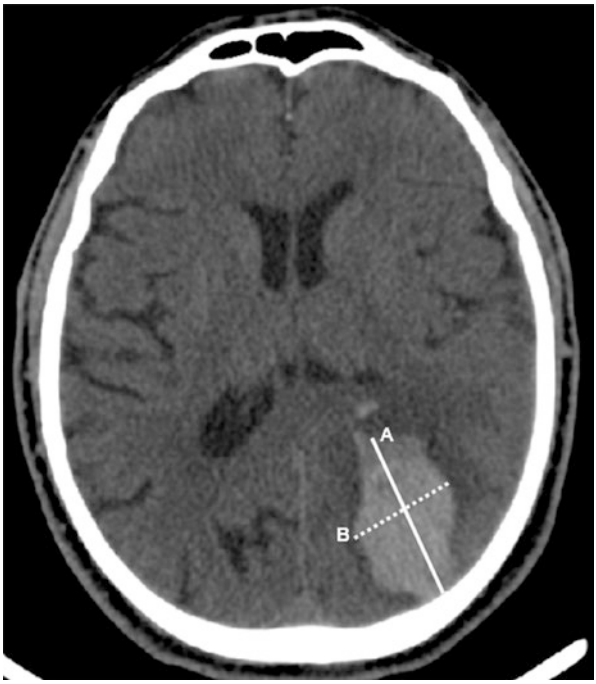

Fig. 26.2 ABC/2 Measurement (**a**). The greatest hemorrhage diameter on the CT slice with the largest area of hemorrhage. (**b**). The largest diameter 90 degrees to line A

hyperintense on T1 due to the presence of methemoglobin; the T2 appears initially dark, later becoming bright. Finally, with the production of hemosiderin, both T1 and T2 become hypointense.

We can estimate the hemorrhage volume by applying the ABC rule (Fig. 26.2).

A is the greatest hemorrhage diameter on the CT slice with the largest area of hemorrhage.

B is the largest diameter 90 degrees to A on the same (index) CT slice.

C is the approximate number of CT slices with hemorrhage multiplied by the slice thickness in centimeters.

ABC/2 gives the ICH volume in milliliters.

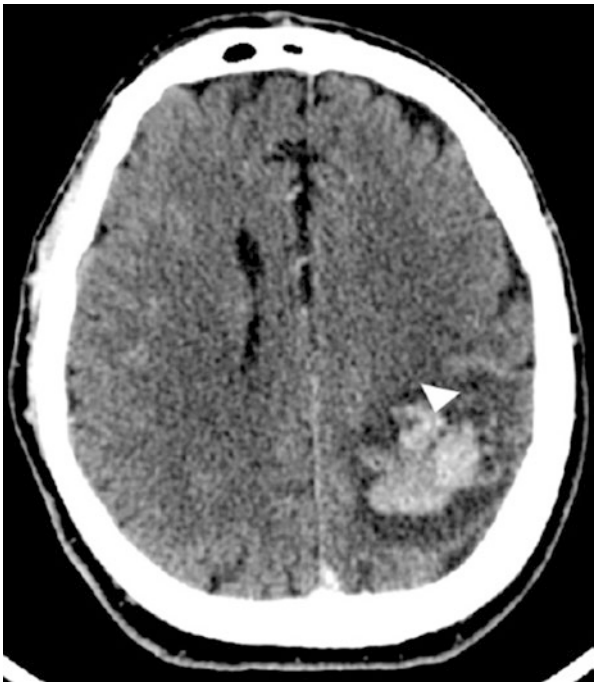

Fig. 26.3 Spot sign. CT scan showing a small area of contrast enhancement on computed tomography angiography (CTA)

Slice with ≥ 75% area of hemorrhage counts as 1 slice; slice with 25–75% area of hemorrhage counts as 0.5 slices; slice with < 25% area of hemorrhage counts as 0 slices.

Some imaging features such as the spot sign, the swirl sign, and the black hole sign are important predictors of hemorrhage expansion. The spot sign is a small area of contrast enhancement on computed tomography angiography (CTA) – Fig. 26.3. The presence of CTA spot sign is inversely related to ICH onset-to-CTA time [20]. The blend sign is defined as blending of a hypo-attenuating area within the hyper-attenuated ICH with a well-defined margin [21]. The black hole sign (Fig. 26.4) is defined as a hypodense area encapsulated within the hyperdense ICH with a clearly defined border [22].

There are several scores to predict hematoma expansion. The most used are the BRAIN score [23] and the BAT score [24]. The first, outlined in Table 26.3, includes baseline ICH volume, recurrent ICH, anticoagulation with warfarin at symptom onset, intraventricular extension, and number of hours to baseline CT from symptom onset. The maximum score is 24 and represents 85.8% chance of hematoma expansion. The second (Table 26.4) is composed of the presence of the blend sign, any hypodensity within the hyper-attenuating hematoma, and time from onset to non-contrast CT. A dichotomized score (of 3 or more than 3) predicted hematoma expansion with 50% sensitivity and 89% specificity.

The most widely used prognostic score is the ICH score (Table 26.5). It is composed of consciousness level, hematoma volume, age, intraventricular hemorrhage,

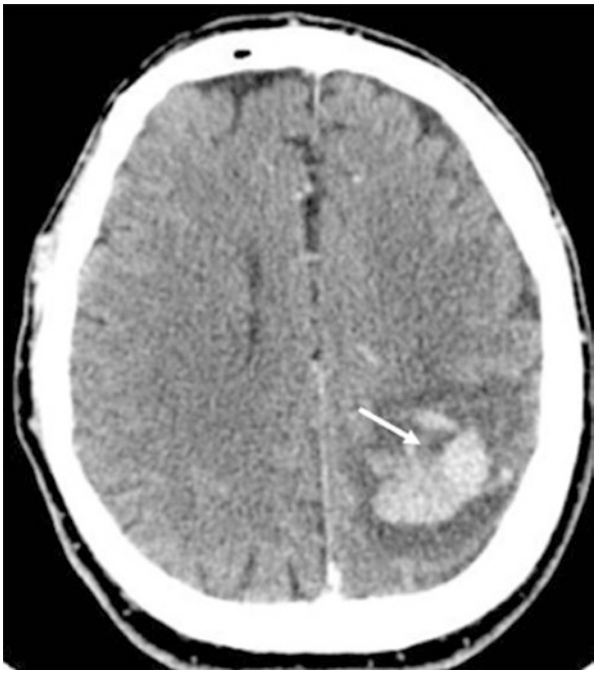

Fig. 26.4 The black hole sign. CT scan showing the black hole sign, defined as a hypodense area encapsulated within the hyperdense ICH with a clearly defined border

Table 26.3 BRAIN score for prediction of ICH growth within 24 h

BRAIN score component	Variable	Points
Baselined ICH volume	<10 mL	0
	10–20 mL	5
	>20 mL	7
Recurrent ICH	No	0
	Yes	4
Anticoagulation with warfarin at onset	No	0
	Yes	6
Intraventricular extension	No	0
	Yes	2
Number of hours to baseline CT from symptom onset	<1	5
	1–2	4
	2–3	3
	3–4	2
	4–5	1
	> 5	0

ICH Intracerebral hemorrhage

Table 26.4 The BAT score for prediction of ICH growth with head computed tomography

Components	Points
Blend sign	Yes = 1
Any hypodensity	Yes = 2
Time from onset to non-contrast computed tomography	<2.5 h = 2
Total score	0–5

ICH Intracerebral hemorrhage

Table 26.5 ICH score per 30-day mortality

Components	Variables	Points
Glasgow Coma Score	13–15	0
	5–12	1
	3–4	2
Age > 80	No	0
	Yes	1
ICH volume > 30 mL	No	0
	Yes	1
Intraventricular hemorrhage	No	0
	Yes	1
Infratentorial origin of hemorrhage	No	0
	Yes	1

and infratentorial origin of hemorrhage. It predicts 30-day mortality, and it ranges from 0% with ICH score of 0 points to 100% with ICH score of 5 or 6 points [25].

The workup is also important to determine the etiology of the bleeding. Age under 65 years, female sex, non-smoking status, lobar ICH, intraventricular extension of hemorrhage, and lack of history of hypertension or bleeding diathesis should set the alarm for the presence of underlying vascular abnormalities and prompt the realization of an angiography study, either CTA or MRA. Angiographic studies can detect vascular malformations, aneurysms, and Moyamoya disease, as well as cerebral venous thrombosis and underlying brain tumors. Laboratory tests can uncover bleeding diathesis and past medical history, and medication use may provide clues to previous systemic hypertension.

A proposed etiological classification of ICH is the SMASH-U (Fig. 26.1), which encompasses structural vascular lesions (S), medication (M), amyloid angiopathy (A), systemic disease (S), hypertension (H), or undetermined (U). On the initial cohort, amyloid angiopathy (20%) and hypertensive angiopathy (35%) were the most common. Patients with structural lesions had the smallest hemorrhages (median volume, 2.8 mL) and best prognosis (3-month mortality 4%), whereas anticoagulation-related ICHs were largest (13.4 mL) and most often fatal (54%) [26].

26.5.1 Clinical Management of ICH

26.5.1.1 Blood Pressure

Blood pressure management is a key point of the clinical treatment of patients with ICH. Elevated blood pressure is common and dangerous in patients with acute ICH. High blood pressure levels may lead to hematoma expansion due to increased bleeding and to elevated ICP from worsening brain edema [27]. On the other hand, quick lowering blood pressure in patients with ICH could theoretically lead to secondary brain ischemia in the perihematomal region, impairing neurological status. Elegant studies using PET CT demonstrated that perihematomal ischemia is not a common finding; therefore clinical trials evaluating blood pressure reduction in ICH were proposed.

Two randomized clinical trials, ATACH [28] and INTERACT [29], stated out that acutely lowering systolic blood pressure (SBP) within 24 h from ictus to below 140 mmHg is safe. A phase III trial (INTERACT-2 [30]) found that patients in the intensive arm (SBP < 140 mmHg for initial 7 days after ICH occurrence) had modest better outcomes with about 3% fewer patients having death or severe disability (defined as a modified Rankin Scale score of 3–6). The ATACH 2 trial randomly assigned eligible participants with ICH (volume, <60 cm^3) and a GCS score of 5 or more (on a scale from 3 to 15, with lower scores indicating worse condition) to a systolic blood-pressure target of 110–139 mm Hg (intensive treatment) or a target of 140–179 mm Hg (standard treatment) [31]. In the ATACH 2 trial, the treatment of participants with ICH to achieve a target systolic blood pressure of 110–139 mm Hg did not result in a lower rate of death or disability than standard reduction to a target of 140–179 mm Hg [31]. Based on these findings, the current American Heart Association (AHA) recommends that it may be reasonable to maintain SBP between 140 and 180 mmHg with the specific threshold determined based on patient comorbidities and level of chronic hypertension [27, 32].

Some drugs might be used to treat blood pressure in patients with ICH. For instance, intravenous (IV) beta blockers and calcium channel blockers have been widely adopted for this indication in the emergency department and the intensive care unit (ICU) [27]. For patients with baseline bradycardia, hydralazine as a bolus 10–20 mg every 4–6 h may be adopted. Nicardipine dose of 2.5–5 mg/h is often used, with up-titration every 15 min as needed up to 15 mg [27]. If possible, nitroprusside should be avoided in patients with recognized impaired cerebral autoregulation, large hematomas, and elevated ICP – however, there are few data to support this recommendation. Especially in low- and middle-income countries, nitroprusside is widely adopted to control elevated blood pressure and was used is several patients included in the Interact III trial.

26.5.1.2 Anticoagulants and Antiplatelets Agents

The use of anticoagulants increases the incidence of ICH and also increases the risk of hematoma expansion, unfavorable outcome, and death. In patients with ICH using anticoagulants, a quick identification of this condition and the reversal of the

drug effect is of utmost importance – in particular, before any surgical procedure [27, 33]. ICH associated with antivitamin K agents should be treated with the quick use of prothrombin complex concentrates (30 IU/kg) or fresh frozen plasma (10–20 ml/kg) plus vitamin K aiming for levels of International normalized *ratio* (INR) ≤1.4 [27, 28]. If an external ventricular drain (EVD) placement is necessary, no INR threshold has been established, and an INR of ≤1.5 is considered safe in general [27]. In such cases, the main goal is to normalize the INR as soon as possible (within minutes) [27, 28].

The impact of concurrent antiplatelet therapy is still unclear in terms of hematoma expansion and outcomes in patients presenting with ICH [34]. Thus, platelet transfusion is not recommended for most patients with ICH on a concurrent antiplatelet therapy [33]. However, platelet transfusion is recommended for patients on antiplatelet medications who are undergoing a neurosurgical procedure [27, 33]. As an option, a single intravenous dose of 0.4 mcg/kg of desmopressin is also recommended in antiplatelet medication-related ICH. Patients in use of the direct anticoagulants, such as direct thrombin inhibitors or factor Xa inhibitors, should be treated with specific reversal agents if available (Idarucizumab for patients using dabigatran and andexanet alfa for patients using anti Xa). In addition, for those patients in use of dabigatran, activated charcoal (50 mg) should also be given if ICH occurs within 2 h of the most recent dose. Patients receiving IV unfractionated heparin should be treated with protamine sulfate, administered 1 mg for every 100 units of heparin received in the prior 2 h, with a maximum dose of 50 mg [27, 33].

26.5.1.3 Deep Venous Thrombosis Prophylaxis

Once the hematoma is radiologically stable in size for at least 24–48 h (at least a follow-up neuroimaging should be obtained within this time period), pharmacological thromboprophylaxis with unfractionated heparin or low molecular weight heparin is recommended. At admission, pneumatic compression devices should be started [35].

26.5.1.4 Seizures

Prophylactic anticonvulsants reduced seizure occurrence in patients with lobar ICH [46]. However, the incidence and impact of seizures on outcomes are still unclear in these patients [30, 46, 47]. In two recent studies, patients who received prophylactic anticonvulsants (mainly phenytoin) had a poorer functional outcome when compared to patients not receiving the drug [48, 49]. The most recent clinical guidelines do not recommend offering prophylactic anticonvulsants for patients with ICH [18]. Clinical seizures should be promptly recognized and treated, and continuous EEG monitoring is suggested for those patients with inadequately explained decreased and/or fluctuating level of consciousness without a major metabolic reason [18, 27].

26.5.1.5 Intracranial Pressure (ICP) Management

Within the first 24 h, in addition to an intensive blood pressure control, avoidance of fever, hypoxia, and hyperglycemia/hypoglycemia is crucial as well as maintaining a secure airway, identifying seizure, and controlling ICP [27]. On the other hand, data about the incidence and impact of elevated ICP upon prognosis in ICH patients is still unclear [27, 36]. The American Heart Association Guidelines recommends that patients with a Glasgow Coma Scale (GCS) score of ≤8, those with clinical evidence of transtentorial herniation, or those with significant IVH or hydrocephalus might be considered for ICP monitoring and treatment. A CPP of 50–70 mm Hg may be reasonable to maintain depending on the status of cerebral autoregulation. A goal of ICP < 22 mmHg is reasonable, aiming at a minimal cerebral perfusion pressure (CPP) of 60 mmHg [27]. If the patient has hydrocephalus requiring an EVD, this kind of catheter may be useful to measure ICP and drain cerebrospinal fluid (CSF). This catheter may be superior to intraparenchymal fiberoptic monitors which have a lower risk of hemorrhage and infection but cannot be used to drain CSF. Any coagulopathy should be corrected prior to ICP monitor insertion; an INR ≤ 1.5 is recommended prior to EVD insertion [27].

26.6 Surgical Management of ICH

Despite significant progress in the clinical evaluation and management of ICH, the ideal surgical management and its efficacy are still unclear [37]. Intuitively, hematoma evacuation could have a therapeutic impact on clinical outcomes. This hypothesis is based on a theoretical advantage of preventing the acute effects of hematoma such as edema, intracranial hypertension, and impaired cerebral hemodynamics [37]. Figure 26.5 portrays the potential impact of surgical evacuation on the ICH pathology.

However, the most common sites of spontaneous ICH are subcortical structures. Therefore a large layer of intact brain must be crossed (and potentially injured per consequence) during the surgical procedure. Moreover, surgical procedures might be associated with both periprocedural and postprocedural adverse effects such as hemorrhages, infection, delirium, and pulmonary embolism [37, 38]. Many surgical and invasive approaches have been proposed, but none lead to improved clinical outcomes. In this scenario, decompressive craniotomy with/without hematoma drainage has been widely studied. In addition, image-guided stereotactic endoscopic aspiration and minimally invasive catheter evacuation followed by thrombolysis have also been attempted without clinical outcome improvement when compared to best clinical management [37] at this moment. On the other hand, large lobar hemorrhage or hematomas in the posterior fossa may lead to a quick clinical deterioration associated with brainstem herniation, which may require life-saving emergent surgical evacuation.

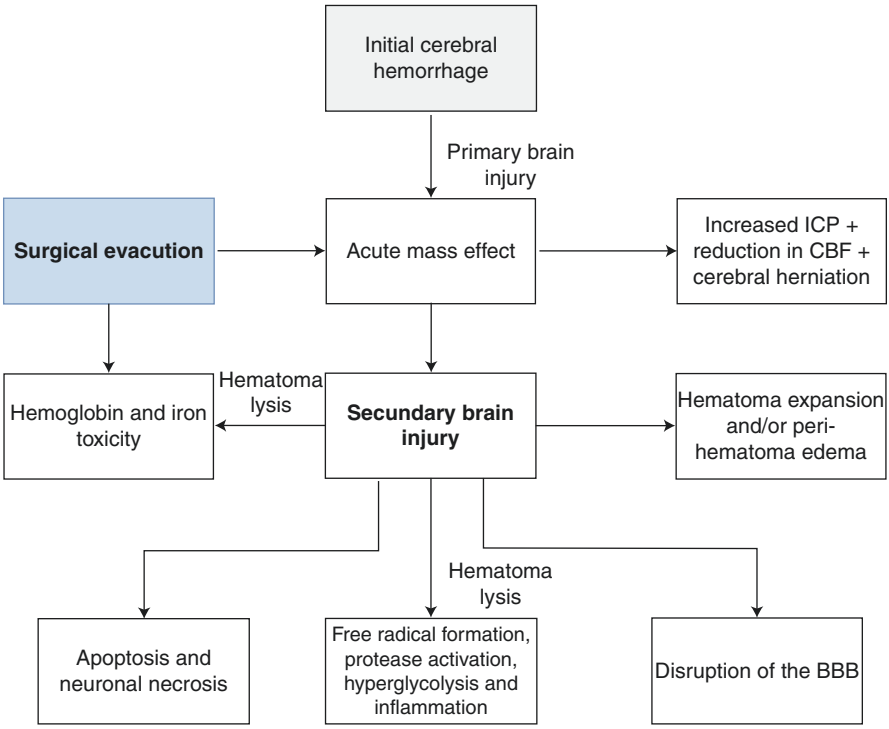

Fig. 26.5 Potential impact of surgical evacuation on the ICH pathology. ICP Intracerebral pressure, CBF cerebral blood flow, BBB blood-brain barrier. (Adapted from De Oliveira [37])

26.6.1 External Ventricular Drain (EVD) for Intraventricular Hemorrhage Management

Intraventricular hemorrhage occurs in about 45% of patients with ICH – which may represent an independent predictor of poor outcome [39]. Intraventricular hemorrhage may impair the normal flow of cerebrospinal fluid, which may cause acute hydrocephalus, leading to clinical deterioration and intracranial hypertension [40]. Thus, patients with acute hydrocephalus due to intraventricular hemorrhage or large intraparenchymal hematoma with mass effect associated with impaired level of consciousness (GSC < 8, for instance) are eligible for urgent placement of an EVD, aiming to drain intraventricular blood and to maintain ICP < 20 mmHg and a CPP > 60 mmHg. An INR ≤ 1.5 is recommended prior to EVD insertion [27]. If a patient needs to be transferred to other units, EVD management should be clearly stated (whether the drain should be clamped or open, and if open, what level it should be set at) [27]. Recently, some procedures to improve clot clearance have been tested. The CLEAR-III trial compared a low intraventricular dose of recombinant tissue plasminogen (tPA) (1 mg, every 8 h, up to 12 mg) to saline in patients

with small ICH (volume less than 30 ml) and intraventricular hemorrhage in the third and fourth ventricles [27, 40, 41].

The CLEAR-III trial found that the irrigation with tPA did not substantially improve functional outcomes measured by the modified Rankin Scale (mRS) at 180 days from the bleeding compared with irrigation with saline. The authors stated out that the protocol-based use of tPA seems safe and might increase the rates of survivorship with severe disability [41]. The use of dual EVD combining intraventricular fibrinolysis with lumbar drainage significantly reduced the shunt dependency (caused by hydrocephalus) after intraventricular hemorrhage [37, 42]. In addition, the clot removal by neuroendoscopy in combination with EVD placement has been tested. A meta-analysis of 11 studies suggests that neuroendoscopy + EVD is superior to EVD + tPA approach in achieving good clinical outcomes (favorable clinical function and lower mortality) and need for ventriculoperitoneal shunt [43]. However, the efficacy of such procedures remains unclear, as the methodologies for the studies included in the meta-analysis are quite heterogeneous [27, 42].

26.6.2 Craniotomy for Supratentorial Hemorrhage Drainage

The use of craniotomy for supratentorial hemorrhage drainage is the most common surgical procedure in patients with ICH and also the most studied strategy [44]. However, the role of this procedure remains unclear, despite the publication of numerous studies, including well-designed clinical trials [40]. The Surgical Trial in Intracerebral Hemorrhage (STICH) [45] included 1033 patients from 83 centers with lobar or ganglionic spontaneous supratentorial hematoma who were randomized to undergo or not early hematoma evacuation within 72 h from symptoms onset. The primary outcome was death or disability according to the Glasgow Outcome Scale at 6 months. No overall benefit in functional outcome was found with early hematoma drainage [45]. The mortality rate was similar in both groups (best medical management with delayed surgery if necessary, versus early drainage) at 6 months. On the other hand, in a prespecified subgroup analysis, patients with superficial hematomas were benefited by early hematoma drainage. A second study was performed including patients with superficial hematomas (within 1 cm from the cortical surface) [46]. Patients with intraventricular hemorrhage (IVH), hematoma <10 mL or >100 mL, comatose patients (i.e., motor Glasgow Coma Score (GCS) < 5 and eye GCS < 2 at randomization), and patients admitted beyond 48 h of symptoms onset were excluded [46]. The same primary outcome from STICH was evaluated [45]. No overall benefit in functional outcome was observed (62% unfavorable outcome in the surgical group versus 59% in the initial conservative treatment). Mortality was also not different between groups (18% in the surgical group vs. 24% in the best medical care group) [46]. Combining the SITCH trials results with other 13 studies, a meta-analysis stated out that patients with predicted poor prognosis, delayed clinical deterioration, or superficial lobar ICH without IVH may have a potential survival benefit without improved clinical outcome if treated with craniotomy for supratentorial hemorrhage drainage [37].

26.6.3 Minimally Invasive Surgery

Open craniotomy exposes the patient to several risks and clinical complications. In addition, healthy brain tissue may be injured during the procedure. Thus, some minimally invasive techniques have been tested around the world. The theoretical benefit of these procedures is producing minimum surgical trauma response and lower rates of healthy brain tissue damage [37]. The Intraoperative Stereotactic Computed Tomography (CT)–Guided Endoscopic Surgery for Brain Hemorrhage trial (ICES) [47] is a pilot multicenter randomized controlled trial which tested CT-guided endoscopic drainage of ICH. This trial included adults with supratentorial ICH (volume > 20 ml) within 48 h of ictus with GSS > 5 and NIHSS >5 [47]. The surgical group had non-significant higher rate of favorable mRS at 12 months. As a limitation, however, the study was not powered to assess functional outcome and mortality [47]. Minimally invasive catheter evacuation followed by thrombolysis (alteplase protocol (0.3 mg or 1.0 mg every 8 h for up to nine doses) has been tested as well. Controlled and randomized phase II [48] and phase III [49] trial showed a significant reduction of hematoma (up to 69%) and perilesional edema, but non-significant results in terms of improving clinical outcome and mortality at 12 months.

26.6.4 Posterior Fossa Hematoma

Many case series advocate that patients with cerebellar ICH > 3 cm in diameter or with compression of the brain stem (evident or imminent) or hydrocephalus may benefit from surgical hematoma evacuation [27]. The current recommendation from the AHA guidelines is that patients with cerebellar hematomas with acute neurological deterioration (GCS ≤ 13) regardless of the volume should be treated with an urgent suboccipital craniectomy ± hematoma drainage [27, 37].

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Chapter 27
Cerebral Hemorrhage and High INR

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27.1 Introduction

Anticoagulants are important options in the treatment of a significant number of clinical settings, from venous thrombosis to primary and secondary prevention of arterial cardiovascular events (heart valves, atrial fibrillation) [1]. Regarding the established benefit of oral anticoagulants (OAC) in the prevention of stroke and taking the increasing number of aging population into account, application of OAC is expected to increase the number of patients who suffer intracerebral hemorrhage [2]. As of 2014, 2.83 million Americans were taking oral anticoagulants, with coumarins being prescribed in almost two thirds of patients [3]. However, they entail the risk of potentially life-threatening hemorrhagic complications, especially in the central nervous system [4], not to mention the significant drug interactions which are associated with its use [5].

Intracerebral hemorrhage (ICH) is the subtype of stroke with the highest degree of mortality and morbidity, compared to ischemic forms [4]. The incidence of spontaneous intracranial hemorrhage ranges from 10 to 20 per 100,000 population per year. The report incidence of OAC-ICH ranges from 0.25% patient-years; approximately 70% of OAC associated intracranial bleedings are ICH [6]. ICH was the only

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cause of fatal bleeding complications of warfarin therapy in one series where the cumulative risk of a fatal hemorrhage was 1% at 1 year and 2% at 3 years [7].

Hypertension, a common risk factor for ICH, is also prevalent among patients with ischemic cardiovascular events [4]. Treatment of these patients sometimes requires OAC, especially coumarins. Understanding the effect of these therapeutic measures on the natural history of an ICH and knowing the options to minimize its effects are of utmost importance.

In this chapter, we review the clinical context of this group of patients, as well as the management and outcomes of intracerebral hemorrhage in patients taking vitamin K antagonists (VKA-ICH).

27.2 Coumarins, Warfarin

Coumarins are antagonists of vitamin K, inhibiting reductases involved in the synthesis of several coagulation factors essential for the extrinsic pathway – II, VII, IX, and X. While affecting their production, it has no effect on the molecules already in circulation. As a consequence, coumarins only reach their full effect after 3–5 days – in the meantime, protein S and C, vitamin K-dependent, are also affected, leading to a temporary pro-coagulation state that requires therapeutic bridging with other anticoagulants [1, 4]. Coagulation is initiated by the binding of FVIIa to the exposed tissue factor (TF) on the subendothelium at the site of vascular injury. TF-FVIIa complex activates FX. FXa, in turn, rapidly converts prothrombin to thrombin, generating small amounts of thrombin. Sufficient amounts of thrombin are continuously generated to convert fibrinogen to fibrin. Thrombin activates fibrin monomers to form a stable fibrin clot (Fig. 27.1).

Warfarin is the most commonly used anticoagulant of its class. It is a racemic mixture, enantiomers S and R, with the former being the most active [1]. Several important enzymes (CYP2C9, CYP1A2, CYP2C19, and CYP3A4) are involved in warfarin metabolism, leading to important drug interactions with other molecules – tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, antibiotics, and others [1, 4].

These drugs prolong prothrombin time (PT) and international normalized ratio (INR) through their effect on factors II, VII, and X, making these essays essential in the baseline work-up of suspected ICH patients [4]. The essays for the intrinsic pathway, namely, activated partial thrombin time (APTT), are not affected by warfarin and other vitamin k antagonists.

27.3 Clinical Presentation and Radiological Findings

ICH should be considered a medical emergency. Sixty percent are of hypertensive origin, with rupture of a small basal ganglia arteriolar vessel, with the remainder occurring due to amyloid angiopathy, vascular lesions (aneurysms, AVM, cavernous

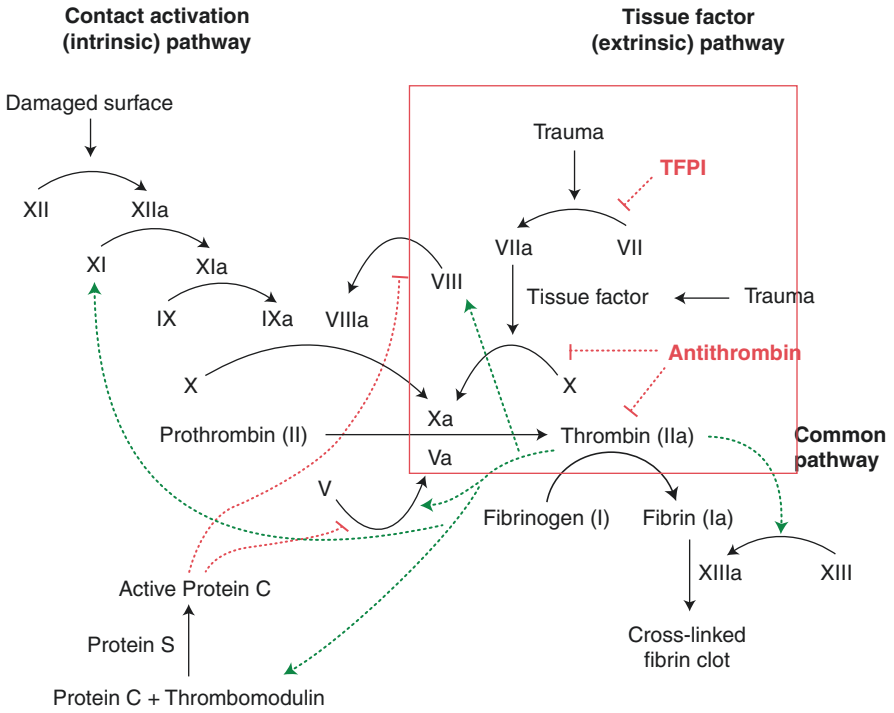

Fig. 27.1 Coagulation cascade: the extrinsic pathway, dependent on factors II, VII, and IX, is the branch of the cascade most affected by vitamin K inhibition. (Adapted from Paul [64])

malformations), and drug-related, both illegal (cocaine) and therapeutic (hemostasis altering drugs) [8].

At presentation, VKA-ICH is similar to other forms of ICH. ICH presents clinically in a variety of ways, depending primarily on the location and size of the hematoma. These features determine a set of clinical findings that occur regardless of location, as they reflect the intracranial mass effect that characterizes ICH (Fig. 27.2). Headache is common at the onset of ICH, reported in 36% of the cases and more common in subjects with cerebellar hemorrhage (58%). Seizures at onset of ICH are rare, reported in less than 10% of the cases. Progression of neurological deficits correlates with the common observation of early enlargement of ICH [9]. Alteration of conscience is a common symptom – 20% of patients will decrease their Glasgow Coma Scale (GCS) by 2 or more points in the pre-hospital setting, with 15–23% further deterioration [8]. Seizures, motor deficit, and sensorium abnormalities are also common clinical features. ICH may present with acute hydrocephalus, a number that increases if intraventricular extension occurs [10, 11].

Clinical features specific to intracerebral hemorrhage location present a large spectrum, depending on the location: putaminal, caudate, thalamic, frontal lobar, temporal lobar, parietal lobar, occipital lobar, cerebellar, midbrain, pontine, and medullary hemorrhage [9].

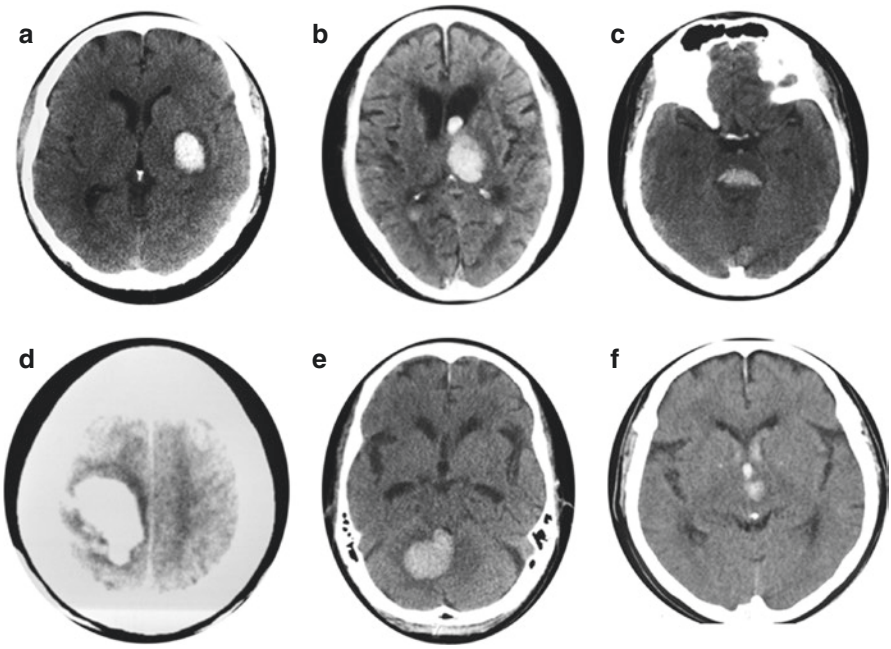

Fig. 27.2 Noncontrast head CT scan is the usual initial imaging procedure of choice. It is rapid, has few contraindications, and easily demonstrates blood as high density within the brain parenchyma immediately after hemorrhage. (**a**) Putaminal; (**b**) thalamic; (**c**) pontine; (**d**) lobar; (**e**) cerebellar; (**f**) midbrain. (Author's departmental archive)

It is important to exclude traumatic events, though the clinician must remain aware that a primary ICH followed by secondary trauma may occur, confounding the diagnosis. The clinician should actively assess for medications that may affect the evolution of an ICH, mainly OAC. Previous clinical records and prescriptions besides inquiring relatives about these drugs are of paramount importance. A high degree of suspicion is warranted in search of other conditions that may alter hemostasis, including pharmacological (antiaggregant drugs) or pathological (hemophilia, Von Willebrand disease). None of these measures, however, precluded the appropriate laboratory studies. Routine blood samples should be immediately taken – hemogram with platelet count, renal function, ionic measurements, and appropriate coagulation study. This should include APTT, PT, INR, anti-Xa activity, and PFA-100, when available – different mechanisms of altered hemostasis should be sought as well, for they may affect the effectiveness of the treatment of these patients. Regardless of clinical data, it is mandatory to assess the current hemostasis status of the patient with suspected ICH, whether or not associated with VKA.

Several clinical and severity scores have been validated, improving communication in the emergent setting. The National Institutes of Health Stroke Scale (NIHSS) score, used for ischemic stroke, can also be used for ICH, with the caveat that impaired conscience frequently encountered in these patients may hinder clinical

evaluation [12]. The ICH score [13], along with its modified versions [14, 15], were designed as tools of risk stratification of 30-day mortality based on GCS, age, ICH volume, intraventricular hemorrhage (IVH), and infratentorial location of ICH. It has been validated [16–20] and has served as a standard in literature for other grading scales [21]. The ICH score is a simple clinical grading scale that allows risk stratification and permits use of uniform terms and clear communication between physicians. Its usefulness has been validated in predicting 30-day mortality. The mortality rates for scores of 0, 1, 2, 3, 4, and 5 are 0%, 13%, 26%, 72%, 97%, and 100%, respectively. Other scores, such as the modified GRAEB scale for ICH with intraventricular extension, are also invaluable tools to assess prognosis and perform management decisions [22].

Cranial tomography scan (CT) is the gold standard for ICH diagnosis. It is highly sensitive, is easily available to most emergency departments, and is extremely important in planning treatment as well as accessing prognosis (Fig. 27.3). CT-angiography and angiography may be useful in suspected cases of vascular lesions. Their identification is highly relevant as the rational for management is distinct from a "spontaneous" ICH [23]. Importantly, some authors have described signs on initial CT scans which may allow assessment of the likelihood of hematoma expansion, such as irregular and dichotomized shapes [23], different densities, and most importantly, spot sign which is known to be a significant predictor of poor prognostic [24, 25]. These are important, for they are more common in patients taking anticoagulants [26]. Hematoma progression may continue for up to 72 hours, aggravated by the OAC effects [27].

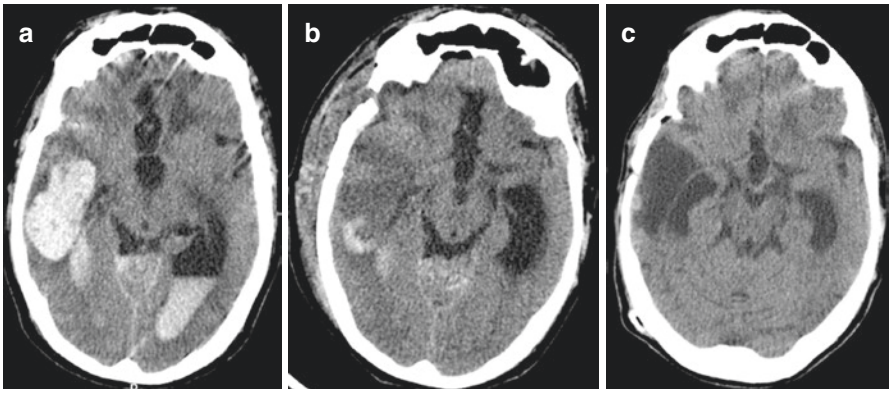

Fig. 27.3 Spontaneous right temporal ICH with intraventricular extension (**a**), in a 50-year-old male. He was taking warfarin, INR 2.21 for a deep venous thrombosis (DVT) 4 months earlier. Angio-CT did not disclose any vascular lesions. Due to its superficial topography, it was decided drain the hematoma with a craniotomy and placement of an EVD (**b**). 13 months after the event, with a shunt procedure for hydrocephalus having been carried out, the patient presented with an mRankin of 3, with some degree of dependence, mainly because of cognitive dysfunction. (Case from author's departmental archive)

Though it provides high sensitivity and specificity, MRI is of limited availability in the acute setting in several centers across the globe [23]. This factor, along with costs and the existence of an effective imaging tool, prevents MRI from taking head CT scan's place as the preferred option to study these patients in their primary approach. Nonetheless, it can be instrumental for secondary study, and in selected cases in the acute phase to rule out vascular lesions and venous thrombosis [23].

27.4 Invasive Interventions and Rationale

Intracerebral hematomas are secondary to chronic vasculopathy and evolves in three stages: hematoma formation, expansion, and edema (Fig. 27.4). Vascular rupture leads to rapid accumulation of blood within the brain parenchyma, which in turn leads to increase of local pressure and disruption of the normal anatomy. Extravasation of glucose and osmotically active electrolytes may play a role in rapid edema formation. Activation of the coagulation cascade leads to clot formation by activation of thrombin and fibrinogen. Activated platelets secrete VEGF, increasing vascular permeability and production of nitric oxide. Stable clot is achieved by interaction of thrombin, fibrin, and platelets. Recruited leukocytes within the hematoma promptly secrete IL-1, IL-6, and TNF-a, potentiating a local and systemic inflammatory response. Autolysis of RBCs within the hematoma increases the concentration of blood degradation products such as iron, CO, and biliverdin. Iron in conjunction with free radicals potentiates membrane damage and excretion of neurotoxic excitatory amino acids such as glutamate. Activation of cellular scavengers

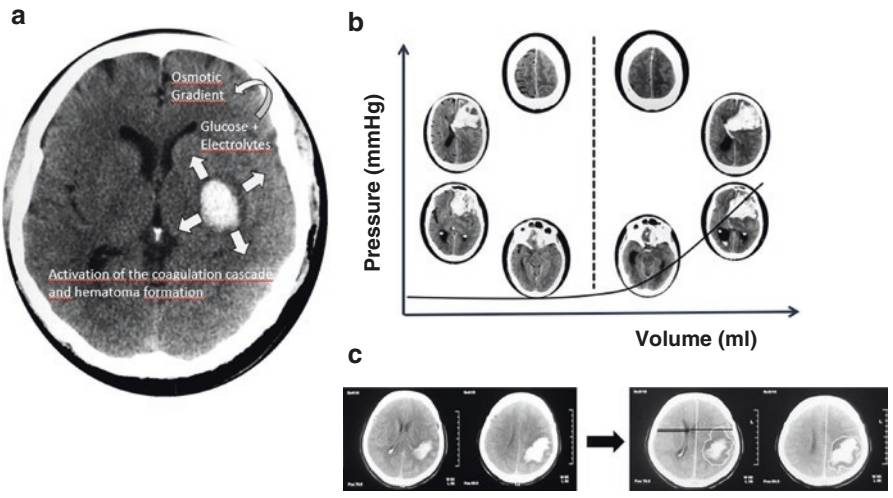

Fig. 27.4 Pathophysiology of intracerebral hemorrhage [65]. (**a**) Vascular rupture and hematoma formation; (**b**) hematoma expansion; (**c**) edema formation. (Author's departmental archive)

leads to upregulation of MMPs, contributing to cellular damage, tissue remodeling, apoptotic responses, and final scarring [28].

Long-standing vascular risk factors, namely, hypertension, induce structural changes in the arterial walls, with greatest impact on small caliber vessels, typical of the most common locations for ICH: thalamus, basal ganglia, deep periventricular gray matter, pons, and cerebellum. The sudden rupture of a vessel, weakened over the years, leads to the formation of the hematoma, which will expand until a balance of pressure is achieved between brain parenchyma and vascular pressure. At this stage, several mechanisms are responsible for the secondary injury characteristic of these hematomas:

- Mass effect: the hematoma itself, edema – both vasogenic and later cytotoxic – plays a significant role, leading to both local and widespread injury [29]. It leads to ischemia by diminishing cerebral blood flow (CBF) – this in turn exacerbates edema, in a cycle of metabolic injury and cell death that severely cripples an already beleaguered cerebral parenchyma after the primary lesion [30, 31].
- Direct toxicity: extravascular red blood cells, outside their normal environment, will readily be deprived of energy sources. As they die, they release ions and molecules, namely, potassium, glutamate, and heme groups, which are toxic for cerebral parenchyma [32].
- Inflammatory response: blood, ischemia, coagulation factors, and disruption of the blood-brain barrier (BBB) lead to a pro-inflammatory state, local and systemic, which aggravates biochemical conditions in parenchyma surrounding the hematoma [33, 34]. These osmotically active proteins (interleukin-1, interleukin-6, intercellular adhesion molecule, tumor necrosis factor, vascular endothelial growth factor) help create an osmotic gradient that will contribute for the edema that surrounds the hematoma [28].

27.5 Management

The basic neurointensive care of a patient with ICH starts with proper control of the airway, breathing, and circulation. To maintain an adequate oxygenation and gas exchange, emergent intubation and mechanical ventilation must be achieved in those comatose patients who are at risk of aspiration or unable to maintain a patent airway. Intubation also allows potentially useful ventilatory techniques such as hyperventilation for the treatment of intracranial hypertension. High and low blood pressure should be immediately corrected to decrease hematoma expansion and edema formation and to keep an adequate cerebral perfusion pressure. Resuscitation with isotonic fluids and vasopressors is indicated in those patients in shock. Placement of a central venous line and an arterial line helps to monitor hemodynamic parameters. In addition to controlling the airway, breathing, and circulation, a detailed laboratory evaluation should be obtained including biochemical, hematologic, and coagulation profiles [28].

VKA-ICH patients should be managed in dedicated neurointensive care units (NICU), or equivalent considering the reality of each institution, staffed with properly trained medical and nursing personnel [10, 35]. Alterations in INR due to pharmacological interventions should be corrected, with class I, level C evidence in its favor as per the 2015 AHA/ASA guidelines [10].

Surgical treatment is an important option for a subgroup of patients with ICH, including those taking coumarins. It may have a role in alleviating intracranial pressure and reducing the pro-inflammatory state with removal of the blood clot. Pathophysiological concepts based on Monro-Kellie doctrine and applied to intracranial hemorrhage favor neurosurgical treatment. After the formation of the hematoma, a proportional amount of liquor (CSF) is extruded from the skull toward the spinal space. In this phase, while the volume of the hematoma is equal to the volume of the extruded CSF, the intracranial pressure does not rise. Increases in intracranial volume due to rebleeding, perilesional edema, and hyperemia are associated with increased intracranial pressure, reduced cerebral perfusion pressure, and consequently cerebral blood flow. The reduction in cerebral blood flow functionally alters (electrical dysfunction) brain tissue and can, in a second moment, cause an irreversible lesion. The pathophysiological concept of neurosurgical intervention interferes in the Monro-Kellie doctrine by reducing the size of the hematoma and avoiding secondary injuries such as perilesional edema and hyperemia. Which patients to treat surgically and how is still under debate in literature.

Craniotomy has been the classical surgical option to treat ICH, whether or not followed by decompression. The well-known STICH trial [36] compared early craniotomy (<24 hours after randomization) against initial conservative treatment. It included patients with GCS > 5 at presentation and with hematomas above 2 cm in diameter. No statistical superiority was found in outcomes for early surgery when compared to optimized conservative treatment. The second trial (STICH II trial [37)] showed clinical benefit for patients under 65 years with superficial (>1 cm depth) spontaneous ICH, 10–100 ml of volume, when compared to conservative treatment. Despite several authors agree with theoretical benefits of surgical drainage [10, 38, 39], mainly regarding the mass effect and improving biochemical and inflammatory conditions, there is no consensus [10, 35], with important criticism related to craniotomy-associated morbidity. An exception is posterior fossa ICH, where evidence favors craniotomy [10, 35], with improvements in both survival and functional outcomes.

Decompressive craniectomy (DC) has also been studied [40, 41]. Yao et al. [40], in their meta-analysis comparing DC against non-DC treatment, found a reduction in mortality, as well as improved outcomes. It did not report higher levels of procedure-associated morbidity (PAM), namely, rebleeding or hydrocephalus, countering what could be expected from a procedure with higher invasiveness, with the authors stating the need for further studies.

Procedure-associated morbidity has led to the search for minimally invasive procedures (MIS) which could combine the theoretical benefits of clot removal and decompression with a procedural with a lower risk profile (Fig. 27.5). Several studies have described endoscopic procedures, either with endoscopy-assisted tubular

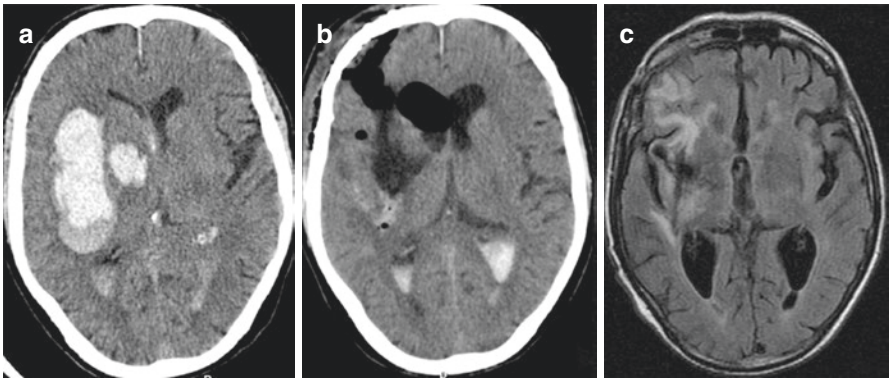

Fig. 27.5 Right putaminal ICH with intraventricular extension (**a**), in a 61-year-old male, on acenocoumarin for atrial fibrillation (INR 2.78). The senior surgeon opted for CT-guided endoscopic treatment, with a supraorbital key-hole approach to minimize procedure-associated morbidity and preserve cerebral cortex directly superficial to the hematoma. (**b**) Demonstrates a good drainage of the hematoma, and the patient evolved favorably, with mRankin of two 14 months after the event (**c**), with minor cognitive dysfunction and grade IV+ left hemiparesis. (Case from author's departmental archive)

approaches or full endoscopic MIS, with significant benefit when compared either against conservative treatment or craniotomy [42–45]. The ICES trial [42], a prospective randomized controlled study published in 2016, compared CT-guided endoscopic drainage of ICH (>20 ml, operated <48H after the event) in 20 patients against 36 patients of the medical cohort of the MISTIE trial. The authors concluded for its safety and effectiveness, with a greater proportion of patients with modified Rankin 0–3, defined as favorable. Other studies, comparing endoscopy against craniotomy or stereotactic aspiration, found superior survival rates at 6 months for the former, especially for ICH >40ml [46]. Though more studies are under way, endoscopy seems to be a step toward better drainage of ICH with lower morbidity.

Other approaches include catheter-based approaches, such as stereotactic procedures for parenchymal hematomas under, or EVD in case of intraventricular hemorrhage. The 2016 MISTIE-II randomized trial found MIS drainage plus alteplase (0.3 mg or 1.0 mg every 8 h for up to nine doses) to be safe and effective compared to optimized medical treatment [47]. It did report an increase in asymptomatic hemorrhages, which was to be expected due to the use of alteplase. MISTIE-III [48] on the other hand did not achieve superiority, with a higher dose of alteplase (1.0 mg every 8 h for up to nine doses).

Intraventricular hemorrhage also has received attention. Beyond the known risk of hydrocephalus, demanding an external ventricular drain (EVD) which could help in draining intraventricular clots, other therapeutic options were studied. The CLEAR-IVH trial [49] focused on the use of intraventricular recombinant tissue Plasminogen Activator (rtPA) (dose protocol – 0.3 mg, 1 mg, or 3 mg of rtPA twice daily) through an EVD, when compared against placebo. The results were encouraging, with acceleration of clot resolution, higher effect with incremental doses, and more impact upon the midline ventricles.

Though none of these major trials focused specifically on the issues of anticoagulation, it is unknown the potential effect on outcomes of administering fibrinolytics to patients taking OAC, namely, coumarins. More studies are in order to address these significant issues.

27.6 Coagulation Reversal

Proper hemostasis should be maintained in patients who suffered an ICH, and abnormalities should be corrected in all patients taking drugs that alter coagulation – either by suspending the drug or by supplying blood clot factors to correct hemostatic deficiencies [4, 8, 35]. These measures should be considered urgent – as described before. OAC and coumarins in particular are significant risk factors in the progression of these hematomas. Reversal may improve outcomes, reduce mortality, and limit hemorrhage expansion [27]. Most regimens for deep vein thrombosis (DVT) or atrial fibrillation demand an INR 2–3, with evidence suggesting that INR > 2 in ICH patients is a significant factor in hematoma progression [49, 50].

A proposed protocol for reversal is displayed in Fig. 27.6. It articulates reversal with monitoring measures, since our clinical expertise has shown on occasion that the first line measures instituted were not enough to correct the hemostasis. A high degree of suspicion is required.

