# Textbook of Neuroanesthesia and Neurocritical Care

Volume II - Neurocritical Care

Hemanshu Prabhakar
Zulfiqar Ali
*Editors*

Springer

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# Foreword

Neuroanaesthesia and neurocritical care continue to evolve and develop as specialities, presenting those of us responsible for patient care with ever more challenges. Within the operating theatre, technological advances in surgical techniques and imaging have necessitated changes both in the way we work and also where we work. Advances in interventional neuroradiology have led to a greater demand for anaesthetic and critical care input outside of the operating theatre, often in remote sites, with all the associated challenges. An ever-increasing number of surgical procedures of greater complexity alongside an aging population have led to increased demands on the neurocritical care unit. Fortunately, advances in neuroanaesthesia, neurocritical care and neuromonitoring have recognised and facilitated these changes.

It has often been said that neuroanaesthesia is a speciality where the knowledge and skill of the anaesthetist directly influences patient outcome. This remains true today. To this end, the *Textbook of Neuroanaesthesia and Neurocritical Care* edited by Hemanshu Prabhakar covers all aspects of patient care. Volume I rightly begins with the fundamentals of neuroanaesthesia including anatomy, physiology and pharmacology, an understanding of which is essential to underpin good care. There is detailed guidance on the process of anaesthesia for neurosurgery including coexisting problems, special considerations, pain management and near misses. A special topics section includes recent innovations such as robotic surgery, gene delivery and expression, intra-arterial drug delivery and simulation in neuroanaesthesia. In volume II, the complexities of critical care are thoroughly addressed, starting with the fundamentals of neurocritical care through to the intensive care management of specific conditions, neuromonitoring, pain management, ethical considerations and near misses. Again, there is a special topics section on recent advances including research and evidence-based practice.

This comprehensive textbook is an authoritative and practical clinical text. It covers the breadth and depth of the complex specialities of neuroanaesthesia and critical care and includes chapters by many leading names in neuroanaesthesia who have lent their expertise to this work. It will be essential reading for trainees, clinicians and researchers involved in neurosciences. Despite the ever-increasing challenges facing us, this book should provide the reader with the necessary knowledge to enhance their practice and provide optimal neuroanaesthesia and neurocritical care.

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# Preface

The editors feel pleased to present the first edition of *Textbook of Neuroanesthesia and Neurocritical Care*. This book has tried to cover the basic concepts of neuroanaesthesia and neurocritical care along with the major changes that have evolved in the field of neurosciences in the last decade. An attempt has been made by the authors to present an updated presentation of the subject. The book is available in two volumes: volume I focuses on the foundation of neuroanaesthesiology, and volume II focuses on the understanding of the neurocritical care. We hope that this book will be of immense use for readers, who are more focused on gaining an advanced understanding in the field of neurosciences.

We thank the authors for doing an outstanding job of producing authoritative chapters. We feel privileged to have compiled this first edition and are enthusiastic about everything it offers to our readers. We learned much in the process of editing this textbook and hope that you will find this textbook a valuable source of educational resource in the field of neurosciences.

New Delhi, India — Hemanshu Prabhakar
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# Part I

# Fundamentals of Neurocritical Care

# General Principles of Neurocritical Care

1

Vishank Shah and Jose I. Suarez

## 1.1 Introduction

Critical care has evolved in the last decades resulting in significant improvement in patient outcomes with previously fatal illnesses such as sepsis, cardiogenic shock, and respiratory failure. Similarly, with advances in neurologic monitoring and therapeutics, there has been a marked improvement in outcomes in patients with life-threatening neurologic disorders such as stroke, traumatic brain injury (TBI), intracerebral hemorrhage (ICH), and aneurysmal subarachnoid hemorrhage (SAH) among others. This has led to the evolution of neurocritical care (NCC) as an independent discipline.

Ropper defined NCC as care and examination of the comatose patient; treatment of raised intracranial pressure (ICP) and neuromuscular respiratory failure; use of therapies specific for acute stroke, ICH, SAH, TBI, and status epilepticus, among other conditions; and treatment of medical complications typical for acute neurologic illness [1].

The pivotal aspect of NCC involves providing intensive monitoring to critically ill neurological patients and thus requires the support of specially trained personnel with skills to identify subtle neurologic changes which remain the best markers for worsening injury. More recently with newly available therapeutic strategies and monitoring technologies, the focus of NCC has shifted from monitoring to salvaging massive brain injuries which were previously thought to be unsalvageable. This is achieved by optimizing cerebral perfusion, limiting intracranial hypertension, and preventing secondary brain insults. Thus, in addition to having general critical care skills, NCC specialists, called neurointensivists, require a comprehensive understanding of cerebral and cerebrovascular anatomy and physiology and its interaction with the remaining organ systems. Such specialized services are best provided in a dedicated neurocritical care unit (NCCU) by a specially trained NCC team. In this chapter, we will review the evolution of NCC and the general principles involved in providing specialized intensive care to critically ill neurological patients.

## 1.2 Evolution of Neurocritical Care

### 1.2.1 History of Neurocritical Care

The exact origin of NCC is a topic of contention although most will agree that this field originated with the advent of neurosurgery. Harvey Cushing, the pioneer of neurosurgery, quickly realized the

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need for close monitoring of his surgical patients to reduce the high postoperative mortality. However, the first NCCU was established at the Johns Hopkins University in 1932 by neurosurgeon Walter Dandy, but this was solely dedicated to intensive postoperative monitoring of neurosurgical patients under the watchful eye of anesthesiologists [2].