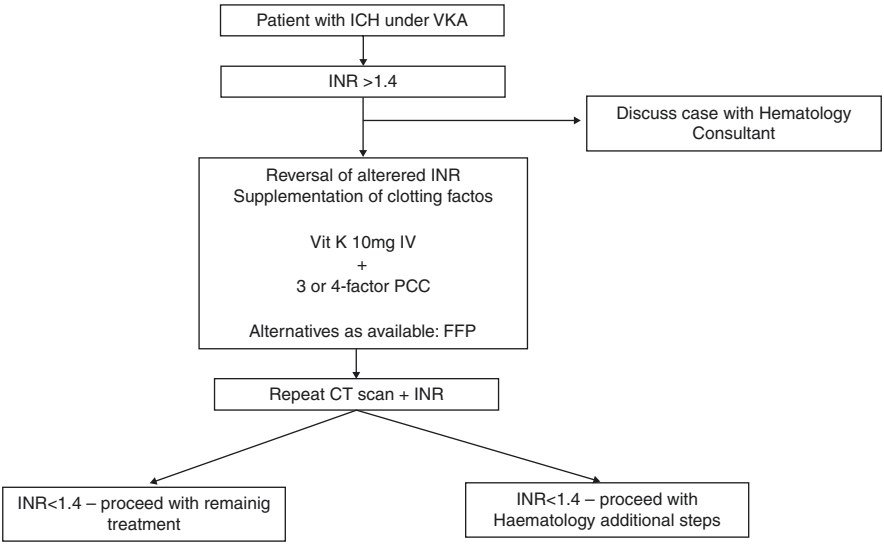

Fig. 27.6 Departmental protocol for INR correction in VKA-ICH. The same protocol is also in place for traumatic brain injury patients (TBI). Reassessment is mandatory, for failure to fully reverse the drugs' effects increases chances of hematoma expansion and worsens outcome. (Protocol in place in author's Department)

Table 27.1 Doses of drugs to counter-act the effects of coumarins

Anti-coumarin drug	Dose
Vitamin K (phytonadione)	10 mg IV
Fresh Frozen Plasma	5–20 ml/Kg 30 ml/Kg in more severe cases[a]
Prothrombin Complex Concentrates	25–50 IU/kg[b]

[a]Discuss doses with hematology consultant according to initial coagulation blood work
[b]May vary according to 3- or 4-factor

The goal of INR correction is to provide the patient with the clotting factors whose production was interrupted by these drugs. VKA reversal agents may act either by providing the liver with vitamin K to produce new clotting factors, or to supply them directly (Table 27.1):

- *Vitamin K supplementation* – it acts by providing the necessary substrate to synthesize new clotting factors (II, VII, IX, X) [27]. While it corrects INR within the first 24 hours [51], it should not be used alone in the acute setting – it will take days until new factors are in circulation, what may be too late. Indeed, in monotherapy, it has been associated with hematoma expansion [52]. A single dose of 10 mg IV of vitamin K is enough to correct INR in most cases [53], with further doses of 10 mg as needed according to repeat coagulation studies. Patients treated suffer anaphylactic reactions in 3/10.000 doses [54].
- *Fresh Frozen Plasma* (FFP) – It replaces all clotting factors, whether they depend or not upon vitamin K for its production. It is widely available and at a lower cost when compared to PTC or rFVII [27]. It has proven to be effective [55] in correcting hemostasis in patients under coumarins, though several studies have shown it to be inferior and slower in action to prothrombin complex concentrates (PCC) in this capacity [56–58]. It is also associated with risks to the patient: volume overload, with cardiac dysfunction and lung-related injury [59], infections [27], and thrombosis [60].
- *Prothrombin Complex Concentrates* **(PCC) (3 or 4 factors)** – PCC contain variable amounts of factors II, VII, IX, X; proteins C, S, and Z; and heparin [27]. 4-factor complexes differentiate themselves from the 3-factor option by including greater concentration of Factor VII [27]. Benefits of PCC include fast preparation and reconstitution time, rapid INR reversal, and small volume of infusion, with little risk of volume overload of infection [27]. Several studies showed lower mortality rates in VKA-ICH patients treated with PCC when compared to FFP [56–58, 61, 62]. The choice between 3- and 4-factor PCC has also been studied, and while both appear to be effective, 4-factor PCC showed a trend toward faster correction of INR [57, 63]. Nonetheless, in their guidelines for reversal of anticoagulation of 2016, Neurocritical Care Society makes a strong recommendation toward the use of either 3- or 4-factor PCC (according to local availability) in VKA reversion [27].

The option of reversal with recombinant Factor VII (rFVII) has also been studied. rFVII provides quick reversal, comparable to PCC [64]. However, it failed to

show consistent gains in hemostasis, mortality, or functional outcomes [65, 66]. On the other hand, it has been associated with a pro-thrombotic state (12–24%), particularly arterial thrombosis [27]. Further studies are in order, but there is no recommendation at this moment for first-line use of rFVII for VKA-ICH [27].

According with the protocol described in Fig. 27.6, literature [27] recommends that the effectiveness of the reversal measures be monitored. Blood tests should be repeated at 6 hours, and further tests after that if the INR require additional correction, until it is reduced to 1.4. We also recommend a repeat of the CT scan, especially if the first scan showed signs suggestive of hematoma progression.

27.7 Outcomes

Outcomes in patients who suffer an ICH while taking warfarin or other coumarins are generally worse when compared to other subgroups [68]. Up to 30% of patients who present with ICH and face a delay in VKA reversal experience hematoma progression [67]. Both initial hematoma volume and hematoma growth are independent predictors of clinical outcome and mortality, and VKA increase significantly the risk of hematoma progression [23].

Current treatment aims the normalization of the iatrogenic coagulation disorder and the risk of thromboembolism that is associated with current hemostatic strategies. As the aging population is increasing, the number of patients with atrial fibrillation who require prophylactic OAC will increase. Consequently, the frequency of OAC-ICH is expected to rise as well. Hence, identifying an effective treatment for controlling the bleeding will lead to decreased mortality and improve outcome [69].

There is conflicting information regarding the safety profile of the new OAC (NOAC) when compared to VKA, despite general assumption, based on IDE studies, of a better safety profile for the NOAC. While this is supported by some clinical trials [70], there is also some evidence suggesting the differences may not be significant [71], considering 90-day mortality and functional outcome.

Though necessary, coumarins are potentially dangerous tools. Constant monitoring is advised to keep the INR within therapeutic limits. Risk factors for ICH, mainly diabetes and hypertension, should be kept under strict control. If an ICH does take place, quick action is demanded to mitigate the consequences, and aggressive treatment may diminish the chances for a poor outcome.

27.8 Conclusion

Intracerebral hemorrhage associated with the use of anticoagulants represents an organizational challenge for hospital institutions and requires a quick and effective interaction between different sectors, especially the emergency room, operating room, laboratory, and intensive care unit. Teamwork with multi-professional and

multidisciplinary assistance adds better expertise, shares responsibilities, and improves outcomes. As a consequence, the use of institutional protocols should be encouraged as a tool to improve the prognosis of these patients.

27.9 Highlights

- Antithrombotic associated ICH is expected to become more common.
- Antithrombotic associated ICH have higher risk of hematoma expansion, higher mortality, and worse outcome.
- Urgent reversal of vitamin K antagonists in patients with intracranial hemorrhage is part of medical treatment.
- Neurosurgical procedures with INR reversal could be a fundamental tool in the treatment of these patients.
- An institutional treatment protocol could improve prognosis in this patients.

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Chapter 28
Ischemic Stroke

Mateus P. Pellegrino, Felipe Moreira, and Adriana B. Conforto

28.1 Introduction

"Apoplexia" ("to strike suddenly") was a term used at least 2500 years ago to describe the sudden onset of loss of consciousness [1]. It is likely that many of the cases of "apoplexia" were caused by cerebrovascular diseases. Over the centuries, the causes of mechanisms of these conditions have been progressively unveiled. Within the past decades, remarkable advances in stroke diagnosis and treatment have been witnessed.

Stroke is still a leading cause of death and disability worldwide but is widely recognized as a preventable and treatable condition. Worldwide, men are slightly more frequently affected than women. Stroke can occur at any age but is more common in the elderly [2]. The burden from stroke is expected to increase, in parallel with global ageing. It is estimated that 80% of all strokes occur in developing countries and that 80–85% of all strokes are ischemic (IS) [3].

28.2 Pathogenesis of Ischemic Stroke

Irreversible brain injury may occur when there is a decrease in cerebral blood flow due to arterial occlusion or hemodynamic mechanisms. Arterial occlusion may occur due to thrombosis or embolism. The irreversibly injured area due to decreased perfusion is called the "ischemic core". Around the core, there may be an area in which function is compromised in the absence of cell death. This area, the "ischemic penumbra", is potentially salvageable if perfusion is restored within a critical

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time window [4]. The efficiency of the collateral circulation is key to ensure that the penumbra does not become irreversibly injured. The main pathways of collateral circulation are the Willis circle, leptomeningeal anastomoses, as well as connections between branches of the external and internal carotid arteries [5]. One of the main goals of acute stroke treatment is to rescue the penumbra area by early reperfusion. Despite the evolving concept of a "tissue clock" that varies across subjects and determines how fast the penumbra may evolve to a core, the dogma that "time is brain" remains valid. Efforts should be made to limit the interval between onset of symptoms and reperfusion, as much as possible.

28.3 Diagnosis

Ischemic stroke is characterized by the sudden onset of neurologic symptoms and signs such as hemiparesis, sensory loss, dysarthria, aphasia, hemianopia, diplopia, vertigo, ataxia, and headache [6]. The clinical features vary according to the affected territory (carotid = anterior or vertebrobasilar = posterior) and the extension of ischemia. Specific syndromes point to distinct lesions, such as the Wallenberg's syndrome in patients with lateral medullary infarcts [7].

The National Institutes of Health Stroke Scale (NIHSS) standardizes fast neurological assessment for patients with ischemic stroke and should be always performed. The scale ranges from zero to 42 and larger scores indicate greater stroke severity [8]. Online certification in NIHSS performance is available in several languages.

Differential diagnosis between ischemic and hemorrhagic strokes cannot be based on clinical grounds alone. Neuroimaging (non-contrast computed tomography, NCCT or magnetic resonance imaging, MRI) is essential for diagnosis [9]. During the first hours after IS, NCCT is often normal or shows sudden changes such as loss of the contrast between gray and white matters or effacement of sulci. Hours to days later, the infarct becomes apparent as a dark hypointense area.

In MRI, diffusion-weighted images (DWI) may show infarct areas, starting at around 30 minutes after onset of ischemia. In patients with brain stem or cerebellar strokes, the sensitivity of NCCT is lower than the sensitivity of MRI. However, during the first 48 hours, posterior fossa strokes may not be diagnosed by NCCT or MRI [10]. *Fluid Attenuation Inversion Recovery"* (FLAIR) MRI typically show infarcts, starting at around 4.5 to 6 hours after onset of ischemia. Susceptibility-weighted images (SWI) are useful to exclude hemorrhagic stroke. CT or MR perfusion imaging may be necessary in order to assess eligibility for thrombectomy. The mismatch between the DWI volume (to assess the "core") and the volume of decreased perfusion is used as a surrogate of the ischemic penumbra.

Brain NCCT is the most widely used imaging test in the acute phase, but MRI may also be performed for differential diagnosis between IS, hemorrhagic stroke, and mimics. NCCT can be performed more quickly than MRI and is often preferred in the acute setting. In addition, NCCT requires less collaboration from the subject than MRI. Remaining still inside the scanner may be challenging in subjects with confusion or decreased level of consciousness. Yet, MRI may be useful

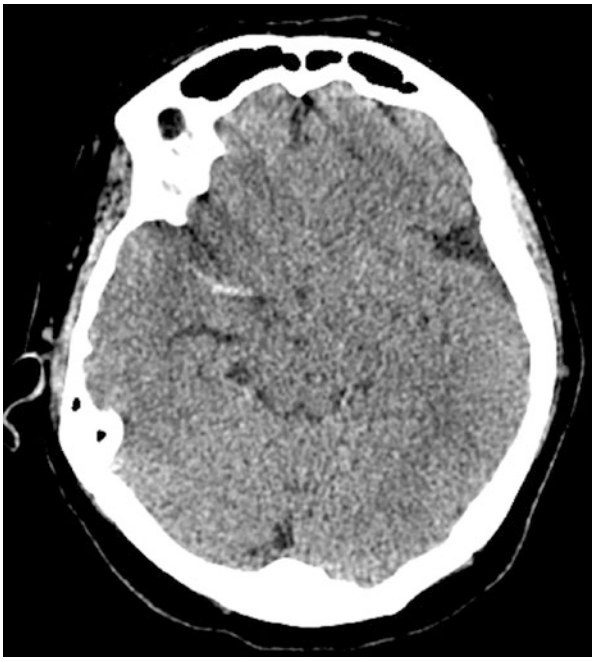

Fig. 28.1 Hyperdense middle cerebral artery sign

to select patients for thrombectomy and also for differential diagnosis between IS and mimics.

In particular, in the acute phase of ischemic strokes in the middle cerebral artery territory, the *Alberta Stroke Program Early CT Score* (ASPECTS) may be used to assess the extent of the ischemic core on NCCT. The score ranges from 0 to 10 (http://www.aspectsinstroke.com). Lower scores indicate greater extension of infarcts. This score is relevant for therapeutic decisions about reperfusion with thrombectomy. NCTT may also show other signs, such as the hyperdense middle cerebral artery that represents a thrombus inside this vessel (Fig. 28.1). Computed tomography angiography (CTA) or, less often, MR angiography (MRA) is also indicated in the acute phase in order to diagnose large-artery occlusions that may be amenable to thrombectomy (Fig. 28.2).

28.4 Differential Diagnosis

"IS mimics" can be divided in two categories [11, 12]:

- Vascular conditions: transient ischemic attacks, cerebral venous thrombosis, and hemorrhagic stroke.
- Nonvascular conditions: psychogenic disorders, seizures, migraine, hypo/hyperglycemia, encephalitis, brain abscess, brain tumors or metastases, hypertensive encephalopathy, hepatic encephalopathy, Wernicke's encephalopathy, and drug toxicity.

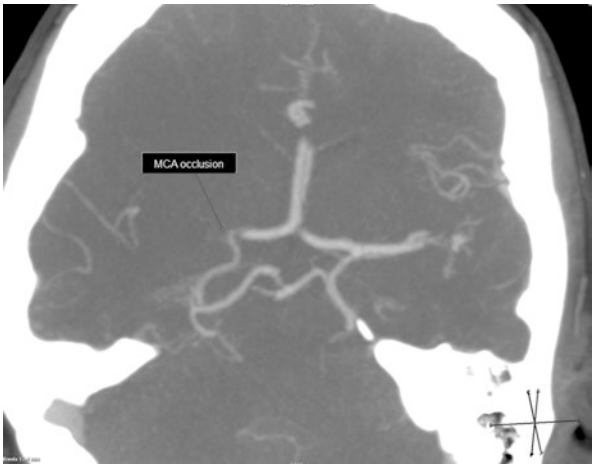

Fig. 28.2 Computed tomography angiography shows middle cerebral artery occlusion (arrow)

In particular, posterior reversible encephalopathy syndrome (PRES) is caused by reversible subcortical edema that presents as an acute neurological deficit in the setting of renal failure, blood pressure fluctuations, cytotoxic drugs, autoimmune disorders, and pre-eclampsia or eclampsia. Neuroimaging assessment reveals changes consistent with vasogenic edema predominantly in bilateral parieto-occipital regions [13]. There is no specific treatment for PRES but the disorder is usually reversible when the precipitating cause is eliminated or treated.

28.5 Acute Treatment

The two main objectives of treatment in the acute phase of IS are to maintain clinical stability and to decide whether the patient is a suitable candidate to reperfusion therapy such as intravenous thrombolysis and mechanical thrombectomy. In a typical middle cerebral artery IS, it is estimated that, for each minute without reperfusion, 1.9 million neurons, 14 billion synapses and 12 km (7.5 miles) of myelinated fibers are lost, making the goal of achieving reperfusion in the shortest time possible an urgent matter: time is brain! [14].

The first step, as in every critical patient, is to make sure that the patient is stable, ensure adequate airway support and ventilatory assistance, if necessary. Supplementary oxygen should be provided only to maintain an oxygen saturation of at least 94%. It is common that patients in the acute phase of a stroke present with high blood pressure. However, unless there are other clinical comorbid conditions that require lowering the blood pressure (i.e., acute heart failure, acute coronary event, aortic dissection), blood pressure levels up to 220/120 mmHg can be tolerated in the first 24 hours after stroke onset in patients not submitted to

intravenous thrombolysis. For those treated with intravenous alteplase, the blood pressure should be kept below 180/105 mmHg. In hypotensive/hypovolemic patients, adequate fluid replacement and even vasoactive drugs should be used in order to maintain adequate brain perfusion. Blood pressure and heart rate should be monitored [15].

Assessment of peripheral pulses should be performed in the four limbs in order to assess the possibility of aortic dissection, a contraindication to intravenous thrombolysis. An intravenous line should be installed. The first complementary test that should be ordered is the blood glucose level because hypo- or hyperglycemia can mimic stroke symptoms and also are linked to worse prognosis of ischemic stroke. Blood glucose levels under 60 mg/dL should be promptly treated with intravenous 50% glucose until correction. In the hyperglycemic patient, blood glucose levels of 140–180 mg/dL should be targeted.

The HeadPoST clinical trial [16] showed no difference in outcomes in patients lying flat or with the head elevated to 30° in the first 24 hours after stroke onset. Overall, a 30° head elevation should be maintained. However, for patients with occlusion/subocclusion of proximal vessels and a possible hemodynamic mechanism responsible for the stroke, a lying-flat position in the first 24 hours may be beneficial, as long as it is tolerated.

After or during clinical stabilization the stroke rapid-response team (code stroke), if available, should be activated aiming to reduce any delay in the evaluation for reperfusion therapy. NCCT should be promptly performed to exclude intracranial hemorrhage, intraparenchymal brain tumors, signs of recent head trauma, alternative diagnosis and assess IS volume.

28.5.1 Intravenous Thrombolysis

The first effective treatment described for acute ischemic stroke was intravenous thrombolysis with alteplase (rtPA), which should be considered for patients with less than 4.5 hours of interval from the last time known well and any disabling deficit. Blood glucose level and head NCCT are the only tests required before starting intravenous thrombolysis in most cases. Their results are relevant to exclude hypo/hyperglycemia and intracranial hemorrhage. Coagulation tests are necessary prior to thrombolysis if there is history of coagulopathy or use of anticoagulants. Other recommended tests in the acute phase are partial thromboplastin time, EKG, troponin, complete blood count, urea/BUN, creatinine and electrolytes. Yet, intravenous thrombolysis should be started prior to results of these tests.

The number needed to treat (NNT) to achieve an excellent functional outcome (modified Rankin Scale score of 0–1) in 90 days of intravenous thrombolysis is time-dependent, ranging from 4.5 in the first 1.5 hours from stroke onset to 14,

between 3.0 and 4.5 hours [17]. The shorter the time until treatment, the greater are the chances of a good outcome.

Greater flexibility has emerged for several conditions previously considered as contraindications. For example, in the case of an intracranial extra-axial tumor (i.e., meningioma) or unruptured intracranial aneurysm with less than 10 mm, intravenous rtPA is considered "probably recommended" in the last American Heart Association/American Stroke Association (AHA/ASA) Guidelines [9, 15]. The procedure also "may be considered" in case a lumbar puncture has been performed within the past 7 days. In some other conditions of great interest in the neurosurgical field, the use of intravenous alteplase should be discussed in an individual basis. For intracranial vascular malformations and giant aneurysms, the indication of thrombolysis is "not well stablished" according to AHA/ASA guidelines. For intracranial intra-axial tumors, intracranial or spinal surgery in the last 3 months or previous history of intracranial hemorrhage, thrombolysis is considered "potentially harmful". Under these circumstances, the benefit of rtPA treatment should be weighed against the risks. A list of the main contraindications for intravenous thrombolysis is shown in Table 28.1 and a complete list can be found in the AHA/ASA guidelines [9, 15].

The dose of intravenous alteplase for ischemic stroke is 0.9 mg/kg (10% given as a bolus infusion and the remaining 90%, over 1 hour), a dose that is inferior to that used for acute myocardial infarction. The percentage of patients without any symptomatic intracranial hemorrhage after thrombolysis is around 94% [18].

If the new neurologic deficits are identified upon awakening or the onset of the neurological deficits are unknown and the last time seen well time is longer than 4.5 hours, advanced imaging techniques can be used to assess eligibility for intravenous thrombolysis. Considering that acute strokes may appear on diffusion-weighted MRI but not on FLAIR images up to 4.5–6 hours after the onset of symptoms, the WAKE-UP trial randomized patients with normal FLAIR but abnormal diffusion-weighted results, to either thrombolysis or no treatment. In this study, alteplase was beneficial in patients who fulfilled the eligibility criteria for the protocol [19]. The EXTEND trial confirmed the benefits of intravenous thrombolysis in wake-up strokes [20].

The most feared complication of intravenous thrombolysis is symptomatic intracranial bleeding. Neurological worsening during thrombolysis should prompt the following measures [15]: interruption of alteplase infusion; complete blood count, prothrombin time/international normalized ratio (INR), activated partial thromboplastin time, fibrinogen, blood type and cross-match; head NCCT. If bleeding is confirmed, 10 units of cryoprecipitate should be infused over 10–30 minutes; if the fibrinogen level is below 150 mg/dL, then an additional dose should be administered. Tranexamic acid (1000 mg) should be infused intravenously over 10 min, or 4-5 g of epsilon-aminocaproic acid should be administered intravenously over 1 hour, followed by 1 g until bleeding is controlled. Neurosurgical drainage of the intracranial hematoma may be required. Intensive care should be provided at all times.

Table 28.1 Main contraindications for IV thrombolysis

Absolute contraindications
Severe head trauma within 3 months
Symptoms and signs most consistent with subarachnoid hemorrhage
Systolic blood pressure (BP) > 185 mmHg or diastolic BP > 110 mmHg at the initiation of IV alteplase
Platelets <100,000 or INR > 1.7 or aPTT >40s or PT > 15 s
Use of direct thrombin inhibitors or direct factor Xa inhibitors within 48 h, if normal renal function (Alteplase could be considered when appropriate laboratory tests such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal)
Treatment dose of low molecular weight heparin in the last 24 h
Infective endocarditis
Aortic arch dissection
Active internal bleeding
Relative contraindications
History of intracranial hemorrhage
Ischemic stroke within 3 months
Intracranial or spinal surgery within 3 months
Intra-axial intracranial neoplasm
Unknown/not well established
Intracranial arterial dissection
Giant unruptured and unsecured intracranial aneurysm
Intracranial vascular malformations
Is reasonable/may be considered
Dural puncture in the preceding 7 days
Procedural stroke—complication of cardiac or cerebral angiographic procedures
Probably recommended
Extracranial arterial dissection
Extra-axial intracranial neoplasm
Small and moderate-sized (<10 mm) unruptured and unsecured intracranial aneurysm

28.5.2 Mechanical Thrombectomy

A major issue of intravenous thrombolysis is the low reperfusion rates in patients with proximal large-vessel occlusions. The rate of recanalization may be as low as 6% in occlusion of the intracranial internal carotid artery, 30% in the M1 segment of the middle cerebral artery (MCA) and 44% in the M2 segment of the MCA [21]. Mechanical thrombectomy emerged as an intervention capable of enhancing reperfusion rates. Several clinical trials around the world proved the benefit of mechanical thrombectomy within the first hours after stroke onset: MR CLEAN in the Netherlands, ESCAPE in Canada, EXTEND-IA in Oceania, REVASCAT in Spain, SWIFT-PRIME in the USA, among others in developed countries; and more recently the RESILIENT trial, in Brazil, the only conducted in a developing country [22–27].

The *Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials* (HERMES) collaboration pooled data from the first five clinical trials cited above and concluded that the NNT for thrombectomy to reduce disability by at least one level on the modified Rankin scale for one patient was 2.6, one of the best NNT in Medicine. According to AHA/ASA guidelines, patients with proximal occlusion of the intracranial internal carotid artery or M1 segment of the middle cerebral artery, less than 6 hours from stroke onset, with a NIHSS score of at least 6 and an ASPECTS of at least 6 should receive mechanical thrombectomy. If also eligible to IV alteplase, the patient should receive it even if mechanical thrombectomy is being planned [9]. Within the 6-hour window there is no need for advanced imaging techniques. NCCT and CTA are sufficient to evaluate imaging eligibility criteria.

Two recent clinical trials extended the time window of possible eligibility to mechanical thrombectomy until 24 h after the last time known well, mainly by selecting patients who are "slow progressors" (still have a big area of salvageable penumbral tissue after several hours). To select those subjects, they assessed either a clinical radiological mismatch using MRI diffusion sequence or CT perfusion to estimate the core of the ischemic stroke compared with the clinical severity of the stroke, or an estimate of the salvageable penumbral area using CT or MRI perfusion. The intervention is highly effective (NNT = 2) in patients who fulfill eligibility criteria up to 6–24 hours after onset of symptoms or after having been seen well for the last time, but only a small percentage of patients typically meet these criteria in clinical practice [28, 29].

Besides the change in the paradigm of time for the classical indication of mechanical thrombectomy, other important questions are being addressed by new research regarding the use of endovascular techniques for occlusions of the M2 or M3 segment of the MCA, for patients with low NIHSS, for large core strokes with low ASPECTS scores, to cite a few examples. These clinical scenarios are still an area of debate between specialists and should be evaluated in an individualized basis. A few clinical trials are currently ongoing to address some of these issues about effectiveness of thrombectomy: TESLA, TENSION and IN EXTREMIS (LASTE) are studying MT in the patients with large cores. ENDOLOW and IN EXTREMIS (MOSTE), in patients with low NIHSS scores.

28.6 Summary—Reperfusion Therapies

According to current guidelines, specific neuroimaging tests are required to define indication of reperfusion therapies. Advanced neuroimaging is necessary to define whether thrombectomy should be offered to patients who present more than 6 hours after onset of symptom but should not delay intravenous thrombolysis in eligible patients. In summary, in addition to neurological evaluation:

- For intravenous thrombolysis up to 4.5 hours after onset of symptoms, NCCT is sufficient.
- For thrombectomy up to 6 hours after onset of symptoms, NCCT and CTA are sufficient.

- For thrombectomy later than 6 hours after onset of symptoms, either DWI-MRI or CT/MRI perfusion are currently recommended.
- For wake-up strokes, MRI for assessment of DWI and FLAIR images are currently recommended if thrombectomy is not planned.

28.7 Complications in the Acute Phase

Neurological or systemic complications may occur after stroke. Progressive neurological worsening after stroke may occur due to recurrent embolism, increase in thrombosis extension or failure of the collateral circulation. Stroke progression may occur in up to 43% of the patients, more often within the first 48 hours after stroke [30–32]. There are neither strong evidence-based data to support treatment of an early single seizure, nor to support lack of treatment. Current guidelines recommend that antiepileptic drugs should be administered for patients with recurrent seizures. Drugs should be tailored to individual patients´ characteristics. Prophylactic treatment with antiepileptic drugs is not recommended [15].

Given that the patient's neurologic status may fluctuate rapidly, serial neurologic assessments are required to identify possible urgent situations. Drowsiness that starts between the first and the fourth day after the onset of symptoms may be the only sign of brain edema, can occur in addition to or be followed by asymmetry in pupillary size, periodic breathing, or new neurological signs [33]. NCCT can confirm mass effect due to edema in infarcts in the internal carotid artery territory as well as in cerebellar strokes. Midline shifts may occur in "malignant" infarcts affecting the territories of the carotid or middle cerebral arteries.

A pooled analysis of the DECIMAL (*Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarcts*), DESTINY (*Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery*) and HAMLET (*Hemicraniectomy after Middle Cerebral Artery Infarction with Life-threatening Edema Trial*) studies showed that, in patients aged 60 years or less with brain swelling due to large unilateral middle cerebral artery infarcts, who evolve with neurological deterioration within 48 hours after stroke onset, decompressive craniectomy with dural expansion significantly decreases mortality [34]. In untreated patients, mortality rates can be as high as 80%. The NNT are: two for survival with a modified Rankin scale score of four or less; four, for a modified Rankin scale score of three or less; and two, for survival irrespective of functional outcome. The pooled analysis indicated that 14% of surgically treated patients may evolve with mild disability, none with no disability and 86%, with moderate to severe disability or death. Considering the high rates of disability for survivors, individual wishes and beliefs should be taken into account before performing surgery by consulting advanced directives or, in the absence of such directives, family members. Patients typically have a decreased level of consciousness by the time surgery is considered. For patients aged more than 60 years, decompressive surgery also decreases mortality but the burden of disability is higher, compared to younger treated patients [35, 36].

For subjects with large cerebellar infarcts that compress the brain stem, decompressive suboccipital craniectomy with dural expansion is indicated. This procedure is associated with good survival and disability outcomes. In patients with obstructive hydrocephalus, ventriculostomy may be recommended [15, 37].

Medical complications such as pneumonia, venous thromboembolism, urinary tract infection, cardiac complications and pressure ulcers may also occur within the first weeks to months poststroke and decrease the likelihood of a good recovery [38]. Organized treatment in stroke units contributes to prevention, diagnosis and treatment of these events.

28.8 Stroke Units

In the acute phase, patients with stroke should be admitted to stroke units, specialized wards where multidisciplinary teams exclusively manage stroke patients. Typically, the team includes neurologists, nurses, physical, occupational and speech therapists. Social workers, psychologists, rehabilitation medicine physicians as well as nutritionists may participate in patient care. Rates of death, dependency and the need of institutional care are significantly lower in patients admitted to stroke units, compared to other models of care [39, 40]. Benefits apply to all types of strokes, across all levels of severity.

28.9 Investigation of Etiology

After the acute phase, clinical features and results of different tests are assessed, in an effort to determine the most likely cause of the IS and thus, plan appropriate measures for secondary prevention. Overall, the following steps are necessary:

- Review the main risk factors for ischemic stroke: age, arterial hypertension, diabetes mellitus, hypercholesterolemia, obesity, physical inactivity, atrial fibrillation and other heart conditions, smoking, alcohol abuse, sleep apnea and family history of stroke [41, 42].
- Review the circumstances in which the symptoms started: after cardiac surgery or digital subtraction angiography, history of major or minor trauma, among others.
- Search for clues of systemic disease on the physical examination including assessment of peripheral arterial pulses, heart murmurs, lesions in the eyes, skin or joints.
- Tests for cardiac evaluation: electrocardiogram, echocardiogram (transthoracic or, if an atrial abnormality is suspected, transesophageal), rhythm monitoring

with Holter or more prolonged evaluation with in-patient/outpatient telemetry or implantable loop recorders.

- Tests for evaluation of the aorta as well as cervical and intracranial segments of arteries that supply the brain: CTA, MRA, cervical Doppler for evaluation of carotid and vertebral arteries, transcranial Doppler for evaluation of intracranial arteries. Transcranial Doppler can also provide other useful information such as evidence of paradoxical embolism by means of the bubble test. Digital subtraction angiography is rarely performed for diagnostic purposes if non-invasive tests are available.
- Specific blood tests for investigation of autoimmune, hematological and infectious diseases such as lupus, temporal arteritis, sickle cell anemia, HIV, syphilis, Chagas disease in endemic areas, and other conditions.
- Urinalysis to assess proteinuria. Nephrotic syndrome, for instance, is a risk factor for thrombosis.
- Other tests: cerebrospinal fluid analysis may be required if autoimmune or infectious vasculitis is suspected. Genetic tests may confirm diagnoses of CADASIL [43], Fabry disease [44], or inherited thrombophilia—for instance due to prothrombin mutations [45]. Investigation of systemic cancer may be performed if thrombophilia secondary to an occult neoplasm is suspected.

The most likely cause of IS can be determined after clinical, laboratory and imaging features are interpreted. Different classification systems have been developed for research purposes and may help to define etiologies in clinical practice. The TOAST (*Trial of Org 10,172 in Acute Stroke Treatment*) criteria were published in 1993 [46] while the Causative Classification System (CCS) [47] and the ASCOD criteria [48] were published more than a decade later. Overall, all these systems have in common the classification of ischemic stroke in five subtypes: atherosclerosis affecting large arteries, cardiac or aortic embolism, small-vessel disease ("lacunar" lesions), other determined etiologies or undetermined etiologies. The criteria to define the likelihood of belonging to one of these groups vary according to the chosen classification system. The frequencies of different etiologies vary in different countries but "other determined etiologies" are always the less frequent. Examples of such etiologies are [49]: cervical or intracranial artery dissection, Moyamoya syndrome, reversible cerebral vasoconstriction syndrome, sickle-cell disease, migraine-induced stroke, illicit drug abuse, inflammatory arteriopathies (Takayasu arteritis, giant cell arteritis, primary angiitis of the central nervous system, polyarteritis nodosa, Behçet disease, Churg-Strauss syndrome, Kohlmeier-Degos disease), infectious arteriopathies (syphilis, HIV, herpes zoster, tuberculosis, among others), inherited arteriopathies (Fabry's disease, Susac syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, fibromuscular dysplasia), inherited or acquired thrombophilias, primary hematologic disorders (e.g., polycythemia vera, essential thrombocythemia, thrombotic thrombocytopenic purpura, among others).

28.10 Secondary Prevention

Control of risk factors for vascular diseases is a main goal of secondary prevention. At the moment, the target for blood pressure is to achieve levels below 140/90 mmHg after the acute phase. Statins are prescribed for patients with IS due to atherosclerosis. For other causes, prescription of statins can be managed according to local guidelines [50–52].

Diabetes, obesity and physical inactivity should be treated. Treatment of sleep apnea might be considered [53]. Smoking and excessive alcohol intake should be discontinued.

In addition, before etiology is determined, aspirin (50-325 mg qd) is widely used in the absence of contraindications [53]. Alternatively, aspirin 25 mg in combination with extended-release dipyridamole twice a day may be considered. For patients who have stroke recurrence despite these medications and in those allergic to aspirin, clopidogrel 75 mg qd can be prescribed. The choice of the antiplatelet drug should be influenced by individual characteristics of the patients. For specific etiologies, other interventions are necessary.

For instance, if stroke etiology is cardiac embolism due to non-valvular atrial fibrillation, anticoagulation with vitamin K antagonists (such as warfarin) or direct anticoagulants is required in the absence of contraindications [53]. A number of variables must be taken into account to decide if/when to start these drugs, such as extension of the stroke, disability and presence of hemorrhagic transformation. Levels of evidence are lower for other possible indications of vitamin K antagonists, such as: recent myocardial infarction with ventricular akinesis or dyskinesis; left atrial or ventricular thrombi; dilated cardiomyopathy; rheumatic mitral valve disease; prosthetic mitral or aortic valves; Chagas disease.

For patients with minor strokes (NIHSS <4), dual antiplatelet treatment with aspirin and clopidogrel for 3 weeks may be considered [15, 53]. In addition, for patients with intracranial atherosclerosis (70–99%), dual antiplatelet for 90 days is considered reasonable [53]. Angioplasty is not indicated in these patients [54], who should be submitted to aggressive control of risk factors.

In patients with >50% symptomatic stenoses of the cervical internal carotid artery and modified Rankin scores up to two, angioplasty or endarterectomy must be considered as long as the periprocedural rate of periprocedural stroke or death is lower than 6% [53].

For patients with patent foramen ovale (PFO), there are still controversies about the best therapeutic strategy. Three studies contributed to change the overall view about the lack of benefit of endovascular PFO closure in patients in whom no other causes of stroke were found: CLOSE (*Patent Foramen Ovale Closure or Anticoagulants* versus *Antiplatelet Therapy to Prevent Stroke Recurrence*), RESPECT (*Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment*) and Gore REDUCE (*GORE® HELEX® Septal Occluder / GORE® CARDIOFORM Septal Occluder for Patent Foramen Ovale (PFO) Closure in Stroke Patients—The Gore REDUCE Clinical*

Study) [55–57]. Despite indications that endovascular closure may be beneficial to patients with large PFOs or atrial septal aneurysms, the risks of IS recurrence were low in these studies, whether or not this intervention was performed.

For patients with arterial dissections, the best approach for secondary prevention is also controversial. In the CADISS (*Cervical Artery Dissection in Stroke Study*), no significant differences were found between risks of ipsilateral stroke or death after 3 months of treatment with either antiplatelet or anticoagulant drugs in patients with cervical dissections but limitations in the study limit generalization of conclusions and therapy should be tailored according to individual characteristics [58].

For patients with meningovascular syphilis, penicillin is the treatment of choice. For autoimmune vasculitis, steroids and immunosuppression are typically prescribed. Patients with strokes of undetermined etiology are treated with aspirin but the optimal therapeutic strategy for these subjects is still unclear. In particular, it is unknown whether anticoagulation may benefit patients with embolic stroke of undetermined source (ESUS), a particular type of stroke of undetermined etiology. The proposed diagnostic criteria for ESUS are [59]:

- Non-lacunar IS detected by NCCT or MRI;
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia;
- No major risk cardioembolic source of embolism such as permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction <30%, valvular vegetations, or infective endocarditis;
- No other specific cause of stroke identified (for instance, arteritis, dissection, migraine/vasospasm, and drug abuse).

The following conditions have been implicated as possible causes of ESUS [60]: myxomatous valvulopathy with prolapse, mitral annular calcification, aortic valve stenosis, calcific aortic valve, sick-sinus syndrome, atrial appendage stasis with reduced flow velocities or spontaneous echodensities, atrial septal aneurysm, Chiari network, covert paroxysmal atrial fibrillation, covert non-bacterial thrombotic endocarditis in patients with cancer, aortic arch atherosclerotic plaques, cervical and cerebral artery non-stenotic plaques with ulceration, PFO, and atrial septal defect.

28.11 Rehabilitation

Interventions to prevent complications and possibly facilitate plasticity mechanisms should be provided as soon as possible, when patients are medically stable. Some of the recommendations from the American Heart Association/American Stroke Association are outlined below [61]:

- Prophylactic-dose subcutaneous heparin (unfractionated or low-molecular weight heparin) should be prescribed during acute and rehabilitation hospital stay or until the patient regains mobility.
- Patients diagnosed with poststroke depression should be treated with antidepressants in the absence of contraindications; effectiveness of treatment should be monitored.
- Formal evaluation of basic and instrumental activities of daily living, communication and functional mobility should be performed before discharge. The results should be used to plan the discharge process.
- Early dysphagia screening is recommended for acute stroke patients to identify dysphagia or aspiration, which can lead to pneumonia, malnutrition, dehydration, and other complications.
- Nasogastric tube feeding should be used for 2–3 weeks to provide nutritional support for patients who cannot swallow safely. Gastrostomy should be performed if safety is not expected in the chronic phase. Behavioral interventions may be considered to treat dysphagia.
- Speech therapy is indicated for aphasic patients.
- Intensive mobility-task training is recommended to improve gait.
- Task-specific training is recommended to improve upper limb motor function.

It is considered that there is not enough evidence to support the efficacy of routine very early mobilization after stroke compared with conventional care. In the randomized, controlled trial of the efficacy and safety of very early mobilization within 24 hours of stroke onset (*A Very Early Rehabilitation Trial* [AVERT]), the high-dose, very early mobilization protocol was associated with a reduction in the odds of a favorable outcome at 3 months [62]: Therefore, this type of intervention is not currently recommended.

28.12 Quality of Care

Over the past decades, measures of quality of care for IS have been developed. Certification systems and methods for evaluation of care vary across countries. In the United States, for instance, hospitals in selected regions were instructed to collected data about the following seven performance measures in the "Get with the Guidelines" program: intravenous rtPA in patients who arrived less than 2 hours after symptom onset, antithrombotic medication within 48 hours of admission, deep vein thrombosis prophylaxis within 48 hours of admission for nonambulatory patients, discharge use of antithrombotic medication, discharge use of anticoagulation for atrial fibrillation, treatment for low-density lipoprotein >100 mg/dL in patients meeting National Cholesterol Education Program Adult Treatment Panel III guidelines, and counseling or medication for smoking cessation [63].

The Joint Commission's Primary Stroke Center Certification Program, based on the Recommendations for Primary Stroke Centers published by the Brain Attack

Coalition and American Stroke Association statements for stroke to evaluate hospitals that function as Primary Stroke Centers, assessed ten performance measures (https://www.jointcommission.org/measurement/measures/stroke/): deep venous thrombosis prophylaxis, discharge on antithrombotics, anticoagulation therapy for patients with atrial fibrillation, assessment of eligibility for intravenous thrombolysis, initiation of antithrombotic medication within 48 hours of hospitalization, assessment of lipid profile, screening for dysphagia, smoking cessation, stroke education, and plan for rehabilitation.

Monitoring of performance measures is encouraged in centers that provide stroke care. Identification of gaps and opportunities for improvement are powerful tools to optimize pathways, daily care and hence, contribute to enhance outcomes.

28.13 Highlights

- Stroke is a leading cause of death and disability worldwide.
- Thrombolysis and thrombectomy can decrease the burden from stroke.
- Time is brain. Reperfusion therapies should be administered as early as possible to eligible patients.
- The gold standard for acute stroke care is treatment provided by a multidisciplinary team in a stroke unit.
- Decompressive craniotomy may be life-saving in large middle cerebral artery or cerebellar ischemic stroke.
- Definition of the most likely etiology of ischemic stroke is necessary to provide appropriate prevention measures and thus avoid stroke recurrence.

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Chapter 29
Emergencies in Neuro-oncology

José Marcus Rotta, Afonso Henrique Dutra de Melo, and Rodolfo Casimiro Reis

29.1 Introduction

The incidence and survival of patients with neurological cancer have been increasing over the past decades. Both primary central nervous and other types of cancer patients live longer due to early diagnosis and better treatment options. According to the Global Burden Disease Study 2016, there were 330,000 incident cases of CNS cancer and 227,000 deaths worldwide on that year. It reflects 17.3% increase in incidence between 1990 and 2016 [1].

Extension of life expectancy and on the incidence of cancer itself predisposes to an increment in the occurrence of a variety of neurologic complications that can result in high morbidity and mortality [1, 2]. These conditions often result in hospital admissions, generally in an intensive care unit (ICU), creating a heavy burden to the healthcare system since primary cancer patients' treatment costs 20 times more than age-matched controls without cancer [2].

The complications could occur due to a direct result of the tumor itself, due to an indirect effect of cancer, or as a result of chemotherapy, radiotherapy, and other medical interventions [3] (Table 29.1). Recognition of these mechanisms helps to achieve early diagnosis and initiate prompt treatment in a scenario that usually demands expedite management.

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Table 29.1 Direct, indirect, and iatrogenic causes of neuro-oncological emergencies

Cause	Complication	
Direct effect of tumor	Elevated ICP	Cerebral edema
		Hydrocephalus
	Status epilepticus	
	Leptomeningeal dissemination	
	Spinal cord compression	
Indirect effects of cancer	Cerebrovascular disease	
	Paraneoplastic syndromes	
	CNS infections	
Iatrogenic	Radiotherapy complications	
	Chemotherapy complications	

29.2 Increased Intracranial Pressure (ICP)

29.2.1 Mass Effect and Cerebral Edema

The ICP is regulated according to the Monro-Kellie doctrine that theorizes that the cranial vault is rigid and its volume is constant. The brain constitutes approximately 80% of this volume, and blood and CSF account for 10% each [4–6].

The first compensatory mechanism for the maintenance of a normal ICP involves displacement and reduction of the CSF compartment, reduction of cerebral blood flow, and lastly, displacement of cerebral parenchyma causing herniation. The slower the increment in ICP, the more efficient this regulatory system. Therefore, rapidly growing masses like malignant gliomas have a higher risk of causing brain herniation than slow-growing tumors like meningiomas or nerve sheath tumors [3].

The most common symptom is headache, present in almost half of all patients with primary and secondary brain tumors. In the classic description, it is worse in the morning due to overnight hypercarbia leading to cerebral vasodilation, although only 17% of patients present that characteristic of pain, as stated by Forsyth and Posner [5]. Other symptoms are vomiting, nausea, CN VI palsy leading to diplopia, optic disc swelling, and Cushing's reflex lately, which suggests brain stem involvement.

29.3 Etiology

Primary and secondary brain tumors cause an increase in ICP because they occupy space in the cranial vault, but also because of the edema that can accompany them [5–7].

This cerebral edema is usually vasogenic, and not cytotoxic, mediated by VEGF (vascular endothelial growth factor) with creation of aberrant vasculature and impaired endothelial tight junctions [6]. Cytotoxic edema can also be present and may be the result of ischemic injury, radiation injury, and cytotoxic chemotherapy (both discussed later).

Tumors can also be complicated by intratumoral hemorrhage. Metastatic lesions like melanoma and lesions in the lung and breast are the most frequent in that scenario [7]. However, some types of cancer, like thyroid and hepatocellular carcinoma that rarely metastasize to the brain, are especially prone to it [8]. Intraparenchymal hemorrhage is the most common, followed by subdural, subarachnoid, and epidural hemorrhages. Coagulopathy, present in a significant number of hemato-oncologic patients, is the second cause of intracerebral hemorrhage [7–9].

Several patients develop hydrocephalus, either due to blocking of the CSF pathways causing obstructive hydrocephalus or due to impaired CSF absorption generally because of leptomeningeal carcinomatosis. Obstructive hydrocephalus occurs when expansive lesions compress the ventricular system. Third ventricle tumors obstruct the foramen of Monro leading to dilation of the lateral ventricles. Hemispheric lesions can block the lateral ventricles and cause isolated ventriculomegaly. Posterior fossa tumors obstruct the fourth ventricle and the aqueduct causing supratentorial hydrocephalus [6, 8]. Communicating hydrocephalus generally develops leading to normal pressure hydrocephalus like syndrome with apraxic gait, urinary incontinence, and mental confusion as main symptoms [9].

29.4 Treatment

The cornerstone of the treatment is lowering the ICP and understanding the severity of the situation. Patients with clinical or radiological signs of elevated ICP should be admitted to ICUs and underwent periodic neurological evaluation. Since those patients are admitted in a state of intracranial hypertension, on the edge of the intracranial compensatory mechanisms, any minor changes in ICP can mean rapid deterioration of the mental status, coma, and death [10].

Despite the etiology, there are generic measures that should be carried for all patients. There should be an initial evaluation assuring adequate circulation and airway. The patient's head should be elevated between 30 and 45 degrees. That guarantees optimized venous outflow from the brain. Hyponatremia, if present, has to be correct, and serum osmolarity should be maintained in the normal range. Hyperthermia has to be avoided with the use of antipyretics if necessary. Since cerebral pressure perfusion (CPP) is the difference between mean arterial pressure (MAP) and intracranial pressure (CPP = MAP – ICP), blood pressure should be kept as to target a CPP in the range of 60 to 80 mmHg [11]

Those patients with a decreased level of consciousness should be intubated, sedated, and put into mechanical ventilation. Hyperventilation to a PCO2 of 26–30 mmHg is sometimes indicated, since it causes cerebral vasoconstriction, reducing cerebral blood flow [6, 10, 11]. However this measure is transient and should not be prolonged.

Corticosteroid therapy is the main nonsurgical treatment in a patient with expansive lesions accompanied by vasogenic edema. Dexamethasone, a corticosteroid that is 30 times more potent than cortisol, with low mineralocorticoid activity, is effective in reducing vasogenic edema and hence reducing mass effect-related symptoms. Usually, a loading dose of 10 to 20 mg is prescribed, followed by 8–16 mg daily, divided into two to four doses. Dexamethasone shall be prescribed in the lowest dose necessary to relieve patients from mass effect-related symptoms. Care has to be taken when lowering the doses since quick withdrawal may lead to adrenal insufficiency [3, 5, 6].

Osmotherapy is the cornerstone of medical treatment for elevated ICP. It is used as a bridge until definitive treatment is possible. The goal of therapy is to create an osmotic gradient between blood and brain tissue, removing fluid from the latter. Hypertonic saline and mannitol are the two agents used in this context. Both can be used with similar results, but in transtentorial herniation, there is evidence that hypertonic saline is more effective than mannitol [6].

Choosing the definitive treatment and when it is going to take place are complicated questions. Several points must be considered. Patient's characteristics such as age, clinical condition (performance status, Karnofsky index), and associated morbidity may preclude surgical treatment. Management, of course, is dictated by the specific diagnosis. For example, a central nervous system lymphoma benefits from radiotherapy and corticotherapy, and conversely, large malignant gliomas have a better prognosis if aggressively resected [12, 13]. Characteristics of the cerebral disease, miliary metastatic disease, and unresectable lesions due to the location are not candidates for surgical resection since it can create unbearable neurological deficits or even accelerate the natural history of the disease. Generally, the Karnofsky index superior of 70 and performance status less than two is considered [6].

Therefore, patients selected for surgical treatment need to be in a clinical condition that fits them for a neurosurgical procedure. The lesion, or lesions, has to be approachable from a surgical point of view, assuring both a longer survival and quality of life. Ideally, the disease should be controlled, and, after surgery, there must be options of oncological treatment left addressing the primary disease or as adjuvant therapy to primary CNS tumors.

Obstructive hydrocephalus is an emergent situation and has to be managed accordingly. In those patients with good clinical conditions and resectable lesions, the best option is the placement of an external ventricular drain followed by definitive surgery for the tumor. Patients with poor clinical status, uncontrolled primary disease, or unresectable lesions may benefit from a definitive shunting strategy, preferably a ventriculoperitoneal shunt. It carries the risks of disease dissemination to the peritoneum and all other shunt complications but addresses adequately the emergency of the moment and offers better probability of survival for those poor surgical candidates [6, 10].

29.5 Status Epilepticus (SE)

Epilepsy in the brain tumor patients accounts for 6–10% of all cases of epilepsy, and its frequency in the brain tumor population varies from 35% to 70%. It is considered the most important long-term disability risk factor since its economic and social impact may significantly aggravate the oncological disease [14, 15].]

The fact that oncological subjects are often using several medications and are under chemotherapy makes the treatment of epilepsy more complicated. Antiepileptic drugs (AED) can have essential interactions with many of those medications. Also, AED have side effects that can negatively impact the quality of life, therefore requiring individual treatment [14, 16–21].

For all the burden of epilepsy in brain tumor patients, prophylactic treatment is not recommended based on several trials that demonstrated no benefit of phenytoin, phenobarbital, and valproic acid. There is no evidence to support the use of newer AEDs as prophylactic agents thus far [21–26].

Tumor-related status epilepticus accounts for 3–12% of all adult SE, and it is an emergency. Between 15 and 22% of patients with epilepsy secondary to brain tumors develop SE. Studies suggest that SE due to brain tumors carries higher mortality than SE by other causes (17.2% vs. 11.2%) However, it is unclear whether this difference is because of SE itself or due to the underlying oncological disease since its occurrence is an indication of tumor growth, reappearance, or other complications such as intratumoral hemorrhages [15].

SE can develop with no history of prior seizures. A study of 2019 analyzing characteristics of SE in brain metastases patients showed that only 36.8% had previous seizures [14].

All brain tumor patients with altered mental status should be investigated for nonconvulsive status epilepticus (NCSE). A single-center study that observed all EEG performed in brain tumor patients found that 2% had nonconvulsive status epilepticus (NCSE), which makes it an important and reversible cause of the depressed level of consciousness [22].

There is no difference in response to treatment between brain tumor-related SE and other etiologies [16]. As soon as it is recognized, treatment should be initiated. Benzodiazepines, anticonvulsants, and other anesthetic agents are the medication of choice.

Patients must be screened for electrolyte disorders and infections and who underwent brain images as mentioned before. Those subjects are often using several medications, including chemotherapy that can modify serum levels of AED, so the medical records are also essential. Even though in this emergency setting, one should, if possible, try to choose drugs that do not have important interactions with others in use, the crucial goal is to stop seizures, overcoming the less immediate risk of pharmacological interactions. In those cases of refractory SE, surgical resection should be considered as a way to obtain seizure control [13, 27].

Prescribing prophylactic AED for patients with cerebral tumors is not rooted in evidence-based decision-making. Seizures may be associated with cerebral tumors in newly diagnosed brain tumors. Relying on the additional evidence of a

prospective, randomized trial that involved 100 patients with brain tumors, Sirven et al. summarized the convincing body of literature demonstrating a lack of efficacy of prophylactic AED treatment in this context. Phenytoin (PHT), phenobarbital, and valproate are the only AEDs subjected to prospective, randomized, controlled trials of seizure prophylaxis in patients with cerebral tumors, and no benefits have been demonstrated [28].

AEDs not only are ineffective in seizure prophylaxis but also may pose more risk of complications than in other patients. First, mutual interactions between enzyme-inducing AED and other drugs commonly used in these patients may be significant. Corticosteroids and the chemotherapeutic agents bischloroethylnitrosourea, cisplatin, carboplatin, and taxol can reduce AED serum concentrations by enzyme induction or reduction in bioavailability. Conversely, PHT levels are increased by concomitant use of 5-fluorouracil. Valproate can inhibit the metabolism of nitrosoureas and etoposide, causing clinical toxicity, and PHT may increase the dose requirement for corticosteroids and tamoxifen [16–21, 23].

Besides, the risk of potentially severe allergic reactions to AEDs is increased in patients receiving treatment for brain tumors. Skin rashes with PHT or carbamazepine have been reported in 25% of patients with malignant gliomas. Severe erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been described in patients taking PHT, usually in association with tapering doses of corticosteroids. The observation that some of these rashes begin within the treatment field on the scalp suggests that the radiation may play a direct role in enhancing allergic responses, perhaps by depressing T-suppressor activity. However, no studies have examined the prophylactic effects of any of the newer generation of AEDs, and the risks of allergic reactions, as well as complications related to drug interactions [16–19, 23].

Because the purpose of treatment may be antiepileptogenic as much as antiepileptic, investigation of neuroprotective agents that may have an antiepileptogenic effect also is relevant. Observations on the relative intractability of tumor-associated epilepsy, however, suggest that some of the failures to demonstrate benefit from prophylactic treatment from older AED may be related to epileptogenic processes that may already have occurred before the diagnosis of the tumor [16–28].

Finally, the different tumor types in various studies may have resulted in low power to detect a prophylactic drug effect in some tumor types. The cumulative incidence of seizures in patients with metastatic melanoma, for example, is about 50%, and the risk/benefit ratio of AED use in these cases has not been independently investigated. A prospective, placebo-controlled trial seems ethically acceptable, given the current state of knowledge [27, 28].

A pioneer meta-analysis addressed the merit of seizure prophylaxis for supratentorial craniotomies. They found that “no empirical data supporting the attitude of using AEDs prophylactically with supratentorial intracranial surgery, have been presented on a scientific basis” [24, 25]. The scope of that meta-analysis was more global, and its conclusions did not apply to people with brain tumors.

At a meeting of the American Society of Clinical Oncology in 1998, an abstract presented the results of a meta-analysis that later evolved into the practice parameters endorsed by the American Academy of Neurology [21]. This meta-analysis set out to answer a more specific question about the efficacy of antiepileptic drugs to prevent seizures in people with brain tumors. The focus was no longer on postoperative seizures. The AAN review concluded that seizure prophylaxis was not effective in patients with brain tumors. Therefore, the panel did not recommend its routine use and recommended that AED be tapered off after the first postoperative week. There are four pitfalls in the AAN review that weaken the strength of its conclusions. First, the reviewers misclassified eight studies as level II evidence (evidence provided by one or more well-designed observational studies with concurrent controls) instead of level III evidence (evidence provided by studies with nonrandomized historical controls), since all those studies were retrospective chart reviews and not clinical trials [19, 23, 27, 29].

Second, there was no exploration of clinical or statistical heterogeneity despite acknowledging the importance of heterogeneity as background noise in the interpretation of meta-analytic results. Randomized, controlled clinical trials are less susceptible, but not immune, to multiple sources of bias and can suffer from heterogeneity. Third, the adverse event rate quoted in the AAN review (23.8%) is the pooled result from three randomized trials and four retrospectives study with historical controls [19, 23, 27, 29].

Based on these analyses, one conclusion of the review was that AEDs were not effective in preventing seizures in people with gliomas, metastases, or meningiomas. The best data originate from a collection of different brain tumors with different seizure risks, each subgroup with few participants. Therefore, the strength of the evidence showing that antiepileptic drugs are ineffective for seizure prophylaxis is not as robust as stated in previous reviews on this topic and is primarily based on two trials, only one of which had enough statistical power. Evidence of this nature is inconclusive, and hence we prefer to say that the best evidence available at present is neither in favor of nor against seizure prophylaxis in brain tumors [20].

However, it is unlikely from these results that there is a clinically relevant effect of phenytoin, phenobarbital, and valproate in preventing seizures in the absence of careful drug-level monitoring. Therefore, it is essential to test the efficacy of newer antiepileptic drugs in this setting, beginning with phase II studies. Levetiracetam could be a promising candidate because it has an intravenous formulation and can be used preoperatively and in the immediate postoperative period. The design of these trials should include random allocation maintained throughout the trial, control with the use of placebo, double-blinding, and follow-up for 1–3 months to avoid the problem of high mortality rates present in at least one trial and no outcomes after a concise follow-up [17, 20, 30, 31].

29.6 Cerebrovascular Disease

Cancer patients are at an increased risk of ischemic stroke due to many conditions, as listed in Table 29.2. Both the disease itself and the treatment options may be the cause of thromboembolic events.

Approximately 15% of cancer patients have a concomitant cerebrovascular event, ischemic and hemorrhagic events presenting a similar frequency. Direct tumor effect includes arterial and venous sinus invasion by tumor or leptomeningeal disease, vessel compression by tumor mass or edema, tumor emboli, and hemorrhagic stroke [32, 33].

The relationship between cerebral ischemia and glioma is still ambiguous based on molecular mechanisms, but several studies have indicated that glioma and cerebral ischemia can facilitate each other concerning the occurrence [32]. It has been reported that the location of the tumor within the brain (insula, operculum, and temporal lobe) and repeated resection during treatment with glioma may increase the risk of ischemic injuries and other neurological deficits [34]. A clinical cohort suggests that the chance of diseases occurring together reaches 9% compared to 2.7% in the control population.

The risk of developing brain cancer (especially glioma) is also higher in patients with a history of cerebrovascular disease [35]. Patients who presented with cerebral infarction may develop brain cancer (glioblastoma) with a mortality rate three times higher than that of the control cohort in the post-ischemic period.

The most accepted model that correlates ischemia and glioma is based on the common hypoxic condition that occurs in both situations [32–37]. Cerebral ischemia due to local vasculature obstruction causes low oxygen tension in the ischemic regions and results in hypoxia. In contrast, a highly proliferative glioma cell mass has embryonic vasculature within its nucleus, leading to a central hypoxic region

Table 29.2 Causes of thromboembolic events in cancer patients

Cause	Complication
Direct effect of tumor	Arterial and venous invasion and blood vessel compression
	Central venous thrombosis
	Embolic events
	Intratumoral hemorrhage
Treatment	Chemotherapy
	Radiotherapy
	Invasive procedures
	Cancer supportive therapies
Coagulopathy	Disseminated intravascular coagulation
	Production of mucin
	Thrombocytopenia
	Hypercoagulable state
	Nonbacterial thrombotic endocarditis

that is deprived of oxygen. The exact mechanisms of this co-occurrence or interaction are still unclear. However, possible mechanisms, such as activation of astrocytes [38], reactive gliosis [39], angiogenesis [40], and changes in perivascular and perinecrotic niches [41] due to cerebral ischemia, are considered as facilitators for the development of glioma.

Glioblastoma (GBM) is associated with an increased risk of developing dural venous sinus thrombosis (DVST), which is often not diagnosed, as the symptoms are easily attributed to the tumor. In a retrospective study that included 163 patients, DVST was identified in 12 patients (7.4%). In patients who developed DVST, thrombosis was more likely to develop ipsilateral to the side of the tumor ($P = 0.01$). It was associated with a higher likelihood of developing extracranial venous thromboembolism ($P = 0.012$) [42].

Tumor cells express tissue factor and cancer procoagulant and release inflammatory cytokines and vascular endothelial growth factor creating an environment prone to intravascular coagulation [43–46]. In the specific situation of adenocarcinomas, Dearborn et al. (2014) described the thrombogenic effect of the production and intravascular secretion of mucin, a glycoprotein with a high molecular weight that is secreted by epithelial cells [47].

Cerebrovascular disease (CVD) is an increasingly recognized long-term toxicity of radiotherapy [1]. This toxicity is particularly devastating because it usually occurs in patients with no previous history of vascular disease. There is a large body of evidence of ischemic cardiovascular disease after radiation therapy [44]. The most previous reports of CVD after radiotherapy (RT) have focused on the pediatric population in which we know that there is a well-established correlation between radiation dose and chances of developing a stroke [44], and the same occurs in adults with head and neck cancer [10–12]. The medium- and large-sized vessels are the most affected. RT leads to vascular wall thickening, atherosclerotic and inflammatory plaque formation, and vascular damage. The risk of internal carotid stenosis ranges from 12 to 60% [45].

Pediatric cancer patients who receive cerebral RT are also at risk for CVD, and a cohort study found a dose-dependent relationship between radiation and stroke [45]. RT carries a not insignificant risk of death from CVD in patients with tumors close to the central arterial circulation (Willis polygon). This effect was not seen in tumors located in other parts of the brain. Radiotherapists who treat patients with primary brain tumors with a reasonable life expectancy should consider limiting high doses of radiation to the central vasculature when possible. At-risk patients should be alerted to the risk of CVD associated with radiotherapy before and after receiving radiotherapy, and the dose close to the circle of Willis should be minimized. In these patients, treatment of other comorbidities, such as hypertension, must be previously optimized. Most importantly, the risk of CVD mortality associated with RT should be considered when determining whether or not to treat patients with brain tumors adjacent to the Willis polygon [44].

Chemotherapy agents can cause stroke due to endothelial toxicity and effects on the coagulation factors. Certain drugs like sunitinib, bevacizumab (BVZ), and cisplatin are known as prothrombotic agents. Also, they predispose to opportunistic

infections due to induced immunosuppression, increasing the risk of stroke by bacterial endocarditis, sepsis, and other infectious conditions [46].

Randomized trials of antiangiogenic therapy (AAT), including BVZ for malignancies unrelated to the CNS, have reported an increased risk of intracerebral hemorrhage (ICH). It is assumed that antiangiogenic therapy leads to disturbance of endothelial cells, increasing the incidence of stroke. As VEGF is inhibited, apoptosis of nonphysiological endothelial cells has been associated with ischemic stroke. Therefore, different studies have suggested an increased risk of ischemic stroke and ICH, in GBM patients treated with BVZ [43].

Other cancer supportive therapeutics like stem cell transplantation and hematopoietic growth factor that are used mainly for the treatment of nonsolid tumors can lead to CVD due to alterations in coagulation, infections, and graft-versus-host disease [43].

Treatment of ischemic stroke on oncological patients differs from non-oncological ones. The burden of cerebral infarction is higher in this group of patients: the survival rate is worse, and they have an inferior neurological condition at the discharge. Active cancer is not a contraindication for thrombolysis, and cancer patients should still be considered for intravenous tissue plasminogen if that is the case. Although the original NINDS trial considers the presence of an intracranial neoplasm a contraindication, a populational study done by Murthy et al. [48] found that thrombolysis was not an additional risk factor for ICH in patients with primary CNS tumors.

Unfortunately, these patients usually present with other contraindications to intravenous tPA, such as thrombocytopenia and prior major surgery. Mechanical thrombectomy can be an alternative and a representative and is lifesaving. Although evidence for the endovascular treatment of acute ischemic stroke has grown strong in the last years, there is still a paucity of data for its use in active cancer patients. A retrospective study done by Lee et al. (2019) demonstrated similar National Institutes of Health Stroke Scale (NIHSS) and rate of recanalization for patients with active cancer and patients without cancer that underwent mechanical thrombectomy <24 hours after onset. But the same study found that the active cancer group mortality was 30.8% at 90 days, versus 8.8% of the control group, suggesting that candidates for intraarterial thrombectomy must be cautiously selected [49].

The management of intracerebral hemorrhage in cancer patients does not differ from that of non-cancer patients. Thrombocytopenia and coagulopathy have to be reversed if present. Blood pressure has to be maintained within a normal range. It is advisable to realize an MRI to investigate the underlying cause, but even if an expansive lesion is the responsible, products of degradation of hemoglobin may mask the diagnosis. In this setting, MRI should be repeated a few months later [49–51].

Surgery arises as the main treatment in the setting of a sizeable intraparenchymal hematoma with mass effect, or in the scenario of ventricular hemorrhage causing hydrocephalus.

As regarding venous sinus thrombosis, one can choose just to observe selected cases. In those cases that need treatment, anticoagulation with low-molecular-weight heparins is indicated, even in the presence of intraparenchymal hemorrhage.

29.7 Metastatic Spinal Disease

Metastatic spinal cord compression (MSCC) affects 20% of oncological patients, and around 5 to 10% will become symptomatic due to spinal cord compression [52]. As mentioned before, all types of metastatic disease are expected to increase their incidence due to better diagnosing and treatment options.

Malignant spinal cord compression is a neurological emergency that, if left untreated, evolves in all cases to neurological deficit. MESCC most commonly occurs in the thoracic spine (60%), lumbosacral spine (25%), and cervical spine (around 15%). Prostate, breast, and lung cancer account each for 15 to 20% of all cases, followed by non-Hodgkin's lymphoma, renal cell cancer, and multiple myeloma (5 to 10% each) [52]. MESCC is usually diagnosed in patients with primary cancer but can be the first manifestation of the disease in around 20% of patients. The first symptom is back pain (83–95%), and the time from onset to MESCC diagnosis is around 2 months [53] Table 29.3.

Table 29.3 Spinal instability neoplastic score

SINS component	Score
Location	
Junctional (C0–C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–C6, L2–L4)	2
Semirigid (T3–T10)	1
Rigid (S2–S5)	0
Pain	
Yes	3
Occasional	2
Pain-free	0
Bone lesion	
Lytic	3
Mixed (lytic/blastic)	2
Blastic	0
Alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50%	3

Table 29.3 (continued)

SINS component	Score
<50%	2
No collapse (>50% body involved)	1
None of the above	0
Posterior element involvement	
Bilateral	3
Unilateral	1
None of the above	0

Table 29.4 Tomita score

Primary site	Prognosis parameter score
Slow growth (breast, thyroid, etc.)	1
Moderate growth (kidney, uterus, etc.)	2
Rapid growth (lungs, stomach, etc.)	4
Visceral metastasis	
None	0
Treatable	2
Not treatable	4
Bone metastasis	
Solitary	1
Multiple	2

When treating patients for metastatic spinal disease, the fundamentals are to preserve or restore neurological function and achieve adequate pain control, thus improving life quality. A comprehensive analysis of each case must be performed, and characteristics of the patient, systemic disease, and local tumor should be evaluated together [53].

The main factor associated with neurological recovery is the duration and severity of the deficit. Hence, early diagnosis and intervention are the rule. There is low-level evidence that corticosteroids administered immediately after diagnosis followed by definitive treatment may increase the odds of maintaining 1-year ambulation posttreatment. All data concerning steroids and MSCC involve RT. There is no data regarding corticosteroids and decompressive surgery [53, 54].

When choosing the definitive treatment, the life expectancy and the systemic burden of the disease should be balanced. The outcomes may be predicted with scores like the Bauer [55], Tomita (Table 29.4) [56], and revised Tokuhashi score (Table 29.5) [57]. Especially for patients with primary lung cancer, there are limitations to the revised Tokuhashi score [52]. One of the main reasons is that in the initial elaboration of the score, injuries from several primary sites were included in the analysis, and for example, there were only 48 patients with primary lung cancer. Other prognostic models are being created, and Cai et al. demonstrated that tumor markers could be added as a prognostic tool [58].

Table 29.5 Tokuhashi score

Characteristic	Score
General condition (performance status)	
Poor (PS 10–40%)	0
Moderate (PS 50–70%)	1
Good (PS 80–100%)	2
Extraspinal bone metastasis (numbers)	
> = 3	0
1–2	1
0	2
Metastases to major internal organs	
Unremovable	0
Removable	1
No metastasis	2
Prior site of the cancer	
Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0
Liver, gallbladder, unidentified	1
Others	2
Kidney, uterus	3
Rectum	4
Thyroid, breast, prostate, carcinoid tumor	5
Palsy	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
None (Frankel E)	2

Although surgery still plays an essential role in MSCC, there has been a shift in the last years from big excisional surgeries to more limited surgeries that aim for the decompression of neural structures and create space for radiotherapy. The term "separation surgery" that has been frequently used refers to a posterolateral approach that allows circumferential decompression and stabilization if needed [53].

Complementarily, the spinal instability neoplastic score (SINS) was designed to unify evaluation and decision-making among physicians dealing with metastatic spinal disease. It evaluates six parameters: location of lesions, pain, alignment, characteristics of lesions (blastic or lytic), vertebral body collapse, and posterior element involvement. High SINS scores (13 to 18) are associated with spinal instability, while low scores (0–6) are considered stable. Scores from 7 to 12 are potentially unstable and require additional information to differentiate which patients need stabilization. It should be emphasized that it has near-perfect inter- and intraobserver reliability in determining three clinically relevant categories of stability. The sensitivity and specificity of SINS for potentially unstable or unstable lesions were 95.7% and 79.5%, respectively [54].

RT plays a central role in the treatment of MSCC. It is indicated in all patients that are candidates for palliative treatment, whether or not they were operated. The main issue is that due to the proximity of the lesions to neural structures, the thresholds between therapeutic and toxic dose are too small. In that context, stereotactic radiosurgery allows for higher doses to be more safely delivered, hence enabling more tumors that were previously considered radioresistant to be appropriately treated [59].

29.8 Cerebral Radiation Necrosis

Cerebral radiation is an indispensable cornerstone in the treatment of many primary and metastatic brain tumors. However, besides its desired therapeutic effect on tumor cells, a significant proportion of patients will experience neurotoxic side effects [60].

Radionecrosis that is cerebral necrosis due to radiotherapy can also manifest with signs of elevated ICP. It occurs between 6 months and 2 years in general, and it is thought to happen due to injuries to small and medium vessels, demyelination with the death of oligodendrocytes, and an allergic response from antigens by the glial cells that were damaged. It is diagnosed based on clinical and imaging data. However, conventional radiological methods can be misleading, and only surgery can assure the diagnosis. The management depends on the presence and intensity of symptoms. For symptomatic patients, dexamethasone is the medication of choice. It restores the blood-brain barrier and reduces the inflammatory response, hence reducing the edema and ICP [61].

BVZ and humanized monoclonal antibody against VEGF can also be used in patients with significant contrast-enhancing lesions. BVZ blocks the activity of VEGF, a key mediator of radionecrosis, thus inhibiting angiogenesis and counteracting the inflammatory response [62]. A pooled analysis of 71 patients showed 97% of radiological response and 79% of clinical improvement, associated with a median 6 mg decrease in dexamethasone. The same analysis shows a median decrease of 60% in FLAIR signal and contrast-enhancing volume. Unlike corticosteroids, BVZ improves edema after days to weeks. Therefore, it should not be used in the setting of imminent herniation or other emergencies [61–64].

29.9 Pituitary Apoplexy

Pituitary apoplexy is a rare condition that results from sudden expansion (hemorrhage or infarction) of intra-sellar contents, including the pituitary gland itself or other lesions such as adenomas and Rathke's cleft cysts. It occurs in 2 to 12% adenomas, specially nonfunctioning, which is more frequent in men and the fifth

decade. The classic symptoms are sudden severe headaches associated with visual field defects, ophthalmoparesis, or other cranial nerve deficits. Altered mental status is relatively frequent, occurring in 20% of the patients, and can be the result of subarachnoid hemorrhage, elevated ICP, obstructive hydrocephalus, hypothalamic compression, and arterial hypotension secondary to adrenal insufficiency. There are known precipitating factors such as anticoagulation therapy, recent surgery, pregnancy, and arterial hypertension, but in approximately 60% of the cases, no factor is identified [65].

MRI is the method of choice if pituitary apoplexy is suspected. It detects pituitary hemorrhage in 88% of times, against 21% in CT scans [65, 66].

Emergency management should include the evaluation of fluid and electrolyte balance, replacement of corticosteroids, and measures to maintain hemodynamic stability. Unstable patients or patients that have other signs of adrenal insufficiency should be given intravenous hydrocortisone as soon as possible. There is an ongoing debate over whether conservative versus surgical management is most appropriate. Due to the rarity of the disease, there are no randomized controlled trials, and the uncontrolled retrospective trials suggest that there is no difference in the endocrine and visual outcome between the two groups. There is a general agreement that patients with significant visual deficits or altered level of consciousness should be operated as soon as possible, although the threshold to consider the visual deficit important is not clear [65–67].

29.10 Conclusions

With the increase in the prevalence of cancer, neuro-oncological emergencies will be more and more frequent. Those could occur due to a direct result of the tumor itself, due to an indirect effect of cancer, or as a result of chemotherapy, RT, and other medical interventions. Management of these emergencies is a fundamental requirement for neurosurgeons and neurointensivists.

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Chapter 30
Hemorrhage into a Pituitary Tumor

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30.1 Introduction

The fully developed pituitary gland normally weighs approximately 0.6 g and resides within the sella turcica above sphenoid bone, close to the optic chiasm superiorly, that is located inside the suprasellar cistern, separated from the pituitary by a tough dural reflection, the diaphragm sellae [1]. Laterally there are the cavernous sinus in both sides that contains internal carotid artery and III, IV, VI cranial nerves besides the ophthalmic branch of V cranial nerve [2].

Pituitary tumors account for 10–20% of all intracranial neoplasms [3]. Magnetic resonance imaging (MRI) images and autopsy studies found the average frequency of pituitary adenomas varying from 11 to 20% [4–6]. Adenomas represent 90% of sellar and suprasellar lesions [4]. Pituitary adenomas develop from one of the five cell types of adenohypophysis [3]. Prolactinomas are the most common type of

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pituitary adenomas representing about 50% of all pituitary tumors, followed by nonfunctioning pituitary adenomas (28–37%) [5].

Pituitary tumors may cause endocrine dysfunction and/or mass effect on surrounding structures that can be related to a significant morbidity and mortality [2]. In some cases, an hemorrhage inside the tumor can occur after the diagnosis, but can also be the first presentation, sometimes resulting in a life-threatening condition [7].

30.2 Definition of Pituitary Apoplexy

Besides clinical findings related to hyperfunction/ hypofunction of pituitary hormones or mass effects, adenomas may also present with acute vascular events (hemorrhage and necrosis) that can contribute to increase morbidity and mortality of these tumors [5].

Pituitary apoplexy is a clinical syndrome of sudden onset of headache, visual disturbance, and altered mental status due to presence of sudden hemorrhage and/or infarction of pituitary gland [1]. As the primary event most often involves a preexisting adenoma, the syndrome should be referred, for some authors, to as pituitary tumor apoplexy, but infarction of an apparently normal gland may occur and has also been reported [8, 9].

Many conditions can present with ischemic necrosis or hemorrhage of pituitary gland including stroke, thrombocytopenia, hemorrhagic shock, and head trauma, but it is encountered most frequently in the setting of a pituitary adenoma [10].

30.3 Physiopathology and Precipitating Factors

Physiopathology of pituitary apoplexy is not completely understood, with some proposed mechanisms possibly being implicated. These include the fragility of tumoral blood vessels (that show incomplete maturation and poor fenestration), misbalance between the high energy requirement of pituitary adenomas and their relative low blood supply, and ischemia after compression of infundibular or superior hypophyseal vessels against sellar diaphragm by the adenoma [11].

Many precipitating factors have been proposed and are identified in 10–40% of cases [11]. Some of them were proposed in single case reports and, therefore, much uncertainty exists whether they are true precipitating factors [11–13]. Those with more data in literature are angiographic procedures, major surgeries (especially cardiac and orthopedic), head trauma, dynamic endocrine tests, and anticoagulation therapy [11]. Other possible predisposing factors with more conflicting data in literature are arterial hypertension, diabetes mellitus, intense physical activity, radiotherapy, and use of cabergoline [11, 12, 14–16].

30.4 Epidemiology

Pituitary apoplexy can be an endocrine emergency in which acute hemorrhagic infarction of a sellar tumor can lead to a partial or complete destruction of the pituitary gland [11]. Although pituitary apoplexy can be acute and present with neurologic signs that must be evaluated at emergency, it's a rare vascular event and affects only 0.2 to 0.6% of the general population [17]. Patients with pituitary tumor are prone to present this condition as it occurs in 2 to 12% of patients [11, 18, 19].

There is a slight overall preponderance in male to female (2.3 /1) in the reported cases in the literature [11]. Although patients of all ages have been described with pituitary apoplexy, it seems to be more prevalent in those older than 50 years of age [20].

30.5 Clinical Presentation

More than 90% of patients present with acute and sudden headache and nearly 45% describe it as a thunderclap headache (defined as a very severe headache of sudden onset that reaches its maximal intensity within a minute) probably due to dural traction or to extravasation of blood into the subarachnoid space, leading to meningeal irritation [21].

Visual disturbances are present in approximately 70% of patients in the acute setting of pituitary apoplexy and are probably due to sudden hemorrhage leading to mass effect and compression of surrounding structures [22–24]. Variable degrees of visual impairment can be observed and bitemporal hemianopsia is the most common. The upward expansion of the tumor is the main mechanism and more rarely may cause loss of visual acuity or blindness [22].

A series of studies observed the presence of oculomotor palsies in nearly 50% of cases, mainly due to functional impairment of III, IV, and VI cranial nerves [11]. The III cranial nerve is the most commonly affected in patients with cranial nerve palsies (approximately 50% of cases). This can be due to intracavernous sinus expansion of the tumor mass or to an abrupt pressure increase in pituitary region [22, 25]. Patients present with ptosis, ocular paresis, and/or diplopia [26].

In the presence of large tumors, hemorrhage leads to compression of third ventricle and intracranial hypertension, characterizing a medical emergency that requires rapid treatment [27].

Hypopituitarism may be the result of mass effect and/or destruction of anterior pituitary or compression of pituitary stalk [28]. Some degree of hypopituitarism is present in the majority of patients in the acute phase of pituitary hemorrhage. A compilation of studies observed that it could be present in 13 to 89% of patients after pituitary apoplexy [11]. The most clinically significant deficit is related to corticotroph axis that can lead to acute glucocorticoid insufficiency [22]. Available

published endocrine data show adrenocorticotropic deficiency in 40% to 100% of cases, thyroid-stimulating hormone (TSH) deficiency in 25% to 80%, and gonadotrophic deficiency in 60% to 100% [8]. Hyponatremia can be present and in most cases is related to the syndrome of inappropriate antidiuretic hormone (SIADH) that is most frequently due to glucocorticoid deficiency and hypothyroidism, but hypernatremia due to diabetes insipidus can also be observed [8, 22, 29, 30].

In about 10% of cases, the onset of symptoms is less prominent. Some degree of visual impairment can be present, but is only detected on medical examination and partial hypopituitarism can be discovered on a laboratory investigation. These patients may have subacute signs of hemorrhage found on MRI [11, 27].

30.6 Radiological Findings

Magnetic resonance imaging is the most important radiologic tool to study pituitary apoplexy, with sensitivity ranging from 80 to 90% [31, 32]. Computed tomography (CT) can be used in the absence of available MRI, but is less sensitive in diagnosing apoplexy [11].

Typical MRI description in literature includes a mass in the pituitary region in more than 90% of cases [33]. Hyperintense signal on T1 weighted image (T1WI) is the most frequent feature in pituitary hemorrhage (Fig. 30.1), but this image can only appear more than 7 days after the acute event and other conditions may present the same characteristics, for example, aneurysms and dermoid cysts, that have to be considered in each case [34].

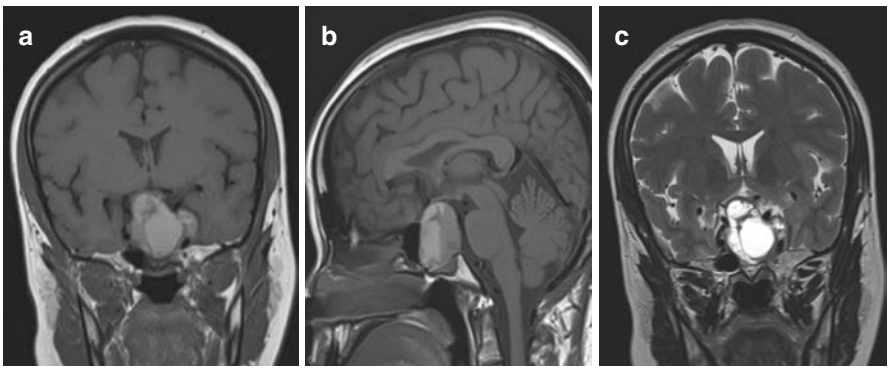

Fig. 30.1 Pre-contrast enhancement coronal (**a**) and sagittal (**b**) T1-weighted magnetic resonance image (T1WI) and T2-weighted magnetic resonance image sequences. (**a**): Sellar, infra and suprasellar lesion with areas of spontaneous hyperintense signal in T1WI. (**b**): Evidence of fluid and debris with hyperintense signal in upper layer and hypointense signal in lower layer. (**c**): Heterogeneous lesion with predominant areas of hyperintense signal and others of hypointense signal. These images were performed in a patient with classical sign and symptoms of pituitary apoplexy 20 days after pituitary apoplexy

Table 30.1 Stages of pituitary apoplexy as seen at magnetic resonance image

Stage	Time since apoplexy	Hemoglobin	T1WI	T2WI
Acute	≤7 days	Deoxyhemoglobin	Hypointense or Slightly Hyperintense	Very Hypointense
Subacute	>7 days to ≤21 days	Methemoglobin	Hyperintense	Hyperintense
Chronic	>21 days	Hemosiderin	Hypointense	Hypointense

T1WI T1-weighted imaging, *T2WI* T2-weighted imaging

Imaging evolution of pituitary apoplexy on MRI is classically described in literature in three phases: acute (up to 7 days), subacute (7–21 days), and chronic (>21 days). Table 30.1 describes the most accepted description of imaging evolution at MRI after pituitary apoplexy.

The acute phase is characterized by an hypointense or slightly hyperintense image in T1WI and hypointense signal in T2WI. MRI cannot detect fresh blood and is not the better exam in the first approach at emergency room [11, 34]. There are two other images highly related to pituitary apoplexy in acute phase. One is the sphenoid sinus mucosal thickening that can appear even before the vascular event, suggesting an engorgement caused by large adenomas or large collections of blood [35, 36]. Pituitary ring sign is the other image and represents the pituitary gland with peripheral gadolinium enhancement surrounding a hypointense gland [36].

In subacute phase, a hyperintense signal on T1WI and T2WI due to presence of methemoglobin is observed [34]. Also, presence of fluid debris in T1WI with hyperintense signal in upper fluid, due to free extracellular methemoglobin, and hypointense signal in lower layer, representing the blood residue, can also be observed and is very suggestive of a pituitary apoplexy that occurred at least 1 week before [24, 34].

After 21 days (chronic phase), both T1WI and T2WI usually show a pituitary mass with hypointense signal.

In addition to the classic proposed evolution of image in T1WI and T2WI, other sequences support the differential diagnosis. Pituitary apoplexy usually presents restricted diffusion due to the presence of accumulated blood products, and this sequence can help in differential diagnosis at acute phase [34]. T2-star weighted gradient-eco (T2*W) MRI is the most sensitive technique to identify hemorrhage in neuroimaging and can be useful in the differential diagnosis when analyzed together with those previously described radiological patterns [34, 37].

30.7 Differential Diagnosis

Pituitary apoplexy is an acute event and differential diagnoses include diseases that present with acute neuroophtalmological deficits and headache. The main differential diagnosis is subarachnoid hemorrhage [11]. Clinically, patients can present

symptoms that can also mimic migraine or meningitis like intense retroorbital headache, associated with nauseas and vomiting [14, 22, 38]. Other neurological diseases, like cavernous sinus thrombosis and midbrain infarction, can also present similar symptoms and need to be considered in differential diagnosis [11].

Cerebrospinal fluid can present high red cell blood count, increased protein level and pleocytosis in patients with pituitary apoplexy, especially if meningeal irritation is present and, therefore, lumbar puncture is not helpful in differential diagnosis [11].

Differential diagnosis relies on combination of clinical picture and imaging study (MRI or CT) showing a pituitary adenoma with, in the majority of cases, the classical findings previously described [11].

30.8 Treatment

Treatment of a pituitary apoplexy episode can be surgical or conservative depending on the clinical picture. Pituitary apoplexy may present as a medical emergency, and in these cases emergency surgery is mandatory [39]. In addition, surgery is generally performed in the presence of progressive or severe and nonimproving neuroophtalmological symptoms, like visual loss or intractable headache [15, 27, 39]. However, in the majority of cases, patients present with stable neuroophtalmological symptoms, however stable. Therefore, conservative treatment can also be tried [27].

Conservative treatment consists in the administration of glucocorticoid to those patients with adrenal insufficiency (hydrocortisone 50 mg intravenous every 8 hours in the acute setting with progressive reduction to physiological replacement doses), analgesia and observation of case evolution, without surgical intervention [27, 39]. Different centers adopt different management protocols, as there is still controversy in literature if endocrinological and visual outcomes are different with conservative vs surgical management [40, 41]. The option for conservative management relies on the fact that many tumors are completed infarcted and will resorb resulting in decompression of surrounding structures without a need for intervention [27].

Two recent meta-analysis were published in 2016 and 2019 including studies that compared surgical and conservative management of patients presenting with pituitary apoplexy [40, 41].

The first meta-analysis included six studies with 210 patients and showed that there was a higher rate of recovery of ocular palsy and visual field with surgical treatment in comparison with conservative management, but there was no difference in the recovery of visual acuity and pituitary function [40]. However, the most recent meta-analysis included 14 studies comprising 457 cases (259 surgical treatments and 198 conservative treatments) and did not observe differences in outcomes of endocrine dysfunction, visual field defect, ophthalmoplegia, or ocular nerve palsy [41]. None of the studies included in these meta-analyses were randomized controlled trials and, therefore, it is not possible to exclude a selection bias, with patients presenting more severe episodes of apoplexy being treated with surgery.

Another controversy in the literature is if there is difference in surgical outcome if surgery is performed early (up to 7 days) after the pituitary apoplexy episode or if it is performed in a latter phase [42]. A recent meta-analysis including 12 studies analyzed the visual outcome after early and late surgical treatment. Surgery was performed before 7 days from the episode of apoplexy in 93 patients and after 7 days in 79 patients. Visual recovery was observed in 97.8% of the patients in the early surgery group and in 84.8% of the patients in the late group ($p = 0.07$).

Considering the controversy in literature, the majority of centers consider conservative management in patients with no visual deficit or with stable visual impairment, with patients presenting progressive or clinically intractable neurological symptoms being treated surgically [27]. The UK guidelines recommend using a score that considers visual acuity, visual defects, cranial nerve palsies and the Glasgow coma scale and ranges from 0 to 10 [39]. In this score, surgical treatment is indicated for scores ≥ 4 [39].

Independent of the approach (surgical vs conservative), it is important to immediately access the hypothalamic-pituitary-adrenal axis function, as adrenal insufficiency can be a life-threatening condition [27, 39]. Glucocorticoid should be replaced for all patients, except for those who are stable and who have documented serum cortisol levels above 18 mg/dL at admission [39]. Hydrocortisone is the steroid of choice due to it similarity with endogenous cortisol. Central hypothyroidism may also be present and should also be replaced, but levothyroxine should not be prescribed before an adequate glucocorticoid replacement due to the risk of precipitating an adrenal crisis [39].

30.9 Conclusions

Pituitary apoplexy can occur in up to 12% of pituitary adenomas, being sometimes an emergency medical condition that requires rapid treatment. However, it can also have a milder presentation and in these cases medical management should rely mainly on the severity and persistence of neuroophtalmological symptoms.

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Chapter 31
Status Epilepticus

Christiane Cobas and Eliana Garzon

31.1 Introduction

An epileptic seizure represents an isolated and self-limited episode, usually of short duration, characterized by synchronous and abnormal depolarization of a given group of cortical neurons. Occasionally, central inhibitory mechanisms fail to abort this phenomenon, or excitatory mechanisms are triggered, leading to abnormal prolonged seizures. This condition can cause neuronal injury, neuronal death, and long-term consequences. In the early sixties, status epilepticus (SE) was defined as an epileptic seizure which, due to its prolonged duration or frequent recurrence, generates a neurological damage [1]. Later, the International League Against Epilepsy (ILAE) Task Force for the classification of SE developed a revised definition of SE, but did not establish a seizure length for a definitive diagnosis of SE [2, 3]. Thus, several definitions can be found in the literature and an operational definition was adopted. For most investigators, SE is a single epileptic seizure or several recurrent seizures without recovery of consciousness, lasting at least 30 minutes [4, 5].

The length of an epileptic seizure considered SE was a topic of discussion in the literature [4]. Epileptic seizures with a minimum duration of 30 minutes were compared with seizures lasting between 10 and 29 minutes [5]. Although both groups of patients demonstrated similar epidemiological characteristics, 93% of seizures lasting 30 minutes or more required administration of antiepileptic drugs to cease them. In the group of patients with seizures lasting 10 to 29 minutes, the seizures ceased spontaneously in 43% of the patients. Mortality was also significantly different

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between the two groups, being 19% for the group with crises during at least 30 minutes, and 2.6% for the group with crises during 10 to 29 minutes. These data demonstrated that the 30-minute length seems to be ideal to define SE, although there is no rationale for waiting 30 minutes to start a specific therapy in the clinical practice. Treatment should start as soon as possible in the pre-SE phase, in order to avoid the evolution to established and refractory SE. However, from the point of view of classification, prognosis, and evolution, it should be considered that seizures lasting up to 29 minutes differ from those with minimal duration of 30 minutes [5].

In 2015, the task force came out with the following definition [6]: "Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" [6] This new definition of SE gives a good guidance on when to consider an emergency treatment. In general, t1 is the time point when treatment should be started, which is at 5 minutes for generalized tonic–clonic seizures, and at 10 minutes for focal seizures with or without impairment of consciousness. On the other hand, t2 marks the time point at which neuronal damage or self-perpetuating alteration of neuronal networks may begin, indicating that SE should be later controlled by that time (30 minutes in case of generalized tonic clonic seizures).

Operational definitions have been established to conduct the treatment appropriately, in each phase.

31.2 SE Classification

In 1962, during the "X European Conference of Epileptology and Clinical Neurophysiology", SE was first subdivided into subtypes convulsive and nonconvulsive [1].

More recently, there have been several proposals in the literature for new classifications encompassing all types of SE and, at the same time, incorporating information on semiology, anatomy, and etiology [7, 8], or even more specific classifications, as SE clinical presentation (focal or generalized onset, and either convulsive or nonconvulsive presentation) [9]. Although interesting, these classifications are complex and often ineffective for clinical purpose. Treiman et al. [10] introduced the term "subtle generalized convulsive" SE to identify patients who remain unresponsive after the apparent interruption of generalized epileptic crises. These patients are usually stuporous or comatose, showing subtle clinical manifestations such as minimal eyelid, facial or mouth movements, nystagmus, tremor or focal clonic movements of the trunk or limbs, or even total absence of movement.

In 2015, ILAE proposed a new classification considering semiology, etiology, electroencephalography (EEG) correlates, and age [6]. From the clinical perspective, the presence or absence of prominent motor symptoms and the degree

(qualitative or quantitative) of impairment of consciousness are used, which may be summarized as the initial classifications in convulsive SE (with motor signs) and nonconvulsive SE (NCSE) (without evident motor signs). Table 31.1 shows in detail the semiology-based classification.

Based on etiology (underlying cause), SE can be classified into SE with *known* or *symptomatic causes* (structural, metabolic, inflammatory, infectious, toxic, or genetic); *SE in defined electroclinical syndromes;* and *unknown SE.* The *known* group can be further subdivided according to its temporal relationship, into *acute* (e.g., stroke, intoxication, and encephalitis), *remote* (e.g., posttraumatic, postencephalitic, and poststroke), and *progressive* (e.g., brain tumor, Lafora's disease and other progressive myoclonic epilepsies, dementias) [6].

The EEG is very useful in SE and, although there is no specific pattern, its findings are crucial in the diagnosis of NCSE. It is recommended to describe the EEG

Table 31.1 Classification of status epilepticus (SE) based on semiology

With prominent motor symptoms
Convulsive SE (CSE or tonic–clonic SE)
Generalized convulsive
Focal onset evolving into bilateral convulsive SE
Unknown whether focal or generalized
Myoclonic SE (prominent epileptic myoclonic jerks)
With coma
Without coma
Focal motor
Repeated focal motor seizures (Jacksonian)
Epilepsia partialis continua (EPC)
Adversive status
Oculoclonic status
Ictal paresis (i.e., focal inhibitory SE)
Tonic status
Hyperkinetic SE
*Without prominent motor symptoms (*i.e.*, nonconvulsive SE, NCSE)*
NCSE with coma (including so-called "subtle" SE)
NCSE without coma
Generalized
Typical absence status
Atypical absence status
Myoclonic absence status
Focal
Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/ psychic/experiential, or auditory symptoms)
Aphasic status
With impaired consciousness
Unknown whether focal or generalized
Autonomic SE

findings according to the *location* of critical activity (generalized, lateralized, bilateral independent, multifocal), *pattern* (periodic discharges, rhythmic delta activity, or spike-and-wave/sharp-and-wave plus subtypes), *morphology* (sharpness, number of phases [e.g., triphasic morphology], absolute and relative amplitude, polarity), *time-related features* (prevalence, frequency, duration, daily pattern duration and index, onset, and dynamics) *modulation* (stimulus-induced or spontaneous), and *effect of the intervention* on EEG (e.g., medication) [6].

It is also recommended to classify SE according the age groups, in *neonatal SE* (0 to 30 days), SE of *infancy* (1 month to 2 years), SE of *childhood* (>2 to 12 years), SE of *adolescence* and *adulthood* (>12 to 59 years), and SE of *elderly* (≥60 years) [6].

The development of more detailed and specific systems to classify SE has been encouraged, since there is no classification system encompassing clinical and research needs so far.

31.3 Incidence and Mortality

It is very difficult to obtain accurate data on SE incidence grounded in community-based studies. The first population study on SE conducted in the USA [11] estimated an incidence of about 50 episodes of SE per 100,000 individuals per year. The cases of SE showed a bimodal distribution, with one peak occurring in the first year of life and another after 60 years of age [11]. This finding is in contrast to previous studies that identified only one peak in childhood [12].

The projection of the incidence of SE reported by DeLorenzo and collaborators in Richmond, Virginia [11], for the Brazilian population suggests the occurrence of approximately 100,000 cases of SE per year, which is much more frequent than usually assumed.

The highly variable mortality rate associated with SE can reach up to 58%, depending on the etiology, mostly in SE secondary to acute factors such as stroke, CNS infection, and metabolic disorders [13]. It is very dependent on the etiology and the age group of the patients [13]. The mortality exclusively related to prolonged epileptic seizure is fortunately much lower (between 1 and 2%) [11].

31.4 Pathophysiology

The systemic effects of convulsive SE can be divided into two stages: Stage I or Compensated Phase (0–30 minutes) and Stage II or Decompensated Phase (30–90 minutes).

In Stage I, the brain autoregulation and homeostasis are still preserved. The brain area in which the crisis originates requires a greater supply of glucose and oxygen, in addition to an adequate blood flow, to remove water and carbon dioxide. The

prolonged epileptic seizure causes a massive release of catecholamines and increases blood glucose, heart rate, and blood pressure, initially keeping cerebral perfusion at adequate levels and providing the muscles with the necessary substrates for exhaustive contraction. The increase in muscle activity produces large amounts of heat, as well as hyperthermia above 40 °C. The presence of hyperthermia may cause brain damage and worsen the prognosis [14, 15].

In Stage II, the mechanism of autoregulation of the cerebral blood flow is compromised, becoming dependent on blood pressure. The lactic acidosis leads to lack of responsiveness of peripheral vessels to circulating catecholamines and this effect, added to the drop in the levels of catecholamines, causes progressive hypotension, compromising the cerebral blood flow and further reducing the supply of glucose and oxygen. Hypoglycemia also occurs due to the exhaustion of glycogen stocks and the increased secretion of neurogenic insulin.

Experimental studies on pathophysiology also show that: (1) hippocampal activity is activated during SE; (2) loss of GABA-mediated inhibitory synaptic in the hippocampus is fundamental to establish the SE, and finally, (3) glutamatergic synaptic transmission maintains SE and causes cell death [15, 16].

The hippocampal CA1 and CA3 pyramidal neurons and the dentate hilus are highly and selectively vulnerable to SE neuronal injury, while other regions, such as neurons in the CA2 region and the granular cells of the dentate gyrus, are more resistant. Other cortical regions are affected in varying degrees, and the neuronal injury is similar to that observed in severe hypoxia and ischemia.

Epileptogenesis alone leads to neuronal hyperexcitability, and the excitotoxicity is mediated by glutamate and aspartate. The epileptic activity produces abnormalities in the neuronal membrane and failure of the calcium pump, leading to calcium influx into the cell; this, in addition to acidosis and the action of excitatory amino acids, can lead to cell death. In summary, diverse mechanism of action of several factors would lead to the common final pathway of cell death and brain inflamation[14,15.16].

31.5 Clinical Manifestations and Physical Examination

The clinical diagnosis of convulsive SE is straightforward. Patients present “episodes of excessive abnormal muscle contractions, usually bilateral, which may be sustained or uninterrupted” and last 5 minutes or more; alternatively, they can have recurrent seizures without complete recovery of consciousness between the events, lasting at least 30 minutes [17]. On the other hand, the diagnosis of both focal and generalized nonconvulsive status epilepticus requires identification of the impairment of consciousness associated with the finding of an ictal electrographic pattern.

Operational definition is important for classifying SE in stages based on seizure duration and to guide treatment.

Considering seizure duration, SE can be divided into four stages:

- *Stage I*—Pre-SE or imminent SE—epileptic seizures lasting more than 10 minutes and less than 30 minutes
- *Stage II*—Established SE—epileptic seizures lasting 30 minutes or more and less than 60 minutes
- *Stage III*—Refractory SE—epileptic seizures lasting longer than 60 minutes
- *Stage IV*—Super-refractory SE—epileptic seizures lasting more than 24 hours, despite the use of anesthetic drugs

Clinical signs depend on the semiology of the crisis, as well as of the SE stage. In convulsive SE, the tonic phase is usually followed by clonic movements, with massive sympathetic outpouring such as pupillary dilatation, tachycardia, hypertension, and hyperglycemia. Consciousness is impaired at the beginning and should be recovered as soon as the SE ends. Sometimes, convulsive SE evolves to an ongoing nonconvulsive seizure activity, that is referred to as subtle status epilepticus. Common manifestations include nystagmus, blinking, eye deviation, speech arrest, and stereotyped automatisms.

In nonconvulsive SE, the clinical manifestations are variable. In stage I, if the seizure does not compromise the consciousness, patients can be completely oriented and report their medical history, while patients in stage IV are in drug-induced coma.

Other clinical and neurological signs will depend on the etiology of SE. The neurological examination of a patient with a focal lesion may reveal focal signs, depending on the location of the lesion. Nuchal stiffness, fever, and mental confusion are data that can be found in patients with infection of the central nervous system (CNS).

31.6 Neuroimaging/ Electroencephalogram

Imaging exams such as noncontrast computer tomography (CT) scans of the head are useful to identify structural lesions in patients suspected of having hemorrhage or ischemic stroke, malformation, calcified lesions, tumor, or traumatic brain injury. The magnetic resonance imaging (MRI) of the brain has a higher sensitivity for identification of structural abnormalities such as cortical development malformation, heterotopia, small lesions not identified by CT scan, or even hippocampal sclerosis.

EEG is essential for the differential diagnosis and the clinical follow-up, especially in refractory SE, when its findings influence the choice and the aggressiveness of the treatment, as well as dictate the prognosis. In patients under treatment with benzodiazepines, barbiturates, general anesthetics, or similar drugs, it is practically impossible to determine, based only on clinical data, the persistence, or resolution of SE [18, 19]. Therefore, in this very critical condition, it is recommended to

monitor patients with EEG recordings as early as possible. This very easy and simple technology will help to properly handle these patients.

EEG can also be useful in differentiating focal SE with disperceptive seizures and generalized nonconvulsive SE, as well as to help diagnose "subtle" tonic seizures with axial movements only (ocular deviation or mild cervical tonic contraction) [6]. We also recommend that all patients suspected of having refractory SE should be submitted at least to a single EEG recording, in order to rule out another possible and often misdiagnosed condition, like psychogenic nonepileptic seizures or nonepileptic events [20].

Other important exams to identify the etiology of SE are glycemia, urea, creatinine, electrolyte imbalances (sodium, potassium, calcium, phosphorus, magnesium), arterial gasometry, complete blood count, aspartate and alanine aminotransferase, gamma-GT, alkaline phosphatase, coagulation tests, antiepileptic drug levels (in patients with known epilepsy, if taking any), blood and urine screening with tests (culture and antibiogram), and toxicological analysis. In specific cases, consider obtaining a virus screening panel, blood culture, antiperoxidase, antithyroglobulin, and screening for inborn errors of metabolism.