The earliest involvement of neurologists in critical care dates back to the 1950s, during the poliomyelitis epidemic in Europe, when respiratory care units were developed to provide long-term ventilator support to these patients with bulbar and neuromuscular respiratory failure. The most notable of these units included the Spalding and Crampton respiratory-polio unit at Radcliffe Infirmary, Ibsen unit in Copenhagen, and Batten respiratory unit among others [3]. These units were staffed by neurologists and pulmonologists with neurologists playing an active role providing critical care services and performing procedures such as rigid bronchoscopies and tracheostomies [4]. However, it would have to wait until decades later for such collaborative intensive care to extend to other acute neurologic diseases.

As the field of neurosurgery progressed, the high volume of surgical cases prevented neurosurgeons from providing the necessary care to their critically ill patients. As a consequence, neurologists, intensivists, and anesthesiologists started consulting on these patients. This led to a unique multi-professional collaboration triggering a deep interest in NCC among some neurologists. In the 1980s, neurologists started rounding in some of the first combined NCCUs in the United States, namely, Allan Ropper at Massachusetts General Hospital, Daniel Hanley at Johns Hopkins University, and Matthew Fink at Columbia University [2]. Eventually, in 1988, the American Academy of Neurology established a separate section for critical care and emergency neurology headed by Daniel Hanley [4].

The 1990s saw a marked rise in publications dedicated to the NCC field. For the first time, several "best practice" guidelines were developed for the management and prognostication of acute brain injuries. Many randomized clinical trials were initiated by neurointensivists during this period. The Society of Critical Care Medicine also established a separate neuroscience section in 1996 to recognize the rising interest in this field [4].

In 2002, for the first time, neurointensivists got together and established the Neurocritical Care Society (NCS) with Thomas P Bleck as its first president [4]. The NCS also started its first dedicated publication, the *Neurocritical Care* journal. Multiple fellowship programs were established to train neurologists and other specialists including anesthesiologists, internists, pediatricians, and emergency medicine physicians in the field of NCC. The United Council for Neurologic Subspecialties established a curriculum for the 2-year fellowship and started administering a certifying examination in 2007.

More recently, with advances in care for both ischemic and hemorrhagic strokes, the Joint Commission (an accrediting organization in the United States) has mandated the need for an NCCU in any facility that seeks to be certified as a comprehensive stroke center. Accordingly, there has been a rapid increase in the number of NCCUs being established in both academic and nonacademic hospitals. Simultaneously, with the establishment of the NIH-sponsored Neurological Emergencies Treatment Trials (NETT) consortium, there has been a steep rise in clinical and translational research in the NCC field care, which has led to the formation of the Neurocritical Care Research Network which serves as a channel for the design and implementation of multicenter trials in the NCCU setting. With the arrival of these exciting avenues, it is safe to say that the NCCU field is booming rapidly and has a long prosperous path ahead.

### 1.2.2 Organization of a Neurocritical Care Unit

The distinctive feature of NCC is the unique collaboration between neurologists and neurosurgeons. Patients with acute neurological diseases benefit from neurosurgical consultation; for example, patients with malignant ischemic strokes who need decompressive craniectomies. Similarly,

neurosurgical patients benefit from neurologic consultation; for example, patients with subdural hematomas or brain tumors who experience status epilepticus. Thus, it makes most sense that NCCUs combine both neurological and neurosurgical patients under the care of a multidisciplinary team that comprises neurologists, neurosurgeons, neurointensivists, and neuroradiologists.

There are three models of organization of care teams in an intensive care unit (ICU): closed, open, and hybrid. A closed unit involves an intensivist managing all cases, functioning as a team leader, leading formal ICU rounds in the presence of house staff or physician extenders. This model facilitates better standardization of care and nursing satisfaction. On the contrary, an open unit involves the primary admitting physician managing the patient, often without the involvement of an intensivist, facilitating better continuity of care considering the primary physician has a long-term relationship with the patient prior to, during, and after the ICU stay. However, Multz et al. [5] showed that when compared, a closed ICU model led to better resource utilization, shorter ventilator days, and a shorter ICU stay. Moreover, Ghorra et al. [6] showed that mortality and morbidity were higher in an open unit.

A hybrid model utilizes an intensivist team that cares for all patients in conjunction with a primary admitting team, thus maintaining standardization and continuity of care. Since NCC evolved as a subspecialty of neurosurgery and neurology, most NCCUs are hybrid with a neurointensivist coordinating care with the assistance of neurosurgeons and neurologists.

The neurointensivist plays a central role, directing medical care, triaging patients, and managing ICU resources. In addition, the critical care provider team also consists of residents, fellows, and/or physician extenders. Ideally such a team should be available 24 h a day to provide continuous monitoring and care. However, there continues to be a lack of in-house medical staff in most NCCUs making it essential to rely on excellent nursing services. Thus, the most essential component of an efficient NCCU is a central core of nurses with NCC training [7]. In addition to providing critical care nursing and operating advanced monitoring technologies, a unique skill the NCCU nurses must possess is performing and interpreting the neurologic examination to detect worsening injury. Like any other critical care unit, the nurse to patient ratio favored is 1:1 or 1:2 depending on the acuity of the patient.

Structurally, an NCCU should have private rooms, 200–330 $ft^2$ per bed area to accommodate equipment and personnel, adequate oxygen, suction, and lighting. The room layout should allow access to the head for minor surgical interventions such as ventricular drain placement, electroencephalogram (EEG) monitoring, and other cerebral monitoring such as ICP measurement.

### 1.2.3 Impact of Neurocritical Care on Patient Outcomes

From inception, the need for the specialized field of NCC has been questioned, many arguing that it does not further improve outcomes when compared to general critical care. However, data published by neurointensivists strongly suggest otherwise.