For suspected central nervous system (CNS) infection, a lumbar puncture is recommended for cerebrospinal fluid (CSF) sampling, besides pressure measurement. The analysis of CSF should include cell count, glucose, protein, lactate, Gram stain, microbiologic serologies, bacterial and fungal cultures plus polymerase chain reaction (PCR) for enterovirus and herpes simplex virus types 1 and 2. Consider evaluating protein electrophoresis, CSF-exclusive oligoclonal bands, additional viral PCR, and autoantibodies for diagnosis of autoimmune encephalitis.

31.7 Differential Diagnosis

Any neurological disease with alteration of consciousness or torpor, such as toxic or metabolic encephalopathies, infections of the central nervous system, and stroke, may be distinguishable from nonconvulsive SE. In a patient with impaired consciousness, certain EEG patterns suggest metabolic, toxic, or infectious encephalopathy; drug intoxication; or focal brain injury (Figs. 31.1 and 31.2).

Among various epileptic or nonepileptic paroxysmal disorders that mimic SE, the psychogenic crises are probably the most frequent. Nonepileptic psychogenic seizures (NEPS) are a diagnostic finding often misdiagnosed and treated as epileptic seizures. The clinical manifestations can be very similar to the epileptic seizures and, therefore, have a variable semiology, with prolonged duration or recurrence within short intervals. It is estimated that about 20% of patients referred to epilepsy centers have psychogenic seizures [20]. However, it should not be forgotten that an epileptic patient may also have psychogenic seizures [20].

EEG recording during NEPS seizure is normal, with movement artifacts, but without any epileptiform discharges.

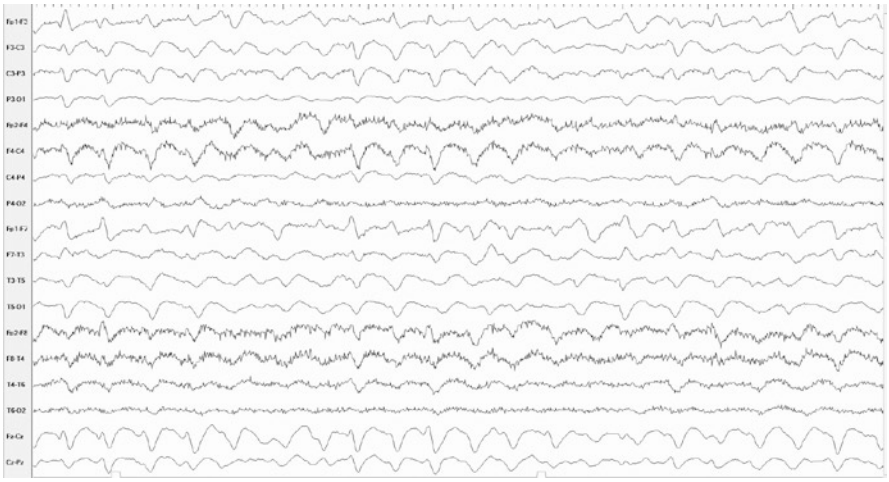

Fig. 31.1 Male, 49 yrs. Stupor and liver failure. EEG showing generalized triphasic waves, which suggests that the stupor condition is metabolic

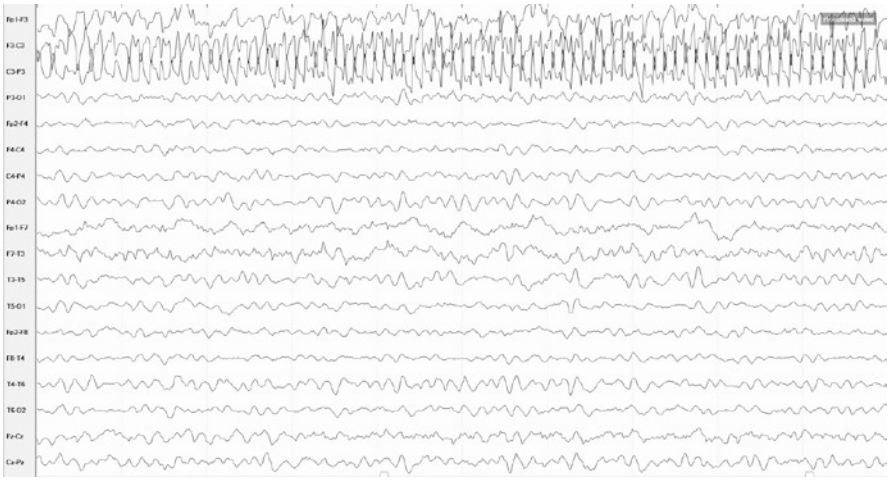

Fig. 31.2 Female, 52 yrs. Brain trauma with subdural hematoma on the left (frontal region). Patient is comatose and occasionally showing subtle jerks on her face, at right side. EEG shows continuous discharges in the central left region, suggesting SE with a pattern of continuous discharges

31.8 Treatment

All treatment protocols include a staged approach to treatment, with different drugs used in early (stage I), established (stage II), refractory (stage III), and super refractory SE (stage IV) (Fig. 31.1), and also emphasize the prompt recognition and treatment of persisting seizure activity at each stage, aiming to reduce morbidity,

mortality, and long-term consequences of the status epilepticus (beyond t2). The most recent reviews focus on the pharmacotherapy of the status, but the general measures for neurological emergencies, as well as a thorough search for the causes, are equally important [21, 22].

Status epilepticus is a medical emergency with the potential for significant morbidity and mortality. It requires immediate treatment and an individualized management plan, based on the specific patient needs, combined with antiseizure drugs [21, 22].

31.9 Initial Care

The initial treatment strategy for SE includes simultaneous assessment and management of ABCs (airway, breathing, and circulation), identification and correction of life-threatening causes, and initiation of seizure abortive drug treatment. In near half of the cases, there is an acute etiology that is potentially treatable [21, 22].

A supportive treatment should be provided, and the patients should remain in bed with bars or lateral protection to avoid falls or head trauma. During the clonic phase, a Guedel's cannula should be inserted between the teeth, preventing bites and lacerations of the tongue. They must be constantly aspirated to avoid aspiration and pneumonia. The vital signs and the temperature should be frequently monitored. The airways must be kept clear to ensure proper ventilation. Whenever necessary, orotracheal intubation and oxygenation should be performed to prevent hypoxia.

31.10 Antiseizure Drugs

A staged approach using operational definitions for diagnosis has been advocated. Consider initiating most appropriate therapy for each stage [21, 22] (Fig. 31.3).

31.10.1 Stage I or Pre-SE (Epileptic Seizures Lasting >10 min and < 30 min)

Intravenous diazepam (0.2 to 0.3 mg/kg). It can be repeated if the seizures persist (up to two doses, with a 5 to 10 minutes interval between doses). Maximum infusion rate: 1 mg/kg/min (risk of respiratory depression).

Diazepam can be replaced by *intravenous Midazolam (0.2 to 0.3 mg/kg).* Maximum infusion rate: 4 mg/min.

If seizures are continuous for 20 minutes, first-line antiseizure drugs can be started.

Alternatives for a difficult venous access:

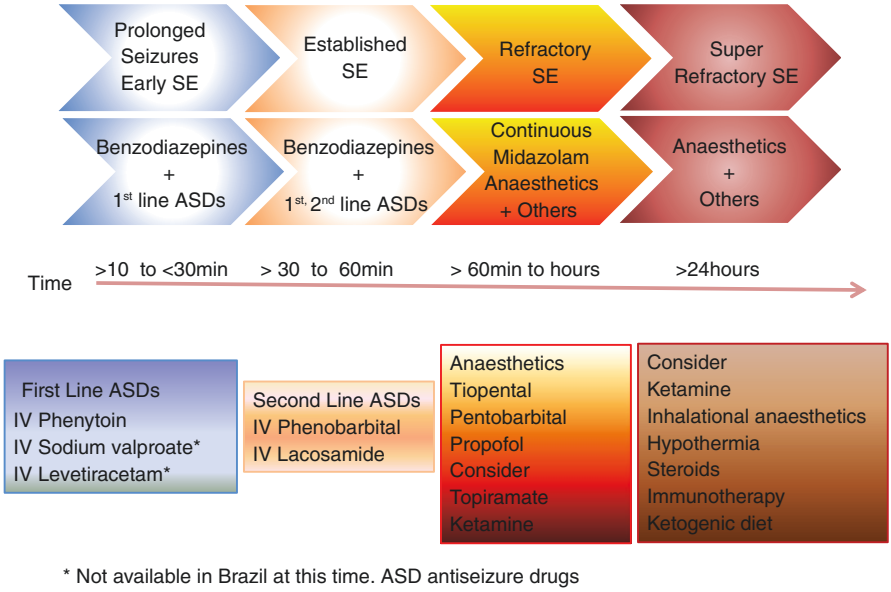

Fig. 31.3 Status epilepticus. Guidelines for treatment

Intranasal, buccal, or intramuscular midazolam (0.2 to 0.5 mg/kg). You can use the intravenous solution.
Rectal diazepam (0.5 to 0.75 mg/kg).

31.10.2 Stage II or Established SE (Epileptic Seizures Lasting >30 min and < 60 min)

If a benzodiazepine has not been administered yet, it should be done at least once, while preparing phenytoin.

Intravenous phenytoin (bolus of 18 to 20 mg/kg) (from 10 to 20 mg/Kg). Infusion rate: 1 mg/kg/min; maximum 50 mg/min). An additional 10 mg/kg can be given if crises persist, 20 minutes after the initial dose. Dilute it with saline solution or distilled water, and use equipment with filter, because it precipitates.

Alternatives to phenytoin:

Phenobarbital (10 to 20 mg/Kg). Especially in young children. For neonatal SE or febrile SE, phenobarbital should be the first option.
Lacosamide (7 to 10 mg/kg). Consider using *intravenous pyridoxine (100 mg)* in infants up to 18 months of age.
Intravenous levetiracetam and valproic acid are good options but they are not available in Brazil.

31.10.3 Stage III or Refractory SE (Epileptic Seizures Lasting Longer than 60 Minutes)

Start coma-inducing drugs. The patient should be at the intensive care unit (ICU), intubated and mechanically ventilated, on complete hemodynamic support, and under continuous EEG (cEEG).

First option
Intravenous Midazolam (bolus of 0,2 mg/kg). It can be repeated every 5 to 10 minutes, up to 2 mg/kg (total), and the infusion is started at 0.05 to 0.4 mg/kg/h.

Second option
Intravenous pentobarbital 5 mg/kg. The loading dose can be repeated to burst the suppression effect (suppression interval of 20–30 s); start infusion at 0.5 mg/kg/h and titrate up to 3 to 5 mg/kg/h.

For both drugs, if there is a need to increase the dose, it is preferable to give an additional bolus rather than increasing infusion rate.

Third option
Intravenous propofol (bolus of3–5 mg/kg). The loading dose is followed by infusion at 5–10 mg/kg/h.

Coma-inducing drugs should be titrated until cessation of seizures (both clinical and electrographic) or a certain degree of suppression of cerebral activity, as assessed on cEEG. The drug-induced coma should be continued for at least 24–48 hours after the seizures have ceased. Gradually tapper coma-inducing drugs, and keep the patient on one or two antiseizure drugs, intravenously, at therapeutic levels.

31.10.4 Stage IV or Super Refractory SE—Epileptic Seizures Lasting More Than 24 Hours Despite the Use of Anesthetic Drugs

It is necessary to continue investigating the underlying etiology, seeking for unusual causes of SE, and, if possible, target the treatment to a specific etiology.

Maintain two (no more than three) antiseizure drugs at therapeutic levels, avoiding frequent changes [23].

Options: phenytoin, phenobarbital, levetiracetam, sodium valproate, topiramate, lacosamide.

Phenobarbital (you can choose to maintain high dose phenobarbital-induced coma).

Ketamine. Give a loading dose (0.5 to0,45 mg/kg), followed by continuous infusion up to 5 mg/kg/h.

Alternative therapies can be used in refractory and super refractory SE, when SE have not stopped despite adequate treatment at therapeutic levels with lidocaine (bolus of 1 to 2 mg/kg as loading dose, followed by a maintenance dose of 1.5 to 3.5 mg/kg/h in adults, or 6 mg/kg/h in children), halothane, and isoflurane anesthetics (requires the presence of an anesthesiologist, and an inhalation is often impracticable due to the duration of SE (hours or days). In children, consider using pyridoxine, pyridoxal-5-phosphate, folinic acid, and biotin.

In specific and very refractory cases, a neurosurgical resection of epileptogenic focus, ketogenic diet, vagus nerve stimulator, immunomodulation (immunoglobulin, methylprednisolone, plasmapheresis), hypothermia, repetitive transcranial magnetic stimulation, and electroconvulsive therapy can be used.

31.11 Complications

The main systemic complications are apnea, hypotension, hypoxia, hyperkalemia, pulmonary hypertension, and rhabdomyolysis [24].

Rhabdomyolysis causes intense release of proteins such as myoglobin, and may lead to acute tubular necrosis. Leukocytosis is a common finding, even in the absence of infection. Also, a mild CSF pleocytosis may occur. Autonomic symptoms such as vomiting, loss of fluids and electrolytes, fecal incontinence, urinary incontinence, increased salivation, sweating, and increased tracheobronchial secretion may be part of the clinical manifestations. An aspiration pneumonia is a common complication.

The metabolic acidosis can be severe and should be immediately corrected with sodium bicarbonate, but it must always be kept in mind that administration of sodium bicarbonate represents an additional load of sodium that may eventually worsen cerebral and pulmonary edemas. Hypotension can further aggravate the clinical situation and should be corrected with vasopressor drugs, if necessary. Antiarrhythmic drugs may be needed, and it is recommended to monitor the ECG for 24 hours after SE has been controlled. The hyperthermia eventually associated with convulsive SE can also be an aggravating factor (it may contribute to increase the brain injury) and should be treated with antipyretics and hypothermia, whenever necessary. The hypoglycemia that may appear at a later stage of SE should be approached very carefully, and should only be routinely corrected when very intense. There is evidence that the hyperglycemia at late-stage SE may lead to a higher degree of brain injury, and that a mild hypoglycemia would even function as a neuroprotective mechanism. Airway clearance should be provided and an adequate ventilatory support ensured. In case of aspiration pneumonia, broad-spectrum antibiotics should be prescribed. Several factors may compromise renal function including myoglobinuria, hypoxia, and hypotension. In the early stages of renal failure, dopamine and mannitol may be useful. Electrolytes and renal function should be continuously monitored. Cerebral edema may occur secondarily to structural damage or simply due to the presence

of prolonged seizures. There are no clinical evidences of the efficacy of steroids or mannitol in SE, but the administration of mannitol or methylprednisolone for 24 hours could be considered in those cases with imaging studies showing significant brain edema.

31.12 Pearls/Tip

Status epilepticus has heterogeneous clinical presentations, and the nonconvulsive SE especially represents a diagnosis challenge. EEG is essential for diagnosis in such cases. Patients with intellectual deficiency, psychiatric diseases, and especially those with critical illness in the ICU are potential candidates for diagnostic delays due to their underlying conditions. All emergency rooms and ICU should a have a written protocol for rapid diagnosis of SE, correction of the underlying etiology, treatment, and attention to potential complications.

Despite the efforts of specialists and epileptology researchers to precisely define and classify SE, additional work is still needed to delineate an optimal management, as well as to improve outcomes.

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Chapter 32
Systemic (Non-neurological) Complications in the Neurocritical Patient

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32.1 Introduction

Non-neurological complications in neurocritical patients are common. It is paramount to establish its etiology since those complications can result from either the neurological injury itself, its systemic effects, or as a consequence of the ongoing therapy. Understanding the impact and development of organ dysfunction starts by

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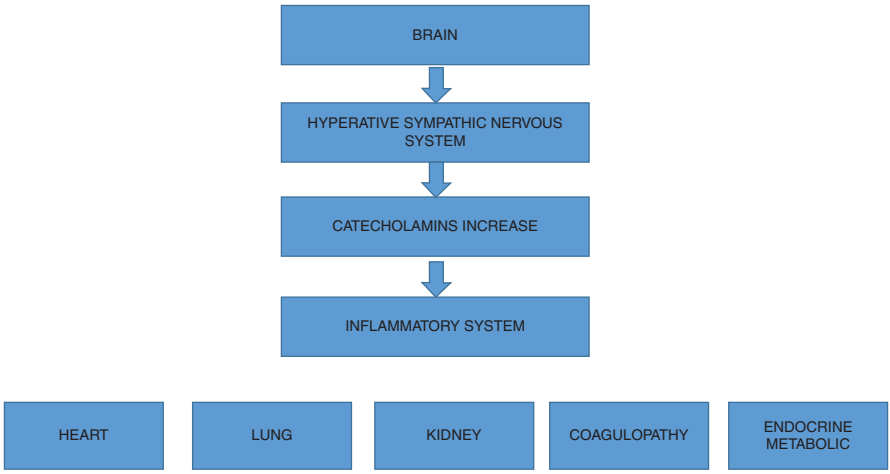

Fig. 32.1 Pathophysiology resume in interrelation with brain injury and rest of systems as they are compromised for example brain injury, sympathetic release inflammation. We have overload of left ventricule that leads to low cardiac output, renal injury aggravated by arterial hypotension, and clotting disorders that aggravate excessive bleeding

comprehending both the pathophysiological process and clinical aspects of those conditions. The management of non-neurological complications involves multidisciplinary teams, including neurosurgery, neurology, cardiology, intensive care, nursing, physiotherapy, and nutrition (Fig. 32.1).

The non-neurological complications include organ dysfunction in patients diagnosed with subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), ischemic stroke, hemorrhagic stroke, and seizures. Cardiovascular complications include atrial and ventricular cardiac arrhythmias, QT interval prolongation, ST-segment depression, presence of U wave, and left ventricular dysfunction.

32.2 Cardiovascular Complications

Experimental models show that SAH can cause electrocardiographic changes by stimulating structures such as the hypothalamus, anterior hippocampus, medial amygdala, and ascending reticular system [1]. Catecholamine increase causes myocardial alterations since it precipitates tachyarrhythmia occurrence and coronary spasm with ST-segment depression and QT interval prolongation [2]. There is a correlation between higher scores on the Hunt-Hess scale and higher troponin values, and the elevation of troponin itself is an independent predictor of mortality and is related to left ventricular cardiomyopathy [3] (Fig. 32.2).

Excess catecholamine release due to therapeutic strategies such as the introduction of vasoactive drugs in order to optimize mean arterial pressure and cerebral

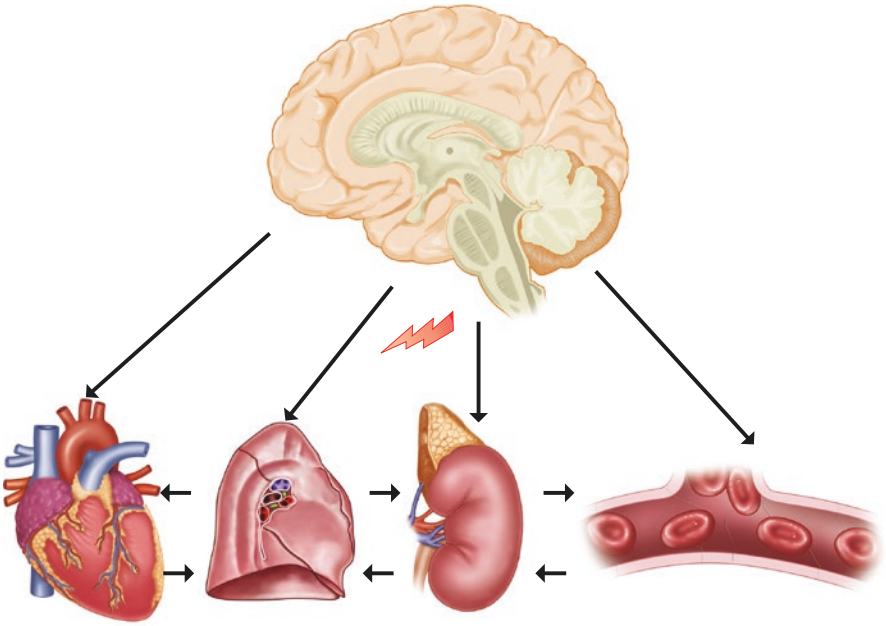

Fig. 32.2 Shows the involvement of systems after brain injury

pressure perfusion can also cause cardiac injury with ischemic cardiomyopathy and transient left ventricular dysfunction [4].

Electrocardiographic changes in patients diagnosed with stroke have been already described since 1954 [5]. Brain injuries such as ischemic stroke, hemorrhagic stroke, TBI, brain tumor, and other causes of intracranial hypertension can lead to cardiac damage in days after the neurological event. In most cases, comorbidities as systemic arterial hypertension, diabetes mellitus, and hypercholesterolemia are present [5] (Table 32.1). Increased sympathetic activity has been described in patients during the course of SAH [6].

Necropsies analysis of patients with ventricular dysfunction identified myocytolysis and myocardial necrosis [7]. Patients diagnosed with SAH who developed ventricular dysfunction did not have previously established coronary disease that could justify the cardiac evolution [8].

About 73% of patients diagnosed with TBI have electrocardiographic changes, including tachycardia, ST-segment alterations, QT interval enlargement, pathological T wave, and U wave. These alterations were identified in patients without previous coronary diseases and corresponded to greater severity in trauma [10, 11]. Thus, cardiovascular complications observed in patients diagnosed with TBI are independent mortality predictors [9].

After ischemic stroke, cardiovascular complications are the second most common cause of mortality. Excess catecholamine and consequential left ventricular dysfunction are related to increased myocardial necrosis markers and Takotsubo cardiomyopathy [12, 13]..

Table 32.1 Non-neurological alterations

Cardiovascular	Arrhythmias	Electrocardiographic changes	Hypotension (SAP <90 mmHg)	Hypertension (DAP >160 mmHg)	Left ventricular failure
Pulmonary	Infiltrate on radiography	Acute respiratory distress syndrome	Atelectasis		
Renal	Increase in creatinine >50% of baseline	Reduction in creatinine clearance			
Gastrointestinal	Increased bilirubin value	Paralytic ileus	Gastric bleeding		
Electrolytes	Hypernatremia Na > 150 mEq/L (hypovolemia)	Hyponatremia (SIADH/SWS)	Hyperkalemia K > 5 mEq/L	Hyponatremia K < 3.5 mEq/L	Hypocalcemia
coagulopaty					

SAP Systolic arterial pressure, *DAP* diastolic arterial pressure, SIADH syndrome of inappropriate antidiuretic hormone secretion

To evaluate cardiac changes is necessary to dose myocardial necrosis markers and perform electrocardiograms and for echocardiography analysis. When the ventricular function is affected, invasive hemodynamic monitoring is also necessary.

Patients diagnosed with subarachnoid hemorrhage who progress to hypotension should be hemodynamically compensated by the use of vasoactive drugs in order to maintain adequate mean arterial pressure and consequent cerebral perfusion pressure above 60 mmHg [14]. Dobutamine and milrinone are inotropic drugs, which optimize cardiac output and are efficient in patients with cardiogenic shock [15]. The use of levosimendan, a non-adrenergic drug, can be considered in the treatment of Takotsubo cardiomyopathy [16].

Circulatory assistance through intra-aortic balloon (IAB) introduction is useful in optimizing cerebral flow in patients who develop vasospasm in subarachnoid hemorrhage [17, 18].

32.2.1 Measurement Cardiac Parameters

32.2.1.1 Lactate

The lactate measurement is a parameter to assess hypoperfusion in the tissues. In the presence of low flow, the end product of anaerobic glycolysis is the pyruvate, which turns into lactate and does not enter the Krebs cycle.

In surgical patients, regardless of their hemodynamic status, lactate assesses the prognosis and is related to increased incidence of complications and mortality. In multiple unstable trauma patients, it also assesses the degree of resuscitation.

32.2.1.2 Central Venous Pressure (CVP)

CVC is indicated when using vasoactive drugs and allows obtaining central venous pressure (CVP) and central venous saturation oxygen ($ScvO_2$). CVP should be used as a safety endpoint, but not as a therapeutic target for fluid replacement.

CVP indications are states of shock, major surgery, sepsis, and renal and respiratory failures. When CVP has a variation of 3 mmHg with breathing, it suggests that the patient will benefit from volume, and when there is alteration after volume replacement, it shows that the ventricular function is preserved.

32.2.1.3 Mean Arterial Pressure (MAP)

MAP monitoring is indicated in every patient who is on vasoactive drugs, like vasopressors or vasodilators, patients in shock, or neurological patients, where we must accurately measure the mean arterial pressure so we can calculate the cerebral perfusion pressure (Fig. 32.3).

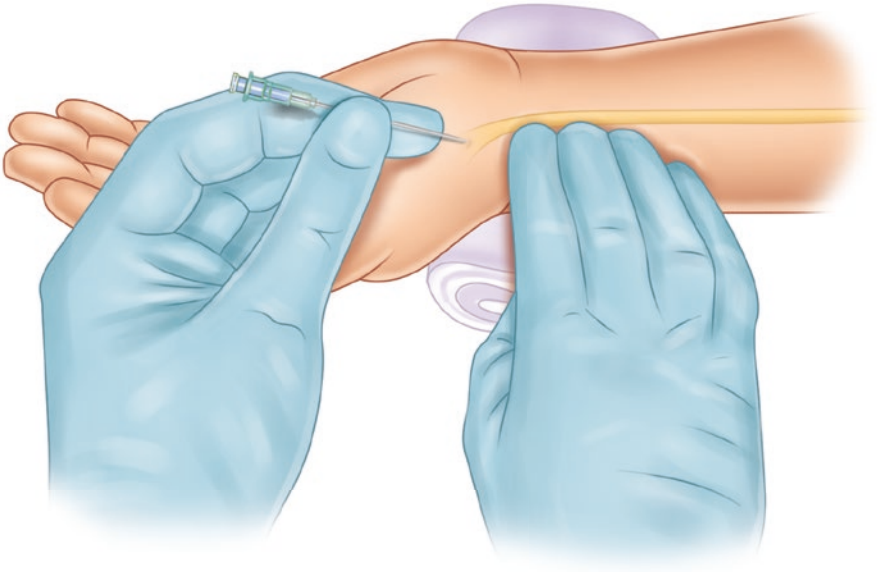

Fig. 32.3 Radial artery catheterization

32.2.1.4 Invasive Hemodynamic Monitoring

Catheter monitoring of the artery should be performed on neurocritical patients with hemodynamic instability who need vasoactive drugs and those with a deterioration of ventricular function. It allows us to check volume changes and intracardiac shunting, assess blood pressure on the pulmonary artery, and calculate vascular resistance to guide our therapy. There are several ways to measure the cardiac output, including the method of Fick based on oxygen consumption, which calculates the difference between the concentration arterial and venous oxygen.

The transpulmonary thermodilution can take benefit of measuring the transpulmonary water, especially in the context of acute respiratory distress syndrome (ARDS). A randomized study showed that the management of fluids guided by the measurement of transpulmonary water versus pressure pulmonary artery occlusion resulted in a better-maintained water balance and a shorter duration of mechanical ventilation and ICU stay in critically ill patients. In patients on mechanical ventilation, with PEEP below 10 cmH_2O, the changes in pulmonary artery pressures occluded are minimal. However, larger PEEP can produce changes in pulmonary pressure measurements. FloTrac®/Vigileo (contour method pulse rate) is related to the maximum arterial pressures obtained in the inspiration and minimal blood pressures on inspiration; a PP delta greater than

13% tells us that the patient responded to the volume (normal range between 8% and 13%).

To use this method, the patient must be stable and on controlled mechanical ventilation, sedated, with a tidal volume of 8–10 mL/kg and PEEP less than 8 and without arrhythmia.

PiCCO, a method of analyzing pulse contour, uses the technique of thermodilution. It has evaluation limitations in patients with severe aortic valve disease, intra-aortic balloons, and intracardiac shunts. The latest technology is the EV1000, which presents as an additional measure of the overall final diastolic volume and the pulmonary extravascular water. Such technology requires a central venous access as well as a medium arterial line to be used (Tables 32.2 and 32.3) [45].

Table 32.2 Hemodynamic monitoring reference values

Hemodynamic monitoring reference values
Systemic blood pressure
Diastolic – 60–80 mmHg
Systolic – 100–140 mmHg
Medium – 70–100 mmHg
Pulmonary artery pressure
Occluded pulmonary artery pressure (PAPO)
Diastolic – 6–12 mmHg
Systolic – 25–35 mmHg
Medium – 15–20 mmHg
Right atrial pressure
Medium – 5–10 mmHg
Cardiac index (CI) DC/SC: 2.8–4.2 lt/min/m^2
Stroke volume index: IC/FC – 30–70 ml/m^2
Left ventricular systolic labor index
ITSVE = SVI : (MAP- PAOP) 0.0136: 40–65 m/m^2
Right ventricular systolic labor index

Table 32.3 Management of cardiac injury and how to monitor and treat

Management of heart injury of neurological cause	Patient with hemodynamic changes
Myocardial necrosis markers dosage	Transthoracic echocardiogram to evaluate cardiac function and absent alterations at admission
Electrocardiogram at admission and daily	Invasive or minimally invasive monitorization
Transthoracic echocardiogram at admission and daily	Circulatory support in patients with low cardiac output and not responding to vasoactive drugs
Daily hemodynamic evaluation	

32.3 Pulmonary Complications

In neurocritical patients, pulmonary complications such as atelectasis, pneumonia, lung injury, and acute respiratory distress syndrome have been described since 1908 [19]. Shanahan et al. described pulmonary edema development in 11 epileptic patients. Pulmonary edema may be present in patients diagnosed with SAH, TBI, and epileptic seizures [19, 20]. The pathophysiology of pulmonary edema results from an increase in hydrostatic pressure in the pulmonary vessels and a significant increase in capillary permeability [21].

There is an increase in cytokines on the cerebrospinal fluid in patients with SAH [22, 23]. In cases of intracranial hypertension, the compensatory response tends to increase sympathetic and adrenergic activity by the release of catecholamine, in order to increase cerebral perfusion pressure. Vasoactive drugs, used with the same purpose for optimizing cerebral perfusion pressure, are related to the development of acute respiratory distress syndrome [24]. The incidence of neurogenic pulmonary edema is estimated at 2–49% [25].

The most frequent non-neurological complications of patients with TBI are the pulmonary ones, with 61% of them evolving with aspiration bronchopneumonia or nosocomial pneumonia, which increases the staying period in the intensive care unit [9].

TBI patients whose Glasgow coma scale is less than 6 have a more significant clinical deterioration compared to those with higher scores since they have more respiratory, gastrointestinal, and infectious complications such as sepsis, which consequently prolongs the stay in the intensive care unit [9]. Lung injury and mortality are related to the Glasgow coma scale score and age [9].

The absence of airway protection during seizures increases bronchoaspiration and respiratory tract infection risk. Thus, orotracheal intubation and mechanical ventilation are essential to provide adequate supply to the increased oxygen demand due to exacerbated muscle contractions during the crisis episode [12].

Some precautions are necessary for spinal cord trauma, especially in association with facial injury. Several techniques can be applied to perform the orotracheal intubation procedure, without superiority between them. However, actions to keep the spine stable are essential to prevent or to avoid worsening the injury. The use of succinylcholine for neuromuscular blocking in orotracheal intubation should be avoided in patients with more than 72 hours of trauma due to the risk of hyperkalemia [26].

32.4 Hematological Complications

Patients with major TBI can develop coagulation disorders, initially induced to hypercoagulability [30, 31, 32]. Astrocytic cells, which are rich in tissue factors, release excessive amounts during the injury, leading to hypoperfusion and

endothelial dysfunction. Besides, there is an increase in the thrombin production inside microcirculation and consumption of coagulation factors, causing a hypercoagulability condition [13].

Endothelial injury increases protein C activity, an endogenous anticoagulant, culminating in fibrinolysis and anticoagulation [13]. Based on the fibrinolysis principle, the CRASH-3 (trial) study recommends using tranexamic acid to prevent bleeding [33].

Tranexamic acid use is safe in patients diagnosed with TBI, according to reports in the literature, due to clot and bleeding stabilization. However, its use increases the risk of pulmonary thromboembolism [34]. Studies have demonstrated a mortality rate of 3.13–7% and an incidence of coagulopathy of 33% in TBI [9].

Patients diagnosed with SAH commonly present anemia after the event, and its etiology varies among bleeding during the surgical procedure, systemic inflammatory response syndrome complication, or successive phlebotomies. Thus, hemoglobin levels should be maintained above 8 in patients with SAH and in those who develop late cerebral ischemia [35].

32.5 Renal Complications

Kidney injury incidence in patients with TBI ranges from 0.098% to 17.3%, which may increase mortality [9]. TBI triggers catabolic processes that culminate in kidney damage, which is aggravated by hypovolemia and hypoperfusion from shock [27, 28]. Rhabdomyolysis is a complication of tonic-clonic seizures since myocyte damage and consequent increases in myoglobin levels result in kidney injury [12]. Furthermore, rhabdomyolysis may also be a complication resulting from the use of sedative medications, such as propofol syndrome [29].

Sedative drugs should be used in an isolated or associated way, preferably with opioids. It is crucial that in every choice of sedatives, analgesia must precede sedation.

32.6 Metabolic-Endocrine Dysfunctions

Metabolic-endocrine changes can occur in trauma due to hypothalamic-pituitary-adrenal axis imbalance. Such disorders result from primary or secondary insufficiency or as a consequence of the treatment. In thyroid disorders, a small number of patients require hormonal treatment. About 15% of patients with pituitary-adrenal dysfunction and low cortisol levels require the use of vasoactive drugs [13].

Sodium is the main extracellular cation and has osmotic and electrostatic activity. Dysnatremias should be interpreted according to patient volemia and serum and urinary osmolality to define its etiology and treatment. Changes in serum sodium

are the most common electrolyte disorders in intensive care units, and its incidence ranges around 49%, being considered an independent risk factor of mortality.

Plasma sodium concentration rages from 136 to 145 mEq/L. Its levels are controlled by homeostatic mechanisms involving thirst, antidiuretic hormone, and kidney control of water excretion. Normal sodium levels are kept by urine production through the action of antidiuretic hormone. Antidiuretic hormone is released according to blood osmolality or other non-osmotic factors, such as pain, postoperative nausea, and hypothyroidism. Changes to any of these controlling elements of water and sodium balance can trigger dysnatremia.

Mostly clinical manifestations of hyponatremia arise with dosages less than 130 mEq/L and are considered severe when it is less than 125 mEq/L. Its mortality reaches 15% of hospitalized patients. Mostly, it results from inadequate water retention due to inappropriate antidiuretic hormone secretion or a deficit of sodium in the extracellular fluid. Hyponatremia has clinical significance when it is related to hypo-osmolality. Normal plasma osmolality values vary between 280 and 295 mOsm/kg.

Dilution plasma sodium occurs when water infusion intake exceeds the capacity of fluid excretion from the kidneys, resulting in hypo-osmolality and hyponatremia. This disorder occurs in the presence of persistent antidiuretic activity.

Hyponatremia results in clinical symptoms and signs of contraction of the volume of extracellular fluid. Mostly, urinary sodium concentration is reduced, except when using diuretics, in sodium-losing nephropathy and clinical cases of severe metabolic alkalosis.

According to pathophysiological mechanisms, hyponatremia can be divided as follows:

- Pseudo-hyponatremia or hyponatremia with iso-osmolality (280 and 295 mOsm/kg H_2O), which is caused by the concentration of large molecules of lipids (triglycerides and cholesterol) and proteins (multiple myeloma). These molecules move part of extracellular water, reducing the plasma fraction of sodium.
- Hypertonic hyponatremia or hyponatremia with hyperosmolality (> 295 mOsm/kg H_2O) that occurs due to the presence of osmotically active solutes, such as mannitol and glucose, hence leading to water translocation from intra- to extracellular compartments with loss of Na by osmotic diuresis. In these cases, the hyponatremias are usually asymptomatic. It is common in diabetic ketoacidosis.
- Hypotonic hyponatremia or hyponatremia with hypo-osmolality (<280 mOsm/kg H_2O). These are clinical situations characterized by plasma sodium concentration below 135 mEq/L, which is equal to hypotonicity in the absence of pseudohyponatremia or other osmotically active solutes.

In many clinical cases, hyponatremia is caused by water translocation from intracellular to the extracellular space, resulting in plasma sodium dilution. The transfer is caused by solute excess in the extracellular space (hypertonicity). Therefore, it is necessary to evaluate the extracellular volume.

- Hypervolemia: A consequence of decreased water renal excretion, leading to water expansion, greater than sodium, and decrease in serum sodium. Common causes are heart failure, liver cirrhosis, nephrotic syndrome, and renal failure.
- Euvolemia: Includes clinical situations like hypothyroidism, corticosteroid deficiency, emotional stress, and pain; use of drugs that stimulate the release of prostaglandin inhibitors, nicotine, chlorpropamide, tolbutamide, clofibrate, cyclophosphamide, morphine, barbiturates, vincristine, carbamazepine, tegretol, acetaminophen, fluoxetine, and sertraline; and syndrome of inappropriate antidiuretic hormone secretion.
- Hypovolemia: Evaluate urinary sodium concentration. When sodium is < 20 meq/l. results from tubular reabsorption of sodium by the kidney and when >20 mEq/L, it must be considered that the kidney is responding appropriately, and these losses are the causes of hyponatremia. The most frequent causes are gastrointestinal losses or the third space losses, renal loss (diuretics), salt-wasting syndrome, Addison's disease, osmotic diuresis, ketonuria, and poorly controlled diabetes.
- Mostly, the signs and symptoms of hyponatremia are mild or absent, and laboratory tests confirm the diagnosis. Cerebral edema occurs through the entry of water from the extracellular to the intracellular medium in the central nervous system and symptoms can range from drowsiness, mental confusion, seizures and even coma. The central nervous system has mechanisms of removing excess solutes when compared to the extracellular, preventing water inflow. The severity of cerebral edema is mainly related to the speed on the installation of the disturbance, as well as the damage to its protective mechanisms. The main risk factor for installing this mechanism is hyponatremia. Which determines the speed of migration of free water from the hypotonic (extracellular) medium to the more hypertonic medium (central nervous system). There are also other contributing factors, namely: edema, hypoxemia and female gender.

In acute hyponatremias, usually gastrointestinal and systemic symptoms (such as weakness, anorexia, fatigue, vomiting, and malaise) precede symptoms related to the central nervous system. However, in chronic hyponatremia, clinical manifestation is lighter, in which severe neurological symptoms occur only when hyponatremia is very severe (sodium below 120 mEq/L).

The diagnosis begins with an adequate anamnesis and clinical examination, signs and symptoms of hyponatremia, and possible diseases related to this electrolyte disorder (such as edema, blood pressure, heart rate, mucosal turgor, hepatosplenomegaly). A specific analysis should be done in the medications list in use (discard the existence of drugs known to be related to the appearance of hyponatremia) and the volume and composition of solutions infused. Laboratory tests include calculation of serum osmolality and serum and urinary sodium dosage and determining the volume status of the patient based on their general state. Urinary sodium aims to help differentiate between renal and extrarenal causes (Fig. 32.4). In cases where FENa < 1%, extrarenal loss is considered to occur. For the fraction of excreted sodium calculation, the following formula is used:

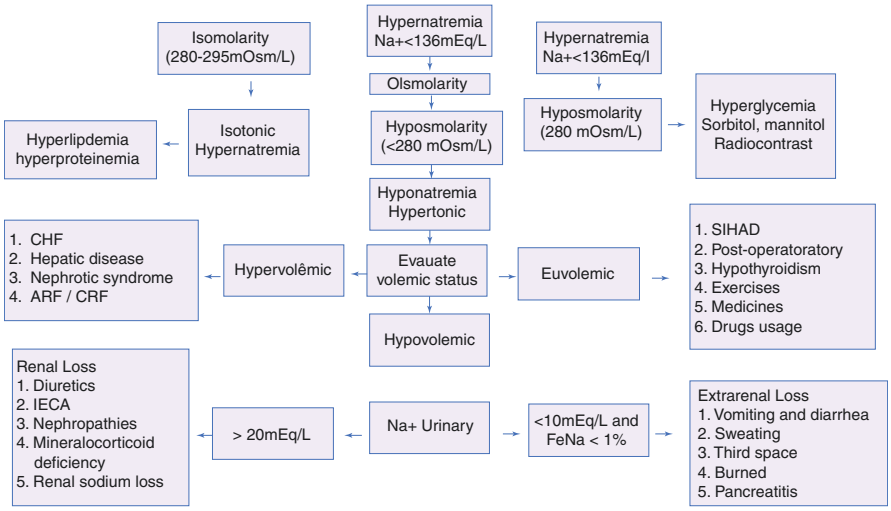

Fig. 32.4 Types of hyponatremia

$$\text{FENa, percent} = \frac{\text{quantity of } Na^+ \text{ excreted}}{\text{quantity of } Na^+ \text{ filtered}} \times 100$$

For the treatment, the hyponatremia has to be classified in either depletion volume (secondary to fluid loss) or isovolemic hyponatremias or hypervolemia. In hypovolemic hyponatremia, the presence of clinical data of hypovolemia such as a history of diuretic use and urinary sodium <30 mEq/L is suggestive of primary adrenal insufficiency. Initially, volume correction should be done by the administration of isotonic physiological saline solution (NaCl 0.9%), in an infusion according to the estimated volume depletion, associated with potassium replacement if there is hypokalemia or history of recent diuretic use. Volume replacement cannot exceed the rate of 12 mEq/L in 24 hours in order to avoid complications like central pontine myelinolysis. American guidelines have a lower limit of replacement – 8 mmol/L in 24 hours – in patients with a higher risk of demyelination of neurons (malnourished patients, with hypokalemia and liver disease).

Osmotic demyelination can occur in a few days after aggressive treatment by any method. The contraction of brain cells triggers neuron demyelination in the pons and extra pons and causes neurological dysfunction, including paralysis, pseudobulbar paralysis, seizures, coma, and even death.

In cases of isovolemic hyponatremia or hypervolemic, the initial management consists of water restriction and, in more severe cases, infusion of sodium 3% solution. An important step in hyponatremia treatment is to classify it as acute or chronic. Given the difficulty of this classification, American and European guidelines use the presence of mild to moderate or severe symptoms to institute therapy.

Acute, severe hyponatremia occurs when serum sodium concentration drops rapidly below 125 mEq/L in less than 48 hours. It commonly occurs during transurethral resection of the prostate surgery – the irrigation process is done with a glycine solution, which predisposes acute hyponatremia. Once brain homeostatic mechanisms cannot react adequately to compensate these rapid changes in plasma osmolality, cerebral edema, irreversible neurological injuries, respiratory failure, brainstem herniation, and death may occur.

In these cases, aggressive intervention is necessary, and both the American and European guidelines indicate intravenous treatment with hypertonic saline. Therefore, for severe (natremia <125 mEq/L) and symptomatic hyponatremia, with concentrated urine (> 200 mOsm/kg) and euvolemia or hypervolemia, or when osmolality greater than that of urine solution (to obtain a negative balance of free water) is used, administer chloride sodium solution 3%. As this solution may not be available at the hospital, it can be obtained by diluting 55 mL of chloride sodium 20% in 445 mL of 0.9% saline. In patients with hypervolemic hyponatremia, hypertonic saline can be combined with diuretics.

The correction begins with 3 mEq/L in the first 3 hours and another 9 mEq/L during the next 21 hours, not exceeding the 0.5 flow at 1 mEq/L per hour. After evaluating the patient, one should calculate the sodium deficit by using the formula:

$$\text{Na} = 0.6\left(0.5\,\text{for women}\right) \times \text{weight} \times \left(\text{expected Na} - \text{current Na value}\right)$$

This formula means the amount of mEq/L of sodium to be replaced and, with the infusion of 1 l of SF at 3%, how much in the serum sodium value will increase.

$$\text{Serum Na} + \text{correction}\left(\text{mEq / L}\right) = \text{Infused Na} + - \text{serum Na} + / \text{total body water} + 1$$

Body water, which can be calculated by multiplying the weight by the beginning of body weight, which varies according to age and sex. The index for adults and children is 0.6. For women and the elderly, this index ranges from 0.45–0.5. The formula estimates the 1-l effect of any solution infused in serum sodium.

Hypernatremia ranges about 45–86.5% in patients diagnosed with TBI, and its cause is attributed to inadequate volume administration and use of mannitol. Desmopressin can be used in doses of 0.5–2.0 mcg to treat hypernatremia [9].

Hypernatremia is defined as a serum sodium concentration (Na +) greater than 145 mEq/L. It is less common than hyponatremia, although debilitated patients with hypernatremia present a risk of very high mortality ([39] 70%). It is a result of relative total body water deficit to total body sodium and can be caused by excessive loss of fluids or actual sodium gain. This represents clinical situations of hypertonicity of extracellular volume, as the sodium concentration in this space determines extracellular osmolality volume. The increase in sodium concentration in extracellular fluid creates an osmotic gradient that induces the movement of water out the cell and hence cellular dehydration leading to extracellular space increase.

The leading causes of hypernatremia are:

- Medicines: diuretic, lithium, amphotericin B, foscarnet, and demeclocycline
- Electrolytic: hypercalcemia or hypokalemia (nephrogenic diabetes insipidus)
- Hyperglycemia with osmotic diuresis
- Intrinsic kidney disease
- Polyuric phase of acute tubular necrosis
- Acute losses (diarrhea, vomiting, fistula, and nasogastric tube)
- Burns

Hypernatremias are common in elderly patients, especially in situations like difficulty of accessing water, insensitivity of thirst mechanisms which is very common in this age group, use of enteral or parenteral nutrition, reduced angiotensin II production (which contributes to changes in thirst mechanism), and urinary concentration deficit.

Diabetes insipidus has the main characteristic of free water loss by kidneys due to the absolute lack of vasopressin (ADH) or tubular resistance to ADH. Important dehydration occurs with increased serum sodium and hypotonic urine (inability to concentrate urine), but urinary sodium increased.

The clinical picture of hypernatremia depends on the intensity and form of installation. The most frequent is dehydration and intense thirst, muscle weakness, confusion or lethargy, focal neurological deficit, seizures, and even coma. The brain adapts to extracellular hypertonicity space due to interstice dehydration and water outlet from the cerebrospinal fluid, with neuron dehydration. In a short period of time (hours), the synthesis and accumulation of small organic molecules, intracellular osmolytes, such as glutamine and glutamate, begins, which will prevent severe dehydration of neurons.

Initial symptoms occur with natremias greater than 160 mEq/L (osmolality greater than 350 mOsm/kg) and are nonspecific, including headache, vomiting, intense irritability, muscle hypertonicity, weakness, lethargy, coma, and seizures.

Patients with hypovolemic or euvolemic hypernatremia may present changes in skin turgor in the supraclavicular region and the arm. In contrast, hypervolemic hypernatremia patients typically present signs and symptoms of volume overload, as polyuria (with natriuresis elevated), edema, jugular stasis, and pulmonary edema.

Hypernatremia is an important differential diagnosis to be made in intensive care health centers in patients with stroke, due to the clinical signs of focal manifestations and a lowering of the state of consciousness, which can be common to both, being computed tomography, mandatory brain for diagnosis. Change in osmotic concentration caused by hypernatremia can cause vascular rupture and subarachnoid or intraparenchymatous hemorrhage.

The diagnosis can be confirmed by the serum sodium dosage greater than 145 mEq/L. However, there are tests that allow us to target the basic cause of hypernatremia:

- Serum/urinary osmolality: useful in the diagnosis of diabetes insipidus. Individuals with central diabetes insipidus or nephrogenic diabetes insipidus

have a reduced capacity of urinary concentration, maintaining osmolality urine less than 300 mOsm/kg and excreting a urine volume close to normal. In the case of central diabetes insipidus, administration of exogenous ADH causes an increase in urinary osmolality, while in nephrogenic diabetes insipidus, exogenous ADH does not cause any change in urinary osmolality. Some patients exhibit urinary osmolality between 300 and 800 mOsm/kg, presenting partial central diabetes insipidus (with increased urine osmolality after administration of exogenous ADH) or Partial nephrogenic diabetes insipidus and osmotic diuresis, in which there is no response to exogenous ADH.

- Serum glucose – diabetes mellitus
- Serum dosage of potassium and calcium
- Cranial tomography – stroke, tumors, traumatic brain injury

The correction of hypernatremia is based on three factors:

- Maintenance of euvolemia and hemodynamic instability correction
- A gradual reduction in serum sodium
- Diagnosis and treatment of the basic cause

In any situation, volume resuscitation is the initial priority, regardless of the severity of hypernatremia, because most patients with hypernatremia also present with hypovolemia, requiring rapid expansion with a hypotonic or isotonic saline solution. The type of solution depends on the patient's volume: if the hypernatremia is in a scenario of pure water loss, for example, in cases of diabetes insipidus, replacement is done with enteral or parenteral water (5% glucose solution). In the scenario of hypothetical liquid losses, for example, in vomiting episodes, diarrhea, and the use of diuretics, the patient will need saline 0.9% isotonic. In arterial hypotension or hemodynamic instability cases, use hypotonic saline solutions 0.2% and 0.45% for correction of hypernatremias of normotensive patients.

Particular attention should be given when using glucose solutions, since critical patients can develop hyperglycemia, worsening the state of prior hypertonicity.

To avoid the main complication correction, iatrogenic cerebral edema resulting from rapid alteration serum osmolality, correction of sodium should be 0.5 to 1 mEq/L per hour or 12 mEq/L in 24 hours. Exceptions to this suggestion are the cases of acute hypernatremia installation (developed in the last 12 hours), where the brain has not had adequate time to adapt to the hypertonicity of the extracellular liquid. The patients are critically ill, acutely symptomatic, potentially requiring intubation to protect airways. In these cases, it is suggested a faster initial correction speed 1, to 2 mEq/L every hour, however still not exceeding the speed of 12 mEq/L every 24 hours.

The use of formulas allows the calculation of sodium correction:

$\Delta Na + \text{estimated} = Na + \text{infused} - Na + \text{measured/Water total body} * + 1.$

This formula will show an estimate of sodium change with 1 l of the chosen solution. The dysnatremia correction should always be accompanied by serial measurement of serum sodium and clinical evaluation of the patient throughout the process of correction.