Mirski et al. compared outcomes in ICH patients treated in an NCCU versus a general ICU and demonstrated that the hospital mortality was significantly lower in the former [8]. Similarly, Diringer et al. performed a multivariate analysis on 1038 patients with ICH admitted to 42 ICUs and demonstrated that not being admitted to an NCCU was an independent predictor of hospital mortality (OR 3.4) [9]. Suarez et al. generated a prediction model for hospital mortality using data on 2381 patients admitted to an NCCU before and after appointment of a dedicated NCC team and showed that the presence of an NCC team was an independent predictor of reduced mortality (OR 0.7). They also demonstrated a reduction in length of ICU and hospital stay with no increase in readmission rates [10]. Varelas et al. [11] also demonstrated a reduction in ICU and hospital stay after addition of an NCC team. There are numerous similar observational studies demonstrating an improvement in mortality, hospital stay, and healthcare costs when patients were treated in an NCCU. Kramer et al. performed a

systematic review combining data from all these studies, including over 40,000 patients, and demonstrated not only a reduction in mortality (OR 0.72) but also in poor neurological recovery (OR 0.7) [12]. Mayer et al. performed a survey and demonstrated that neurological patients in NCCUs had lower rates of mechanical ventilation and intravenous sedation and higher rates of invasive hemodynamic and ICP monitoring and more patients received nutritional support when compared to medical or surgical ICUs [13]. This body of evidence has now led to widespread acknowledgment of the benefits of NCCUs staffed by a dedicated NCC team. Markandaya et al. carried out an online survey among intensivists in North America, and 70% of the respondents acknowledged that NCCUs staffed with neurointensivists would improve quality of care of neurocritically ill patients [14].

Outcomes in NCC are also measured using functional recovery scales such as Glasgow Outcome Scale, modified Rankin score, Barthel Index, and quality of life questionnaires such as SF (Short Form)-36 [15] emphasizing the importance of functional independence in addition to survival in neurological patients. We have limited data on the impact of specialized NCC on long-term functional outcomes and quality of life.

## 1.3 Managing the Neurocritically Ill Patient

Like any other critically ill patient, management of the neurocritically ill patient begins with ensuring a secured airway, adequate ventilation, and circulation. This is followed by a rapid neurological assessment to grade the level of consciousness and elucidate the cause and severity of injury in order to identify immediate interventions such as ICP control. Once stable, appropriate radiological studies are obtained to confirm the suspected diagnosis followed by specific therapies including neurosurgical interventions.

Once acute care is complete, the next phase of management involves close neurologic monitoring in order to prevent secondary brain injury. Ventilatory support, fluid and electrolyte management, appropriate blood pressure control, and cardiac monitoring, all play an important role in preventing secondary brain injury, and an in-depth understanding of how these interact with cerebral physiology is needed. Finally, considering the significant morbidity associated with neurologic illness, an important aspect of neurocritical care is prognostication and assisting families in making informed decisions on behalf of their critically ill family members.

The most common cases admitted to an NCCU include post-neurosurgical patients, TBI, SAH, and ICH. Acute ischemic stroke (AIS) is the next most common followed by status epilepticus, intracranial infections, and neuromuscular disorders.

### 1.3.1 Clinical Assessment of a Neurocritically Ill Patient

The most common clinical presentation of a patient in the NCCU is coma. Coma is defined as a state of unresponsiveness in which the patient lies with eyes closed and cannot be aroused to respond appropriately to stimuli even with vigorous stimulation [16]. The causes of coma can be classified by the presence or absence of structural injury. Nonstructural causes include metabolic, endocrine, and toxic conditions. Structural brain injury leading to coma usually occurs from direct involvement of rostral brainstem, bilateral thalami, diffuse cortex, acute hydrocephalus, and/or nonconvulsive status epilepticus. Unilateral lesions, such as ICH, AIS, and subdural hematoma, may also lead to coma but usually in conjunction with lateral brain tissue displacement. Ropper et al. demonstrated that horizontal displacement of the pineal body on head CT imaging correlated with the degree of alteration in consciousness with >8–13 mm shift correlating with coma [17]. Accordingly, the evaluation begins with a detailed history from family members/bystanders focusing on delineating the possible etiology of coma including identifying the acuity of onset (sudden

onset may suggest vascular conditions); associated trauma; toxic (carbon monoxide poisoning), recreational drug (such as opioids, alcohol) or medicinal (insulin, antidepressant overdose) exposures; and accompanying medical conditions such as hypertension (ICH), atrial fibrillation (AIS), associated cardiac arrest, recent fevers, and headaches (meningitis/encephalitis) among others.

The assessment of the vital signs may provide important diagnostic information. Hypothermia may directly cause coma. Hyperthermia may indicate systemic or intracranial infections or heat strokes. Hypertension, bradycardia, and irregular respirations, the Kocher-Cushing reflex, suggest elevated ICP. Hypotension may indicate sepsis and cardiac or endocrine abnormalities and if severe enough may impair cerebral perfusion and lead to a comatose state. Assessing respiratory patterns may also help localize the potential lesions. Some of the common breathing patterns seen in comatose patients include Cheyne-Stokes respiration (metabolic or diffuse neurologic insults), central hyperventilation (midbrain lesions), apneustic breathing (pontine lesions), and ataxic breathing (medullary lesions). Finally, meningismus may suggest an intracranial infection or subarachnoid hemorrhage.

The next step involves a thorough neurological examination, the primary purpose of which is to localize the lesion and thus identify the etiology. Certain neurological signs may also suggest impending catastrophes and need for urgent attention. The examination begins with assessing the depth of coma. The two most recognized coma scales include Glasgow Coma Scale (GCS) and the Full Outline of UnResponsiveness (FOUR) score (Table 1.1). The GCS [18] was originally developed in 1974 to assess the level of consciousness in patients with TBI but is now widely used in clinical practice to grade coma. With a total score ranging from 3 to 15, it has three components graded independently: eye opening, motor response, and verbal response. It is universally accepted and easily performed by a wide range of providers with an interrater disagreement rate of approximately 20% [18, 19] and has outcome predictive value in patients with ICH [20], SAH, and TBI among others. The inability to grade the verbal score in intubated patients (a substantial proportion of comatose patients) is a major drawback of the GCS. In addition, the GCS has very limited value in localization as it does not account for brainstem reflexes. To overcome these shortcomings, the

**Table 1.1** Advantages and disadvantages of the GCS and FOUR scores

| Coma scale | Components | Advantages | Limitations | Interrater agreement |
|---|---|---|---|---|
| GCS | Eye opening<br>4—spontaneously<br>3—to voice<br>2—to pain<br>1—no response | – Simple, no neurologic expertise needed<br>– Widely accepted<br>– Good interrater reliability<br>– Good predictive value | – Verbal score often not scored as patients intubated<br>– No localizing value<br>– No insight into etiology of coma | Exact: 71%<br>±1 score: 90% |
| | Verbal response<br>5—alert and oriented<br>4—disoriented<br>3—nonsensical speech<br>2—unintelligible<br>1—no response<br>T—intubated | | | |
| | Motor response<br>6—follows commands<br>5—localizes to pain<br>4—withdraws to pain<br>3—decorticate posturing<br>2—decerebrate posturing<br>1—no response | | | |

(continued)

**Table 1.1** (continued)

| Coma scale | Components | Advantages | Limitations | Interrater agreement |
|---|---|---|---|---|
| FOUR score | Eye response<br>4—open spontaneously, tracking or blinking to commands<br>3—open but not tracking<br>2—opens eyes to voice<br>1—opens eyes to pain<br>0—no response | – Takes into consideration brainstem reflexes and thus has localizing value<br>– No verbal score and thus can be performed in intubated patients<br>– Helps further characterize patients with lower GCS scores | – Not widely accepted yet<br>– May require some neurologic expertise (interrater agreement superior in neurologists compared to other staff) [29] | Exact: 82%<br>±1 score: 92% [29] |
| | Motor response<br>4—thumbs-up, fist or peace sign<br>3—localizes to pain<br>2—flexor response to pain<br>1—extensor response to pain<br>0—no response | | | |
| | Brainstem reflexes<br>4—pupil and corneal reflex present<br>3—one pupil wide/fixed<br>2—pupil/corneal reflex absent<br>1—pupil and corneal reflex absent<br>0—pupil, corneal, and cough reflex absent | | | |
| | Respiration<br>4—not intubated, regular breathing pattern<br>3—not intubated, Cheyne-Stokes breathing<br>2—not intubated, irregular breathing<br>1—breathes over ventilator rate<br>0—breathes at ventilator rate or apnea | | | |

FOUR score [21] was developed in 2005 which takes into account eye opening, motor responses, brainstem reflexes, and respirations and ranges from 0 to 16. The FOUR score has been validated with multiple providers including medical intensivists, nurses, and emergency department physicians with an interrater reliability of 0.82. However, when compared prospectively to GCS, the interrater reliability remained only marginally better [22]. Although the FOUR score may provide additional neurological information, especially in patients with lower GCS, and negates the need for a verbal score, it has not gained wide acceptance in clinical practice.

After assessing the depth of coma, brainstem reflexes are assessed which help localize brainstem lesions, provide prognostic information, and may suggest the need for emergent interventions. The pupils are assessed for reactivity, size, shape, and symmetry and indicate integrity of the optic nerve, midbrain, and oculomotor nerve. An acute unilateral wide fixed pupil in a comatose patient suggests transtentorial herniation and the need for urgent medical and surgical intervention

to prevent irreversible injury. Similarly, absent vestibulo-ocular reflexes may suggest injury to the third, fourth, sixth, and eighth cranial nerves as well as rostral brainstem. Corneal reflex tests the fifth and seventh cranial nerves and the mid pons. Cough and gag reflexes, when present, indicate that the ninth and tenth cranial nerves and rostral medulla are intact.

Motor responses to command or pain also provide important information and are included in the GCS and FOUR score. Movement of extremities spontaneously to command or localization to pain (a purposeful movement aimed at removing stimulus) is not consistent with coma. Flexor posturing (reflexive flexion of arms to pain) suggests more rostral lesions when compared to extensor posturing (reflexive extension and internal rotation of arms to pain), which usually indicates lesions involving the lower midbrain and upper pons. However, the localizing value of these findings is limited [16]. Patients with nonconvulsive status epilepticus may also have other important signs suggesting ongoing seizure activity such as eye deviation, fluctuating pupillary asymmetry, facial and finger twitching, and urinary and fecal incontinence among others.

Clinical evaluation remains incomplete without appropriate laboratory studies. Laboratory analysis of all comatose patients may help identify several nonstructural causes of coma and should include a complete blood count, metabolic panel with liver function (hypo- or hypernatremia, uremia, hyperammonemia), blood glucose (hypoglycemia or severe hyperglycemia), arterial blood gas (hypercarbia or profound hypoxemia), urinalysis, toxicology screen (drug overdose), alcohol level, thyroid-stimulating hormone, and cortisol levels. If the etiology of coma is not apparent during the initial steps of assessment, empiric treatment with intravenous dextrose (to treat suspected hypoglycemia) preceded by thiamine (to prevent Wernicke's encephalopathy) and/or naloxone (to reverse opioid overdose) may be warranted [23]. In addition to above, a computed tomography (CT) scan must be obtained and most often will reveal the diagnosis.

A subgroup of neurocritically ill patients need special mention. Although not comatose, patients with spinal cord injury and neuromuscular disorders such as Guillain-Barre syndrome and myasthenic crisis may need close monitoring in the NCC due to their potential for rapid progression and high risk for respiratory and hemodynamic compromise. It is important to frequently assess respiratory mechanics such as single breath count (SBC), forced vital capacity (FVC), and negative inspiratory force (NIF) to predict the need for ventilatory support. Moreover, these patients may have hemodynamic instability from involvement of the autonomic nervous system and may need continuous telemetry and blood pressure monitoring.