Table 32.4 Disorders of sodium in patients in postoperative brain tumor resection

	SWS	SIADH	DI
Hydric balance	Decreased	Normal or increased	Decreased
Urinary volume	Increased	Normal or decreased	Increased
Serum sodium	Decreased	Decreased	Increased
Urinary sodium	Increased	Increased	Normal
Serum osmolarity	Decreased	Decreased	Increased
Urinary osmolarity	Increased	Increased	Normal or decreased
Plasma vasopressin	Normal	Increased	Decreased

SWS Salt-wasting syndrome, *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *DI* diabetes insipidus [45]

Another important step in the treatment of hypernatremia is the recognition of the cause and its treatment. The cause is detectable with a good anamnesis and detailed physical examination:

- Hypovolemic hypernatremia: Correct the water and sodium deficit; treat the triggering condition (hyperglycemia).
- Euvolemic hypernatremia
- Central diabetes insipidus (DI): Desmopressin and correct underlying cause correction.
- Reversible nephrogenic DI: Remove trigger medicine and adjacent electrolytic correction.
- Irreversible nephrogenic DI: Thiazide, non-steroidal antiinflammatory, reduction of the sodium.
- Hypervolemic hypernatremia: Diuretic and dialysis [45].

Cases of syndrome of inappropriate antidiuretic hormone secretion are characterized by free water retention, plasmatic hyposmolarity, and hyperosmolar urine. Sodium replacement at 1.0 mmol/hour with a maximum of 12 mmol/day is the treatment proposed in the literature [13].

In salt-wasting syndrome, patients develop hypovolemia and hyponatremia since there is a greater circulation of pro-BNP natriuretic peptide and, consequently, an increase in natriuresis with urinary sodium greater than 40 mmol/40 liter [13, 36]. In SAH, hyponatremia is commonly related to late cerebral ischemia [37] (Table 32.4).

32.7 Thromboembolic Complications

Deep venous thrombosis and pulmonary thromboembolism are one of the major complications of neurocritical patients. The incidence of deep venous thrombosis is 1.2–31.6%. Risk factors are immobilization and obesity [38]. The use of central venous catheters is associated with an increased risk of deep venous thrombosis

[39]. However, peripherally inserted central catheters have the highest risk of thrombotic phenomenon occurrence [40, 41].

Even when using pharmacological prophylaxis for venous thromboembolism, neurocritical patients have an increased risk of deep venous thrombosis. In order to minimize thrombosis risk, early mobilization and catheter removal should be performed as soon as possible [38]. During the first hospitalization week, searching for thrombosis aided by ultrasonographic examination of deep veins can provide diagnosis, especially in patients at higher risk, who are obese, 60 years old or more, and immobilized using a central venous catheter and have history of neoplasia and thrombophilia or previous history of deep venous thrombosis [38].

Pneumatic compression prophylaxis can be used in neurosurgical patients during the perioperative period to reduce the risk of deep venous thrombosis. The combination of pneumatic compressor and pharmacological prophylaxis is effective in reducing venous thrombosis risk in clinical patients in the intensive care unit. The use of unfractionated heparin is considered in patients with TBI [42].

Prevention of venous thrombosis in ischemic stroke includes enoxaparin in prophylactic dose associated with pneumatic compressors as soon as possible in patients with restricted mobility. In cases of patients with stroke who underwent endovascular procedures, it is recommended an immediate start of pharmacological prophylaxis also associated with a pneumatic compressor. In patients whose APTT is enlarged, prophylaxis can be delayed by 24 hours. In cases of stable intraparenchymal hematoma (IPH), mechanical prophylaxis should be adopted immediately. Pharmacological prophylaxis starts within 48 hours, while pneumatic compression is maintained.

Mechanical prophylaxis should be started in all patients with SAH secondary to aneurysmal rupture, and pharmacological prophylaxis can be performed after 24 hours of surgical or endovascular treatment. Regarding TBI, mechanical prophylaxis begins in the first 24 hours or 24 hours after craniotomy. Pharmacological prophylaxis is introduced in 24–48 hours after trauma or 24 hours after craniotomy. In patients hospitalized for elective craniotomy, we use combined prophylaxis 24 hours after operation.

Pharmacological prophylaxis should start as early as possible in patients with brain cancer. In patients with spinal cord injury with controlled bleeding, it is recommended to start pharmacological prophylaxis within 72 hours. Isolated mechanical prophylaxis is not recommended in thrombosis prevention. In elective spine surgeries, the primary prophylaxis consists of pneumatic compression and early ambulation. In cases of patients at high risk for thrombosis, using combined mechanical and pharmacological prophylaxis has higher benefits. For endovascular procedures, adopt pharmacological prophylaxis within 24 hours [43].

32.8 Gastrointestinal Complications

In trauma, patients can develop paralytic ileus, stress ulcers, and liver dysfunction [9]. Paralytic ileus is also an abdominal complication in cases of seizures and is highly associated with the use of thiopental. Another complication of seizures is pancreatitis since during the crises, intraduodenal pressure increases.

Stress ulcer prophylaxis is extremely important. Neurocritical patients hospitalized in the intensive care unit using prophylaxis have a general bleeding risk of around 0.1–4.0%, and in the absence of prevention drugs, this risk increases by up to 15%.

Patients with a Glasgow coma scale ≤10, using mechanical ventilation and in the presence of coagulopathy, are at greater risk of ulcer. There are higher rates of morbidity and mortality in patients diagnosed with brain injury, ischemic stroke, hemorrhagic stroke, spinal cord injury, and central nervous system infection. Not using prophylaxis for stress ulcers demonstrated a higher risk of bleeding and increased pneumonia rates [44].

32.9 Conclusion

Non-neurological systemic complications are dysfunctions present in neurocritical patients at admission or during their stay in critical care. They can significantly impair the evolution of these patients, and we must develop strategies for prevention, early diagnosis, and effective treatment, which can influence their outcomes.

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Chapter 33
Acute Spinal Cord Disorders

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33.1 Introduction

Spinal cord injury (SCI) is defined as an injury resulting from an insult inflicted on the spinal cord that compromises, either completely or incompletely, its major functions (motor, sensory, autonomic, and reflex). SCI remains an important cause of morbidity and mortality in modern society [1]. This event causes permanent disability and a decreased life expectancy with physical, physiological, and social impact [1–7]. Since it had no curative treatment, the efforts should be taking on preventive actions and rehabilitation therapies. The management of SCIs requires a lot of health resources and generates expenses for patients, families, and the whole society [8–11].

A systematic review revealed that overall mortality of patients with SCI is up to three times higher than in general population when analyzing standardized mortality rates [12]. Acute SCI may be classified according to etiology in traumatic SCI (TSCI) and nontraumatic (NTSCI) with different epidemiology, pathophysiology, and outcomes.

Traumatic SCI is generally caused by motor vehicle accidents, assault, falls, and sports injuries. Nontraumatic SCI have multiple etiologies, with the most frequent being degenerative spinal diseases compression, followed by extrinsic neoplastic involvement, vascular injuries, and finally inflammatory or infectious diseases [13].

In this chapter we aim to discuss the most important etiologies causing acute spinal cord dysfunction, its epidemiology, clinical features, and treatment nuances that are essential from a neurosurgeon's point of view.

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33.2 Traumatic Spinal Cord Injuries

33.2.1 Epidemiology

TSCI affects 54 cases per one million people in the United States or about 17,730 new cases per year [14]. The estimated prevalence is approximately 291,000 people in the USA [15]. In Brazil, the annual incidence is estimated to be 16–26 per million [16].

33.2.2 Age at Injury

TSCI is rare in childhood. Despite an increase in the average age of patients over the last years (from a mean of 29 years during the 1970s to a mean of 43 years nowadays), there are still two peaks of incidence: the first in earlier 20s and the second one at elderly, due to fragility and fall from the heights [17–19]. In developed countries, the age of SCI ranges from 14.6 to 67.6 years, while in underdeveloped countries, these figures vary from 29.5 to 46.0 years [20, 21].

33.2.3 Gender

The prevalence of TSCI was higher in men, once they are more exposed to causative factors, such as violence and motor vehicle accidents. The average male-female ratio is 4:1 [21]. In developed counties, this ratio ranged from 1.10:1 to 6.69:1, while in underdeveloped countries, it varies from 1.00:1 to 7.59:1 [22–26].

33.2.4 Etiology

Motor vehicle accidents are the main cause of TSCI, followed by falls, violence, sports-related accidents, and other causes [20, 21, 27].

33.2.5 Level of Injury and Neurological Impairment

The most common site of injury is the cervical spine, followed by the thoracic and lumbar spine. Although the majority of spinal traumas do not have neurological injury, when present, incomplete tetraplegia is the most common presentation, present in 47.6% of cases, followed by incomplete paraplegia (19.9%), complete

paraplegia (19.6%) and complete tetraplegia (12.3%) [21]. Motor-complete injuries tend to be associated with traumatic SCI, while motor-incomplete injuries are associated with nontraumatic SCI [8, 20, 28].

33.2.6 Pathophysiology

Trauma causes primary injury due to mechanical damage to the spinal cord through compression, laceration, distraction, or shearing [17, 29, 30]. A cascade of events composed by damage to the microvasculature, progressive edema, ischemia, inflammation, and apoptotic process leads to the second injury [31, 32].

The blood-spinal cord barrier is affected, and inflammatory cells, vasoactive peptides, and coagulation factors migrate to a spinal cord leading to thrombosis and spasm of the microvessels and finally hypoxia [32, 33]. The production of oxygen free radicals and mitochondrial impairment cause an imbalanced energy state. This energetic crisis results in excitotoxicity, cytotoxic edema, and apoptotic cascade [34–36].

The definitive extent of spinal cord damage results from primary and secondary injuries started at the moment of the injury and lasts for days or weeks. Neuroprotective measures try to prevent neural damage from secondary injury, while neuroregenerative therapies focus on axonal regrowth [37, 38].

33.3 Neurological Classification

The American Spinal Injury Association (ASIA) impairment scale is the standard tool for neurological and functional classification at initial and follow-up evaluation. It is also used to predict outcome. Eighty-five percent of patients with complete deficits (ASIA A) will not recover function. Only 3% of that 15% who will improve will present a useful motor function. More than half (54%) of ASIA B patients and the majority (86%) of ASIA C–D patients will recover some degree of function [39–41].

This tool is composed of two components, the sensorial and the motor. The sensorial component evaluates the light touch and pinprick sensation on 28 dermatomes (from C2 to S4–5) on both sides. For each sensation modality, a 3-point scale, ranging from 0 (absent) to 2 (normal or intact), is performed.

The motor examination tests the key muscle functions of ten paired myotomes (C5–T1 and L2–S1). Voluntary external anal sphincter contraction should also be tested. The strength is graded according to the Medical Research Council grading system, from 0 to 5.

The neurological level of injury is defined as the most caudal segment of the cord with intact sensation and antigravity muscle function strength (Fig. 33.1).

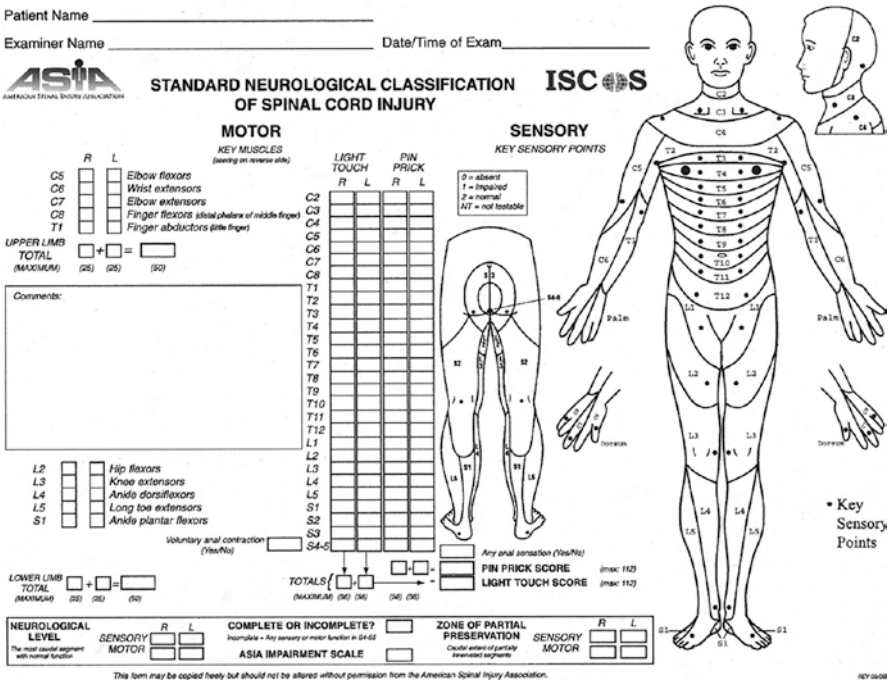

Fig. 33.1 Schematic depiction of ASIA scale. The American Spinal Injury Association (ASIA) scale is the standard tool for neurological and functional classification at initial and follow-up evaluation. It is also used to predict prognosis

33.3.1 Imaging

Trauma patients with neck pain, spinal tenderness, and symptoms or signs of a neurological deficit and those patients whose neurological exam cannot be assessed (unconscious, uncooperative, incoherent, or intoxicated) need a radiological study of the spinal cord [42, 43].

The National Emergency X-Radiography Utilization Study (NEXUS) protocol tries to identify those patients at low risk of cervical injury. It is composed of five criteria: no posterior midline cervical tenderness, no intoxication, alert, no other painful injuries, and no neurological deficits. Patients who complete all of these criteria are at low risk of cervical injury, and imaging study can be waived. The NEXUS protocol has a sensitivity of 99% and a negative predictive value of 99.9% for cervical spinal cord injuries [44].

The Canadian C-Spine Rule is another protocol to define patients who need to be radiologically evaluated. Three questions should be answered: the presence of a high-risk factor that mandates radiography (age > 65 years, dangerous mechanism of trauma, or paresthesia in extremities), the presence of low-risk factors allowing safe assessment of the range of motion, and the ability to actively rotate the neck 45°

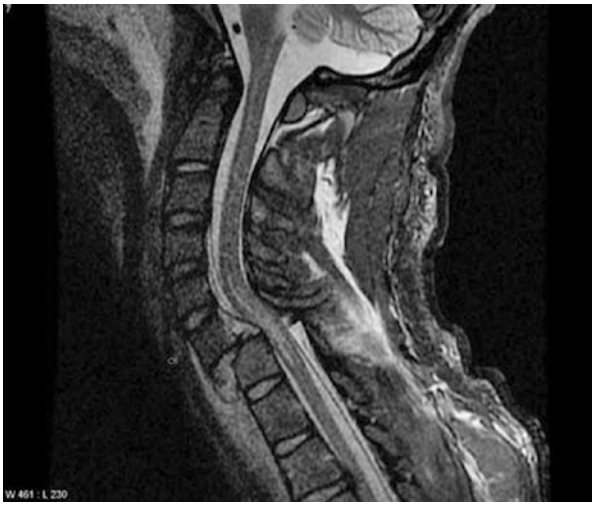

Fig. 33.2 Sagittal T2W sequence MRI of a patient with a fracture and displacement of C6/C7 and a severe spinal cord injury

to both sides. The Canadian C-Spine Rule protocol has 100% sensitivity and 42.5% specificity for cervical spinal injury [45].

Computed tomography (CT) is the main radiographic evaluation tool [46]. Magnetic resonance imaging (MRI) is useful for ligamentous lesions and can detect up to 6% of lesions in which the CT was normal [47, 48]. MRI can also identify the severity and predict the outcome based on the presence of hemorrhage, the extent of edema, and the severity of compression. Worse prognosis is associated with extensive intraspinal hemorrhages (> 1 cm long) and longitudinal T2 signal changes >3 cm [49] (Fig. 33.2).

33.3.2 Medical Management

33.3.2.1 Airway Management

Respiratory issues are the main cause of morbidity and mortality in the acute phase of the SCI, ranging from 36% to 83%. It is caused by reduced vital capacity, accumulation of pulmonary secretion, and autonomic dysfunction [50, 51]. Up to two-thirds of patients are affected by atelectasis, pneumonia, or respiratory failure requiring mechanical ventilation [52].

The injury level and the ASIA classification are the most important predictors for the need for intubation. Because of the phrenic nerve origin (C3–C5), the vast majority of patients with lesions above C5 will require intubation, which should be performed before it becomes an emergency [50]. Special care should be taken during intubation, by avoiding hyperextension, rotation, and other movements of the neck [53].

Only 40% of patients with lesions above C5 are successfully extubated. The need for tracheostomy can be assessed by the extent of the lesion, smoking, and previous lung disease [54, 55]. In those patients, early tracheostomy (<10 days) results in shorter ICU stay and mechanical ventilation [54].

33.3.2.2 Cardiovascular Management

Hypotension in a traumatic SCI patient may occur due to hypovolemia or due to neurogenic shock. It results from the interruption of sympathetic tone and intact parasympathetic mechanisms via the vagus nerve, causing an imbalance in the autonomic control. Finally, it results in loss of peripheral vascular tone and bradycardia [56].

Hypotension intensifies the secondary injury after acute SCI, reducing spinal cord perfusion. Currently, hypotension should be avoided, and the mean arterial pressure (MAP) should be maintained at 85–90 mmHg for 7 days after trauma [57].

In neurogenic shock, a drug with chronotropic and inotropic effects and vasoconstrictor properties might be required. Norepinephrine or dopamine could be a good option [58, 59].

33.3.3 Surgical Management

33.3.3.1 Decompressive Surgery

Progressive edema and hemorrhage contribute to increase the pressure on spinal cord tissue and affect the microvasculature. Surgical decompression tries to relieve this pressure by reducing secondary hypoxia and ischemia. Surgery is indicated to significant cord compression with progressive neurological impairment and unstable vertebral fractures.

The Surgical Timing in Acute Spinal Cord Injury Study compared the timing of surgery in patients with a close cervical spine dislocation and neurological deficits. Those patients operated before 24 hours were twice as likely to have a two-grade ASIA Impairment Scale improvement [60]. The “time is spine” emerged from it, and a recommendation of surgical decompression in the first 24 hours is made by the authors [61].

33.3.3.2 Intravenous Methylprednisolone

Intravenous corticosteroid with methylprednisolone (MP) was attempted to control inflammatory factors and reduce oxidative stress. The National Spinal Cord Injury Study I, published in 1984, could not find any neurological recovery difference between 1000 mg and 100 mg doses per 10 days although a high MP dose was associated with a higher infection risk [62].

The National Spinal Cord Injury Study II, published in 1990, compared MP 30 mg/kg intravenously followed by 5.4 mg/kg/h over 23 hours to naloxone and

placebo. There was no significant difference in neurological function among the groups. However, in subanalysis, patients who received the corticosteroid within 8 hours had a discrete improvement in motor recovery. Wound infections are still more common in MP patients [63].

The National Spinal Cord Injury Study III, published in 1997, compared three treatment groups: MP for 48 hours, MP for 24 hours, and tirilazad mesylate (lipid peroxidation inhibitor). Patients were treated within 8 hours of SCI. Patients treated between 3 and 8 hours from trauma, with the 48-hour protocol, was associated with greater non-function motor recovery. However, the longer use of MP was more associated with severe sepsis and pneumonia [64].

Recently, meta-analysis and systematic reviews do not support routine methylprednisolone use in acute SCI since it has no consistent benefits and increases gastrointestinal hemorrhage and overall adverse events [65].

33.3.3.3 Neuroregeneration

Numerous strategies have been developed to recovery function in SCI patients. Cell-based therapies seem to be promising. Preclinical studies with cellular transplantation were associated with neurological recovery [66]. Few human studies demonstrated some improvement without major adverse events [67]. Cellular transplantation remains an experimental therapy, without formal recommendations.

33.4 Nontraumatic Spinal Cord Injuries

Compared with those with traumatic SCI, survival rates are lower in individuals with nontraumatic SCI (NTSCI). Other factors associated with lower survival rates were associated with older age, higher neurological levels, and completeness of SCI. Causes of death stemmed from secondary complications, with failure of the respiratory system being the leading cause. Runner-ups were disorders of the heart and the circulatory system. The epidemiology of SCIs has undergone substantial changes during recent years. The incidence of NTSCIs is increasing as it occurs more commonly in older age groups [13, 68]. In this section we discuss the most common neoplastic lesions in the spine, as well as vascular lesions.

33.5 Neoplastic Lesions

33.5.1 Epidemiology

Spinal cord compression occurs in 10–15% of patients diagnosed with spinal metastases. It can be caused either by direct tumor compression or by the collapse of a vertebral body by tumor invasion [69]. It is a medical emergency that requires

prompt recognition and treatment, since it can result in permanent neurological deficit [70]. It is estimated that more than 10% of cancer patients will develop some degree of metastatic spinal cord compression (MSCC) during the course of the disease [71].

33.5.2 Pathophysiology

Bone metastases can occur through different forms of propagation, the most frequent being the hematogenous route. Less frequent types of dissemination are contiguity and lymphatic dissemination. Tumor spread through the venous system is the main mechanism of metastasis in the spine [72].

33.5.3 Diagnosis

Initial laboratory workup of patients with MSCC include complete blood count with differential, coagulation tests, and evaluation of renal function and electrolytes, among others. Although simple radiographs and computed tomography may be useful for surgical planning and for assessing spinal deformities, MRI is the imaging modality of choice for the assessment of MSCC [73, 74] (Fig. 33.3).

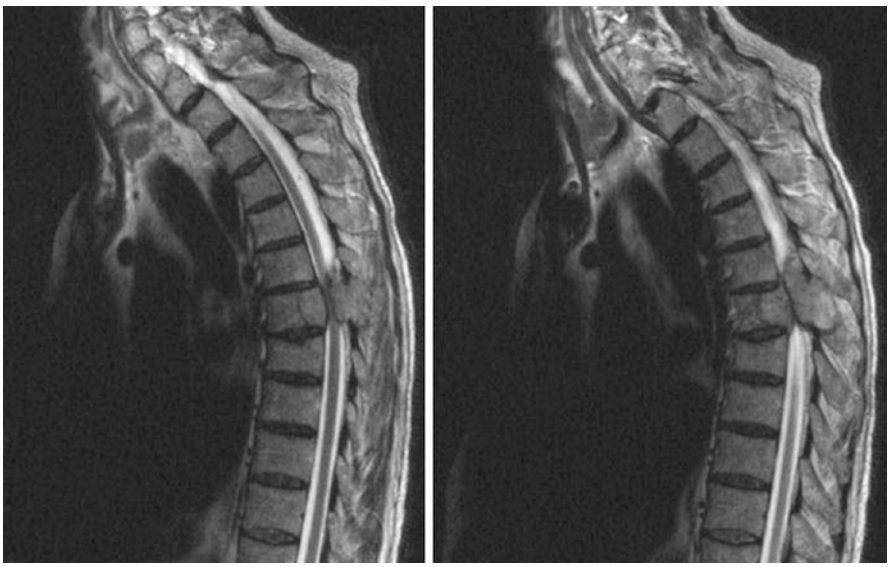

Fig. 33.3 Sagittal T2W MRI of a 60-year-old patient presenting with rapidly progressive paraplegia secondary to an epidural metastatic disease from a renal cell carcinoma

33.5.4 Drug Treatment

Considering pain as the most common manifestation of metastases in the spine, pain treatment is of paramount importance. Patients with metastatic spine usually experience biological pain and/or mechanical instability. Biological pain is the nocturnal or morning pain that resolves throughout the day. The postulated pathophysiology is related to the diurnal variation in the secretion of endogenous steroids that decreases during sleep. Flare pain results from inflammatory mediators secreted by the tumor. Identifying the cause of the pain is important to guide proper treatment: biological pain often responds to steroids and radiation, but pain secondary to spinal instability may require a surgical procedure for stabilization. MSCC medication includes non-steroidal anti-inflammatory drugs and steroids. Steroids can also be used in the context of neurological impairment due to tumor compression: generally, a loading dose of 10 mg dexamethasone, followed by 4 mg every q6, can decrease the neurological symptoms secondary to compression and local pain [73–75].

33.5.5 Surgical Treatment

Surgery in the case of MSCC is considered a palliative treatment, usually reserved for patients with a life expectancy >3 months and who tolerate the procedure. However, patients with severe pain due to instability or in specific selected cases may benefit from minor surgical procedures for stabilization/decompression, after a complete multidisciplinary analysis [74, 76, 77]. Surgical goals are preservation of spinal instability, spinal cord decompression, and local disease control.

33.5.6 Radiotherapy

As surgery is considered only in selected cases, conventional external beam radiation therapy (cEBRT) remains the main treatment modality for metastasis in the spine. Spinal stereotactic radiosurgery (SRS) is a type of radiation therapy developed more recently that delivers a high dose of radiation to the tumor, while minimizing the amount delivered to healthy neighboring tissues, usually for radioresistant tumors or more extensive metastases (one or two levels) [74, 78–80].

33.5.7 Therapeutic Decision

Instead of using algorithms that are fixed in time and limited by the technology available at the time they were proposed, the NOMS framework was developed by analyzing the four points considered fundamental in decision-making [76]. The

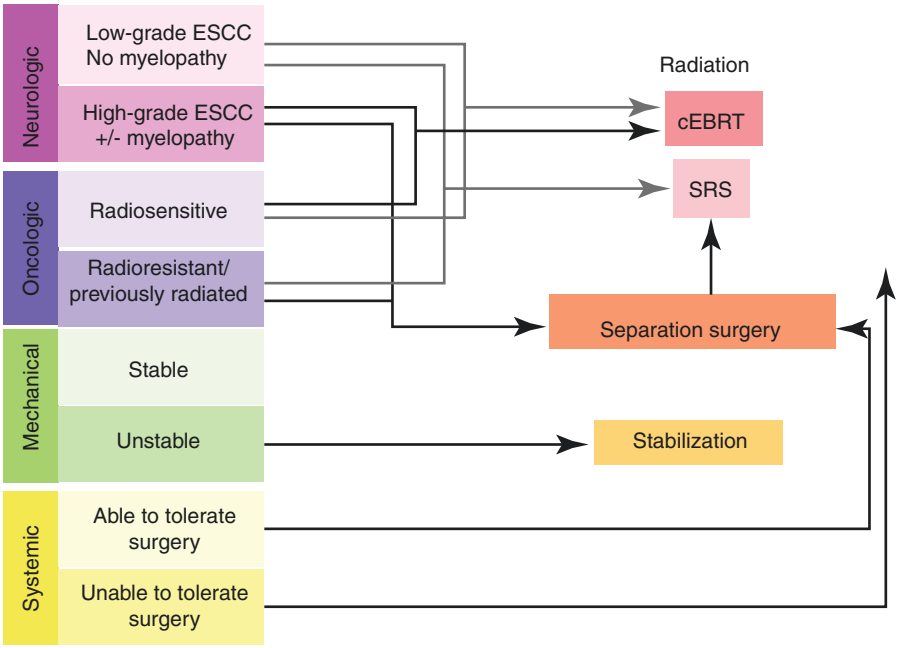

Fig. 33.4 Schematic depiction of the neurological, oncological, mechanical, and systemic (NOMS) decision framework [69]. Abbreviations: cEBRT, Conventional external beam radiation therapy; SRS, stereotactic radiosurgery

NOMS consists of an evaluation of the following criteria: neurological (Epidural Spinal Cord Compression Scale), oncological, mechanical instability, and systemic disease [69]. Unlike Tokuhashi and Tomita's algorithms, the advantage of the NOMS structure is that it incorporates both new technologies and evidence-based medicine as they become available. Considering these four assessments, the interdisciplinary team can determine the ideal treatment consisting of radiotherapy, surgery, systemic therapy, or a combination of these (Fig. 33.4).

33.5.7.1 Outcome

Regarding functional outcome, in a recent publication by our group of a cohort of 40 patients with spinal metastases, 11 patients who presented with incomplete deficit had recovery from their deficits after surgery, and 2 patients with complete neurological deficit had partial recovery. After statistical analysis, we described that the neurological status was improved, as shown by the Frankel scale, in relation to the preoperative status [73].

33.6 Spinal Vascular Disorders

Vascular spinal disorders (VSD) include several diagnoses that are often misdiagnosed or undertreated. Some represent neurologic emergencies, such as spinal cord infarction, and others can be disabling if they remain unrecognized, such as spinal dural arteriovenous fistulas [81].

33.6.1 Etiologies

The three major groups of vascular diseases of the spinal cord are acute spinal cord ischemia syndrome (ASCIS), spinal cord hemorrhage, and spinal vascular malformations [82]. In Table 33.1, we present the most common etiologies of vascular spinal cord injury and its clinical characteristics to help the suspicion of the diagnosis [83].

33.6.2 Epidemiology

Spinal cord infarction is speculated to account for only 1–2% of all ischemic strokes and 5–8% of all acute myelopathies. However, spinal cord ischemia occurs in 4–33% of patients exposed to its most prominent risk factor: thoracoabdominal aortic surgery [81, 83].

Considering spinal vascular malformations, about 60–80% comprises spinal dural arteriovenous fistulas. They predominantly affect men in their 60s and occur most often in the lower thoracic spinal cord. Spinal arteriovenous malformations (AVMs) are the second most common spinal vascular malformation after dural arteriovenous fistulas, constituting up to 15% of all spinal vascular malformations. And finally, spinal cavernous malformations typically occur in the fourth decade and

Table 33.1 Etiologies of vascular spinal cord injury and clinical characteristics

Type of spinal vascular disorders	Risk factors	Vessel involved
Spinal cord infarction	Aortic vascular surgery	Anterior spinal artery
Dural arteriovenous fistula	Male sex	Radiculomedullary artery and vein fistula
Arteriovenous malformation (AVMs)	Genetic syndromes	Anterior spinal artery and/or posterior spinal artery into medullary vein
Cavernous malformation	Family history	Thin-walled dilated sinusoidal vein
Epidural hematoma	Spinal surgery, coagulopathy	Internal vertebral venous plexus

have a slight predominance in men. A family history of cavernous malformations is present in 12% of patients, and 17% of patients have a concomitant intracranial cavernous malformation(s) [83, 84].

33.7 Clinical Presentation

The clinical presentation symptoms depend on the etiology, extension, and topography of the lesion, varying from mild pain or sensorial findings to complete paraplegia [81, 83].

33.7.1 Spinal Cord Ischemia

The clinical scenario is based on the location of the ischemia. More commonly, the anterior spinal artery is the main responsible for ischemia. A complete deficit or a posterior deficit alone is less frequently seen. The symptoms are acute (ictal) and are related with the segment, level, and extension of the lesion [83, 84]. Pain is often present in the onset of cases. The most common syndromes associated with ASCIS are:

A. Anterior cord syndrome (corticospinal, spinothalamic, sympathetic): quadriparesis or paraparesis, bilateral loss of temperature/pain below the level of commitment. Autonomic symptoms in higher injuries may occur.
B. Posterior cord syndrome (dorsal columns): deficit of vibration, proprioception, light touch, sensitive ataxia.
C. Complete cord syndrome (corticospinal, spinothalamic, sympathetic, and dorsal columns): complete sensitive and motor deficit below the lesion.
D. Central cord syndrome (corticospinal and spinothalamic tracts)**: "**man in the barrel syndrome" – weakness worse in upper limbs.

33.7.1.1 Diagnosis:

MRI can reveal a hypersignal on T2-weighted as a result of a long segment of swelling (Fig. 33.5). DWI may not present restriction of signal due to the little size of the spinal cord, although it has capability of identifying hyperacute events (see the image below). Contrast enhancement is not commonly seen in these cases, when it is present should call up suspicious to others etiologies [81, 82].

These alterations often are present within the first 48 hours since the beginning of the symptoms, but patients whose first exam were normal and then were submitted to a second one after 72 h presented tardily signal changes [81].

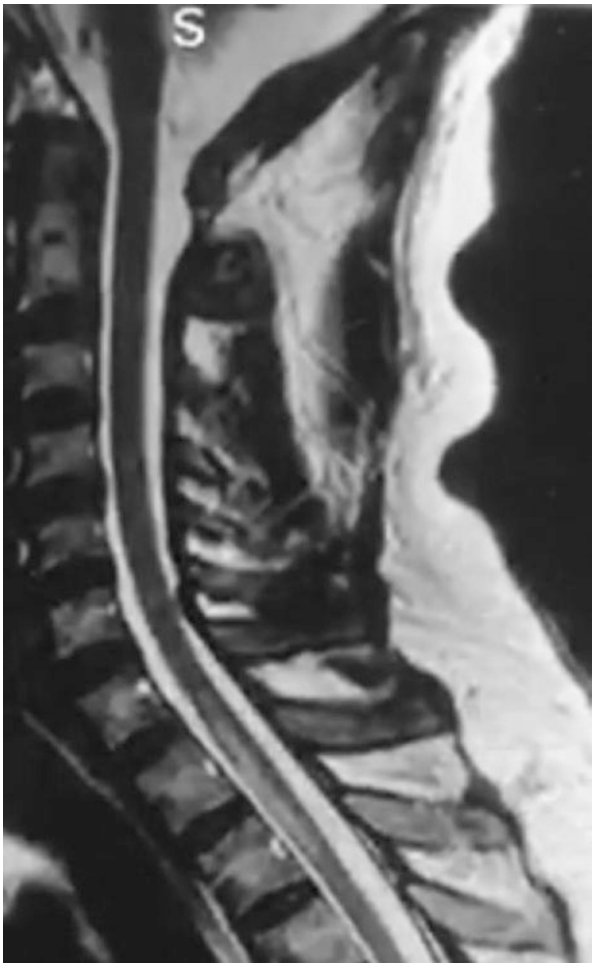

Fig. 33.5 Sagittal T2W sequence MRI with a spinal cord hypersignal from C7 to T2 as a result of a spinal cord ischemia

33.7.1.2 Management

The mainstay of treatment of spinal cord ischemia is to improve spinal cord perfusion through blood pressure augmentation and reducing CSF counterpressure through spinal fluid drainage. Blood pressure augmentation is initiated with volume replacement followed quickly by vasopressor support that is titrated to symptom improvement or adverse effects. Weaning of therapy should be performed while closely monitoring the neurologic examination for deterioration over 24–48 hours [83, 85].

33.7.2 Spinal Cord Hemorrhage

Patients with spinal cord hemorrhage usually present with acute symptoms with back or neck pain that may be intense and knife-like and often show a radicular component. Patients with spinal subarachnoid hemorrhage may additionally show symptoms resembling meningitis, such as meningeal irritation with headache, neck stiffness, disturbance of consciousness, and epileptic seizures and are also often misdiagnosed as having cerebral hemorrhage [82, 86].

33.7.3 Spinal Vascular Malformations

33.7.3.1 Spinal Dural AVF

Spinal dural AVF are more common in men, usually presenting after the forth decade, and are probably acquired. The etiology of spinal dural AVF is unknown. The clinical presentation is mostly a slowly progressive, often stepwise, and rarely acute myeloradiculopathy. A venous congestion caused by arterial overload of venous drainage due to the fistula initiates edema and myelopathy of the spinal cord leading to a broad range of clinical symptoms. Spinal cord hemorrhage is almost never seen in patients with spinal dural AVF [81–83].

33.7.3.2 Diagnosis

Intramedullary T1 hypointensity and T2 hyperintensity extending over 3–7 vertebral levels with peripheral sparing or a rim of T2 hypointensity (indicating the presence of deoxygenated hemoglobin) is characteristic of myelopathy related to a spinal dural arteriovenous fistula. Edema secondary to the venous congestion may be seen, but, in advanced cases, the spinal cord may be atrophic. The myelopathy is often observed first in the conus, and gadolinium enhancement may be seen. Dilated and tortuous veins are seen as flow voids on the ventral or dorsal aspect of the spinal cord [81].

33.7.3.3 Management

Surgical and endovascular options exist for disconnecting the draining vein from its arterial supply. Endovascular therapy to occlude the draining vein with liquid embolic agents is successful in approximately 70% of cases which may be performed during the initial angiography. It is associated with a reduction in hospital stay compared with open surgery [83, 87].

33.7.4 Spinal Arteriovenous Malformation

In spinal arteriovenous malformation, symptoms are usually first seen in adolescence or early adulthood. Damage of the spinal cord is most often caused by acute intramedullary or subarachnoid hemorrhage, venous congestion, and less frequently mass or steal effect [81–83].

33.7.4.1 Diagnosis

MRI is very helpful. It shows mixed intramedullary or extramedullary T1 and T2 signals in the setting of hemorrhage and intramedullary T2 hyperintensity, with spinal cord edema in patients without hemorrhagic symptomatic lesions. Flow voids from dilated vessels are commonly present [83].

33.7.4.2 Management

Endovascular embolization and surgery are options for treating spinal AVMs; however, their success rates are lower than with spinal dural arteriovenous fistulas (33% and 78% for embolization and surgery, respectively). This is because the arterial supply to the AVM frequently also perfuses the spinal cord, increasing the risk of spinal cord ischemia with treatment. Nonetheless, even partial treatment can reduce the hemorrhage rate [81, 83, 88]. Stereotactic radiosurgery can be curative in some cases but more commonly reduces the size of the lesion. Combination therapies and a multidisciplinary approach are frequently used [88].

33.7.5 Spinal Cavernomas

Regarding spinal cavernomas, it can cause a transverse spinal cord syndrome with acute worsening by hemorrhage or mass effect. Most patients present with progressive or stepwise clinical deterioration which is thought to be due to gliosis, microthrombosis, microcirculatory changes, and repeated minor bleedings into the spinal cavernous angioma. Acute and severe neurological symptoms can occur due to hemorrhage into the spinal cord [82, 89].

33.7.5.1 Diagnosis

Well-circumscribed lesions with heterogeneous intralesional T1 and T2 signals are depicted on MRI (“popcorn-like” aspect). Gradient echo sequence is very useful as well [84, 89].

33.7.5.2 Management

Carefully selected patients for surgical resection experience higher rates of symptomatic improvement and clinical stabilization and lower rates of decline with follow-up, even with a partial resection [83]. Better outcomes are associated with surgery within 3 months of symptom onset and with a hemilaminectomy approach. Conversely, conservative management is justified in asymptomatic, mildly symptomatic, or older patients [83, 84, 89].

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Chapter 34
General Principles of Awake Neurosurgery

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34.1 Introduction

The continuous development and improvement of neurosurgery aim to offer better treatments and decrease surgical risks. Particularly in epilepsy surgeries and resections of intrinsic brain tumors, the neurosurgeon faces a dilemma: increasing the brain resection area probably leads to better control of the disease but also increases the chance of causing a functional deficit. Therefore, not only the location of the lesion and understanding the structural anatomy of the region being explored are important, but also the knowledge about the functional role and functional organization of that region are fundamental to achieve the best possible surgical outcome.

Initially, the cortical surface of the brain received more attention in an attempt to explain its functional organization. However, studies with injured patients have revealed that subcortical white matter fiber injuries can also lead to significant neurological deficits. The modern functional theory of the brain accepts the existence

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of dynamic networks within the brain, focusing great attention to the distribution of subcortical white matter fibers that connect different cortical regions. This complementary approach joins topography (study of cortical functional epicenters) with hodology (study of connectivity between areas), creating a so-called hodotopic framework. Some cognitive functions can be related to particular brain networks (e.g., spatial attention, language, memory and emotions, working memory and executive functions, face and object recognition), while most brain functions can result from the interaction of different brain networks.

Deep understanding of structural anatomy of the brain is necessary for performing an effective and safe neurosurgery, but it is not enough to know the functional organization of the brain. The exact same anatomical cerebral regions are not consistently related to the same brain functions in all patients. This significant interpersonal variability makes it impossible to create a functional map that can be generalized, requiring the individual investigation of each patient [17]. This variability is even greater in patients with slow-growing lesions, such as low-grade gliomas, where neuronal plasticity leads to a slow functional reorganization of the brain. Additionally, functional areas can be found within the tumor [24], and only a partial resection of the lesion is preferred in these cases; otherwise the patient may present functional deficits.

Several techniques are available to map brain functions. The most important noninvasives that can be performed before surgery are functional nuclear magnetic resonance (fMRI), tractography (DTI), positron emission tomography (PET), and transcranial magnetic stimulation (TMS). Some invasive methods are available: evoked potential, electrocorticography, subdural electrode grids, depth electrodes, and direct electrical stimulation (cortical or subcortical) (DES). All of them have advantages and disadvantages, but they have sub-optimal sensitivity and specificity when compared to the gold standard (DES), particularly for complex functions such as language (sensitivity, PET = 75%, fMR = 81%; specificity, PET = 81%, fMR = 53%) [9].

Intraoperative brain mapping used in awake craniotomy is the gold-standard procedure for the identification and preservation of eloquent cortical and subcortical structures during surgery for patients with intrinsic brain tumors [4]. The electrical stimulation on the brain (cortical or subcortical) by a probe causes a temporary dysfunction of that specific region, and, if applied at an eloquent area, the patient presents with a temporary functional disturbance. In addition, DES is the only method capable of assessing the subcortical functional organization of each region.

The main goal of the awake neurosurgery should be to have a positive impact on the natural history of disease, especially by increasing overall survival, and to achieve a significant resection in lesions that are in eloquent areas, with preservation of maximum brain function, and without adding new neurological sequelae [2]. The awake craniotomy surgical technique allows intraoperative localization and protection of cortical and subcortical motor and language pathways while having real-time feedback from the patient. This technique allows the surgeon to reduce the risk of morbidity and permanent severe postoperative deficits caused by resection or injuring functional areas.

Brain mapping using DES at neural structures finds its pioneers in Fritsch and Hitzig in 1870. They stimulated the motor cortex of dogs and were able to elicit movements. In 1874 Ferrier characterized the brain's motor centers in macaque and later in 1901 Sherrington and Grunbaum replicated the same experiment in great apes. In 1917 Leyton and Sherrington noticed that different motor area representations such as fingers, forearm, and arm overlap within the precentral gyrus. Krause and Cushing in 1909 were the first to perform DES in the human brain eliciting motor responses, and a decade later, in 1919, Vogt and Vogt tried to link brain functions to anatomy using DES. In 1937, Penfield and Boldrey described a simplified representation of the somatotopy of the body on the cortical surface, calling it "homunculus" [20]. Later, Ojemann showed that language disturbances were not confined to cortical regions but also to subcortical white matter tracts. More recently, Berger applied intraoperative brain mapping techniques in neuro-oncology, and Duffau developed the functional mapping of subcortical pathways [8].

34.2 Brain Mapping

A detailed analysis of the topographical and functional anatomy of the patient's brain as well as of the tumor or epileptic foci unique features is mandatory before attempting surgery. Brain mapping needs to be tailored to patient's cortical and subcortical anatomy, functional dominance, biological characteristics of the tumor or epileptic foci, patient's neurocognitive reserve, pre-existing neurological deficits, and patient's wishes.

Mapping strategies are preoperatively discussed with the neuroanesthetist and neurophysiologist addressing whether the surgery will be conducted purely in awake conditions or asleep/awake techniques will be used. Motor mapping of primary motor cortex and pyramidal tract can be performed in asleep conditions, while cortical and subcortical mapping of the supplementary motor area, language-related areas, and other higher-order neurocognitive functions networks require the patient to be fully awake and collaborative. Constant switching between different parameters and mapping probes during surgery allows dynamic mapping of different functions and networks while simultaneously safely removing the lesion.

Mapping strategies must take into consideration the functional networks potentially affected by the lesion or the selected surgical approach. Therefore the cortical anatomy as well as the subcortical white matter fibers should be integrated in a functional three-dimensional mental imagery which allows the surgeon to appropriately use each neuropsychological test according to the mapped network (Table 34.1).

Intraoperative tractography integrated into the neuronavigational system and augmented reality techniques can be helpful to detect specific tracts during surgery; however direct subcortical mapping with specific intraoperative neuropsychological tests remains the gold standard to accurately detect and preserve those networks. Nonetheless, there is not a strict correlation between anatomy and functions, since

Table 34.1 Cortical and subcortical structures and related networks and functions

Cortical and subcortical structures	Networks	Functions
Central region, SMA, premotor cortex, pyramidal pathways	Motor	Simple and complex motor functions, bilateral motor coordination
Central region, thalamocortical pathways	Somatosensory	Processing somatic sensations
Posterior temporal regions, dorsolateral prefrontal areas (dorsal and ventral), orbitofrontal region, inferior fronto-occipital fasciculus	Language ventral stream	Language (semantic)
Posterosuperior temporal cortex, inferior frontal gyrus, arcuate fasciculus	Language dorsal stream	Language (phonological)
Supramarginal gyrus, ventral premotor cortex, SLF III	Language articulatory loop	Language (articulation)
Dominant anterior insula, ventral premotor cortex, primary sensory motor area of the mouth, operculo-insula fibers, descending pathways from ventral premotor cortex, pyramidal tract, and lentiform nucleus	Language pathway	Language (speech production)
Left inferior frontal gyrus, posterosuperior temporal area, SLF	Language	Language (switching)
Left inferior frontal gyrus, left superior temporal gyrus, SLF	Language	Language (syntactic processing)
Inferior and superior parietal lobules, insula, II and III frontal convolutions, SMA, SLF	Language	Writing
Visual cortex (primary and secondary), ILF	Language	Reading
Temporo-parietal-occipital junction, visual cortex, optic radiations	Visuospatial	Visuospatial cognition (visual)
Right supramarginal gyrus, right superior temporal cortex, right SLF	Visuospatial	Visuospatial cognition (spatial awareness)
Right inferior parietal cortex, posterior insula, posterior temporal cortex, right SLF	Visuospatial	Visuospatial cognition (vestibular)
Inferior frontal gyrus, dorsal premotor cortex, supramarginal gyrus, SLF	Working memory	Working memory
Left dominant prefrontal cortex, left posterior temporal cortex, IFOF	Higher-order integration	Judgment, decision-making, understanding
SMA, cingulum, frontal eye fields, subcallosal medialis fasciculus, head of caudate nucleus	Higher-order integration	

Of note within the same anatomical structures, multiple functional networks can be hosted and potentially mapped to avoid disruption. Careful preoperative analysis of the anatomy involved by the tumor and the surgical approach is mandatory to define the appropriate neuropsychological tests and mapping strategy during surgery. In bold subcortical major fiber bundles and subcortical structures are highlighted

SMA Supplementary motor area, *SLF* superior longitudinal fasciculus, *IFOF* inferior occipitofrontal fasciculus, *ILF* inferior longitudinal fasciculus

a white matter bundle of a supposed network could be silent to a specific mapping, therefore identified as non-essential to the function due to brain plasticity or network redundancies.

Direct mapping strategies are always integrated with continued neuromonitoring modalities in order to have constant feedback of the whole integrity of the corticospinal tracts (MEPs), somatosensory pathways (SSEPs), and visual (BAEPs) and corticobulbar pathways. It is common to position a four- or six-channel strip electrode over the primary motor cortex to accurately monitor the corticospinal pathways or over the primary visual area to monitor the optic function. In fact in the majority of cases, only the integration of the neuromonitoring and direct mapping can guarantee the integrity of the tract, as it is the case for insular tumors when attempting to map the corticospinal tract at the level of the internal capsule potentially leaving undetected the rostral portion of the same tract.

Fatigability of the patient as well as prediction of transient functional intraoperative impairment contributes to the mapping strategy. Patients are routinely positioned supine with the head fixed in the Mayfield holder and the head of the bed elevated at 30–40 degrees. This position allows the patient to have a direct view to the tests administered by the neuropsychologist and to have both hands free to perform complex bimanual motor tests as required for supplementary motor area (SMA) lesions. When motor and language mapping is required, the surgeon might decide to conduct the removal of the lesion toward the primary motor cortex and corticospinal tract in asleep conditions, in order to keep the patient awake for language testing for a shorter period of time reducing fatigability, which might affect higher neurocognitive abilities during surgery misleading the surgeon whether a specific network is clearly essential or not to the function. Functional intraoperative impairment as transient mutism during surgery for SMA lesions has to be predicted in advance in order to avoid resection of the lesion in those areas till all language and higher-order functions mapping has been performed.

34.3 Electroneurophysiology for Awake Neurosurgery

The technique described by Penfield and refined by Ojemann [11, 18] uses a constant current stimulator (Penfield and Boldrey, 1937) with a low-frequency paradigm of 50 Hz (Europe) or 60 Hz (America) [25]. The commonly used stimulation model consists of a single biphasic (anodal/cathodal) rectangular pulse with a duration of 1 msec and 1–6 mA current, applied with a bipolar fork probe (electrodes being 5–10 mm width apart) for 1–4 seconds [4, 6, 11, 14].

The current intensity must be adapted to each patient by starting at 1 or 2 mA and progressively increasing in increments of 0.5–1 mA until either a functional change is observed in the patient or after-discharges are seen on the electrocorticography (ECoG) [7, 11]. If after-discharges are observed from an electrode grid placed

nearby the mapping region [7] at a certain current before a functional change is observed, mapping should performed with at least 0.5–1 mA below that current [11, 18]. Most papers suggest that reliable responses are evoked when after-discharges are not present, avoiding false-positive results [7]; however Szelenyi et al. [25] explains that the threshold for after-discharges varies across the cortex, and for some regions functional mapping may only be present above the after-discharge threshold. To compromise between the after-discharge threshold and effectiveness of mapping, trying different stimulation durations and repetition rates can be done.

A transient deficit in the same site repeated on three separate stimulation occasions is accepted as sufficient evidence that this region is essential for the patient's normal function [7]. These functionally positive areas can be marked with numbered tags [20], and resection is then carried out avoiding these eloquent regions. Mapping with this technique is repeated during the resection, and the same parameters are used to identify the deep functional white matter pathways at the subcortical level [3]. A positive functional pathway is identified by stimulating the subcortical tracts and eliciting a positive response just as it is assessed during cortical mapping [4].

Another electrical stimulation technique, named the train of five (To5) technique, is also available. However, it is more commonly used in anesthetized patients for the mapping and monitoring of motor function using motor evoked potentials. This To5 technique, introduced by Taniguchi in 1993, uses a monopolar probe or electrode to stimulate the cortex or subcortical white matter with a reference placed on the scalp close to the craniotomy. It delivers five square pulses of 0.5 msec duration, with a 2–4 ms interstimulus interval, constant anodal (cortical) or cathodal (subcortical) stimulation, with a current ranging between 1 and 20 mA dependent on the patient and surgical circumstance [25].

This To5 method has been related to a lower risk of intraoperative seizures [25], and some authors have investigated the use of To5 for mapping eloquent language areas instead of the standard Penfield technique [1]. Using electrode grids, both techniques were carried out using language testing in an awake patient around Broca's area, but similar responses to both techniques were reported only for very specific testing methods. Currently the Penfield technique is still the most widely used for functional testing in awake patients; however both techniques can be used simultaneously in some cases [25] – for example, to resect a tumor located at the posterior aspect of the inferior frontal gyrus, the To5 technique could be used to monitor the motor function, while the Penfield technique is used to check for language function, enabling the patient to relax and focus on the language tests only.

The rigorous repetitive patient testing performed during DES is an important advantage of this method, because it diminishes false-negative results and reliably identifies eloquent functional regions which should be preserved during the resection [7]. DES has aided better intraoperative understanding of anatomo-functional organization [5] allowing resections to be based on both anatomical and functional boundaries.