### 1.3.2 Imaging in Neurocritical Care

Neuroimaging serves multiple purposes in neurocritically ill patients depending on the phase of their care. In the acute phase, the primary purpose of neuroimaging is to establish the diagnosis and identify lesions that may need emergent medical and surgical interventions such as large AIS with vessel occlusions, cerebral edema, subdural hematomas, and obstructive hydrocephalus among others. For this purpose, most often, non-contrast head CT scan suffices, although magnetic resonance imaging (MRI) of the brain may be indicated in early identification of smaller ischemic AIS involving the brainstem. During the monitoring phase, imaging modalities may help preempt progression of injury such as transcranial Doppler (TCD) ultrasound and perfusion studies in identifying delayed cerebral ischemia in patients with SAH. Finally, more advanced neuroimaging may be needed to provide more detailed structural and metabolic data to help predict functional outcomes such as diffusion tensor imaging (DTI), MR spectroscopy (MRS), and positron emission tomography (PET) in patients with traumatic brain injury [24]. We summarize in Table 1.2 common neuroimaging modalities and their indications categorized by common neurocritical illnesses.

**Table 1.2** Common neuroimaging modalities used in the NCCU

| | Acute phase | | Monitoring phase | | Prognostication | |
|---|---|---|---|---|---|---|
| Disease | Imaging | Indication | Imaging | Indication | Imaging | Indication |
| Acute ischemic stroke (AIS) | Head CT | Rule out hemorrhage prior to thrombolysis | Head CT | Evaluating hemorrhagic conversion, cytotoxic edema, midline shift to guide osmolar therapy, and need for decompressive craniectomy | MRI brain | Location, size of stroke, and secondary injury from shift/edema provide prognostic information |
| | MRI brain | Location/size of infarct | | | | |
| | CT/MR angiogram (CTA/MRA) | Identify vessel occlusion | | | | |
| | CTP | Identifying infarct core vs. penumbra volume especially in patients 6–24 h from symptom onset prior to thrombectomy | | | | |
| | Digital subtraction angiography (DSA) | Mechanical thrombectomy in large vessel occlusions (0–6 h and select patients up to 24 h) | | | | |
| Intracerebral hemorrhage (ICH) | Head CT | Location, volume of hemorrhage, intraventricular hemorrhage (IVH), obstructive hydrocephalus | Head CT | Hematoma expansion, perihematomal edema, and midline shift to guide osmolar therapy Monitor removal of IVH and hydrocephalus to guide ventricular drainage | Head CT | Initial ICH volume, presence of IVH, and location of ICH (infratentorial/thalamic) are radiologic markers that correlate with short-term and long-term outcomes |
| | CTA | Identify vascular malformation, aneurysm | | | MRI brain | Secondary brain injury may correlate with outcomes for, e.g., thalamic or brainstem injury from herniation |
| | MRI brain | May provide etiologic information such as underlying tumor or amyloid angiopathy | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Traumatic brain injury (TBI) | Head CT | Subdural/epidural hematomas, contusions, countercoup injury, diffuse cerebral edema, hydrocephalus | Head CT | Monitor size of contusions and cerebral edema to guide osmolar therapy; monitor hydrocephalus to guide ventricular drainage | MRI brain with SWI/GRE | Locating subcortical and deep shearing injuries, corpus callosum, and dorsal brainstem lesions which correlate with poor outcome |
| | CTA | Vascular injury | | | DTI with tractography | Diffuse axonal injury-disrupted white matter tracts; severe DAI may correlate with poor outcome |
| | | | | | MRS | Identifies metabolic parameters of damaged brain; N-acetyl aspartate (NAA) levels on MRS correlate with 6-month outcomes in mild to moderate TBI patients |
| | | | | | PET | Evaluates oxidative and glucose metabolism; experimental at this stage Early reduction in oxidative brain metabolism may correlate with chronic brain atrophy |
| Subarachnoid hemorrhage (SAH) | Head CT | Location and severity of hemorrhage (graded by Fisher scale); obstructive hydrocephalus, IVH | Transcranial Doppler (TCD) | Cerebral blood flow velocities to detect cerebral vasospasm and DCI (needed from day 3–14) | Head CT | Higher amount of subarachnoid blood (higher modified Fisher scale) correlates with higher risk for DCI |
| | CTA | Location of aneurysm (MRA not useful as cannot detect small aneurysms) | CTA/CTP | To detect vasospasm, vascular territories "at risk" (sensitivity 75–80%; specificity 90–93%) [40] | MRI brain | Ischemic burden from DCI may correlate with outcomes |
| | DSA | Coiling of aneurysm | DSA | Angioplasty, intra-arterial therapy with vasodilators to treat DCI | | |
| | MRI brain | Rarely needed if head CT negative for blood but suspicion is high and patient presents several days after onset (CT sensitivity can be as low as <50% after 1 week) | | | | |

### 1.3.3 Multimodality Neurologic Monitoring in NCC

Multimodality neurologic monitoring plays an important role in the NCCU, providing adjunct information to the neurological examination to guide therapy. They are broadly categorized into global and regional modalities (Table 1.3) [15]. Global neurologic monitoring technologies include:

(a) *ICP Monitoring*
ICP monitoring is the most widely used multimodal monitoring. Persistent elevation in ICP and corresponding reduction in cerebral perfusion pressure (CPP) correlate with poor outcomes in patients with neurologic injury. The Neurocritical Care Society recommends ICP and CPP monitoring in all patients at risk for elevated ICP based on clinical and imaging characteristics. Guiding interventions to maintain ICP below 20–25 mm of Hg is recommended [25].

The "gold standard" to measure ICP is an external ventricular drain (EVD) coupled with a fluid-filled transducer system that provides the most accurate measurement of global ICP in addition to cerebrospinal fluid (CSF) drainage. However, prolonged monitoring with EVD brings with it an increased risk for infectious ventriculitis.

ICP monitoring devices that use fiber-optic microtransducers (e.g., Camino, Codman, Raumedic, and Pressio-Sophysa) are placed in the brain parenchyma or subdural space and eliminate the need for an external fluid-filled transducer system reducing the risk of infections. Such devices, however, do not drain CSF, provide less accurate readings, may represent compartmentalized pressures rather than global ICP, and have a considerable zero-drift during long-term monitoring making them ineffective beyond a few days [26].

(b) *Jugular Venous Bulb Oximetry ($SjVO_2$ Monitoring)*
$SjVO_2$ monitoring involves placement of a specialized catheter in the bulb of the internal jugular vein which measures the oxygen saturation in the cerebral venous outflow ($SjVO_2$), a measure of cerebral oxygen extraction. It

**Table 1.3** Most commonly used neuromonitoring techniques in the NCCU

| Monitoring system | Indications | Shortcomings |
|---|---|---|
| ICP | Cerebral edema, acute hydrocephalus, midline shift | Invasive; risk of infectious ventriculitis, ICH, IVH |
| Jugular venous bulb oximetry | Severe TBI, diffuse cerebral edema | Measures global brain oxygenation, risk of venous thrombosis, line sepsis, carotid puncture |
| Continuous EEG | Status epilepticus, unexplained altered consciousness or neurologic deficits, therapeutic hypothermia, SAH for monitoring DCI | Qualitative, operator dependent, frequent artifacts, interferes with head imaging studies |
| Cerebral microdialysis | Severe TBI<br>SAH | Sampling of a small region limiting extrapolation to the remaining brain, infection (low risk) |
| Brain tissue oxygen | Severe TBI, SAH, diffuse cerebral edema | Infection, ICH |
| Transcranial Doppler (TCD) | Monitoring cerebral vasospasm, confirming brain death, recanalization after thrombolytic therapy | Operator dependent; limited by cranial anatomy |
| Near-infrared spectroscopy (NIRS) | Severe TBI, cerebral autoregulation | Motion artifact, signal drift, sensitivity to extraneous light |
| Xenon-133 clearance | Severe TBI, SAH | Measures superficial blood flow, unreliable with abnormal blood-brain coefficient |
| Laser-Doppler flowmetry | Severe TBI, cerebral edema | Probe malfunction requiring replacement |
| Thermal diffusion flowmetry | Severe TBI, cerebral edema | Small region monitored, signal distortion, low risk of infection |

can also be used to calculate the difference between arterial and jugular venous oxygen content ($AVDO_2$). A lower $SjVO_2$ (<55%) and a higher $AVDO_2$ (>8 mL $O_2$/100 mL blood) suggest a higher cerebral oxygen demand than supply (i.e., cerebral ischemia) and may indicate the need for interventions to provide a "luxuriant" CBF [27]. The Neurocritical Care Society recommends using $SjVO_2$ monitoring in combination with other modalities to guide therapy in patients with moderate to severe TBI [25].

(c) *Continuous Electroencephalography (EEG)*
EEG helps monitor changes in cortical electrical activity over the cerebral hemispheres and has the ability to identify focal changes as well. The Neurocritical Care Society [25] recommends using EEG monitoring in all patients with or without acute brain injury who have persistent unexplained altered consciousness or neurologic deficits, patients with status epilepticus not returning to baseline and patients undergoing therapeutic hypothermia to identify subclinical seizures. EEG monitoring may also be used in high-grade SAH patients to detect delayed cerebral ischemia by monitoring variability in alpha activity and the ratio of alpha to delta activity over the cerebral hemispheres.

Regional neurologic monitoring modalities help identify focal changes in CBF and metabolism with the goal to preempt permanent injury. These include:

(a) *Cerebral Microdialysis*
Microdialysis involves placing a specialized catheter in the subcortical white matter that monitors brain chemistry at the cellular level. This is most studied in patients with TBI. The most commonly measured interstitial brain analytes are lactate, pyruvate, glucose, glutamate, and glycerol. Increased lactate to pyruvate ratio and low brain glucose strongly suggest increased mortality and unfavorable outcome. Increased glutamate is a marker of delayed injury [28]. Guiding systemic glucose control, transfusions, therapeutic hypothermia, hypocapnia, and hyperoxia using cerebral microdialysis is suggested [25].

(b) *Brain Tissue Oxygen Monitoring ($PbtO_2$)*
PbtO2 monitoring involves measuring interstitial oxygen locally over a probe that is tunneled into parenchyma or subdural space [28]. The literature supports using PbtO2 monitoring in combination with ICP monitoring in patients with severe TBI and SAH. Initiating therapy when PbtO2 is <20 mm of Hg is recommended by the Neurocritical Care Society [25]. The interventions that can help improve PbtO2 include hyperosmolar therapy, hyperventilation, increasing oxygen supplementation, positive end expiratory pressure (PEEP), mean arterial pressure (MAP), and blood transfusions among others.

(c) *Regional CBF and Oximetry Monitoring*
These techniques include TCD and near-infrared spectroscopy (NIRS). TCD measures the CBF velocity in the main vessels such as anterior, middle, and posterior cerebral as well as basilar arteries. TCD is most useful in detecting subclinical vasospasm in patients with SAH in order to prevent delayed cerebral ischemia. TCD is also used to determine cerebrocirculatory arrest in those patients with the clinical suspicion of brain death when flow is completely absent. NIRS provides a continuous noninvasive method to continuously monitor regional cerebral oxygenation but remains a research tool currently and is most studied in TBI.