DES is also related to some disadvantages, including false positives caused by patient fatigue, partial seizures, and the spreading of DES. However, Duffau [7] explains that these limitations can be overcome by combining the responses with preoperative knowledge offered by other techniques, such as diffusion tensor imaging tractography, transcranial magnetic stimulation, and functional neuroimaging. Strict patient selection is important for brain mapping as DES may be very demanding on the awake patient constantly doing functional tests within a stressful environment. Awake neurosurgery using electroneurophysiology also requires a dedicated multidisciplinary team which is not readily available in every hospital.

Cortical mapping techniques using DES have risk of evoking intraoperative seizures [25], although this risk is higher when using the Penfield technique in comparison to the To5 technique [25] due to the shorter stimulus duration [1]. An intraoperative neurophysiologist or an epileptologist may help to prevent the onset of a generalized seizure by monitoring the patient's electroencephalography (EEG) and ECoG throughout the entire procedure, especially during DES [11]. Continuous EEG and ECoG allow recording the patient's baseline cerebral electrical activity and monitor the occurrence of any after-discharges following stimulation, or sub-clinical or clinical seizures throughout the procedure (Fig. 34.1).

ECoG is recorded by an electrode grid of at least 4-by-1 contacts, placed onto the cortex near the DES functional mapping region, referenced against a subdermal needle placed in the midfrontal region, and seen on a computer monitor intraoperatively [7]. EEG is monitored from both hemispheres by placing at least four subdermal needle electrodes over the scalp. If discharges are observed, cold saline irrigation should be applied immediately to the surgical site and cortex [11, 25] which will control and revert the situation and refrain a focal seizure from generalizing. Pausing stimulation is also recommended. The EEG can show whether the seizure has spread to the other hemisphere. As previously mentioned, the current threshold should be at least 0.5 mA below the current which evoked after-discharges [11].

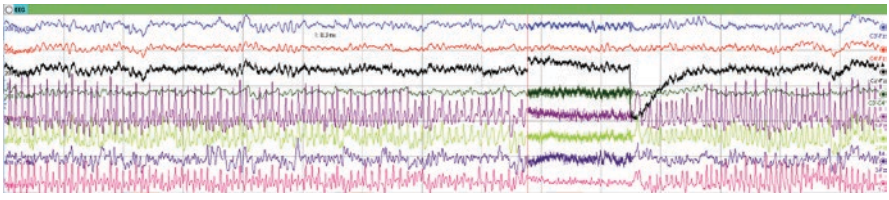

Fig. 34.1 Seizure activity during bipolar fork probe stimulation using the Penfield technique at 5 mA. Recording from ECoG using a 4-by-1 contact grid electrode referenced against Fz as well as EEG using four subcutaneous corkscrews placed over the bilateral scalp (recording was obtained using the inomed Medizintechnik GmbH NeuroExplorer software)

34.4 Intraoperative Neurological and Neuropsychological Testing and the Evaluation of Cognitive Functions in Patients with Brain Tumors

To succeed, brain mapping needs to optimize the selection of appropriate intraoperative tasks given the limited intrasurgical awake time frame. A multidisciplinary approach, involving neurosurgeons, neurologists, neuropsychologists, and speech therapists, is crucial to the building of a tailored and practical intraoperative protocol for each individual patient based on both patient and lesion characteristics [4]. The rationale for selecting the optimal intraoperative tasks is based on the tumor's biology, size, location, and vascularity but predominantly considers the detailed relationship between the connectivity of the tumor and the functional networks [7, 8]. A preoperative discussion with the patient and his/her relatives can search for specific brain functions that are more relevant for the patient, and some neuropsychological tests can be reformulated to fit into intraoperative tasks in order to help preserving this specific ability (e.g., voluntarily switch between different languages for multilingual patients, spatial awareness for sportsmen or dancers, working memory for businessmen) [4].

Neuropsychological assessment is the normatively informed application of performance-based assessments of various cognitive skills. Typically, neuropsychological assessment is performed with a battery approach, which involves tests of a variety of cognitive ability areas. These ability areas include skills such as language, memory, attention, executive functions, processing speed, reasoning, judgment, problem-solving, inhibition, visuospatial cognition, perception, motor, and somatosensory skills, representing functions of both the dominant and the non-dominant hemisphere. In addition to the objective neuropsychological scores, the individual lifestyle must also be subjectively defined by the patient before any treatment on the basis of individual parameters such as job, hobbies, or wishes.

The elaboration of a minimal common protocol includes testing not only language but also other cognitive functions, which could be applied preoperatively, intraoperatively, and postoperatively in awake tumor surgery. A minimal standard pre-and postoperative protocol to test language function may include a subjective questionnaire, complaints inventory, assessment of handedness, spontaneous speech, a naming task with calculation of reaction time, a fluency task, a timed semantic association task, and a timed reading task [4]. Less time-consuming alternatives such as IQ measurement or Mini-Mental State Examination (MMSE) are less sensitive and less valid for adults with brain tumors. The essential neurocognitive domains to be evaluated include attention, executive functions, verbal memory, and motor speed.

In order to protect the patient from fatigue, the mapping must be done in a targeted, systematic, and concise manner. The neuropsychologist, or speech therapist, present in surgery must note the onset of neurological disorders, classify them, and promptly inform the neurosurgeon. The tasks must be trained by the

Table 34.2 Appropriate neuropsychological tests for each brain region

Frontal lobe
Motor function, speech articulation, picture naming task, double task (working memory), semantic task of association and judgment (left), and writing
Occipital lobe
Visual field, picture naming task (left), and reading (left)
Temporal lobe
Picture naming task, Double task (working memory),Semantic task of association and judgment (left), Reading (left posterior) and Visual field (posterior).
Insular lobe
Picture naming task, sensorimotor functions, and double task (working memory)
Parietal lobe
Sensorimotor functions, picture naming task (left), double task (working memory), line bisection task (right), calculation (left)

patient before the surgery, taking note of the percentage of correct answers and response time. A speech therapist or neuropsychologist should inform the surgeon about the result of each test (right, wrong, phonemic or semantic paraphasia, line deviation, hemianopsia, etc.), and the neurosurgeon must mark the functionally essential regions with sterile pieces of paper (marked with numbers). Coello et al. [4] described and discussed brain regions associated with the testing (Table 34.2).

For the mapping of language and cognitive function, the patient's compliance is very important, as is the close cooperation among members of the participating medical team. A psychosocial anamnesis, searching for the general anxiety, humor behavior, and the possibly compliance of the patient [25], is important to select only appropriate candidates.

It is highly recommended to introduce members of the surgical team to the patient and to explain the intraoperative procedure as well as the testing to the patient at least a day prior to surgery. The patient might feel uncomfortable experiencing involuntary movement or the inhibition of voluntary movement and language, which could lead to feelings of fear and might be accompanied by an alteration of vital and vegetative signs such as nausea, hypertonia, and tachycardia. Patients should be carefully examined and asked about any sensation, feelings, or movements, especially the contraction of pharyngeal muscles, which might not be observed by the examiner [25].

Intrinsic cerebral tumors such as gliomas may not only focally interact with the perilesional brain but may also affect the functional connectivity of the whole brain. Nonetheless, when objective neuropsychological assessments have been performed in tumor patients, behavioral deficits have regularly been observed after brain surgery. To prevent this, all the process should be clearly explained to the patient and his or her family before surgery in order to define what the patient would consider "tolerable" and to adapt the extent of resection according to his individual "oncofunctional" balance.

This optimization of the onco-functional balance that aims at improving the quality of life can be conceived only by investigating the organization of the parallel and interactive delocalized cortico-subcortical networks at the individual level, by means of intraoperative electrical mapping and real-time cognitive monitoring in awake patients [7]. In this spirit, surgical resection is pursued until critical structures have been reached, up to functional boundaries but not before. Thus, a perfect understanding of the hodotopical organization of the brain and the dynamics of the neural subcircuits underspinning specific subfunctions, their interactions, as well as their potentials and limitations of functional compensation is mandatory to optimize the benefit/risk ratio of neuro-oncological surgery [5].

Recently, atlases of brain plastic potential have been built from glioma patients, based upon residual tumor voluntarily left because of positive responses obtained during intrasurgical electrostimulation mapping [7]. These atlases demonstrated the pivotal role of the subcortical white matter tracts for postlesional reshaping. From an oncological perspective, these atlases represent a tool to predict functional the degree of resection. In other words, white matter bundles have a lower plastic potential than cortical areas, leading to the description of a "minimal common brain" necessary for the basic cognitive functions [13]. This knowledge is essential in surgery because gliomas diffuse along the subcortical fibers, which constitute the deep limits of surgical resection; therefore, these tracts represent the main obstacle to radical tumor removal.

Assessment of the possible effect of brain glioma on the neurocognitive status at baseline is not a luxury. If a detailed neuropsychological evaluation is done before any treatment, such slight but objective disturbances are very regularly found. In other words, the standard neurological examination is too crude to be capable to detect subtle cognitive impairment, especially tiredness and deficit of attention. Nonetheless, accurate neurocognitive examinations have rarely been reported in glioma surgery, even when the neoplasm involved the presumed language areas. Thus, rate of glioma patients with actual cognitive disturbances is probably underestimated in the classical literature. These deficits seem to be related to the invasion of gliomas along the white matter tracts. Indeed, recent investigations have demonstrated a significant relationship between scores of semantic fluency and the infiltration of the subcortical fibers underpinning the ventrolateral connectivity, that is, the inferior fronto-occipital fasciculus (IFOF). In the same way, impairment in mentalizing (a key function related to understanding and performing complex social interactions) was mostly due to the degree of glioma infiltration of the right frontoparietal connectivity. These data show that the migration of gliomas along the white matter bundles can generate specific cognitive or emotional disturbances depending on the neural subnetworks invaded by the tumoral cells. Thus, with the goal of preserving the neural functions while performing a more radical tumor removal, an original philosophy consists of achieving an individual functional mapping-guided resection and not an image-assisted surgery as classically suggested [7].

34.5 Anesthesiology for Awake Neurosurgery

Neurosurgery with awake brain mapping techniques has advanced over 27 years [11]. Initially, anesthesia was limited to local scalp and regional blocks using lidocaine and bupivacaine, but no sedation was performed [16]. Neuroleptic anesthesia using droperidol was the initial sedation regimen until monitored anesthesia care using propofol was introduced in the early 1990s. Propofol was immediately recognized for its sedating characteristics in addition to its ability to suppress seizure activity [10]. In the early 2000s, dexmedetomidine was identified as another potential alternative for patient sedation with the addition of the short-acting opioid remifentanil [19]. Regardless the anesthetic regimen used, over-sedation during the sleep phase of surgery can lead to carbon dioxide retention, particularly problematic in overweight patients, patients with significant tumor mass effect (greater than 2 cm of midline shift), or in cases with high-volume blood loss risk. The laryngeal mask airway (LMA) became commercially available in the early 1990s and offered a potential solution for this problem, allowing airway management and potential hyperventilation during the asleep phase of surgery. Additionally, a nasal trumpet may be placed for patients who snore excessively or retain carbon dioxide.

Awake craniotomy comprises four anesthetic phases:

- Phase one: Local anesthetic (LA) is injected at the rigid pin fixation insertion sites and at the skin incision site. Relevant scalp nerves are blocked (supraorbital, supratrochlear, zygomaticotemporal, auriculotemporal, lesser occipital, and greater occipital nerves), and the patient is placed in the head holder. Subsequently, the craniotomy and opening of the dura mater are performed.
- Phase two: Brain mapping with the awake patient.
- Phase three: Tumor resection in the either (re-)anesthetized or awake patient.
- Phase four: Closing of the cranium and scalp in the either (re-)anesthetized or awake patient.

Several anesthetic methods can be used for awake craniotomy:

(a) Monitored anesthesia care (MAC): The patient is sedated and remains spontaneously breathing throughout the entire procedure whereby risks related to general anesthesia (GA), e.g., airway issues, are avoided [26]. The disadvantage of this approach is patient discomfort, especially in the first phase of the operation, despite relatively deep sedation. Heavy sedation can lead to airway obstruction, which is a serious complication because it is of paramount importance to avoid hypoxia and/or hyper-capnia in these patients.

(b) Asleep-awake-asleep (AAA) technique: The patient is anesthetized during phase one. A laryngeal mask (LM) or an endotracheal tube (ET) is used for ventilation. During phase two, the patient is awakened and the LM or the ET is

removed. Brain mapping is performed while the patient remains awake. After mapping is no longer required, the patient is anesthetized, and the LM or ET is reinserted [9]. The advantage of this technique is that the heavy sedation and the related airway problems during phase one are avoided. The LM or ET, however, must be replaced under difficult circumstances as the head is fixated and partly covered with sterile draping. Coughing and stress upon removal of LM or ET can increase intracranial pressure or lead to protrusion of the brain. Additional mapping or monitoring of the neurological status during tumor resection is not possible.

(c) Asleep-awake (AA) method: This method has been described in detail by Olsen [4] and is still being used at Glostrup Hospital. First, anesthesia is induced and maintained with infusion of remifentanil and propofol. After anesthesia induction, LA is positioned and the craniotomy is performed. The patient is then awakened and LM removed for brain mapping, carried out by the neurosurgeon in close cooperation with the neuropsychologist. Nasal prongs are placed to administer oxygen and monitor end-tidal CO2. An infusion of a small dose of remifentanil is started if the patient feels any discomfort. Subsequently, tumor resection is performed, guided by further intermittent mapping. If the patient develops neurological deficits, tumor resection is terminated or redirected. The AA technique has advantages if compared to the AAA technique, because it is only occasionally necessary to put the patient under general anesthesia during closure, reducing airway management if compared to AAA. After the surgery, the patient usually is observed at the intensive care department for 24 hours.

Potential candidates for awake craniotomy include those who have eloquent brain areas near the tumor. Once the neurosurgeon has identified a candidate, the patient is informed about the method and its benefits and risks [21] (Table 34.3). A thorough neuropsychological and pre-anesthetic examination is performed. It is essential that patients are well-selected and prepared. Psychologically stable, well-cooperating patients are offered an awake craniotomy.

Sedatives are rarely used as premedication because sedation may interfere with the mapping. Antiemetics and analgesics are administered after the induction of the anesthesia. Remifentanil and propofol can be started or removed rapidly, making these drugs well-suited for awake craniotomy. Often mannitol and dexamethasone are given to reduce the risk of brain edema. If there is a history of seizures, the patient is loaded with phenytoin. Oxygen saturation, electrocardiography, end-tidal

Table 34.3 Intraoperative complication rates during awake craniotomy

Related to anesthesia	Related to surgery
Respiratory depression	Bleeding
Hypertension	Focal seizure
Nausea and vomit	General seizure
Pain	Neurological impairment
Agitation	
Cough	

CO_2, invasive arterial blood pressure, and diuresis are monitored during surgery, and hypotension is treated by means of vasoconstrictor.

Airway management is fundamental for safety. When the patient is sedated and therefore at risk of respiratory depression, it may be difficult to mask ventilate or insert a LM or an ET because the head is fixated in the head clamp. In procedures where the MAC method is used, these problems primarily arise in phase one where heavy sedation is often necessary because the patient is in much pain. The incidence of airway obstruction has been found to range from 0% to 20% and desaturation from 0% to 28% [15, 22]. In comparison, airway obstruction in the AAA and AA procedures was seen in 0–7% of cases, whereas desaturation has not been reported [12, 23].

The selective α-2-receptor agonist dexmedetomidine is also a good option for awake brain surgery. Its main properties include sedation, anxiolysis, and analgesia without causing respiratory depression.

Pearls

- Several techniques are available to map brain functions, but direct electrical stimulation (cortical or subcortical) (DES) is gold-standard technique for the identification and preservation of eloquent cortical and subcortical structures during surgery.
- Brain mapping needs to be tailored to patient's cortical and subcortical anatomy, functional dominance, biological characteristics of the tumor or epileptic foci, patient's neurocognitive reserve, pre-existing neurological deficits, and patient's wishes.
- Deep knowledge of cortical and subcortical anatomy is fundamental to allow the surgeon to understand functional disturbances during surgery and to appropriately use each neuropsychological test according to the network being mapped.
- If Penfield technique is used for DES, a transient deficit induced in the same site repeated on three separate stimulation occasions is accepted as sufficient evidence that this region is essential for the patient's normal function.
- The train of five (To5) technique can be used in anesthetized patients for mapping and monitoring motor function using motor evoked potentials.
- The elaboration of a minimal neuropsychological common protocol includes testing not only language but also other cognitive functions, which could be applied preoperatively, intraoperatively, and postoperatively in awake tumor surgery.
- In order to protect the patient from fatigue, brain mapping must be done in targeted, systematic, and a concise manner. The neuropsychologist, or speech therapist, present in surgery must note the presence of neurological disorders, classify them, and inform the neurosurgeon promptly.
- Specialized neuro-anesthesia is critical for a successful awake craniotomy and requires clear communication between the surgeon and anesthesiologist to ensure ideal intraoperative mapping conditions.

- Several anesthetic methods can be used for awake craniotomy: monitored anesthesia care (MAC), asleep-awake-asleep (AAA), and asleep-awake (AA).
- Remifentanil and propofol can be started or removed rapidly, making these drugs well-suited for awake craniotomy. Airway management is fundamental for safety.
- The team should be flexible and prepared to act with prompt response to perioperative events if and when they occur [2].

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Chapter 35
TBI in Pediatric Patients

Giselle Coelho and Eduardo Varjão Vieira

35.1 Historic/Epidemiology

Traumatic brain injury (TBI) is the leading cause of pediatric morbidity and mortality in the United States (US) and worldwide. In the United States, there are over 2 million cases of TBI per year, resulting in approximately 50,000 deaths [14, 19] and representing an important public health problem [13]. About 75% of all children hospitalized with trauma have a head injury [17].

The annual worldwide frequency of pediatric TBI is evaluated at 691 per 100,000 cases, with a noteworthy increment (60%) of emergency department (ED) visits from 1374.0 to 2193.8 per 100,000 from 2008 to 2010, respectively, in the United States [19, 38].

Severe TBI is a driving cause of mortality and disability in children. In the United States, it accounts for more than 2.8 million crisis office visits, more than 35,000 hospitalizations, and 2200 deaths per year [18, 39]. The estimated costs are colossal. Recently, the National Emergency Department Sample published an estimate of the initial hospital cost associated with TBI in the United States to be nearly $30 billion [34, 37].

It is important to emphasize that disability post-pediatric TBI is approximately 20%. Furthermore, different types of TBI are reported among different pediatric age groups. For example, in young infants, up to 30 per 100,000 babies under 1 year of age (average age 2–4 months) endure non-accidental injury (NAI) per year [29]. Considering patients 1–4 years of age, traumas result from falls, accounting for

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94–132 hospitalized children per 100,000. School-age children are more inclined to being hit by a car and to bicycle-related wounds. The secondary TBI in children reaches the highest peak during adolescence referring to motor vehicle accidents. Mortality rates for pediatric TBI range between 3.1 and 5.7 per 100,000 among different age groups between 0 and 14 years and dramatically increase to 24.3 per 100,000 in the 15–19 age group, according to the Centers for Disease Control and Prevention (CDC) [38, 41].

The pediatric traumatic brain injury (TBI) is remarkable, because the sequelae may extend beyond the evident physical impairment in the affected children to disrupt their psychosocial functioning. Damage may or may not resolve on the short term, often leaving them with long-term, deleterious deficits.

However, children may have very different outcomes when compared to adults, and the mechanism of injury may lead to completely different short-term and long-term results. In this context, it could be related to the concept of neuroplasticity, which is most prominent and active during time-sensitive periods of pre-natal and post-natal development [27, 38].

Aiming to standardize the medical care and therapeutic strategies, in 2003, the first *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents* were published. Since then, the recommendations have been reexamined, and numerous studies have shown that guideline adherence is associated with reduced mortality and improved neurological outcome [22, 28, 34].

In general, the evidence resource used to write the guidelines consists of observational cohort studies and not randomized controlled trials. Therefore, there are some controversial questions in the management of TBI (especially in severe presentations), for example, the usefulness of the placement of an intracranial pressure (ICP) monitoring device and how to manage it and what are the most appropriate ICP therapies [34].

In this chapter, we discuss the main aspects of the TBI and its peculiar management in pediatric population.

35.2 Mechanisms of Injury

Interesting biomechanical and anatomical highlights of the growing cranium and brain lead to recognizing types of TBI in children compared to adults. Considering the proportion of head measure and weight to body between adults and children, it is possible to notice that the pediatric population is bigger than adults, which puts children's heads at higher risk of damage in any sort of trauma. Smaller cranium thickness and open sutures in newborn children allow more versatility and deformation, and then better absorption of the impact effects [11, 23].

Nevertheless, this could be considered unfavorable when combined with the fact that pediatric brains are less myelinated and contain a much bigger water content

compared to adults (89% versus 77%), which makes the pediatric brain more vulnerable to diffuse and shear damages [36, 38].

There are two principal phases of TBI. The first is the *primary injury* which involves the initial mechanical impact, resulting in loss of tissue and neuronal death. This primary injury cannot be repaired, and the damage is permanent.

The second phase is related to a *hyperexcitatory and inflammatory-mediated secondary injury* that occurs during the period of hours to days after the initial injury [43]. Consequently, there is a high blood-brain barrier (BBB) permeability and cerebral edema, resulting in rising intracranial pressure, potentially exacerbating cerebral ischemia [47].

The area of the brain surrounding the primary injury (penumbra) is susceptible to hypoxic events, and preservation of this region is one of the primary objectives in the management of TBI. For decades, secondary brain injury prevention has been the subject of significant research. Despite promising data from numerous preclinical researches, no therapy has improved outcomes in patients thus far.[31] Furthermore, we still have little corroboration about the effectiveness of every perspective of TBI management [13, 35].

The impact-loading mechanism occurs when the head is hit by a moving object or smashes into a stopped object, though impulsive-loading, moreover alluded to as "whiplash," happens when the head moves in reaction to fast movement of another body portion that is affected by an external action. After an impact-loading trauma, contusions, lacerations, and cranial fractures and coup-contrecoup brain damage (central and/or diffuse, parenchymal wounds, subarachnoid hemorrhage, etc.) are frequently observed [24].

The probabilities of injury types differ according to acceleration during an impulsive-loading trauma. Diffuse axonal injury (DAI) is related to coronal plane accelerations, while bridging veins damage and resultant subdural hematomas are more likely to occur in sagittal plane accelerations. The so-called shaken baby syndrome and DAI are representative sequelae of impulsive-loading trauma forced upon a weakly myelinated brain with less density [21, 38]. Once again, the differences between the pathophysiological responses to TBI in pediatrics compared to adults should be highlighted. Children tend to more frequently develop diffuse brain swelling [3] and early post-traumatic seizures after a moderate-to-severe TBI [5]. In addition, there is vulnerability to suffer consequences from low cerebral perfusion pressures, when compared to adults [15, 38].

35.3 Physical Examination/Image

Trauma victim care begins at accident stages. There is a consensus that the outcome for trauma patients is improved with a systematic initial evaluation from prehospital and hospital care teams. The primary assessment and the beginning of therapeutic approach to life-threatening injuries are described as ABCDE (Airway, Breathing,

Circulation, Disability, and Exposure). It is a mistake to initiate the approach of a patient with altered consciousness through neurological assessment. There are causes of coma that can be reversed following the steps of initial care, and it is not always associated with neurological problems. Secondary assessment begins after stabilization of the initial condition to search for other lesions that may endanger life or functionally affect the patient [6].

Children admitted to the emergency department and diagnosed with moderate and severe TBI should receive neurosurgical care. Neurosurgeons must obtain a complete history, sought characteristics of trauma mechanism, prior diseases, medications, and risk factors (i.e., seizures, otorrhagia, rhinorrhagia, unconsciousness, penetrating injury, nausea, vomiting, and headache). After obtaining history, it is important to detail neurological examination.

Neurological examination should begin by inspecting the child. Reactions or spontaneous interaction with the environment, general mobility, and posture will be evaluated. It is not possible to apply the techniques and maneuvers of adult neurological examination in children, particularly in neonates and infants. It is necessary to gain the child's confidence and through play and different maneuvers evaluate the different items of the neurological examination, which were not possible on simple inspection [42]. Pediatric facies, cranial bone, and scalp should be evaluated, searching for open or closed fractures, including signs of basilar skull fracture, and especially hematomas, and lacerations, because these can be cause of blood loss.

Despite some criticism, the Glasgow Coma Scale is still being used to report impairment of the level of consciousness and coma in traumatic injuries even in pediatric population, since some modifiers can be used to patients aged $\leq$2 years [12]. Neurological examination is a challenge in the unconscious child and should be direct to identify differences between focal and diffuse injuries. One of the important findings in infants is the presence of tense fontanelle that leads to intracranial hypertension suspicion. Other important findings are the clinical signs related to acute herniation of brain tissue. As transtentorial herniation progresses, the changes signs include pupillary changes and bradycardia. Foramen magnum herniation causes downbeat nystagmus, bradycardia, bradypnea, and hypertension. Clinical features of subfalcine herniation may be unilateral or bilateral weakness. Inappropriate motor responses such as decorticate or decerebrate rigidity reflect significant brainstem injury [33].

Head computed tomography enables quick detection of intracranial injury, signs of mass effect, and/or cerebral edema for pediatric patients with brain trauma [32]. This kind of image can affect therapeutic strategies, monitor effects of treatment, and evaluate progression or regression of some intracranial infections, although serial CT scans are controversial. Repeating CT scan can be useful when there is no evidence of neurological improvement despite medical and surgical treatment, neurologic deterioration, persistent or increasing intracranial pressure, or a condition that impedes neurologic status assessment, because of sedation or neuromuscular blockade. The adoption of scoring systems is useful to predict outcomes in patients

with severe trauma brain injury, including children. Higher Rotterdam head CT score rates are associated with greater mortality [16, 25, 32, 40], and the Marshall CT score has shown that scores 3 and 6 predict the most unfavorable outcomes [40].

35.4 Differential Diagnosis

Abusive head trauma is an important cause of severe brain injury. Although many of the clinical signs of accidental and abusive head injury are similar, the abusive mechanism should be investigated if suspected, because your diagnosis regards child protection [2].

35.5 Treatment Options

35.5.1 Severe Traumatic Brain Injury (sTBI)

Neurosurgeons have an important role in the TBI care process. The main goal is to recognize when acute herniation of brain tissue is imminent or ongoing to act as soon as possible. The latest released guideline for acute medical management of sTBI in children was published in 2019 [32]. In the following topics, monitoring, thresholds, and interventions are discussed.

35.6 General Recommendations

35.6.1 Ventilation

The cerebral circulation is controlled by homeostatic mechanisms, including partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), cerebral autoregulation, metabolism, and blood viscosity. The sensitivity to changes in $PaCO_2$ makes it the most potent physiologic cerebral vasodilator [46]. Ventilation should be established in children who present deteriorating consciousness, respiratory failure, or decerebrate or decorticate posturing to decrease the incidence of brain impairment [45]. The settings for ventilation should be PaO_2 between 90 and 100 mmHg and $PaCO_2$ between 35 and 40 mmHg [33]. Prophylactic severe hyperventilation with $PaCO_2$ less than 30 mmHg in the initial 48 hours after injury is not suggested [32].

There is little data on the relationship between reversal of transtentorial herniation in children after TBI and the use of hyperventilation, although it is recommended as a component of the approach to the emergency treatment supported by

studies in adults. If hyperventilation is used in the management of refractory intracranial hypertension, advanced neuromonitoring for evaluation of cerebral ischemia may be necessary [32].

35.6.2 Blood Transfusion Therapy

Data suggests that children have higher oxygen consumption and a higher cardiac output to blood volume ratio than adults [9]. Cerebral blood flow rises as a result of improved rheology of the blood flow in cerebral vessel and as a compensatory reaction to decreased oxygen dispensation during anemia [46]. Although only a few studies of hemoglobin target have been published, evidence suggests a minimum hemoglobin target of 7.0 g/dl [33].

35.6.3 ICP Monitoring

Present data confirms that achieving adequately controlled ICP reduces mortality and is associated with better functional outcomes among children between 2 and 12 years with ICH [8]. However, there is not a specific recommendation for infants and children regarding CT and ICP monitoring after sTBI [32]. The presence of an open fontanel in infants does not preclude the development of intracranial hypertension and cerebral herniation [44], although the use of monitoring in children less than 2 years old has been less expected [32]. Importantly, in children younger than 5 years old with TBI, cerebral perfusion pressure (CPP) should be maintained greater than 40 mmHg, whereas in children between 6 and 17 years of age, a target greater than 50 mmHg is suitable [44].

35.6.4 Advanced Monitoring

As discussed earlier, the key issue of neurocritical care management of TBI patients is to optimize cerebral perfusion [33, 44]. Advanced neuromonitoring can improve overall outcomes [31]. Transcranial Doppler (TCD) may be performed within 72 hours of admission, and its frequency and duration will be guided by children clinical presentation and eventualities. It is useful for evaluation of cerebrovascular hemodynamics using measurements of intracranial cerebral arteries. Although there are no criteria for vasospasm for children, TCD appears to be a feasible method for CPP to predict response to medical treatment of intracranial hypertension [1, 32]. Sustaining a level of brain tissue oxygenation ($PbrO_2$) greater than 10 mmHg is

suggested when it is monitored. At this time, there is no strong evidence to support $PbrO_2$ monitoring, although its addition to other advanced neuromonitoring tools (i.e., microdialysis, examination of cerebral autoregulation, and electrophysiology assessments) is helpful to optimal critical care [32].

35.6.5 Hyperosmolar Therapy

Both mannitol and hypertonic saline (HTS) have been commonly used to manage raised intracranial hypertension. However, there is an absence of supportive mannitol clinical trials versus placebo, or other therapies in children. Bolus of 3% HTS has been recommended as hyperosmolar therapy in patients with intracranial hypertension. The dosing for acute use varies between 2 and 5 mL/kg over 10 and 20 minutes, and a continuous infusion of 0.1 and 1.0 mL/kg of body weight per hour can be used varying in accordance to minimum dose needed to maintain ICP less than 20 mmHg. Another option for hypertonic saline is bolus of 23.4% HTS for patients with existing hypervolemia. This has been shown to be effective for refractory ICP, and it can be delivered in a dosage of 0.5 mLkg with a maximum of 30 mL. The physiologic effect of higher serum sodium and serum osmolarity is to pull water from the intracellular and interstitial compartments of the brain, reducing cerebral edema [30]. However, the observation of a sustained high serum sodium greater than 160–170 mEq/L (>72 hour) may lead to complications like deep vein thrombosis, thrombocytopenia, and anemia, and it must be avoided [32].

35.6.6 Analgesics, Sedatives, and Neuromuscular Blocking

With the use of other interventions, the combination of benzodiazepine and opioid for sedative/analgesic therapy allows manipulation of ventilation, optimization of cerebral metabolic rate, cerebral blood flow, and intracranial pressure [20, 33]. Nevertheless, studies documented that bolus administration of midazolam and/or fentanyl during ICP rises has risks of cerebral hypoperfusion. Drugs and dosing should be chosen according to pediatrician experience and knowledge as there is absence of outcome data [32]. Nevertheless, long-term propofol use is not appropriate based on guidance from US Food and Drug Administration, because it may cause propofol infusion syndrome, presenting with lactic acidosis, cardiac dysfunction, and renal failure [20, 32]. Neuromuscular blockage has been demonstrated to achieve and maintain paralysis, and it can optimize patient-ventilator interactions and prevention of shivering, although at the expense of significant increased rates of respiratory tract infection, cardiovascular collapse, and myopathy [26].

35.6.7 CSF Drainage

Often, when ICP is increased, CSF drainage through an external ventricular drain can be used as a therapy. There are concerns regarding the potential for EVD to raise complications such as hemorrhage and infection [32].

35.6.8 Seizures Prophylaxis

A potential advantage of prophylactic treatment may be in decreasing early (within 7 days) post-traumatic seizure (PTS). Many risk factors have been shown to increase occurrence of PTS, including location of the lesion, cerebral contusions, retained bone and metal fragments, depressed skull fracture, focal neurologic deficits, loss of consciousness, GCS greater than 10, severity of injury, length of post-traumatic amnesia, subdural or epidural hematoma, penetrating injury, and age. There is a reduced seizure threshold in children, and it is especially challenging to recognize subtle clinical seizures. Thus, continuous electroencephalogram recording should be used, recognizing seizures occurrence in up to 70% of cases. There is no evidence that levetiracetam may be safe as an antiepileptic drug to use in TBI over phenytoin; therefore either is acceptable [32, 33].

35.6.9 Temperature Control/Hypothermia

Maintaining an adequate temperature between 35 °C and 38 °C after a traumatic brain injury is one of the goals to avoid secondary damage to the injured brain [32, 33]. Guidelines have used hypothermia as a treatment for ICP control, but its use in a prophylactic moderate way (32–33 °C) did not improve overall outcomes over normothermia. Moderate hypothermia therapy has been considered safe in children. It should be implemented at a rate of 0.5–1.0 °C every 12–24 hours or slower to avoid complications, and, if phenytoin is administered, monitoring and dosing have to be adjusted to minimize toxicity, particularly during the rewarming period [32].

35.6.10 Barbiturates

The suppression effects at cerebral circulation caused by high-dose barbiturates can be used if intracranial pressure is suboptimal after 4 hours dosing of osmotherapy and hyperventilation. Nevertheless, high-dose barbiturate therapy can cause hemodynamic instability, including decreased cardiac output, hypotension, and increased intrapulmonary shunt. Thus, barbiturates, particularly pentobarbital and thiopentone, are suggested in hemodynamically stable children, and consequently

vasopressors are commonly needed to maintain adequate CPP [32, 33]. The suggested dose for pentobarbital is a loading dosage of 10 mg/kg and a maintenance dose of 1 mg/kg/hr., aiming a burst suppression on electroencephalography. After 24 hours of reduced ICP, its infusion can be titrated and then withdrawn over 24–96 hours [33].

35.6.11 Decompressive Craniectomy

Decompressive craniectomy is used as a stand-alone procedure or associated with other surgical interventions such as hemorrhage evacuation to treat neurologic deterioration, strong suspicion of herniation, or intracranial hypertension (> 25 mmHg) refractory to optimal medical management [4, 32]. The surgical goal should be an anterior-to-posterior craniectomy diameter of at least 12 cm in children in a similar pattern to adults. There have been series showing that it is reasonable to adapt craniectomy size to age during infancy. However, a gain in a horizontal brain diameter of more than 1 cm might indicate serious brain herniation through the bone gap when an optimal hemicraniectomy is accomplished, associating with unfavorable outcome and long-term neuropsychological disturbances, similar to a post-traumatic pupillary dysfunction at admission [7, 10]. Autologous cranioplasty, even if complicated by bone flap resorption, is the chosen modality of cranial reconstruction, due to osteointegration, growing skull, and cost-effectiveness [10]. Although this can successfully decrease ICP, decompressive craniectomy is also associated with hygroma, hydrocephalus, and multiple types of infection (i.e., ventilator-associated pneumonia, bone flap sepsis).

35.6.12 Nutrition

Physiologically, in children, BTI increases metabolism, which requires caloric support during critical ill phase. Moreover, growing children have more nutritional needs for development. Because of this, early enteral nutritional support (within 72 hours from injury) is beneficial to reduce mortality and improve outcomes [32].

Pearls/Tips

- Considering the proportion of head measure and weight to body between adults and children, there are important population differences regarding cranioencephalic trauma and mechanisms of injury.
- Abusive head trauma should be recognized as a differential diagnosis in pediatric population.
- Autologous cranioplasty secondary to decompressive craniectomy should be chosen as the best option in children due to cranial growth pattern.

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Part III
The Outcomes

Chapter 36
Prognostic Models in Neurocritical Care

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36.1 Introduction

In medicine, prognostication involves an attempt to essay the course of a disease. In rudimentary medicine, any neurocritical patient would have a poor prognosis, and in the eventual need for neurosurgical intervention, the outcome for death was practically inevitable [1, 2]. With evolution, there was a more significant structuring of the medical science and technical knowledge accumulated from observational studies [3, 4]. Anesthesia was developed, which started to provide comfort and stability for surgeries. Operative techniques, surgical instruments, and anatomical and physiological knowledge for neurosurgical intervention were improved [5].

However, a great number of patients undergoing anesthesia and neurological surgical treatment continued to die. Then it was realized that the improvement of postoperative clinical care was necessary to provide higher survival rates for patients affected by brain injuries. Thus, the increasing intensive care units (ICUs) with monitoring of multiple parameters, with advances at each different time with more quantity and quality of information that assist intensive care physicians on details of patients' clinical conditions, have emerged [6]. The development of imaging tests, mainly represented by magnetic resonance imaging (MRI) and computed tomography (CT), provided a better understanding of the structural damage to the brain parenchyma. At this time, only medical history and physical examination were no longer sufficient to interpret the situation and provide adequate medical care. The data provided by imaging exams (added to clinical history and physical examination) allowed a more accurate diagnosis, and consequently, decision-making might be made with greater precision [7].

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The higher number and better quality of information related to clinical history, physical examination, monitoring parameters, and radiological images inspired the emergence of scales to classify patients, subdividing them into groups according to the type and severity of injury and subsequent mortality risk [8–11]. In this way, a quick perspective of the diagnosis evolution and treatment of neurocritical patients may be evaluated. Also, progress has been made, from incipient and fully expectant assistance to a full critical care assessment, including monitors, subsidiary exams, and surgical techniques.

At the same time, epidemiological studies have enabled the analysis of the distribution and determinants of the occurrence of neurological injuries, whether traumatic or spontaneous, and their repercussions on populations or groups of individuals. This contribution characterized the natural history of the neurological disease as regards its onset, duration, recurrence, complications, disabilities, and mortality. Epidemiological studies provide arguments for organizing social programs aimed at disease prevention and treatment. As they change the behavior of agents and causal mechanisms, the identification of the dimensions of mortality and morbidity related to the host, and the relationship between these and the causal environmental factors are evident [12].

The creation of a reliable multivariate prognostic models to quantify the risk of an individual patient is necessary and desirable in order to guide better treatment of the individual affected by neurological injuries. In the neurocritical patient, establishing adequate prognosis is a priority because many diseases are fatal or lead to severe disability. Patients, families, and healthcare professionals want to know what to expect, and these expectations often influence short- and long-term healthcare decisions [13].

In this chapter, we will discuss prognostic models in traumatic brain injury, ischemic and hemorrhagic stroke, and spontaneous subarachnoid hemorrhage.

36.2 Traumatic Brain Injury

36.2.1 Prognostic Models

Since the pioneering study by Jennett et al. for the prediction of mortality and functional outcome after severe traumatic brain injury (TBI), several prognostic models have been developed with the main objective of providing an objective measure of the final prognosis of the individual evaluated at the beginning of his hospitalization [14]. Despite the numerous predictive models, only a few have been developed in large groups of patients with TBI. Most models were developed using small sample sizes and thus have unsatisfactory statistical power, which does not allow generalization [14, 15]. However, the IMPACT and the CRASH models, in contrast, are two examples of prognostic models created for TBI based on large populations, unlike most studies [9].

The IMPACT database includes patients with severe and moderate TBI (GCS ≤ 12) from three observational studies and eight randomized controlled trials conducted between 1984 and 1997 [9]. The primary endpoint for the prognostic analyses (available online – http://www.tbi-impact.org/?p=impact/calc) was the 6-month Glasgow Outcome Scale (GOS), which the outcome is subdivided into five categories: 1, dead; 2, vegetative state; 3, severe disability; 4, moderate disability; and 5, good recovery. In patients whose 6-month assessment was not available, the 3-month GOS were analyzed (611, 19% of the patients).

In the CRASH prediction model (available online www.trialscoordinatingcentre.lshtm.ac.uk), the authors also included patients with mild TBI (GCS > 12 points), finding that advanced age, lower GCS score, absent pupillary reactivity, and the presence of severe extracranial injury were factors associated with poor prognosis. Computed tomography findings were also associated with unfavorable results, including the presence of small hemorrhagic foci, the obliteration of the third ventricle or basal cisterns, the presence of traumatic subarachnoid hemorrhage (tSAH), deviation of the midline brain structures, or an unoperated intracranial hematoma [16].

Rosi et al., in a cohort study, evaluated 1275 patients with TBI and abnormal CT scans upon admission to the emergency unit and analyzed the outcome on mortality. Logistic regression was undertaken to determine the adjusted weight of each independent variable in the outcome. According to this author, four variables were found to be significant in the model: age (years), Glasgow Coma Scale (3–15), Marshall Scale (MS; stratified into 2,3 or 4,5,6; according to the best group positive predictive value), and anisocoria (yes/no). A logistic model (*USP index* to head injury) was developed to estimate the probability of death of patients according to admission characteristics [17].

For the penetrating TBI (pTBI), only one prognostic model has been published: predicting survival after acute civilian penetrating brain injuries (SPIN) score [18]. This score was drawn from retrospective analyses of 413 patients in 2 US level 1 trauma centers, which represent the largest contemporary pTBI cohort. The variables included were self-inflicted injury, transfer from another hospital, sex, injury severity score, motor GCS, pupillary reactivity, and admission INR. While the original publication of the SPIN score did not include external validation, the same group of authors carried out external validation in a cohort of 362 patients from 3 US level 1 trauma centers [19]. In this external validation, both discrimination and calibration were excellent (AUC-ROC 0.88; Hosmer-Lemeshow p value >0.05).

36.2.2 Clinical Predictors

Some clinical predictors are simple and determine the prognosis using the Glasgow Coma Scale only. According to Narayan et al., the low GCS score has a significant correlation with the result of a worse prognosis in the patient with severe TBI. The predictive value for the worst outcome in individuals with an initial score between

6 and 8 was 26%, and for patients with a score between 3 and 5, it was 77% [16]. In another study, Gale et al. found that the death rate was 88% for those with a GCS score between 3 and 5 [20]. Other authors have studied the simplified motor score (SMS), which is a 3-point measure based on the GCS motor response [21]. According to Caterino et al., the SMS has the same predictive power for neurological outcomes, as in full GCS [22].

When it analyzed the pupillary pattern, it is well established that changes in pupillary reactivity indicate damage to the brainstem or its compression, and there is an association with an unfavorable prognosis [23]. Balestreri et al. showed that patients presenting with anisocoria have a 67% higher risk of mortality, and the presence of anisocoria may be enough to deduce that the patient has an intracranial lesion that can be operated or at least a lesion without a surgical indication but severe enough to justify the strict neurological observation [24]. This finding was also demonstrated by Chesnut et al., who found that 43% of individuals with pupillary asymmetry greater than 3 mm in their series had lesions with an expansive intracranial effect [25].

Recently, Sobuwa et al. developed a predictive model for severe TBI, which includes pupil reactivity, GCS score, and peripheral arterial oxygen saturation values which were the predictive factors for the prognosis [26]. According to Hoffmann et al., in a retrospective cohort of 24,115 patients, the best clinical variables for predicting outcomes are the SMS (GCS motor component) and pupil reactivity [27]. Majdan et al. observed the same results in 445 patients who were analyzed to predict mortality after 6 months in patients with severe TBI. In children, non-reactive pupils are also related to higher mortality but in a lower percentage than that detected in adults [28].

The prognostic value of extracranial injury in TBI is controversial [15, 29, 30]. Some studies have shown that the presence of large extracranial lesions was associated with a worse outcome. However, in others, the outcome depended mainly on the severity of primary brain damage and was not aggravated by the presence of extracranial lesions [31, 32]. According to Van Leeuwen et al., the prognostic effect of the extracranial lesion had more influence on the mortality of patients with TBI when the intracranial lesions were not so extensive. That is, they would be patients where potentially death would not occur due to TBI but due to the magnitude of the extracranial lesions, for example, where there are visceral abdominal injuries with significant hemodynamic or respiratory instability [33].

Confirming these data, Lingsma et al., in the POCON study (508 patients), demonstrated that the extracranial lesion did not have a prognostic value in the studied population. However, in subgroups with less severe patients, there was some additional value attributable to an extracranial lesion in the prognosis of the patient with TBI, which therefore makes us a reason that in the evolution of patients to death, extensive brain injury in critically ill patients is responsible for the outcome. In contrast, in patients with TBI but without extensive injury and in a less severe neurological state, extracranial lesions were the leading cause of the bad evolution [34].

According to Chesnut et al., age is a significant predictor of mortality and functional outcome in patients with TBI [25]. Other studies show that advanced age is associated with a worse outcome, and threshold values range from 30 to 60 years. The likelihood of a poor outcome gradually increases with the patient's age, especially after the age of 60 [13, 30]. Luerssen et al. published a relevant study that compared the impact of age on patients with TBI, where severe pediatric patients had lower mortality when compared to adults (28% versus 47%) [35].

The association between sex and the fatal outcome has been described in some studies. However, there are discrepancies between them [34, 36]. It should be noted that men are more likely to have severe TBI in car accidents and assaults, and interestingly there is evidence that women who survived after severe TBI have a worse quality of life and worse functional results when compared to men. Despite this, the individual's sex has not been well established as a reliable prognostic factor [34].

According to Sorani et al., ethnic origin and results after TBI have an association with outcome after TBI. They showed that black patients have a worse outcome than Caucasian or Asian patients. However, among the reasons for this association are access to the emergency medical unit and to rehabilitation care, which may justify the differences [37].

36.2.3 Tomographic Predictors

The CT scan classification of TBI was introduced in 1991 by Marshall et al.. It evaluates the presence or absence of lesion with an expansive effect, compression of basal cerebrospinal cisterns, and deviation of brain structures from the midline [38]. Since then, studies have analyzed their data according to this tomographic classification. According to the *Brain Trauma Foundation*, the obliteration of the basal cisterns and the presence of subarachnoid hemorrhage are the strongest predictors of the patient's prognosis by CT [39]. It should be noted that many studies have joined their efforts on analyzing abnormalities in the CT used, with broad and complex categorizations that make interpretation difficult for non-imaging specialists.

The importance of the Marshall scale is reflected (Table 36.1) by its presence in the CRASH model [36]. In addition to Marshall, there are other systems developed to assess cranial CT, such as the Rotterdam score (Table 36.2) (validated externally in some studies) [40, 41] and the Helsinki score (Table 36.3), which has been externally validated [42].

The prognostic models in the TBI have several limitations, one of the main ones being that in the analysis, only admission variables are included, disregarding the generally long hospital period. These restrictions are secondary to the lack of standardized data collection during hospitalization in the studies from which these models were developed. Additional variables, such as infectious complications, as well as the trajectory of improvement or worsening during medical care, can improve the actual models.

Table 36.1 Marshall scale – for traumatic brain injury

Marshall Score	CT findings
Diffuse injury I	There is no visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift of 0–5 mm and/or lesions densities present; no high or mixed density lesion >25 cm^3 may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift of 0–5 mm; no high or mixed density lesion >25 cm^3
Diffuse injury IV (shift)	Midline shift >5 mm; no high or mixed density lesion >25 cm^3
Evacuated mass V	Any lesion surgically evacuated
Unevacuated mass VI	High or mixed density lesion >25 cm^3; not surgically evacuated

Marshall et al. [38]

Table 36.2 Rotterdam CT score – for traumatic brain injury

CT findings	Score
Basal cisterns	
Normal	0
Compressed	1
Absent	2
Midline shift	
No shift or shift <5 mm	0
Shift >5 mm	1
Epidural mass lesion	
Present	0
Absent	1
Intraventricular blood or SAH	
Absent	0
Present	1
Sum score	Total + 1

Maas et al. [10]

Table 36.3 Helsinki score – for traumatic brain injury

CT findings	Score
Mass lesion type(s)	
Subdural hematoma	2
Intracerebral hemorrhage	2
Epidural hematoma	−3
Mass lesion size	
Hematoma volume < 25 cm^3	0
Hematoma volume > 25 cm	2
Intraventricular hemorrhage	
Absent	0
Present	3
Suprasellar cisterns	
Normal	0
Compressed	1
Obliterated	5
Sum score	−3 to 14

Yao et al. [42]

36.3 Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is responsible for 10–15% of all strokes. It is a significant cause of injuries related to morbidity, mortality, and disability worldwide [43, 44]. Despite advances in medical knowledge, treatment for this most deadly and disabling stroke remains strictly favorable, with no evidence-based interventions currently available [45]. Medical and surgical treatments, such as blood pressure control, osmotherapy, and hematoma evacuation, have not shown definite benefits for improving the outcome [46]. Also, several promising neuroprotective agents for ICH have failed to demonstrate efficacy in phase III studies.

There are more than 20 prognostic models in ICH, most of which were developed in cohorts of isolated centers. The ICH score (in this case, the "original" ICH score) was the most validated in independent cohorts (Table 36.4). As in the initial publication in 2001, the primary objective was to define mortality within 30 days [47]. In 2009, this score was validated as a prognostic model of functional outcome in 12 months [48]. Alternative models to the oICH include the ICH Grading Scale (ICH-GS) which compares whether the bleeding is supra- or infratentorial [49], the modified ICH [50], and the Essen ICH score that incorporates the clinical examination using the National Institutes of Health Stroke Scale (NIHSS) instead of the Glasgow Coma Scale (GCS) [51]. There are also the ICH Functional Outcome score (ICH-FOS) that incorporates the GCS and NIHSS [52] and the modified Emergency Department ICH (EDICH) score that incorporates the values of the international normalized ratio (INR) [53], Functional Outcome in Patients with Intracerebral Hemorrhage (FUNC) score [54], and the maximally treated ICH (Max-ICH) scores [55].

Table 36.4 ICH score – for hemorrhagic stroke

Variables	Score
GCS	
3–4	2
5–12	1
13–15	0
ICH volume	
>30	1
<30	0
Intraventricular hemorrhage	
Present	1
Absent	0
Infratentorial origin	
Yes	1
No	0
Age	
>80	1
<80	0

Hemphill et al. [47]

The modified ICH score, ICH-FOS, Essen ICH score, ICH-GS, and the Max-ICH score assess in-hospital mortality and poor functional outcome characterized by a modified Rankin scale from 3 to 6 in up to 12 months of follow-up. The EDICH score assesses mortality in 48 hours, risk of neurological worsening in 48 hours, and poor functional outcome (mRs > 3) at hospital discharge. The FUNC score was developed to predict functional independence in patients who survived [53, 54].

In the last decade, these scales were compared in the most varied ways. It was observed that the determination of a more reliable prognostic model is difficult. According to Bruce et al., in a study of 67 patients with intracerebral hemorrhage, the comparison of the 8 prognostic scales observed that the Essen ICH score had better discrimination to predict intrahospital mortality, mortality in 3 months, and functional outcome in 3 months. Despite this, the differences between the scales were minimal [56]. In a study of 501 patients, it was observed that the FUNC score and the ICH-GS presented better discrimination in mortality and functional outcome in 3 months than the oICH [57]. In a meta-analysis published in 2015, it was concluded that the oICH and ICH-GS presented more considerable evidence and predict early mortality [58]. However, a retrospective analysis with 2556 patients from the INTERACT2 trial observed that the modified ICH score presented better discrimination for adverse outcomes in 90 days than oICH and ICH-GS [59]. In a study carried out in Singapore with 1338 ICH patients, it was observed that the ICH-GS is slightly better than the oICH in predicting outcomes [60]. In an Italian cohort of 170 ICH patients, it was observed that the modified EDICH score was a better model than the oICH, ICH-GS, and FUNC score when assessing early in-hospital deterioration, mortality, and poor functional outcome [61].

Currently, it is not clear what importance should be attached to prognostic scores in daily practice. The use of prognostic scores to guide decisions about care goals has been increasing [62]; however, so far, the available scoring systems have not been superior to clinical judgment in terms of predicting functional results [63]. Although prognostic scores typically include hospital admission variables, the score's timing should be applied to more accurately predict outcomes during hospitalization of a patient with ICH is currently unclear. As the medical literature evolves from a simple warning against premature withdrawal from care [46], recent studies have suggested that reassessing the patient within 24 hours [64] or even 5 days [65] dramatically improves the accuracy of the prognosis. New studies can explore optimal prognostic periods, including when, on average, patients with ICH achieve "prognostic stability." Besides, there is a growing appreciation for how patient comorbidities and systemic diseases associated with patients with ICH during hospitalizations in intensive care units (i.e., infections) can ultimately determine the patient's outcome [66]. There have been some recent attempts to include physiological measures, such as the APACHE II Score, in the ICH prognostic models, with variable success (e.g., the Prognosticating Functional Outcome after the ICH score) [67]. Although these attempts can make subsequent rating scales more complicated to calculate, there is a possibility that further research will help to increase prognostic accuracy.

Finally, while the subjective clinical judgment of physicians with experience in neurocritical care units correlates well with the scores described, it is not clear whether the judgment of intensive care physicians not exclusively dedicated to neurocritical patients would be the same. In this context, the development of more accurate prognostic models is essential.

36.4 Subarachnoid Hemorrhage

Clinical outcomes after subarachnoid hemorrhage have improved significantly in the past four decades [68, 69]. The first widely used scales of clinical classification, such as the Hunt and Hess Scale (Table 36.5) [70] and WFNS (Table 36.6) [71], are still the most reliable predictors of death and long-term poor functional outcomes [72]. When comparing both, there is no difference in forecasting the results using the modified Rankin scale and the Glasgow Outcome Scale at discharge, at 6 and 12 months. However, on the WFNS scale, there was a substantial overlap between grades II and III, III, and IV, with similar results for the grades awarded [73]. The original scales, Hunt and Hess and WFNS, have been modified to allow a more accurate and reliable distinction between notes. The modified WFNS scale was the one that obtained the highest discrimination between grades I, II, and III, as well as IV and V when attempting to predict the average GOS and mRS at 90 days [74]. Another scale based on the GCS (Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage-PAASH scale) was able to predict outcomes in 6 months

Table 36.5 Hunt-Hess clinical grading in subarachnoid hemorrhage

Grade	Clinical findings
1	Asymptomatic or mild headache
2	Moderate to severe headache, or oculomotor palsy
3	Confused, drowsy, or mild focal signs
4	Stupor (localizes pain)
5	Coma (posturing or no motor response to pain)

Hunt and Hess [70]

Table 36.6 WFNS clinical grading in subarachnoid hemorrhage

Grade	Glasgow Coma Scale	Motor deficit
1	15	Absent
2	13–14	Absent
3	13–14	Present
4	7–12	Present or absent
5	3–6	Present or absent

Teasdale et al. [71]

with the GOS and mRS scale [75]. The FOUR (Full Outline of UnResponsiveness) score that assesses eye-opening, eyelid movements (E), motor examination (M), brainstem reflexes (B), and breathing patterns (R) was designed for further evaluation of level of consciousness [76]. The application of this score on the day of the ictus and on the 7th and 14th days after the hemorrhage also showed a good correlation with mortality and functional outcome (mRS and GOS) at 1 and 6 months [77].

The SAH Physiologic Derangement Score (SAH score) was conceived to identify potentially harmful disorders during the acute phase of subarachnoid hemorrhage. According to Claassen et al., this score is an excellent predictor of death and severe disability (mRS) 3 months after SAH [78]. There are few prognostic models developed to predict the long-term outcome after SAH. While the SAH score is based on the patient's age, admission GCS, and comorbidities [78], the HAIR score [79] composed of Hunt-Hess score, age, presence of intraventricular hemorrhage, and rebleeding within 24 h and the ABC score, including GCS, troponin I, and protein S-100ß [80] obtained on admission, focus on predicting hospital admission, the possibility of discharge, and long-term mortality.

Two new models have recently been developed: the Functional Recovery Expected after Subarachnoid Hemorrhage (FRESH) score and the Subarachnoid Hemorrhage International Trialists (SAHIT) score. Both aim to predict the long-term functional outcome and are considered the most comprehensive [81, 82]. The FRESH score is composed of the Hunt-Hess graduation, APACHE II of admission (only the physiological sub-score), age, and the presence of rebleeding within 48 hours. This score aims to predict the functional outcome through mRs at 12 months after SAH, physiological sub-score of APACHE II on admission, up to 48 hours to add up to 9 points, and the prognostic functional result (mRS) in 12 months after SAH. The score was developed based on 1526 SAH patients, and those in which care was limited or withdrawn were excluded. After the elaboration of this score, its validation was performed in a different cohort with 413 patients. Subsequently, additional scores for cognitive impairment and quality of life in 12 months were developed (FRESH-cog and FRESH-Quol) [82].

The SAHIT score was derived from grouped data from 10,936 patients from various randomized clinical trials, prospective observational studies, and hospital records and validated externally in 3355 and 338 patients. The result was evaluated by GOS in 3 months. This model includes age, hypertension, WFNS classification (in the central model), aneurysm size and location, and Fisher's classification (in the neuroradiology model) and treatment modality (if microsurgery or endovascular in the complete model). The addition of these variables to the primary model slightly increased the accuracy of the results [81].

The Hunt-Hess, WFNS, and Glasgow Coma Scale are still the most widely used to predict long-term prognosis in clinical practice and clinical trials. Most of these scores were developed in cohorts of <500 patients with SAH in single centers or few centers and some with retrospective data. More recently prognostic models, such as the FRESH score and the SAHIT score, have a higher discriminative capacity, and their results have been validated externally. There are still several gaps in the prognostic models of SAH, such as the lack of clinical status of the patient before

cerebral hemorrhage. The elaboration of prognostic models is generally based on retrospective analyses of a large population of patients, and those patients whose restrictive life support measures have been implemented are not excluded. Also, scores are based on admission variables, but hospital complications are not considered. Parallel to the fact that there is no ideal model, it will still be necessary to define the main time to include the variables in the prognostic models.

36.5 Ischemic Stroke

Prognostic scores after acute ischemia (AIS) aim to predict mortality, as well as short- and long-term functional recovery [83]. Also, some models can predict the expected outcomes at discharge and after 90 days based on the treatment instituted in the acute phase [84, 85]. Considering the observed cohorts in which the neurological deficits are very heterogeneous, delay in treatment, as well as the level of assistance provided, especially in those centered on patient preference, makes the existence of a single and widely applicable model practically non-existent. In this context, the generalization of the available models is not feasible. Several items can be considered, especially if neuroimaging is included, making the scores very complicated in daily clinical practice [86]. The most relevant ethical question is whether there is an accurate model for decision-making, especially concerning limiting life support [87]. Although there are more than 100 published papers describing scores to predict functional outcome and mortality after AIS [88], these scores should not be an integral part of the clinical routine and are not included in the main stroke guidelines [89]. Every prognostic model has strengths and weaknesses. Therefore, a quantitative comparison of the models' prognostic accuracy is a challenge and allows for an incorrect interpretation [83, 87].

A recent review looked at several scales to predict the outcome 30 days after stroke. The eight scales (PLAN, iSCORE, iSCORE-r, ASTRAL, SPI2, THRIVE, SOAR, and modified SOAR) include clinical admission data and, however, exclude neuroimaging data [87]. In their external validation using the Virtual International Stroke Trials database, it was observed that these scales have different discriminative power. In detail, in the ASTRAL score, there was a significantly better prognostic discrimination in mortality, the modified Rankin scale, and the Barthel Index 90 days after the event ictus [87, 88]. Another study, which looked at prognostic models that included imaging methods in their scores have been published. Seven scales (DRAGON, MRIDRAGON, SAD, NAV, HAT, HIAT, HIAT2) were evaluated in which the neuroimaging data of the acute phase or during outpatient follow-up were compared with seven scales based on clinical information (ASTRAL, BOAS, iScore, NIHSS, sNIHSS-4, SPAN, THRIVE) [90]. As a result, no discriminatory power was detected in the analyzed scales and concluded that it should apply specific choices for the most varied clinical situations. In internal and external validation, the discriminating power of a prognostic model is also a fundamental issue. When we analyze the most different cohort studies, countless prognostic models,

with countless variables included, we observe that the best predictor of the prognosis is the application of the NIHSS clinical scale of admission [83, 87, 88, 90, 91].

Besides, it is essential to highlight the need for periodic recalibration of the model since there is always impact of new therapeutic approaches (such as thrombectomy) that might affect the outcome. Despite methodological improvements recently [88], even better-validated stroke models with good prognostic value should not be used exclusively for clinical decision-making, especially in the acute phase [91]. In this context, new models are needed to reduce the chance of individual classification errors in patients with stroke [87, 88].

36.6 Conclusion

The implementation of predictive models in neurocritical patients is a great challenge, and physicians must adopt these models in general clinical application but be aware of the observation of their professional technical limitations. Thus, the model must be straightforward and secure so that it becomes, in fact, a tool of medical assistance practice. It should be considered that studies on traumatic or non-traumatic brain injury, especially prognostic models, tend to have many variables, due to the heterogeneity of the brain injury per se. Thus, they induce errors that may not detect an effect that is present and that interferes with the prognosis. An adequate prognostic model must be simple and, therefore, of general use, feasible, and at the same time including prognostic factors of real importance, without being contaminated by confounding factors inherent to the conditions of the social environment in which the data are collected.

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Chapter 37
Rehabilitation and Palliative Care in Neurocritical Patients

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37.1 Introduction

Neurocritical illness, defined as critical illness primarily involving the brain, spinal cord, or neuromuscular system, is often a sudden event for patients and their families. The onset of neurocritical illness is usually abrupt, and although advances in neurocritical care continue to improve outcomes, mortality rates for common conditions are high. Moreover many patients never achieve functional independence [16, 19]. Patients often experience significant physical and cognitive impairment in quality of life [7, 8]. Even for those who survive without permanent disabilities, recovery from neurological injury can be prolonged and accompanied by physical and psychological distress for patients as well as for families. For these reasons, rehabilitation and palliative care are important components of high-quality care in the neurocritical care environment.

Rehabilitation medicine is based on the "bio-psycho-social" approach to the individual in an attempt to integrate him or her into society in a productive and independent manner. In the WHO international classifications, health states (diseases, disturbances, lesions, etc.) are mainly classified in the ICD-10 (International

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Classification of Diseases, Tenth Revision), which supplies an etiological structure. In addition to these aspects, rehabilitation medicine encompasses some components relevant to health related to well-being and quality of life and describes them as health domains and health-related domains. These domains are described based on the perspective of the body, of the individual, and of society and include functionality and disability. Functionality is a term that includes all the functions of the body; similarly, disability is a term that includes the limitations to activities or restrictions in the social participation of the individual. Functionality and disability associated to the health states are classified in the ICF. Therefore, the ICD-10 and the ICF complement each other. Together, the information on the diagnosis and on functionality provides a broader and more significant image of the health of the person or population, which can be utilized in the decision-making process. According to the American National Consensus Project for Quality Palliative Care [1], palliative care means patient- and family-centered care that optimizes quality of life by anticipating, preventing, and treating suffering. Palliative care throughout the continuum of illness involves addressing physical, intellectual, emotional, social, and spiritual needs.

In this way all patients and families with a neurocritical condition that adversely affects daily functioning and independence or will predictably reduce life expectancy and quality of life should have access to rehabilitation or palliative care services appropriate to their needs.

In general, the literature shows that functional improvement of the disabilities after a neurological condition happens in most cases in the first months after the acute event regardless of the etiology of the lesion and recommends that the evaluation by the medical rehabilitation professional be done while still in the acute intrahospital phase, after clinical stabilization. We must remember, though, that the evolution and prognosis will depend on numerous factors such as lesion etiology and location, patient's age, associated clinical comorbidities, and acute phase treatment among other key points. Therefore many patients can have good evolution and new functional gains even after many years post-lesion [2, 4, 23]. In this sense specific clinical and radiographic tools are predictive of neurological outcome [24]. The Glasgow Coma Scale (GCS) is a highly reliable predictor of in-hospital mortality but has limited use for predicting long-term functional outcome of survivors [21, 22]. The NIH Stroke Scale and Rankin Score [20] are two of the most reliable instruments to predict outcome after ischemic stroke [3, 10, 11]. But predictors of functional outcome and quality of life are heavily weighted toward motor ability and do not take into account other important outcomes such as cognitive and emotional function and quality of life, which are very important to patients and families [5].

Moreover the patient's values, goals, and preferences provide important key points for communication and decision-making for rehabilitation and palliative care introduction. The community of providers, researchers, educators, payers, and policymakers should promote patient- and family-centered care as its own quality dimension that requires measurement and improvement.

37.2 The Multidisciplinary Approach

The teams must be interdisciplinary so that the treatment develops the motor, cognitive, emotional, social, and family areas at the same time. Apart from variations, the literature recommends a minimum team composed of physicians, physiotherapists, occupational therapists, psychologists, nurses, nutritionists, and speech therapists. Other professionals such as art therapists or physical trainers can also contribute [6]. The team must develop realistic and achievable goals within the limitations imposed by disease, environment, and social support. These objectives are dynamic and are reprogrammed according to the clinical evolution, favorable or not. The team acts in an interdisciplinary manner, that is, in a collaborative effort between members, where they integrate services and work with the patient.

There are categories of this therapeutic model:

1. Preventive interventions: Mitigate the effects of expected disabilities. These include approaches to improving physical functioning and overall health and guidelines for preserving strength and flexibility.
2. Restorative interventions: Procedures that seek the return of the patient with a good prognosis to the physical, psychological, social, and vocational functional level prior to the disease.
3. Supportive interventions: Designed to teach patients to accommodate their disabilities, maximize their autonomy, and minimize debilitating changes in their progressing illness.
4. Palliative interventions: When disability increases and disease is advanced, actions and goals focus on minimizing or eliminating complications and providing support and comfort.

So the rehabilitation and palliative care of neurocritical patients are processes that seek the following [13, 14]:

1. Prevention of physical or cognitive secondary complications
2. Reduction and early recovery of sensory, motor, and cognitive disabilities
3. Acquisition of new neurological functionality (neuroplasticity and relearning)
4. Maximum utilization of the residual potential of body functions (training and improvement)
5. Compensation for and adaptation to physical and cognitive disabilities
6. Independence, reintegration into the community, and quality of life for patients and family members
7. Relief of disabled conditions or symptoms as pain, fatigue, dyspnea, dysphagia, urinary or fecal incontinence, spasticity, emotional lability, contracture, and pressure ulcer among others
8. Effective communication about goals of care
9. Alignment of treatment with patient preferences
10. Family and caregiver support
11. Planning for transitions

The determiners for choosing the treatment intensity and goals are different for each patient and depend on [13]:

1. Patient expectations
2. Motivation
3. Degree of attention
4. Seriousness of deficits
5. Functional prognosis
6. Strength for physical activity

It is important to highlight the use of effective communication techniques as a critical core competency to improve the quality of treatment as well as patient and family satisfaction and good outcomes.

37.3 Main Clinical Complications Found in Neurocritical Patients

1. Immobility syndrome: Neurological lesions can induce physical inactivity. The effects of inactivity and physical deconditioning generate the so-called immobility syndrome in the intensive care unit (ICU) which is associated with neuromuscular weakness, post-intensive care syndrome, functional limitations, and high costs. Early mobility-based rehabilitation in the ICU is feasible and safe [9, 12]. The consequences of the immobility syndrome are numerous:
    - Muscles: With bed rest, lean mass loss is 10% per week, with muscle torque reduction 24% after 5 weeks. With inactivity, myotendinous shortening and periarticular and intraarticular changes occur, stimulating collagen proliferation in the presence of hemorrhages and edema. Reduced activity levels, coupled with muscle weakness, generate dynamic muscle imbalance, worsening the risk of contractures. There is also an increase in urinary calcium excretion after 3 days of rest (disuse osteoporosis).
    - Respiratory tract: Weakness and reduced intercostal and diaphragmatic activity and supine posture favor altered breathing pattern, resulting in decreased functional capacity, atelectasis, worsening cough efficacy, and hypoxemia. Breathing deeply becomes painful; pleural effusions and increased risk of pneumonia are common.
    - Genitourinary apparatus: Urinary stasis, hypercalciuria, lithiasis, urinary retention, and infections.
    - Gastrointestinal tract: Inactivity leads to reduced peristalsis and sphincter hypertonia. Radiopaque studies show increased colonic traffic and a decline in propulsive waves. Nausea, vomiting, and anorexia are frequent and, combined with negative nitrogen balance, contribute to cachexia and hypoproteinemia.

- Cardiovascular system: Hemodynamic effects occur from a few days of rest, with plasma losses of up to 500 mL in 1 week. As a result, there is an increase in blood viscosity, orthostatic hypotension, tendency to hypotension, reduction in cardiac output, increased risk of syncope, and low cerebral perfusion. Hemodynamic responses to physical exercise are also affected after 10 days of rest, with lower systolic volume, cardiac output, and maximum O2 consumption. It is estimated that it takes 3–4 weeks to reestablish physiological hemodynamic responses.
- Hypercoagulability states, higher blood viscosity, and venous stasis lead to increased risk of thrombosis.
- Nervous system: Deficits in balance, coordination, and perception, leading to increased risk of falls. Bed confinement and immobilization lead to sensory deprivation, attention/concentration deficits, delirium, and other cognitive deficits.
- Skin: Low mobility associated with malnutrition, incontinence, and sensory deficits increase the risk for pressure ulcers.

2. Pain: Pain is highly prevalent among patients, reaching a rate of 40% to 90%. Knowledge of the etiological history and therapeutic management help in symptomatic control. Rehabilitation techniques complement the therapeutic drug arsenal and facilitate analgesia .
3. Malnutrition, dysphagia, and cachexia: Muscle cachexia reflects myofibrillar protein degradation, and it is an important clinical picture among neurological patients. The musculoskeletal catabolic response in these patients results in muscle loss and weakness, represented by increased gene expression and activity of the ubiquitin and calcium/calpain pathways, which degrade sarcomeric myofilaments. Due to the presence of malnutrition, dysphagia, cachexia, and other associated metabolic conditions, functionality is very compromised.
4. Impairment of cognitive functions (attention, executive, memory) and self-care skills: Neuropsychological exams many times are necessary for a quantitative evaluation. Cognitive or emotional deficits ranging from moderate to serious will interfere notably in the functional reorganization and in the learning of new abilities.
5. Motor, sensory, and walking disorders, tremors, risk of falling, and incoordination for appendicular and axial movements: Motor function evaluation must include the complete evaluation of motor control and muscle strength, mobility, balance, sensitivity alterations, lack of coordination, altered patterns of synergy of movement, tonus alterations such as hypo- or hypertonia, alterations in joint range or in the muscular or articular biomechanics, involuntary movement, or postural alterations such as Pusher syndrome.
6. Consciousness level: Disturbances in the consciousness are more likely when the cerebral lesion is either extensive or when there is a cerebral edema or increase in intracranial pressure.
7. Sensory and visual disturbances: Many sensory and visual impairments can occur. The most common are homonymous hemianopsia and olfactory and

auditory acuity disturbances. Pupil response exams, ocular motility test, direct observation of retina, and corrected measurement of auditory and visual acuity and visual field are important. There can be also complex visual deficits such as diplopia, vertigo, visual distortions, as well as color and forms disturbances and anosmia. Severe visual disturbances increase the complexity of the treatment.
8. Osteoporosis
9. Communication, speech, and language deficits: Ability for functional communication is essential for a good outcome of the rehabilitation and palliative process. The evaluation of alterations in communication encompasses a detailed routine of the sensory-motor exam of the speech, medical anamnesis, functional evaluation of language and communication, and the utilization of standardized tests. The aphasias occur due to vascular events in the dominant hemisphere and can cause disturbances in the comprehension and verbal expression, reading, and writing. The evaluation includes naming objects, fluency content, speech prosody, grammatical forms, repetition, and comprehension abilities. Other alterations in communication such as dysarthrias, speech apraxias, dysphonias, and alterations in speech prosody and pragmatics need to be distinguished from aphasia.

37.4 The Principles of Therapeutic Treatment

1. Occupational therapy to guide compensatory strategies and use of adaptations to preserve functional independence in self-care.
2. Provision of assistive technology as crutches, canes, wheelchairs, walkers, ramps, and other architectural adaptations for improve mobility.
3. Orthotics (cruropodalic, suropodalic, upper limb positioning, elbow and knee extensors) assist in segment stability, prevent deformities, assist in gait, and correct reducible shortening. Dynamic orthoses assist in grips and fine motor activities.
4. Multisensory stimulation: for sensory, allodynia and proprioceptive recovery.
5. Physical therapy such as thermotherapy (heat and cold) is adjuvant for analgesia and reduction of inflammatory processes.
6. Manual therapies such as massage and myofascial sliding for muscle relaxation and anxiety control.
7. Neuromuscular electrical stimulation is auxiliary in the work of strengthening and endurance gain mainly in central nerve injuries.
8. Botulinum toxin neuromuscular blocks and phenol neurolysis to reduce focal spastic tone and prevent deformities.
9. Prescription of specific rehabilitation medicines such as antispastics, analgesics, psychostimulants, anticonvulsants, and opioids.
10. Active and passive kinesiotherapy are mandatory for joint amplitude gain, balance and proprioception control, postural changes, orthostatism, and gait.

11. Swallowing therapy and language for diagnosis and treatment of dysphagia, aphasia, and linguistic-cognitive disorders.
12. Neuropsychological assessment to investigate cognitive deficits and executive functions.
13. Psychological accompaniment.
14. Personalized nutritional monitoring, dietary adjustments regarding the introduction of physical activities and variations of energy expenditure, as well as the prescription of supplements and modified diet.
15. Early active and passive mobilization, with aerobic and resistive exercises, transference exercises, and postural changes associated with sensory stimulation, cognitive training, and care for pulmonary expansion and clearance of secretions [9]. Growing evidence supports early mobilization and physical therapy to improve both short- and long-term physical function in patients who are critically ill. In a recent systematic review, early mobilization of patients who required mechanical ventilation improved muscle strength, increased ventilator-free days, and decreased length of hospital stay [15]. Patients who received physical therapy while critically ill had improved long-term outcomes, including the ability to perform independent activities of daily living after hospital discharge. Importantly, physical therapy can be performed safely for most patients who are critically ill [15, 17, 18].

37.5 Summary

Rehabilitation and palliative treatment in neurocritical care is a process that seeks early recovery from deficits and the preparation for reintegrating into community life, in search of the best functional outcome possible, independence, quality of life, and decreased suffering. The literature emphasizes the need for structuring of services specialized in these approaches. Among other recommendations the literature suggests the following:

1. The need to early interventions in the acute phase, aiming to facilitate the recovery and prevention of future complications.
2. The importance of establishing a real prognosis starting at the acute phase.
3. The importance of establishing individualized program or service respecting the needs and the functional prognosis of each individual patient.
4. The importance of utilizing interdisciplinary teams, so that the motor, cognitive, emotional, social, and family areas are treated at the same time.
5. The importance of evaluating the expectations, motivation, degree of attention, grade of deficits and functional impairments, and physical strength for activities as determiners in the process for choosing the type and intensity of the program.
6. The importance of a documented, periodic rigorous, and consistent evaluation in each recovery phase to direct the treatment decisions and monitor the patient's progress.

7. The importance of the presence of family members in the therapeutic process helping patients to actively participate.
8. The need to assistive technology.
9. More studies are necessary in the future for the discussion of questions such as measurements of quality of life, prognosis, the stratification of patients in relation to their response to rehabilitation and palliative care, the intensity of rehabilitation, and measurements of the quality of rehabilitation services.

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Chapter 38
Brain Death and Management of the Potential Donor

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38.1 History

When analyzing the history of medicine and its technological development, as well as in anthropology and philosophy, two subjects have always generated apprehension in the general population. How can the heart beat in a dead person and how to use organs from people who already died to bring life to others waiting for a transplant?

Cardiorespiratory arrest invariably follows brain death (BD). Victor Horsley, in 1894, described cases of cerebral hemorrhages, tumors, and traumatic brain injuries in which there was death due to respiratory failure before the cardio-circulatory arrest [1]. The development of the iron lung in the 1930s, in Boston, and its application in the 1950s, during the polio epidemic, allowed artificial delay of the dynamic process that involves the brainstem dysfunction, respiratory arrest, and subsequent cardiac arrest [2]. In other words, the installation of positive pressure mechanical ventilation prevents respiratory arrest and delays cardiorespiratory death. In addition, vasoactive drugs and metabolic corrections replace vegetative functions of the brain. These measures complete the support of some vital functions of the body in BD [3, 4].

Two French neurologists, Mollaret and Goulon, published in 1959 an article entitled *Le Coma Dépassé*, which defined some aspects of what is evolution to BD at the initial phase. The *coma dépassé*, which can be translated as a state of impaired consciousness "beyond" the coma, was described through the presentation of 23

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patients with severe neurological conditions ventilated artificially. It was characterized by the immobility of the eyeball in the neutral position, mydriasis not reactive to light, absence of a blinking reflex, absence of a swallowing reflex, chin drop, absence of motor response to any stimulus, muscle hypotonia, tendon areflexia, plantar reflexes mistaken, sphincter incontinence, absence of spinal automatism, absence of spontaneous breathing after discontinuation of artificial ventilation, immediate cardiovascular collapse after discontinuation of noradrenaline infusion, disturbance of thermoregulation, and electroencephalographic silence [5].

If from a neurophysiological perspective, the recognition of brainstem function arrest can be understood, the clinical evaluation and the possibility of having some residual neurological function have improved the clinical criteria for defining BD in the last 50 years [6].

After the description by Mollaret and Goulon, the first set of criteria for BD was published by Hockaday et al. in 1965, including the absence of spontaneous breathing for 30 minutes, absence of tendon reflexes of any kind, absence of pupillary reflexes, absence of oculocardiac reflex, and isoelectric electroencephalogram (EEG) for at least 30 minutes [7].

In 1968, an ad hoc Harvard Medical School committee proposed the first definition of BD. It has included clinical features (irresponsive coma, absence of reflexes, and any movements) after 1 hour of observation, absence of breath after 3 minutes of disconnection of the respirator. Isoelectric EEG, exclusion of hypothermia (below 32° C), and suspension of central nervous system depressants (CNSD) were also necessary. Complementarily, the aforementioned clinical tests were repeated within 24 hours [8, 9].

In 1971 the Minnesota Code of Brain Death Criteria included the need for diagnosis of irreparable intracranial injury and the exclusion of metabolic causes. The authors reduced the observation time to 12 hours, established 4 minutes of disconnection of the mechanical ventilation without breathing movements for apnea. They also restricted the need for evaluating only the reflexes that pass through the brainstem, featuring, for the first time, that the injury to this region would be the moment of irreversibility [10].

The next step in the evolution of the BD concept was a document that would have significant international influence. The Uniform Determination of Death Act (UDDA), approved in Hawaii in 1980 by the National Conference of Commissioners on Uniform State Laws, has been the recommendation for use in all US states [11] as it affirms that:

> An individual who has maintained an irreversible arrest of circulatory and respiratory functions or maintained an irreversible arrest of all functions of the entire brain, including the brainstem, is dead. The determination of death must be made according to accepted medical standards.

Irreversibility was established by diagnosing the cause of the coma, which was irrecoverable and sufficient to justify the dysfunction. Regarding observation time, 6 hours was considered enough. For cases of exogenous intoxication, hypothermia, shock, and children, more time was necessary. In 1995, the American Academy of Neurology reaffirmed these criteria, specifying how to perform the apnea test and a series of possible clinical observations which do not invalidate the BD diagnosis,

like Babinski's sign, normal blood pressure, and absence of diabetes insipidus, among others [12].

Although not universally accepted, the equivalence of BD and death is a legal standard throughout most of the Western countries, and even the undeveloped countries are following. There is an increasing prevalence of its legal standard in practice [6, 11, 13].

Despite most countries have a legal provision for BD, institutional protocols for diagnosis are not universal and are often absent, particularly in lower-income countries and in those without an organized transplant network. Even among countries with an organized diagnostic protocol, there is substantial variation in the criteria that are used [3, 4, 6, 11–13]. The most significant differences between the criteria adopted in each country are the number of clinical examinations (ranging from one to three different examiners); intervals between exams (1–24 hours, for adults); mandatory complementary examination (being optional in several countries); preferential type of complementary test to be performed; and qualification of the doctor who performs the examinations (requirements in several countries are previous experience with the clinical tests, minimum time since graduation, and having some medical specialization) [3, 14–16].

38.2 Diagnosis

BD is defined as the determination of human death after irreversible cessation of all clinical brain functions. Its diagnosis is clinical, made at the bedside. When the clinical examination is inconclusive, or the patient has any peculiarity, ancillary tests are required. In some countries, like Brazil, ancillary tests are mandatory by law [3, 4, 14].

Practice parameters of BD have been established in 1995 and revised in 2010 by the American Academy of Neurology. These parameters are the basis of diagnosis protocols worldwide. Some differences exist between countries and even between US states. In adults, there are no published reports of neurologic recovery after a diagnosis of BD, using the criteria published in 1995. In the 2010 revision, the authors observed that confirmatory tests were less reliable and useful than has been suggested in 1995 [6, 11, 12]. According to Shewmon et al., BD diagnosis depends on this triad: the presence of pre-conditions excluding reversible causes of neurological impairment (e.g., traumatic brain injury, subarachnoid hemorrhage, extensive ischemic stroke), clinical examination, and ancillary tests (when necessary) [13].

38.3 Pre-conditions

The diagnosis of coma etiology must be established in clinical evaluation and confirmed by neuroimaging or other diagnostic tools (Fig. 38.1). The uncertainty of the presence of an irreversible lesion, or its cause, makes it impossible to determine

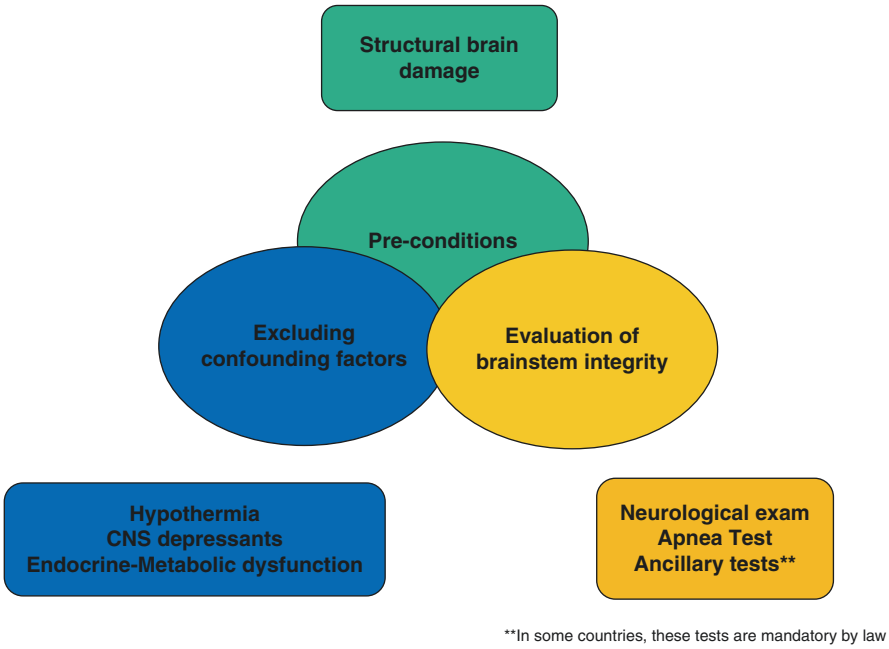

Fig. 38.1 Brain death diagnosis. Pre-conditions, confounding factors, and brainstem integrity are interconnected to correct brain death diagnosis

BD. A minimum period of observation and intensive care treatment in a hospital environment for at least 6 hours in a coma state must be respected. When hypoxic-ischemic encephalopathy is the primary cause enrolled, a minimum period of 24 hours after cardiac arrest or rewarming in therapeutic hypothermia should be expected before starting the BD diagnosis protocol. The cause of the coma must be known and registered [3, 16–18].

38.4 Excluding Confounding Factors

Some clinical conditions can simulate BD or worsen a critical neurological state, confusing the clinical exam. One example is hydroelectrolytic disorders. It is the responsibility of the team involved in BD diagnosis to determine whether these abnormalities are secondary to the natural evolution to BD or a confounding variable that impairs the neurological examination. Severe hypernatremia refractory to treatment does not preclude BD determination, except when it is the only cause of the coma [3, 4, 14–16].

Also, hypothermia can confound the clinical exam. Normothermia must be a goal and sometimes needs external warming. The exact temperature that is appropriate to BD diagnosis is not known, but a minimum core temperature of

Table 38.1 CNS depressants drugs: half-life (in hours)

Classification	Drug	Half-life (hours)
Benzodiazepines	Diazepam	40 hs
	Clonazepam	20 hs
	Lorazepam	15 hs
	Midazolam	6 hs
Other hypnotics	Propofol	2 hs
	Ketamine	2.5 hs
	Etomidate	3 hs
Opioids	Fentanyl	6 hs
	Morphine	3 hs
	Codeine	3 hs
Antidepressants	Amitriptyline	24 hs
	Fluoxetine	24 hs
	Paroxetine	21 hs
Muscle relaxants	Succinylcholine	0.2 hs
	Atracurium	0.5 hs
	Cisatracurium	0.4 hs
	Rocuronium	1 hs
	Vecuronium	2 hs
	Pancuronium	2 hs
Anticonvulsants	Phenobarbital	100 hs
	Thiopental	20 hs
	Primidone	20 hs
Inhalational agents	Halothane	0.3 h
	Isoflurane	0.2 h
	Sevoflurane	0.2 h

32° C (90° F) seems to be adequate, since brainstem reflexes may disappear at lower temperatures [3, 4, 17].

Severe exogenous intoxication, including those by CNSd (e.g., opioid analgesics and other sedatives) commonly used in the ICUs, needs to be ruled out. When CNSd are used in continuous infusion and habitual dosages, it will be necessary to wait for a minimum interval of four to five half-lives after the drug suspension before starting procedures for determining BD (Table 38.1) [14, 16].

If CNSd are used in the presence of liver failure or renal failure, after therapeutic hypothermia, or when intoxication is suspected due to higher than the usual doses, more time is necessary to start the protocol of BD diagnosis. The exact time should be individualized. It takes into consideration the severity of liver and kidney dysfunctions, the doses, and for how long it has been used [14, 16].

38.5 Clinical Evaluation (Neurologic Assessment)

The three cardinal findings in BD diagnosis are coma or unresponsiveness, absence of brainstem reflexes, and apnea [3, 4, 14].

A. *Coma*

Patients must lack all evidence of responsiveness with no motor response to pain. It should be tested in all extremities and cranial segments (usually nail-bed pressure on the four limbs and supra-orbital pressure). The latter is essential in situations of spinal cord injury, in which the synaptic reflex may be absent if spinal shock is suspected.

B. *Absence of brainstem reflexes*

Absent pupillary light reflex: Pupils should be fixed and unresponsive to intense light stimulation (flashlight) and may have an irregular contour and variable or asymmetric diameters.

Absent corneal reflexes: The absence of a blinking response to direct stimulation of the lower lateral corner of the cornea with a drip of cold saline or cotton wool soaked in saline or distilled water.

Absent oculocephalic reflexes: The absence of deviation of the eye(s) during rapid movement of the head in the lateral and vertical direction. Do not perform on patients with suspected or confirmed cervical spine injury.

Absent oculovestibular reflexes (caloric responses): No deviation of the eye(s) during 1 minute of observation, after irrigation of the external auditory canal with 50–100 ml of cold water (±5 °C), with the head placed in a supine position and at 30°. The minimum examination interval between both sides should be 3 minutes. Perform otoscopy before verifying the absence of tympanic perforation or occlusion of the external auditory canal.

Absent gag reflex: Should be absent on stimulation of the posterior pharynx.

Absent cough: With tracheal suctioning (cannot be evaluated only with the manipulation of the orotracheal tube).

C. *Apnea*

This test is the last one to be performed since the apnea test can per se harm the patient [3, 4, 18]. The three steps are described in Fig. 38.2.

Plum and Posner, two of the leading researchers in the comatose patient investigation, suggested the use of blood gas analysis during the apnea test. They established that if $PaCO_2$ were in the normal range 1–2 minutes without artificial ventilation, then it would be enough to produce CO_2 tension elevation to stimulate the respiratory center. Speeds of $PaCO_2$ increase in apnea patients were estimated at 4.1 mmHg/min in the first 4 minutes and 2.7 mmHg/min in the subsequent 6 minutes. Therefore, a patient who starts the test with $PaCO_2$ of 30 mmHg will need 8 minutes of apnea to overcome 55 mmHg; if started with $PaCO_2$ of 35 mmHg, he will need 6 minutes, and if started with $PaCO_2$ of 40 mmHg, he will need 4 minutes of observation [19].

In some patients, ventilatory conditions do not allow a persistent increase in $PaCO_2$ to be achieved without concomitant hypoxia. In these situations, apnea testing can be performed using the connection of a "T-piece" to the orotracheal tube coupled to a continuous positive airway pressure (CPAP) valve with 10 cm H_2O and oxygen flow at 12 L/minute. The apnea test should not be performed on ventilators

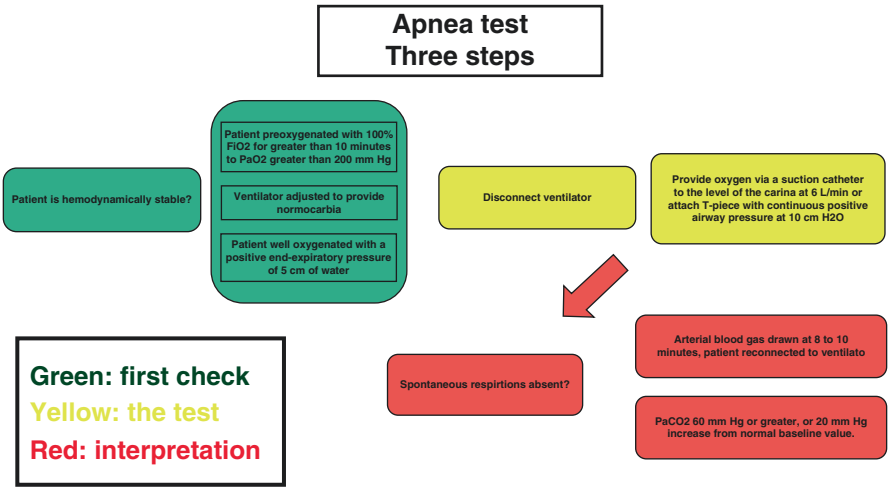

Fig. 38.2 Apnea test. The three basics steps

that do not guarantee oxygen flow in CPAP mode, which results in hypoxemia [3, 4, 11, 14, 16, 18].

38.6 Pitfalls and Special Situations

Some conditions can make clinical BD's diagnosis a difficult task. In cases of severe facial trauma, preexisting pupillary abnormalities, and high-level spinal cord injuries, it is sometimes impossible to assess brainstem reflexes. Exogenous intoxication, especially in the presence of renal or hepatic insufficiency, makes the diagnosis a challenge. In patients with chronic dioxide carbon retention (e.g., COPD and other pulmonary pathologies), the trigger for respiratory incursion can be higher than standardized in several protocols. Some authors recommend that 20 mmHg raise above the baseline $PaCO_2$ value is necessary for situations of chronic carbon dioxide retention. Spinal cord reflexes, including complex-spontaneous motor movements, can be present in BD patients, and it can be clinically difficult to differentiate them from cerebral motor-induced movements. Besides, false triggering of the ventilator can commonly happen and compromise apnea diagnosis [4, 14–16].

One of the most frightening movements for family members and health professionals that does not exclude the diagnosis of BD is Lazarus sign. It is a sequence of movements that lasts a few seconds and can occur spontaneously, during the apnea test, by the passive movement of the head or right after the disconnection of the mechanical ventilation device. It begins with the extension of the arms, followed by crossing or touching them in the chest and finally resting next to the trunk, and flexion of the trunk may also occur. However, not just this movement pattern may occur

[6, 11]. Saposnik et al. describe innumerous movement patterns, including plantar flexor or extensor responses, cremasteric reflex, myoclonus, abdominal cutaneous reflex, and facial myokymia, among others [20].

38.7 Ancillary Tests

Usually, with a known cause of coma and excluding the confounding factors, the clinical exam is sufficient for BD diagnosis. However, some situations can bring doubts, as explained above. In some countries, these tests are mandatory by law as a complement of the clinical diagnosis [3, 4, 14].

The choice of test must be individualized. All tests have their own limitations, and the selection depends on the patient's clinical conditions, transport availability, feasibility of the test in the institution, and expertise of the medical staff. Confirmatory tests are divided in two essential types: brain blood flow and electrophysiological exams [14, 21, 22].

Essentially, if brain blood flow is absent, the brain is considered dead. It occurs when intracranial pressure, due to tissue edema or mass effect, raises and exceeds systemic arterial pressure obstructing blood flow completely.

BD extinguishes all cerebral electric activity also, and this is the basis of electrophysiologic assessment.

Both methods have limitations. Brain blood flow can be nonexistent in hypotensive states leading to a "false positive" diagnosis. "False negatives" also can occur in "open cranium" situations like traumatic skull fractures, decompressive craniectomy, or ventricular drains. Electrophysiologic tests are probably a best option in these situations. On the other hand, blood flow tests are not affected by hypothermia, exogenous intoxication, or metabolic disorders, which can mimic the absence of cerebral electric activity, being a false positive isoelectric electroencephalogram [14, 16, 21].

Brain blood flow tests include cerebral angiography, transcranial Doppler, magnetic resonance angiography, computed tomographic angiography, and nuclear medicine radionuclide scanning. Electrophysiological tests include electroencephalography and somatosensory evoked potentials [4, 16, 21].

38.8 Brain Blood Flow Tests

Four-vessel cerebral angiography is considered the "gold standard" method on BD diagnosis. It is expected no blood flow at carotid bifurcation and beyond at the circle of Willis. External carotid flow is normally present. A minority of BD patients can still have minimal arterial flow (especially in "open skull situations"), delaying the diagnosis and the needs of repeated exams for confirmation. Other disadvantages include the ionic contrast infusion and transportation until the hemodynamics suite.

These aforementioned disadvantages can be a problem in unstable patients. Mean arterial pressure should be monitored strictly during the cerebral angiography [14–16].

In contrast, transcranial Doppler (TCD) is non-invasive and safe and has lower cost than angiography. It can be performed at bedside but demands expertise. Approximately 9% of patients do not have an adequate bone window for Doppler insonation, so the confirmatory test needs to be changed. Small systolic peaks without diastolic flow or a reverberating flow pattern are suggestive findings of BD. The exam sensibility is 70% and specificity is near 100% [3, 4, 6, 9, 16, 23].

There are other possible brain blood flow confirmatory tests not usually standardized in most protocols. Magnetic resonance angiography (MRA) is one of the alternatives. Absence of brain blood flow supports the diagnosis. Small studies suggest good sensitivity, but specificity is still uncertain. Computed tomographic angiography (CTA) is also an alternative, and its sensitivity seems to be similar to other ancillary tests. However, there are many doubts regarding test specificity. Other disadvantages include use of contrast and the needs for transportation [6, 11]. Nuclear medicine seems to be a good alternative for diagnosis, but it is not widely available. Studies using 99mtc-labeled hexamethylpropyleneamine oxime (HMPAO) and subsequent imaging with single-photon emission computed tomographic (SPECT) brain scintigraphy show excellent specificity (no false positives) and sensitivity that are similar to transcranial Doppler [11, 21].

38.9 Electrophysiologic Tests

Electrocerebral silence or a flat electroencephalogram (EEG) has been included in the first guidelines for BD diagnosis. It is still recommended as an ancillary test in most countries, especially in the USA. This silence is defined as the absence of any electrical potential >2 microvolts, non-artifactual, in a 30-minute minimum record time. Nonetheless, it has several limitations. As exposed before, a flat EEG may be present in severe intoxications, hypothermia, and metabolic disorders, what does not imply in an irreversible brain injury, with some studies showing the presence of false positives in these situations. In the ICU environment, the presence of electrical artifacts is common, which can be interpreted as cortical activity leading to false negative results [6, 11, 17, 21].

Evoked potential tests also have limited use in BD diagnosis. Somatosensory evoked potentials (SSEP) and brainstem auditory evoked potentials (BAEP) are the two available modalities for this purpose. Anatomically, these tests show brainstem integrity but cannot test the functional integrity of other CNS structures, which can be a dilemma in brainstem lesions. There are descriptions of patients with evoked potential tests supporting BD diagnosis with preserved EEG. Some authors postulate the combination of evoked potential tests and EEG to BD diagnosis accuracy [22, 24].

38.10 Ethical Aspects

Cerebral death (brain death) is a popular term for the neurological cause of death. Nevertheless, it is doubly mistaken: first for inducing the false interpretation that the brain and not the individual is dead and second for the anatomical mistake, since conceptually in the vast majority of other countries, the loss of function is necessary for the whole brain (from the Greek word enkephalos) and not exclusively cerebral (from the Latin word cerebrum). The use of the term brain death partially corrects this problem. However, the introduction of the etymological debate on this topic is unnecessary [25, 26].

In the medical literature, there is no conceptual difference between the words cerebral death and encephalic death, since both comprise irreversible dysfunction of the brain, brainstem, and cerebellum. However, there are significant differences with two other anatomically restrictive concepts: brainstem death, used in the UK, which does not require brain damage, and neocortical death, which does not require cerebral and brainstem injury. As already noted, extensive injury to the brainstem compromises both breathing and awakening, involving Christian-Jewish fundamentals of life. However, the most striking criticism of the brainstem death criterion is the possibility of diagnostic confusion with locked-in syndrome [27]. Although in locked-in syndrome, tetraparesis and cranial palsy due to pontine lesion coexist with preserved awakening, coma is common in the early stages, making the diagnosis difficult. Also, even though the brainstem lesion is rationally compatible with philosophical-ontological, religious, pathophysiological, and clinical-prognostic concepts of death, the uncomfortable possibility of cortical preservation and consequent maintenance of the content of consciousness, even if inaccessible due to the inability to awakening, makes it a stressful situation [27].

If the acceptance of death criteria anatomically restricted to the brainstem is complex, the criteria for neocortical death are more complicated. This model requires only damage to the brain areas involved in the content of consciousness, affecting what is considered the essence of the human being. The loss of reason and consequent depersonalization would be equivalent to death, implying that patients in a persistent vegetative state are dead, since they maintain breathing and the sleep-wake cycle only.

Although valid, more in-depth discussions on the subject are not the scope of this chapter.

In countries where the legislation is not strict regarding post-BD management, three situations of cardiorespiratory support may occur after BD. The first is the organ preparation for removal and subsequent transplantation. The second, very sad, is a pregnant woman in BD with a viable fetus when life and death cohabit the same body. The third and controversial situation is the maintenance of cardiorespiratory function at the request of family members or the patient himself, given several bioethical arguments in favor of redefining death, as well as its legal repercussions [25].

In the religious sphere, Judaism, Catholicism, and Islamism do not create restrictions to the concept of BD or organ removal [26, 27]. However, Tibetan Buddhism correlates death with decomposition. Gypsies require to keep the body intact for a year after death so the soul can reconstruct its steps. The Shintoism believes that the dead body is impure and dangerous, a fact that contributed to the difficulty in accepting BD and transplants in Japan [17, 28–30].

Despite the robust scientific and philosophical knowledge on the subject, there are indications that its diffusion, both between doctors, other health professionals, and among general population, is unequal. The decision between bioethical duties of non-maleficence and justice, respect for patient's autonomy, and minimization of family suffering belongs to the medical staff. Safety, consistency, clarity, and transparency in information transmission are an essential part.

38.11 Management of the Potential Organ Donor

38.11.1 Monitoring

The monitoring of the potential donor should be as complete as possible. What is observed is often less proactive management, given the severity of the brain injury, in addition to the lack of knowledge about the multiple organ donation processes. The care of a potential organ and tissue donor represents the prospect of, at least, obtaining benefits for many other people. Keeping the donor as close as possible to their homeostasis will enable donation and, probably, good organ preservation in the short, medium, and long terms. These patients should, therefore, receive individualized care, always thinking in the possible beneficiaries. All should be admitted to the intensive care unit, monitored with continuous electrocardiography, peripheral oxygen saturation (SpO_2), necessary vital data, urinary output control, central vein access, and invasive pressure monitoring. The objectives do not differ from those recommended for other critical clinical conditions [17, 29, 31].

38.11.2 Hemodynamic Support

After the establishment of BD, the removal of viable organs for transplantation should occur as soon as possible. Bureaucratic obstacles often delay the entire process. In this context, it is essential to guarantee the supply of oxygen to the tissues, maintaining the physiological functions and eventual dysfunctions that may occur. The longer delay worsens in the inflammatory response and impairs the use of tissues for transplantation. It is recommended that the interval between the diagnosis of BD and the removal of organs should occur 12 to 24 hours [32].

In the hemodynamic management scenario, blood pressure measurement in a non-invasive manner is imprecise in shock situations, usually observed in BD patients. Despite low evidence to support the use of invasive methods to monitor hemodynamic support, the recommendations for this are strong within specialty societies [33, 34].