### 1.3.4 Management of Raised ICP

ICP is defined as the pressure exerted on the dura mater by contents within the cranial vault [29]. According to the Monro-Kellie hypothesis, with an intact skull, the sum of the volume of brain, CSF, and intracranial blood is constant [30] and increases in one component results in the displacement of the others. Once these compensatory changes are maximized, ICP begins to rise in an exponential fashion. This inflection occurs when ICP is approximately 20–25 mmHg

in adults [31]. Elevated ICP has been shown to consistently correlate with poor outcomes. A study in severe TBI patients demonstrated an increased odd for death when the ICP was >20 mmHg (OR 3.5 if ICP 20–0 and 6.9 if >40) [32]. However, brief spikes in ICP above 20 mmHg may occur with coughing, agitation, and Valsalva maneuver, which are well tolerated. Thus, for treatment purposes, intracranial hypertension is defined as sustained elevation (>5 min) in ICP above 22 mmHg [29].

CPP is the difference between the mean arterial pressure (MAP) and the mean ICP [33]. Thus, when the ICP increases, there is a resultant decrease in the CPP. However, as described by Lassen [34], the relationship between CPP and CBF is sigmoid. Provided cerebral autoregulation is intact, CBF is maintained over a wide range of CPP by maximal cerebral vasodilation and vasoconstriction. Below the lower limit of autoregulation (CPP < 40–60 mmHg), cerebral ischemia ensues, while above the upper limit of autoregulation, cerebral hyperemia, vasogenic edema, and hemorrhage might occur.

The Brain Trauma Foundation recommends treating ICP if >22 mmHg and maintaining CPP >60–70 mmHg in patients with TBI [35]. This is extrapolated to other neurocritical illnesses, and targeting ICP below 20–25 mmHg is also recommended by the NCS [25].

Therapies that lower ICP, and thus raise CPP, target one or more of the three intracranial components, i.e., brain parenchyma, CSF, and intracranial blood (Table 1.4). Stocchetti et al. suggest following a "staircase" approach with the more aggressive measures restricted to refractory ICP elevations [36]. After ensuring a secure airway, adequate ventilation, and hemodynamics, the first step is proper positioning, ensuring that the head of bed is elevated and neck midline. This permits cerebral venous outflow and CSF drainage. Initiating sedation lowers ICP by reducing the cerebral metabolic rate ($CMRO_2$) and consequently intracranial blood volume. CSF drainage through EVD also lowers ICP but is most useful when ICP elevation is due to ventricular obstruction.

Hyperosmolar agents, the next line of management, lower ICP by generating an osmolar

**Table 1.4** Therapeutic maneuvers to decrease elevated ICP

| Intervention | Intracranial compartment targeted | | | Risks |
|---|---|---|---|---|
| | Brain parenchyma | CSF | Intracranial blood volume | |
| Positioning: head of bed elevation, neck midline | – | + | + | None |
| Sedation and analgesia-propofol, midazolam, pain control with fentanyl, etc. | – | – | +++ | Inability to reliably monitor neurologic examination, hypotension, bradycardia,[a] hypertriglyceridemia,[a] propofol infusion syndrome,[a] pancreatitis[a] |
| External ventricular drainage | – | +++ | – | Infectious ventriculitis, intracerebral hemorrhage |
| Mannitol | +++ | – | ++ | Hypotension, dehydration, acute renal failure, volume overload |
| Hypertonic saline | +++ | – | – | Volume overload, hypotension, hypernatremia, hyperchloremia, acidosis |
| High-dose glucocorticoids | +++ | – | – | Hyperglycemia, increased infections, impaired wound healing, gastric ulcers, worse outcomes in patients with intracerebral hemorrhage and stroke |
| Induced hypocarbia: Hyperventilation | – | – | +++ | Cerebral ischemia, strokes, severe alkalosis, seizures |
| Hypothermia | – | – | +++ | Infection, electrolyte disturbances |
| Barbiturates | – | – | +++ | Hypotension, infections |
| Decompressive craniectomy | +++ | – | – | Infections, subdural hygromas or hematoma, syndrome of the trephined |

[a]Side effects of propofol

gradient across the intact blood-brain barrier (BBB) which promotes water egress from the normal brain parenchyma. An osmolar agent creates a gradient effectively only when it is excluded by the BBB, measured by the reflection coefficient (0 = complete permeability and 1 = impermeable). Mannitol has a reflection coefficient of 0.9 lowering ICP effectively by creating an osmolar gradient and also promoting osmotic diuresis. It also has a first-pass rheological effect which involves lowering blood viscosity, causing reactive cerebral vasoconstriction, and reducing intracranial blood volume [37]. Mannitol should be administered in bolus doses of 0.25–1 g/kg body weight during acute ICP elevations. Continuous mannitol infusion results in equilibration of osmoles across the BBB becoming ineffective, worsening cerebral edema and thus should be avoided.

Sodium has a reflection coefficient of 1, making hypertonic saline the most effective osmolar agent that lowers ICP by directly increasing serum osmolarity. When the ICP is acutely elevated, a bolus of 30 mL of 23.4% hypertonic saline can be given. Other concentrations available include 2%, 3%, and 7.5% which can be given in boluses of 500, 250, and 75 mL, respectively. Concentrations higher than 3% should be administered through a central venous catheter. Continuous 2 or 3% saline infusions to maintain a high serum sodium are often used in practice and, though effective, benefit only transiently.

High-dose glucocorticoids also reduce ICP by targeting vasogenic cerebral edema and are most effective in patients with brain tumors, abscesses, demyelinating diseases, and infections. They have not shown to be effective in cytotoxic edema related to AIS and may worsen outcomes in patients with ICH.