A striking feature of the patient who is evolving to BD is the occurrence of the so-called sympathetic storm. This disturbance occurs in two phases; the first is related to adrenergic hyperactivity and is clinically recognized by tachycardia, hypertension, increased systemic vascular resistance, and increased oxygen consumption by the myocardium. There is characteristically a considerable increase in systolic pressure than in diastolic pressure. This phase lasts approximately 30 minutes, and subsequently, hypotension occurs. In the acute phase, when blood pressure levels are elevated, there is no consensus in the literature as to whether treatment of this hypertensive crisis is necessary or not. As its pathophysiology is related to the increase in systemic vascular resistance, there may be intra-abdominal organ hypoperfusion. This visceral involvement occurs mainly when systolic levels of 160 mmHg or higher occur for more than 30 minutes. If necessary, the use of esmolol or nitroprusside is recommended for blood pressure control temporarily. Attention should be done to the hypotension that spontaneously occurs after adrenergic discharge of the sympathetic storm [32, 35].

The mean arterial pressure target of potential donor patients is between 60–80 mmHg and at least 100 mmHg systolic blood pressure. The exposed values are not a guarantee of tissue perfusion, and the analysis of tissue perfusion markers should be used. It should be noted that in patients already in BD, there is depletion of circulating catecholamines, which is associated with eventual osmotic diuresis due to hyperglycemia or mannitol infusion, as well as diabetes insipidus. These previous factors hinder the blood pressure control. Left ventricular dysfunction often occurs, due to myocardial contusion, hydroelectrolytic disorders, pulmonary hypertension, or neurogenic myocardial stunting [32].

Hemodynamic support is initially performed with volume replacement, but defining how much volume is needed is a greatest task. Insufficient replacement increases the inflammatory response and worsens organ dysfunction. The initiation of vasopressor drugs without adequate volume replacement can lead to arrhythmias or overact vasoconstriction and organ ischemia [36]. In contrast, excess volume leads to acute pulmonary edema and makes this organ unfeasible for transplantation [29, 31, 32, 35].

The central venous pressure monitored in every potential donor is subject to criticism. Values of 8–12 mmHg are not able to define the responsiveness or non-responsiveness to volume replacement. However, CVP <4 mmHg allows more volume infusion. The infusion volume is stopped if the CVP rises more than 2 mmHg. The use of DeltaPp has higher sensitivity and specificity than the CVP measurement and is a good alternative. In a practical way, 20–30 ml/kg of heated crystalloid solution at 43 degrees for 30 minutes is initially infused. If, after volume expansion, and CVP and DeltaPp values define that there is no possibility of more volume infusion, the vasoactive drug infusion is indicated [14, 17, 30, 35].

There is no consensus on which drugs to choose, and there is no dose limit. There are concerns about cardiac viability after using high doses of beta-agonists (dopamine and dobutamine), mainly when used in the context of low cardiac output and secondary hypoperfusion. Despite this, there is no formal contraindication for its utilization. Vasopressin selection is emphasized since it is a hormone with a vasopressor activity that helps in the management of diabetes insipidus. It reduces the need for catecholamines and, consequently, their complications. One unit is used in bolus, followed by 0.5–2.4 U/hour [14, 30].

Lactate levels, as well as central venous saturation, despite useful in situations of trauma and sepsis, are not adequate to assess the response to fluid resuscitation in potential donor patients [17, 35, 37].

Cardiac arrhythmias are also common in patients undergoing BD protocol. They can lead to reduced cardiac output and hypotension. Its etiology is multifactorial, and among the most frequent causes are hypovolemia, hypotension, hypothermia, catecholamine administration, myocardial contusion, acid-base equilibrium, and hydroelectrolytic disturbances. All types of arrhythmias are found, from supraventricular and ventricular tachyarrhythmias to conduction disorders with bradyarrhythmias. Tachyarrhythmias and bradyarrhythmias should be treated according to *American Heart Association* protocols. Atropine should not be used in bradyarrhythmias, and the temporary transcutaneous pacemaker followed by the transvenous pacemaker may even be indicated [14, 16].

38.12 Temperature Control

Keeping body temperature within physiological limits (36–37.5C) is essential for maintaining the homeostasis. The primordial function on temperature control belongs to the hypothalamus, which integrates information through the skin, organs, spinal cord, and brain and, through its efferences, controls thermal physiology [16].

After BD, or in its evolutionary process, the hypothalamus ceases its functions. In this context, there is a tendency for the organism temperature to equalize with the environment. The early identification of hypothermia is essential and preferably through central temperature measurement obtained in the esophagus, tympanic membrane, or nasopharynx. Measurements in the oral cavity, axilla, or rectum are not recommended [28, 36].

38.12.1 Ventilation

BD induces many inflammatory changes that compromise the lung parenchyma. Lung function can worsen suddenly in patients after BD diagnosis. About 30–45% of potential BD donors develop lung injury, most often acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [14, 16].

Despite being related to primary injury, inadequate ventilation strategies are also responsible for tissue damage. Protective ventilation strategies in volume or controlled pressure mode, tidal volume 6–8 ml/kg of ideal bodyweight, and FiO_2 adjusted to obtain $PaO_2 \geq 90$ mmHg, PEEP 8–10, plato pressure < 30 cm H_2O are widely recommended [4, 16, 18, 35, 36, 38].

Alveolar recruiting maneuvers can be useful, but there is no strong evidence to justify their use. Among these, the application of PEEP is recommended, but it should be titrated according to hypoxemia and hemodynamic impairment. The ultimate objectives of mechanical ventilation in the potential BD donor are arterial blood gas normalization, alveolar collapse avoidance, and maintenance of ventilatory mechanical parameters that protect from hyperdistention and potentization of lung injury [35].

38.12.2 Nutritional Support

The exacerbated systemic inflammatory response is correlated to metabolic stress. The hypercatabolic state, very common after severe head trauma, can lead to an energy expenditure up to 2.5× higher than the basal metabolic rate. The massive release of adrenaline, glucagon, and corticosteroids during the "sympathetic storm" is a significant contributor to these metabolic changes [39].

After the sympathetic storm, there is a decrease in baseline energy expenditure due to hypothermia, reduced brain metabolism, and absence of muscle activity. It is estimated a 30% reduction in total energy expenditure.

There are no studies that demonstrate a higher rate of organ utilization in patients submitted to nutritional intake. However, the caloric intake aims not only to prevent the loss of muscle mass but also to influence immune function. One of the few contraindications for nutritional support are those patients with severe hemodynamic instability. According to Dominquez-Roldan et al., nutritional support equivalent to 70–85% of baseline energy expenditure should be offered [29, 37].

38.12.3 Endocrine-Hormonal Therapy

Endocrinological and hormonal disorders are very common in patients with BD diagnosis. There is a decrease in insulin release by the pancreas as well as higher resistance in peripheral tissues. This condition leads to hyperglycemia. Studies on glycemic control in potential BD donors have not yielded conclusive results, and current procedures follow established protocols of American Association of Clinical Endocrinologists and American Diabetes Association in which the measurement of capillary blood glucose should be done every 6 hours. Shorter intervals are necessary if insulin is in continuous infusion. It is observed that persistent blood glucose levels above 180 mg/dl must be corrected according to institutional protocols [40].

Both respiratory alkalosis and metabolic acidosis are frequently observed. The first is consequent to hyperventilation and diuretic treatment in an attempt to reduce intracranial pressure. When increasing the affinity of hemoglobin for oxygen, there is a microcirculation impairment. Metabolic acidosis, often secondary to tissue hypoperfusion, reduces the response to catecholamines and generates more vasodilation and hypotension. The ideal is to maintain the pH between 7.35 and 7.45, but values up to 7.2 are tolerated [28].

Changes in urine output are frequent in the BD donor. The main disturbance is diabetes insipidus. The polyuria occurrence can lead to hemodynamic instability if not properly treated. The main recommendations are to keep serum sodium between 130 and 150 mEq/L and urine output between 0.5 and 4 ml/kg/h. In the case of hypernatremia, its correction should be made with 5% glucose solution or 0.45% saline solution. Other electrolytes such as magnesium, phosphorus, calcium, and potassium must be monitored every 6 hours, and their changes must be corrected since they predispose to the occurrence of cardiac arrhythmias [38, 41].

Regarding the use of corticosteroids, there is evidence that their use contributes to the effectiveness of lung transplantation. Due to its anti-inflammatory properties, some studies demonstrate a reduction in post-transplant liver dysfunction. Besides, adrenal insufficiency that occurs after BD worsens hemodynamic instability, and in this context, the replacement of 15 mg/kg/day of methylprednisolone after confirmation of BD is indicated [29, 37].

Clinical evidence demonstrates that the replacement of thyroid hormones results in better hemodynamic stability and higher uptake of hearts for transplantation. As there are no studies on absorption via the gastrointestinal tract in situations of BD, the preferred route is intravenous. However, some countries do not have an intravenous presentation, and in these cases, 1–2 mcg/kg is recommended soon after BD diagnosis [42].

38.12.4 Antibiotics

One of the emerging concepts is the so-called borderline donors. Until recently, potential donors were excluded due to the presence of an identified infection, whether bacterial, fungal, viral, or parasitic. In these situations, many organs are no longer used, and a review of transplant contraindications has been prepared. Antibiotic indications and which organs may be used differ between protocols in each country. Eventually, even in the same nation, there are differences between states [43].

One of the most emblematic examples of transplantation in infected patients are the hepatitis B or C donors. They have their livers transplanted in patients who have the same virus [44].

Despite this, some systemic viral infections like HTLV I, HTLV II, rabies, adenovirus, enterovirus, measles, West Nile, and parvovirus; herpetic

meningoencephalitis parasitic infections such as leishmaniasis, trypanosomiasis, and malaria; and prionic diseases are contraindications to transplantation. HIV-positive patients, on the other hand, do not have a contraindication for transplantation as long as the recipient is also seropositive. There are even organ donation programs among HIV-positive patients [34].

38.12.5 Transfusions

Oxygen consumption is reduced in the BD donor, but it is not yet known the metabolic needs and oxygen supply to organ demands. In parallel, due to the loss of peripheral vasomotor tone, there is an uneven blood flow distribution, and some organs may be poorly perfused despite hemodynamic stability and systemic oxygen saturation.

Some authors try to correlate BD patients with lower lactate levels as donors with "theoretically" appropriate perfusion. Despite this theoretical basis, there are no studies that demonstrate better results in patients with lower lactate levels. The indication to evaluate lactate is based on critically ill patients' studies, which such a marker helps to orient therapy.

As with critically ill patients, the best strategy for transfusing patients is controversial. Effectively, hemoglobin levels below 7 g/dl are avoided, and patients should receive blood transfusion. In situations where hemoglobin is between 7 and 10 g/dl, blood transfusion is recommended only in order to help hemodynamic stability if the MAP goals are not achieved with resuscitation measures [17, 37].

Concerning coagulation factors, it is known that patients with head trauma develop some type of coagulation disorders in up to 45% of cases. Concomitantly, hypothermia, metabolic, and acid-base balance disorders that occur in the BD patient further worsen the coagulation disorders installed. There is no consensus when to indicate clotting factors or platelet transfusion, and some protocols aim to maintain platelet count above 50,000/mm^3. If disseminated intravascular coagulation is suspected and the fibrinogen value is below 100 mg/dl even after fresh plasma, the cryoprecipitate transfusion is indicated [17, 37].

38.13 Conclusions

BD diagnosis should be performed in all unresponsiveness, absence of brainstem reflexes, and apnea patients. The exclusion of reversible causes for the neurological condition is essential. Such measures must be carried out regardless of the condition of a donor for organ transplantation.

The observed physiological disarrangements turn the BD patient as unique, with many peculiarities. Establishing a management plan in order to avoid futile therapies, providing safe information to family members, reducing costs, and

optimizing the intensive care occupancy are essential. Furthermore, the option for organ donation transforms the intense suffering moment into an altruistic manifestation.

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Chapter 39
New Perspectives

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39.1 Cerebral Microvascular Injury and the Origin of Secondary Neurodegeneration

Traumatic brain injury (TBI) is a prevalent condition worldwide. American statistics report that there are at least 2.8 million medical assessments in emergencies for TBI annually. In middle- and low-income countries, the incidence of TBIs is much higher and is the leading cause of death and disability in young adults. As the young population is most commonly affected, the impairment of productivity is evident. Even mild trauma (mTBI), which accounts for 80–90% of all head trauma, is responsible for long-term damage [1, 2].

Neurodegenerative disease after TBI was first described in the 1920s in professional boxers who suffered repeated head trauma [3]. Called pugilistic dementia, it was observed that a history of head impacts is associated with the development of Alzheimer's dementia (AD) and other dementias, Parkinson's disease (PD), and amyotrophic lateral sclerosis [4–6].

Although far from universal, the possibility of these long-term consequences is understandable of great concern to patients and their families. Epidemiological studies aimed at a better understanding of this relationship have shown controversial results [7]. It has long been recognized that moderate and severe TBI in early and middle age is associated with an increased risk of late dementia, with relative risks (RRs) of the order of 2.5–5.0 [8–11]. Several prospective observational studies have failed to establish a relationship between mild TBI, which is a much more common injury, and late dementia. However, well-designed epidemiological studies indicate

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that mild TBI is associated with an increased risk of dementia, with RRs in the order of 1.3–2.0 RRs for multiple mild TBIs compared to a single severe TBI [10–14].

TBI is conceptualized as a primary injury event caused by an initial mechanical impact, followed by secondary insults due to molecular and cellular responses in reaction to the initial injury. The secondary lesion propagates an inflammatory cascade in the surrounding brain tissue. It was believed that this secondary injury, even in the most severe cases, occurred for a few weeks or, at most, a month, followed by a recovery path that would be completed in months or, at most, a year. Evidence accumulated in the last decade has led to the recognition that, for many patients, the consequences of TBI continue to evolve long after the initial acute recovery period [15]. Longitudinal studies have shown that the results are uncertain because there may be an improvement or deterioration of neurological function many years after the injury [16].

In this context, the TBI can be better conceptualized as a chronic health condition triggered by the initial injury and that by mechanisms still poorly understood, which can affect brain function for decades [15, 16]. Given this complexity, the specific pathophysiological mechanisms that contribute to TBI-related dysfunction in the acute and chronic phases of the disease must be understood [17]. In animal models, interventions aimed at molecular targets involved in secondary lesions have been successful in limiting the extent of the lesion and improving neurological recovery. These results demonstrate that an effective therapeutic intervention is possible, but has not yet been achieved in the human condition [17, 18].

Clinical and pathological evidence indicates that microvascular dysfunction exists across the spectrum of TBI-related injury. Histologically detected ischemic damage is seen in almost 60% of cases of fatal TBI, with no evidence of occlusion of large vessels [19, 20]. In moderate to severe TBI, vasospasm of larger cerebral arteries can precipitate cerebral ischemia, but trauma-induced vascular injury occurs at the level of arterioles and capillaries [21].

Rodrigues-Baezaetal et al. (2003) created vascular injury models to examine brain microcirculation in patients who died after severe head trauma. It demonstrated that the arterioles and capillaries in the middle and deep cortical vascular zones showed extensive lesions characterized by damaged endothelial surfaces, longitudinal folds in the vessel wall, and decreased lumen diameter and undulations, indicating a separation between the endothelium and the smooth muscle cells as well as the rupture of the blood-brain barrier (BBB) [22]. Despite this, larger pial and subpial vessels were histologically normal. In addition to these findings, Stein et al. (2002) demonstrated that cerebral intravascular microthrombosis appears to be an almost universal characteristic [23].

At the endothelial level, endothelin-1, a peptide with a vasoconstrictor effect, is overexpressed after TBI and activates vascularization, endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), and other inflammatory pathways [24–27].

Tomkins et al. (2011) evaluated individuals with head trauma and a Glasgow Coma Scale score higher than 13 in the subacute (1 week) and chronic (3 months) period after the injury. It was observed that individuals who developed

post-traumatic epilepsy were more likely to have BBB disorders than those who did not (82% versus 25%) [28].

Tagge et al. (2018) found focal cortical lesions with a perivascular accumulation of immunoglobulin G in four cases of mild concussive lesion examined in the subacute to the chronic period after the injury. These findings are consistent with extravasation and accumulation of serum proteins at sites of focal microvascular injury [29]. The breakdown of the blood-brain barrier in the acute period after severe brain injury, determined by a cerebrospinal fluid (CSF)/plasma protein ratio greater than 0.007, may correlate with a worse long-term outcome although these findings in prognostic models need to be further explored [30].

It is often claimed that dementia associated with TBI is similar to Alzheimer's dementia (AD), which is the most common type of dementia in the general population. However, studies of dementia associated with TBI used medical records reviews or clinical interviews to determine dementia, which is recognized as having low specificity [9, 31]. No previous study of TBI-associated dementia used pathological confirmation of the dementia subtype, which is recognized as the gold standard [32]. Furthermore, no previous study has used modern neuroimaging diagnostic tools, such as neuroimaging assays or biomarkers in the CSF, serum, or plasma, which are recognized for refining the clinical diagnosis [33].

Since the vascular dysfunction is prevalent and persistent after mild to severe TBI and that neurodegeneration is a late consequence after some TBIs, this association becomes redundant [34]. The more excellent knowledge about vascular dysfunction and neurodegeneration has been described in the context of AD, with evidence that vascular dysfunction has a role in the pathogenesis. Patients with AD and related dementias often exhibit changes in brain microcirculation, including decreased capillary density, fibrohyalinosis of the microvessel walls, loss of tight junctions, and increased BBB permeability [34, 35].

The neuropathological characteristics of AD include plaques containing beta-amyloid and neurofibrillary tangles composed of hyperphosphorylated tau protein. The vascular hypothesis of AD proposes that the rupture of blood vessels and BBB is the initial event that leads to the deposition and accumulation of beta-amyloid in the brain [35–37]. There is evidence of changes in BBB permeability detected in the early stages of cognitive decline. Changes in the CSF pericyte-soluble platelet-derived growth factor (PDGF) receptor B marker can be present before changes in AD and tau biomarkers are evident in individuals with very mild cognitive impairment [7, 38].

Although direct links have not yet been established between traumatic brain vasculature injury and neurodegenerative disease in humans, the evidence presented suggests the hypothesis that TBI-related neurodegeneration may be, at least in part, a consequence of chronic microvasculopathy, similar to dementia and vascular contributions to dementia [39]. Together, these clinical and preclinical observations suggest that therapies targeting cerebral microvasculature are promising areas for an investigation into neurodegenerative disorders related to skull trauma [40]. There are animal models of subdural hemorrhage in which pretreatment with aspirin inhibited thrombosis of the parenchymal vessels, preventing secondary lesions due

to hypoperfusion and ischemia. In another study, activated protein C (APC) has been shown to promote angiogenesis and improve results in a TBI model [41]. In this context and according to Lyden et al., the use of 3K3A-APC, an agonist of the APC receptor protease-activated receptor, has been shown to decrease bleeding rates when administered after human ischemic stroke treated with intravascular thrombolytic agents or mechanical thrombectomy [42].

In parallel with the studies of microvasculature in the pathogenesis of neurodegeneration, some studies define which drugs influence BBB permeability after TBI. Co-treatment with lithium and valproic acid, clinically approved therapies for the treatment of mood disorders and epileptic seizures, has shown some benefit in mitigating BBB damage, as measured by the leakage of immunoglobulins, and also improving long-term functional recovery [43].

Other methods to modulate TBI-induced lesions include inhibition of endogenous degradation pathways of metalloproteinases (MMP-9) and vascular endothelial-derived growth factor (VEGF) [44, 45]. It was found that the acute inhibition of MMP-9 with the use of melatonin reduces the breakdown of the blood-brain barrier and, thus, secondary cerebral edema. Treatment with VEGF inhibitors reduced vascular permeability to albumin and elevated tight junctions proteins [44, 45].

Despite all these data, there is an urgent need for imaging methods and biomarkers that identify subgroups of patients with TBI who can be targeted for specific treatments, further confirming that the proposed molecular target is being achieved and pharmacodynamic assessment of therapeutic efficacy [46].

In this sense, BBB breakage biomarkers and other vascular pathologies are also being developed. The most used biomarker to measure BBB breakdown is the CSF albumin: serum albumin ratio, which is altered in mild cognitive impairment, Alzheimer's disease, and severe TBI, but not altered in the milder forms of TBI. Preclinical models of TBI and neurodegenerative disease should also be used to explore molecular mechanisms and genetic contributions to traumatic vascular dysfunction that cannot be easily explored in studies of human patients [47, 48]. The continuous work to develop serum and image biomarkers specific to vascular lesions related to TBI and that can be safely measured will be essential for us to monitor the vasculature, the therapeutic responses, and recovery. Translating initial scientific observations into effective human interventions has never been closer.

39.2 Selective Hypothermia as Neuroprotection in Cerebrovascular Disease: Are We Getting Too Cold?

Acute ischemic cerebrovascular disease is a significant cause of death and disability worldwide. Therapeutic hypothermia has been considered as one of the most robust neuroprotective strategies. Although the neuroprotective effects of hypothermia have only been confirmed in specific situations such as post-cardiac arrest and neonatal hypoxia, the application of specific protocols could extend the application to other acute neurological situations [49].

The neuroprotective mechanisms of hypothermia in acute ischemic events are extensively studied. Preclinical models of vascular recanalization have demonstrated that hypothermia interferes with cell metabolism, apoptosis, inflammatory mechanisms, and white matter integrity [50].

Hypothermia targets several stages of injury, as well as different types of cells. The primary neuroprotective mechanism is the reduction of the cerebral metabolic rate since it reduces about 10% with each reduced Celsius degree of the basal temperature [51].

The recombinant tissue plasminogen activator was approved to treat ischemic stroke about 25 years ago [52]. More recently, in parallel with the advancement of endovascular techniques, methods that aspirate and remove thrombi have become standard in the treatment of acute stroke in selected cases [53]. But, despite all these advances, ischemic stroke is responsible for severe disability in a large number of people and responsible for almost 10% of deaths worldwide [54].

Numerous studies have proven the effectiveness of therapeutic hypothermia in laboratory settings, but how to successfully translate these exciting findings from basic research into a clinical treatment for stroke patients is still a significant challenge [55]. What is the big difference between bench and bedside? Why does therapeutic hypothermia not benefit stroke patients? How to conduct a quick and straightforward hypothermic therapy in the reperfusion era?

There are numerous completed and ongoing clinical studies on therapeutic hypothermia in stroke patients. In the earlier studies, the failures were due to technical limitations; the patients included in the first clinical studies of hypothermia were unable to obtain vascular recanalization [56, 57]. However, with the emerging concept of vascular recanalization, recent clinical studies have placed more emphasis on opening occluded arteries. Second, most studies have a significant delay in the onset of hypothermia, losing the ideal time to protect the penumbra. In this situation, there is no point in prolonging or intensifying hypothermia [58]. Third, previous studies have tended to use superficial or endovascular cooling as a method of hypothermia, which has many side effects. In recent years, more targeted hypothermia methods have emerged, which reduces the risk of side effects [59]. In the current context, adequate recanalization, exact parameters of hypothermia, and method of cooling the patient are imperative.

One of the significant methodological flaws in the research that used hypothermia after thrombolysis was that recanalization rates were much lower than mechanical thrombectomy, so there was no point in performing hypothermia if the reopening of the vessel did not occur [60]. Another question was when to start hypothermia. It is known that there are several limitations regarding the diagnosis of stroke, so this delay in diagnosis and treatment did not allow the beneficial effects of hypothermia in the penumbra area to be observed [61].

The duration of hypothermia is also directly related to the final neuroprotective effects. Although the ideal duration of hypothermia is not known, since the cascade of harmful events after a stroke can last for hours or even days [62], we must allow the hypothermia time to cover these destructive processes for adequate neuroprotection. The results of experimental studies suggested that a longer duration of

hypothermia may produce better neuroprotective effects [63, 64]. However, it is observed that prolonged hypothermia also increases the risk of infections, which in clinical practice is harmful; therefore, the risks and benefits must be weighed.

The quantification of hypothermia is another topic of debate. There are animal models that show that the temperature of around 34 °C provided the best neuroprotective effects on the size of the infarction, edema, and functional prognosis. In contrast, preclinical models found an inverse relationship, in which more superficial hypothermia was responsible for reducing the volume of the infarction [65]. However, this conclusion is not supported by a recent meta-analysis [66].

As a final stage of hypothermic therapy, rewarming also influence clinical outcomes. The reheat speed is the most critical parameter in this step. Rapid rewarming may be responsible for hemolysis and coagulation disorders [67]. Furthermore, studies in patients with hemispheric infarction have observed that rapid rewarming can induce an increase in intracranial pressure, with cerebral herniation and even death [68].

In the most recent international multicenter prospective clinical trial, the Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR), developed to determine the neuroprotective effects of hypothermia in patients with TBI, the rewarming stage was performed under the monitoring of intracranial pressure [69]. For patients with intracranial pressure below 20 mmHg the reheat rate was fixed at 0.25 C per hour to minimize the risk of increased intracranial pressure [69]. As intracranial pressure monitoring is not routine in ischemic strokes, it is essential to maintain a slow heating speed.

The side effects of hypothermia are much more evident during clinical studies when compared to preclinical studies. Tremor is one of the main side effects, which is a physiological reaction of the body. This reaction increases the metabolic rate, respiratory rate, and oxygen consumption. One of the main measures to combat tremors is to associate meperidine in low doses with enteral buspirone. This combination of treatment is one of the most used and with little impairment of the neurological condition [70]. Other drugs used to fight tremor are clonidine, magnesium, and tramadol [51]. Another feared complication is infection since most patients already have increased risk of pneumonia due to altered pharyngeal reflexes and dysphagia. When associated with hypothermia, the risk of infection increases, possibly due to immunosuppression. The same anti-inflammatory effects that protect the brain "facilitate" systemic infection. According to Hemmen et al., patients undergoing thrombolysis and hypothermia had an increase of 50% in cases of pneumonia but without increasing mortality [71].

Coagulation disorders are also worrisome complications since stroke patients undergoing or not thrombolysis are at risk of hemorrhagic transformations. Although preliminary reports have shown that hypothermia can decrease platelet aggregation and prolong clotting time, serious bleeding events associated with hypothermia have not been observed in clinical practice [72]. It has been questioned in the past whether hypothermia would reduce thrombolytic activity, but due to the short duration of tissue plasminogen activator in clinical practice, this interaction is negligible. Hypothermia also has effects on the cardiovascular system and is related to the

depth of hypothermia, but there is no evidence that the influence on the cardiovascular system is related to any worsening in the clinical outcome.

In parallel to the cardiovascular system, there are changes in urinary output, hydroelectrolytic imbalance, and hyperglycemia. Patients under hypothermia must be monitored continuously in intensive care units to prevent any harm to the clinical outcomes of patients with cerebrovascular disease [51, 72].

In this context, the intra-arterial selective cooling infusion (IA-SCI) is a method that perfuses brain tissue with hypothermic fluid. Theoretical models showed that IA-SCI achieved local hypothermia of brain tissue 18 to 42 times faster than surface cooling and 10 to 20 times faster than systemic transvenous cooling [73]. In 2010, the first study that described the safety and viability of IA-SCI in humans was published. Eighteen patients with a previous diagnosis of vascular malformation received IA-SCI provisionally during the follow-up of cerebral angiography. A 10-minute infusion of hypothermic saline (4–17 C) at a rate of 33 ml/min on one side of the internal carotid artery reduced the temperature of the jugular venous bulb by 0.84 C without causing severe side effects [74]. In subsequent years, several studies have demonstrated the safety of infusing hypothermic solution at 4 degrees before and after mechanical thrombectomy. Wu et al., in a pilot study with 26 patients, demonstrated that the volume of the infarction measured by MRI and the degree of functional independence were higher in the thrombectomy and hypothermia group than in those submitted to thrombectomy alone [75]. A more significant number of patients are still needed for a definitive conclusion, but the current results are auspicious.

39.3 Refractory and Superrefractory Status Epilepticus: What Should We Do? Is It Time for Intravenous Topiramate?

Status epilepticus (SE) is a medical emergency associated with high mortality. It needs immediate medical care, and hospital stay is usually prolonged, with associated impact in healthcare costs. The state of refractory and superrefractory disease is characterized by the failure of first-, second-, and third-line therapies in case of anesthetized patients. There are few controlled or randomized studies on refractory (RSE) and superrefractory status epilepticus (SRSE), so therapeutic management often depends on expert opinions, clinical reports, and pathophysiological assumptions stemming from experimental models [76–78].

In this context, topiramate has being studied as an option in these patients. Because it is a second-generation drug with a mechanism of action against various epileptic syndromes, several pleiotropic effects on different receptors and ion channels, it has become an interesting treatment option. Pathophysiological studies demonstrate that topiramate potentiates the activity of gamma-aminobutyric acid at the level of its GABAA receptor but independently of the action of benzodiazepines,

that is, topiramate can help to overcome resistance to benzodiazepines observed in refractory epileptic status [79].

There are animal models that demonstrate neuroprotection in situations of prolonged epileptic status. Besides, topiramate has good oral bioavailability, little protein binding, and rapid absorption. Although no intravenous solution is available, its use is under investigation [80].

Because there is no intravenous presentation, there is little data on its use in situations of status epilepticus. Recently Fechner et al., in a cohort study with 106 patients, have shown that cessation of the illness was attributed to topiramate in about 27% of cases [81]. The criteria used to attribute topiramate as responsible for stopping seizures were stricter than the literature on the subject, in which topiramate is responsible for ending the illness in up to 80% of cases. The titration of doses was also done more quickly (100 mg/day started; the daily average was 400 mg/day and could reach 900 mg/day); considering the severity of status epilepticus, there is no justification for starting doses of 25 mg/day. As side effects, only was hyperammonemia observed, primarily when associated with valproic acid [82].

Based on these findings, the availability of topiramate in intravenous formulations and new clinical studies are urgent. Would we be one step away from including topiramate in the status epilepticus treatment flowchart, especially before anesthetizing the patient?

39.4 Algorithm for the Treatment of Intracranial Hypertension: Filling in Gaps

The relationship between increased intracranial pressure and reduced cerebral perfusion pressure is a major cause of secondary brain injury and worsening clinical outcomes [83].

The *Brain Trauma Foundation* guidelines were the cornerstones of severe trauma management despite numerous relevant criticisms to the evidence on which they are based. The *Seattle International Consensus* recently described the management of patients with severe head trauma who are already monitoring intracranial pressure [84]. This consensus was developed with the support of 42 experts in the management of intracranial hypertension related to severe head trauma and included 18 interventions considered essential. It is observed that it was done with high rigor and could couple individualized treatments in a single management algorithm. This consensus follows three steps that start from the safest (in the first stage) to the last third with the highest risks (hypothermia, barbiturate coma, and decompressive craniectomy).

There is clarity about the management of levels and what problems should be considered when scaling the therapy needed. Specifically, the authors emphasize that each intervention within a step is equivalent and that there is no need to use all interventions before moving on to the next step.

One aspect of the consensus is the most controversial. The authors recommend raising the mean arterial pressure (MAP) to assess the state of preservation of cerebral self-regulation, and, if the increase in MAP results in a reduction in ICP (confirming that self-regulation is relatively intact), it is considered that the increase in systemic blood pressure is a method to reduce ICP. This recommendation, although "physiologically" adequate, may be somewhat premature since the increase in MAP is not harmless.

Also, a recent study by the *CENTER-TBI* group demonstrated that individual PCI thresholds (identified by brain self-regulation monitoring) are present in two-thirds of adult patients with TBI. The prolonged mean ICP above the individualized threshold of a patient are more strongly associated with mortality compared to values above the empirical threshold defined by the BTF of 22 mmHg [85]. Most studies investigating management guided by self-regulation have been directed toward optimizing CPP instead of PIC [86]. The significant ongoing studies by the *CENTER* and *TRACK-TBI* consortia that investigate the monitoring of self-regulation in severe head trauma may provide new, much-awaited evidence on this critical issue. Meanwhile, the *Seattle Consensus* can fill in the gaps left by the *Brain Trauma Foundation* guidelines.

39.5 Best Biomarkers: A Panel Is Better than an Isolated Marker

Traumatic brain injury is a common cause of disability and mortality worldwide. The pathophysiological responses of the central nervous system include structural and metabolic changes. Excitotoxicity, neuroinflammation, and cell death also occur as secondary damage [87]. Serum biomarkers that can track these lesions and inflammatory processes are explored for their potential to provide objective measures in the evaluation of TBI. However, currently, the clinical guidelines available on the use of biomarkers in TBI are limited. In the elaboration of protocols for the use of biomarkers, it is first necessary to define the purpose of each biomarker. Are we defining the need for cranial tomography in mild head trauma, or do we want to predict severe head trauma and answer questions about functional independence in 6 months?

When we aim to document the existence of a brain concussion, the most used biomarkers are copeptin (the C-terminal part of the arginine vasopressin prohormone – AVP), which reflects the hypothalamic adrenal axis activity of the pituitary as part of the stress response and its effects. Serum levels increase in proportion to the severity of TBI [88]. The other biomarker is CKBB, which is an intracellular enzyme that catalyzes the phosphorylation of creatine into phosphocreatine as part of the homeostasis of cellular energy and is found mainly in oligodendrocytes, which may be due to the high energy requirements in these cells [89]. The excellent performance of these biomarkers suggests that both the activation of the stress axis

and cellular damage in specific brain areas are involved in the pathophysiology of concussion.

Another useful aspect of biomarkers is to assess the need for cranial tomography in people with mild head trauma. Theoretically, they are very sensitive tests (close to 100%) but with low specificity. According to Posti et al. [90], GFAP and UCH-L1 levels remained low in patients with mild head injuries and associated orthopedic trauma. Other biomarkers such as CRP (generalized inflammation), MMP-2 (localized brain inflammation), and CKBB (cell membrane injury) also have high sensitivity regarding the suspicion of intracranial tomographic lesions. According to Gan et al., the biomarkers described above are superior to the S-100b, formally the only biomarker with low levels of recommendation for assessing the need for cranial tomography [91].

In parallel to mild trauma, biomarkers for prognostic purposes after severe trauma are also used. Considering severe trauma as a systemic disease, the presence of coagulation and inflammation markers is taken into consideration. Serum coagulation biomarkers with an excellent ability to predict poor outcomes in severe trauma include D-dimer, thrombospondin-1, and SCUBE1. D-dimer is thought to indicate TCE-induced coagulopathy in which the proposed underlying mechanisms may comprise tissue factor (TF) release, hyperfibrinolysis, shock, and hypoperfusion, triggering the protein C pathway, disseminated intravascular coagulation, and platelet dysfunction [92–94].

Thrombospondin-1 is an antiangiogenic factor sensitive to thrombin whose expression is increased after intracerebral hemorrhage [95]. *SCUBE1* is released from endothelial cells and platelet alpha granules during platelet activation [96].

The most commonly identified and studied inflammatory markers include IL-1beta, IL-6, IL-8, HMGB1, ceruloplasmin, ficolin-3, macrophage migration inhibitory factor (MIF), MBL, galectin-3, S100A12, and suPAR. Among these, the high expression of HMGB1 in the brain [97] may be useful in recognizing patients with critical inflammatory responses to brain injuries associated with severe disability and death. Although these inflammation markers are not specific for insults located in the brain, they can contribute with prognostic information, helping to characterize strong inflammatory responses to TBI that contribute to secondary brain injury and, ultimately, poor outcome [98].

39.6 The End of Hyperosmolar Therapy in Ischemic Stroke and Decompression in Older Patients

Extensive ischemic strokes, also known as malignant strokes, are life-threatening due to their risks of brainstem compression caused by the extent of the lesion or its perilesional edema [99]. In this context, hyperosmolar therapy (HT), primarily indicated for the global reduction of intracranial hypertension, is used in ischemic events either as a temporary measure in situations of neurological deterioration or in

an attempt to avoid neurosurgical decompression. Despite this, countless studies show no benefit in hemispheric strokes. There are systematic reviews (Cochrane in 2007 and the American Heart Association) that show no position in favor or against its use [53, 100].

HT has its most significant effects in situations where the blood-brain barrier is integrated, so in situations of extensive infarction, the contralateral side will be the most "affected" by the osmotic gradient effects created by HT (extraction of water from intracellular to intravascular space) [101, 102]. Based on the concepts that intracranial pressure is not global in focal situations, and that there is a pressure gradient between both hemispheres, the use of HT could theoretically worsen the deviation from the midline.

According to Carhuapoma et al., the increase in intracranial pressure is global at the beginning of the ischemic condition, and as the days progress, the pressure gradient appears, and the pressure difference between both supratentorial compartments may reach 40 mmHg [103].

However, it was Allan Ropper who proposed a plausible explanation, alternative to global intracranial hypertension, for the deterioration of the level of consciousness after the unilateral mass effect [104]. Accordingly, the distortion of the brainstem by the mass effect is the initial mechanism. The anisocoria itself is the result of lateral deviations that generate traction of the third nerve (and not uncal compression as historically taught). Such findings were corroborated by other authors [105, 106].

In a study by Berger et al., the following sequences of events were observed: first the development of anisocoria, followed by dilated pupils and loss of the photomotor reflex that occurred about 12 h before the elevation of the lactate – pyruvate ratio (indicative of ischemia in the hemisphere not affected by stroke) and for last elevation of the PIC>20 mmHg [107]. For comparison, the *BOOST-II* Trial (head-injured patients) found that cerebral hypoxia preceded elevations in ICP over a considerable time [108].

In summary, the findings discussed above support the concept that severe compression of the brainstem and contralateral hemisphere may occur, despite normal or slightly increased ICP values. The supratentorial compartment can function as a bicameral space in the setting of an expanding hemispheric mass lesion, and the ipsilateral or global elevation of the ICP is usually a late phenomenon that occurs when all pressure redistribution mechanisms fail – at that point drug intervention can be useless. When elucidating the mechanisms of neurological deterioration in extensive hemispheric ischemic injuries and considering that HT requires relatively intact physiology to exercise its full therapeutic potential, the inferiority of HT to decompression surgery is apparent [109]. HT preferentially dehydrates healthy contralateral brain tissue, while having minimal effects on the injured hemisphere, with BBB impairment and self-regulation [110]. As a result, it may fail to improve the radiological mass effect and, at least theoretically, exacerbate hemispheric gradients of ICP. In awake patients, we should not perform any intervention with hyperosmolar therapy. In patients with neurological deterioration, HT will serve as a palliative

measure until the surgical intervention. What about patients over 60 who are not candidates for surgery? Should we expand the indications for decompression, especially in patients over 60 and without other significant comorbidities?

39.7 The Midazolam Wake and the Widespread Cortical Depolarization

Cortical spreading depolarization (CSD) describes a class of pathological waves characterized by an almost complete sustained depolarization of neurons and astrocytes that spreads through the cortex. CSD is mediated by the release of glutamate in the extracellular space, activation of glutamatergic inotropic receptors, potassium efflux, and the influx of sodium and calcium, which overloads the adenosine triphosphate-dependent pumps, leading to a complete breakdown of ionic gradients. Subsequently, morphological changes occur that generate cellular edema and retraction of the extracellular space once the water follows the inflow of the cation. As a consequence, there is an electrical silence of neuronal activity, called widespread depression. Objectively, there is a loss of neuronal homeostasis and possibly adverse outcomes [111, 112].

Responses to CSD are different in the healthy and injured brain. In the intact brain, CSD induces a wave of disseminated hyperemia (physiological neurovascular coupling) that provides the tissue with the energy necessary to restore ionic balance. In the injured brain, in a tissue where the neurovascular coupling is compromised, CSD induces a microvascular constriction that leads to transient hypoperfusion (pathological inverse coupling). Considering that CSD occurs in more than 50% of patients with severe traumatic brain injury and about 30–60% of patients with severe traumatic brain injury exhibit impaired cerebrovascular self-regulation, the deleterious effects of CSD may be more significant than imagined [113].

Even in the normally perfused cortex, the effects of depolarization include acidification of tissues, vasogenic edema, and depletion of extracellular glucose. To date, there are doubts as to whether CSD can be modulated pharmacologically in the human brain. However, according to Hertle et al., preliminary conclusions suggest that large doses of analgesics and sedatives influence the occurrence of CSD. Most documented CSDs are made under the influence of GABA agonists such as benzodiazepines and barbiturates. These drugs target receptors that regulate neuronal activity and synaptic transmission and can alter the susceptibility and course of CSD [114].

In the context of CSD, ketamine has been tested again for its potential neuroprotective effect. Ketamine is a non-competitive antagonist of the calcium channel pore of the N-methyl-D-aspartate receptor. Ketamine demonstrates several beneficial pharmacodynamic effects in the hypotension scenario. The primary reported negative effect (increased intracranial pressure) stems from small studies in the 1970s.

Himmelseher and Durieux summarized the available evidence by stating that in a sedated and ventilated patient, ketamine does not increase intracranial pressure and, compared to opiates, ketamine reduces the need for vasopressors to maintain cerebral perfusion pressure when used for sedation [115].

However, the most exciting finding in the analysis by Hertle et al. was a strong and sustained suppression of depolarizations spread by ketamine. Specifically, ketamine administration was inversely correlated with the occurrence of scattered depolarizations. Ketamine has been shown to increase cerebral perfusion pressure and can increase neuronal survival [114].

Recently Carlson et al. conducted a prospective study with ten patients and demonstrated that ketamine reduces the onset of CSD at doses commonly used for sedation [116]. The first clinical studies are emerging, large samples will be needed for definitive conclusions, but ketamine will be the new midazolam?

39.8 Tranexamic Acid? Is CRASH-3 Enough?

Intracranial hemorrhagic injuries are common after traumatic events, and most injuries are not surgical at first. However, there are situations in which the hemorrhagic lesion progresses by different mechanisms [117]. Coagulopathy is a widely recognized contributor, and although many aspects of coagulation function have been studied in this context, fibrinolysis is one of the main factors of coagulopathy associated with skull trauma and the hemorrhagic progression of injuries [118]. In these situations of increased hemorrhagic collections, there is evident neurological damage with increased morbidity and mortality [119]. The clinical evaluation of tranexamic acid as an antifibrinolytic drug to reduce TBI-associated mortality is logical, mainly because of the mortality reductions observed with its use in patients with multisystemic trauma without TBI and in women with postpartum hemorrhage [120]. Recently *CRASH-3*, a multicentric study involving 175 hospitals in 29 countries, included patients suffering from skull trauma who were within 3 h of the injury and had a Glasgow Coma Scale (GCS) score of 12 or less intracranial bleeding on computed tomography and no significant extracranial bleeding. The primary endpoint was death related to head trauma in the hospital within 28 days after the injury in patients treated within 3 h of the injury [121].

When analyzing 12,737 adults with TBI (mean age 41.7 years), those treated within 3 h of the injury, the risk of death related to head injury was 18.5% in the tranexamic acid group, against 19.8% in the placebo group risk ratio [RR] 0.94 [95% CI 0.86–1.02]. There was a significant reduction in mortality related to head injury when tranexamic acid was administered within 3 h of the injury in patients with mild or moderate TBI (RR 0.78 [95% CI 0.64–0.95]), but not in patients with severe head trauma (0.99 [95% CI 0.91–1.07]) [121]. Considering the results of *CRASH-3* [121] with *CRASH-2* [120] (20,211 trauma patients) and *WOMAN* [122] (20,060 patients with peripartum hemorrhage), more than 53,000 patients were

randomly assigned to study tranexamic acid and the drug's effects on patients with bleeding. The results of each study independently and together are precise: tranexamic acid reduces the risk of death from bleeding, regardless of the cause. Also, tranexamic acid must be administered early – within 3 h of bleeding beginning – to be effective. These data suggest a fundamental truth about the pathophysiology of life-threatening hemorrhage in which early activation of the fibrinolytic protease cascade is closely linked to poor results in patients with bleeding [120–122].

CRASH-3 is the first study of a pharmacological intervention applied in acute situations to show better results in patients with TBI [120]. Tranexamic acid is likely to benefit patients at risk of early mortality, while late deaths are unlikely to be affected by tranexamic acid [120]. Future studies for hemostatic interventions should reflect what is physiologically plausible and focus on the goals of early death related to bleeding that links the intervention to the outcome. Although it seems safe, a clot-stabilizing intervention, such as tranexamic acid, can cause an increase in the risk of venous thromboembolism, which was not identified in the study [123]. An additional significant limitation of the *CRASH-2*, *CRASH-3*, and *WOMAN* assays is that the tranexamic acid dosing regimens were very similar. Future studies may be needed to explore the effects of increased doses of tranexamic acid in patients with bleeding or possibly alternative routes of administration, such as intramuscular administration, which may facilitate early intervention. Despite its limitations, *CRASH-3* is an interesting study that may change our clinical the practice.

39.9 Awakening Management After Neurosurgery for Intracranial Lesions

Postoperative complications after intracranial surgery may have devastating effects even after an uneventful neurosurgical procedure. Anesthesiologists and neurosurgeons suppose that physiological changes during anesthesia recovery may cause intracranial bleeding or cerebral edema. These complications are common. In a prospective study of 486 patients, 54.5% of the patients who could be extubated during the 4 h following surgery had at least 1 complication. The most common complication was nausea or vomiting (38%), but respiratory problems occurred in 2.8%, cardiovascular complications in 6.7%, and neurological complications in 5.7% of patients. In Table 39.1 it is presented systemic and cerebral conditions making delayed emergence considered to be a good choice [124].

Rapid emergence from anesthesia may be associated with systemic hypertension. Hypertension during emergence is frequent in neurosurgical patients and has been reported in 70 ± 90% of patients. This is the consequence of sympathetic stimulation demonstrated by an increase in circulating catecholamine and oxygen consumption [125–127].

It is clear that severe hypertension (systemic blood pressure > 200 mmHg) is a risk factor for intracranial hemorrhage in patients recovering from intracranial

Table 39.1 Systemic and cerebral conditions making delayed emergence considered to be a good choice

Systemic	Cerebral
Hypothermia *(T < 35.5 °C)*	Preoperative altered consciousness
Hypotension-hypovolemia	Large tumor resection with midline shift
Hematocrit <25%	Long-lasting surgery (>6 h)
Hypertension *(SBP > 150 mmHg)*	Intraoperative brain swelling
Ineffective spontaneous ventilation	Injury to cranial nerves (IX, X, XII)
Hypoosmolarity *(<280 mOsmol/kg)*	Convulsions during emergence
Disorders of coagulation	
Residual neuromuscular blockade	
Hypoxia or hypercapnia	

SBP Systolic blood pressure

surgery. The risk associated with less severe hypertension, however, is not demonstrated. Basali et al. established a link between perioperative hypertension and intracranial hemorrhage after craniotomy in a retrospective case control study. Patients with postoperative intracranial hemorrhage were 3.6 times more likely to be hypertensive than their matched controls. Of particular interest was the very strong association with intracranial hemorrhage when blood pressure remained in the normal range intraoperatively but became hypertensive postoperatively. This suggested that loose surgical hemostasis performed at a low blood pressure may bleed at a higher blood pressure [128].

Intracranial hypertension is common after neurosurgery. In a retrospective study of 514 patients whose intracranial pressure (ICP) was monitored after elective intracranial surgery, 76 (18.4%) of the 412 patients operated on in the supratentorial region had a postoperative sustained ICP elevation exceeding 20 mmHg. Abnormally high ICP occurred after 13 (12.7%) of the 102 infratentorial operations. Of the 89 patients with elevated ICP, 47 (52.8%) had an associated clinical deterioration. The most common findings on computed tomography scans were cerebral edema and cerebral hemorrhage [129].

It has also been well documented that tracheal stimulation increases ICP, although cerebral perfusion pressure is maintained in most cases. This ICP increase is related to arousal, coughing, and transient cerebral hyperemia. Its duration is variable, depending on brain compliance, but is usually less than 5 min. On extubation, the tracheal stimulation is often associated with hypercapnia due to increased carbon dioxide production and respiratory depression. Thus, large increases in ICP may be anticipated in patients with a "tight brain" at the end of surgery. Laryngotracheal lidocaine is effective for limiting coughing due to tracheal stimulation. Short-acting opioids (remifentanil and alfentanil) decrease coughing, agitation, and cardiovascular stimulation during emergence from anesthesia, showing the importance of postoperative analgesia after craniotomy. These agents, however, may interfere with clinical assessment [130–134].

Another reason for the occurrence of cerebral complications is the postoperative cerebral hyperemia. Tracheal extubation is associated with a 60 ± 80% increase in cerebral blood flow (CBF) velocity from preinduction baseline value, with an increase in the jugular venous bulb saturation in oxygen. This may occur especially after tumor or aneurysm surgery [135].

This complication has also been demonstrated after surgery for chronic subdural hematoma [23, 25] or carotid surgery or stenting. In elderly patients, cerebral hyperemia was significantly associated with postoperative delirium and exacerbated by postoperative systemic hypertension. The significance of postoperative hyperemia after intracranial tumor surgery is unknown; however a provocative study suggested that deep opioid analgesia with a 1 ± 2 h delayed emergence after completion of surgery reduced the incidence of postoperative intracranial hemorrhage. This result was explained by better postoperative hemodynamic control. The study, however, was retrospective and did not include a control group. The same results could probably be obtained with an early recovery including tight hemodynamic and metabolic control. In another study using lower-dose narcotics, 2 h delayed recovery was associated with higher risks of metabolic and cardiovascular abnormalities than an early recovery [136–139].

Rapid recovery may fail or may not be a good choice. This is the case after lengthy surgery (more than 4 h), large tumor resection, injury to the cranial nerves (especially IX, X, and XII), complications during surgery, hypothermia, and severe respiratory or cardiovascular complications during emergence. In a prospective study with 486 neurosurgical patients, 11% remained intubated for more than 4 h after the end of surgery. The main reasons were poor preoperative conditions [140].

In most situations, an assessment of the neurological condition of the patient is possible under close hemodynamic and respiratory monitoring. Then the patient is sedated until emergence and extubation are indicated. This allows the diagnosis of swallowing disorders, the correction of coagulopathy or anemia, adequate ventilation, return to normothermia, and control of pain. Since sedation impairs neurological evaluation, an early computed tomography scan before transfer to the intensive care unit may be indicated, especially after difficult procedures. After stopping sedation in the intensive care unit, the patient should be rapidly awake and alert. Propofol is probably the best choice to perform a reliable clinical assessment a few minutes after stopping the infusion.

The advent of new short-acting anesthetic agents has made perioperative anesthetic management in neurosurgery easier and extubation delays more predictable. These new techniques, however, have shifted some problems from the operating room to the post-anesthesia care unit. There is some evidence that an explosive emergence and the lack of hemodynamic control during extubation may lead to cerebral complications such as worsening of cerebral edema or hemorrhage.

Further studies are needed, however, in order to understand the relationship between cerebral complications and management during emergence. Early recovery should be performed after most neurosurgical procedures because clinical assessment is the best neurological monitoring.

The physiological changes during emergence and associated complications should be anticipated to limit their effects on the cerebral circulation and metabolism. Thus, emergence and extubation should be performed with the same monitoring and the same anesthetic care as during the surgical procedure. This is the necessary condition to perform fast-tracking neuroanesthesia without increasing the complication rate.

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