Induced hypocarbia by hyperventilation effectively lowers ICP by reducing intracerebral blood volume through cerebral vasoconstriction. However, this carries a risk of cerebral ischemia, and hyperventilation is recommended only in the emergent management of life-threatening intracranial hypertension with rapid normalization of $PaCO_2$ once definitive therapy is administered [38]. Moreover, guidelines recommend monitoring $SjvO_2$ or $PbtO_2$ when using hyperventilation to detect cerebral hypoxia [35].

Advanced therapies reserved for refractory intracranial hypertension include cerebral metabolic suppression with hypothermia (target temperature 32–36 °C) and barbiturate infusion (with the goal of achieving burst suppression on continuous EEG). Surgical interventions such as decompressive craniectomy may be pursued in patients with cerebral contusions, subdural hematoma, and hemispheric AIS and ICH among others. Bifrontal decompressive craniectomy for severe diffuse TBI with refractory intracranial hypertension (DECRA trial) has not been shown to provide any benefit and is associated with higher rates of unfavorable outcomes [39].

### 1.3.5 Airway and Mechanical Ventilation in Neurocritical Care

Unlike other critically ill patients, the NCC patient most commonly requires tracheal intubation for "inability to protect airway" due to depressed mental status. This occurs most commonly in patients with impaired consciousness leading to inadequate airway clearance from impaired oropharyngeal coordination, bulbar weakness, and weak cough reflex, leading to aspiration of oral contents. In addition, acute loss of consciousness leads to occlusion of upper airway by the tongue. Also, impaired consciousness is often coupled with hypoventilation and hypercarbia leading to elevated ICP. Thus, promptly securing the airway is essential to prevent secondary brain injury. The corollary, although subjective, is that any neurologic patient at risk for aspiration is a candidate for airway assessment. Guidelines recommend intubating brain injury patients based on low GCS scores [35] (often GCS < 8 or 9), although some argue against this practice. Important factors determining the need for intubation include level of consciousness, presence of gag and cough reflex, swallowing mechanisms, amount of secretions, and how long the patient is likely to be neurologically impaired [40, 41].

A special mention must be made regarding patients with spinal cord and neuromuscular disorders. Apart from having bulbar dysfunction and consequent failure to protect their airway, these patients may rapidly progress to respiratory failure from intercostal muscle and diaphragmatic weakness. Hypercarbia and hypoxemia occur late and can be catastrophic. Bedside pulmonary function tests such as negative inspiratory force (NIF) and forced vital capacity (FVC) better predict the need for mechanical ventilation in a timely manner and should therefore be followed serially. Mechanical ventilation is indicated with a declining NIF or FVC, NIF <−20 $cmH_2O$, or FVC <20–25 mL/kg body weight [42].

Rapid sequence intubation (RSI) using a high-dose sedative and paralytic is the preferred method for securing the airway in neurological patients at risk for elevated ICP [43]. The presence of coma does not exclude the need for general anesthesia as laryngoscopy often induces a reflex sympathetic response (RSR) which can lead to hypertension and elevation in ICP. Preloading patients with fentanyl (2–5 μg/kg) has been shown to prevent this and is recommended in neurological patients [44].

Induction should be performed using agents that are less likely to cause hypotension, maintaining MAP between 80 and 100 mmHg and preserving CPP >50 mmHg [43]. Etomidate is the most hemodynamically neutral agent, but propofol (2 mg/kg) is also favored as it lowers ICP through reduction in $CMRO_2$. Propofol leads to hypotension unless combined with a vasopressor. Ketamine also has a favorable hemodynamic profile but has been associated with ICP elevations in the presence of hydrocephalus. However, systematic review of ketamine use showed no effect on cerebral perfusion and neurologic outcomes in brain injury patients without hydrocephalus [45].

Succinylcholine is the preferred paralytic due to its rapid onset and short duration of action. Transient elevations in ICP with succinylcholine may occur but are clinically insignificant [46]. Due to its depolarizing nature and consequent risk for hyperkalemia, succinylcholine should be avoided in chronic denervation (prior stroke, spinal cord injury, neuromuscular disease) or prolonged immobilization (>72 h). In these patients, non-depolarizing neuromuscular blockers such as rocuronium or vecuronium are recommended despite their slow time of onset and longer action. In patients with elevated ICP, care must be taken to minimize the duration the head of bed is lowered for intubation. In fact, head of bed should be lowered only after induction. In patients with cervical spine injury, manual in-line stabilization should be provided, and cricoid pressure should be avoided to prevent posterior displacement.

After intubation, mechanical ventilation should be initiated with the goal of maintaining normoxia, normocarbia, and a normal arterial pH with hyperventilation and induced hypocarbia limited to acute ICP crisis. There is no literature guiding the use of ventilator modes in neurocritical illness. Volume-cycled ventilation is preferred [43] as it ensures a fixed minute ventilation thus permitting better $PaCO_2$ control. Controlled mandatory ventilation (assist control) is the most commonly used ventilator mode in neurocritical care. Synchronized intermittent mandatory ventilation (SIMV) may be used if patient comfort and ventilator synchrony is an issue. Pressure-controlled (PC) ventilation involves fluctuating tidal volumes to deliver a fixed airway pressure, leading to $PaCO_2$ fluctuations and, theoretically, ICP elevations. Pressure-regulated volume control (PRVC), while regulating airway pressure, ensures adequate tidal volume delivery, minimizing $PaCO_2$ fluctuations. However, Schirmer-Mikalsen et al. [47] compared PC to PRVC in TBI patients and did not show any significant difference in mean ICP and $PaCO_2$ levels. They did, however, demonstrate more fluctuations in these parameters in PC versus PRVC modes.

Regardless of the mode, lung-protective ventilation is preferred with tidal volumes set at 6–8 mL/kg of predicted body weight and plateau pressures maintained below 30 $cmH_2O$ to prevent acute respiratory distress syndrome (ARDS) [48]. Respiratory rate is guided by the minute ventilation needed to achieve the desired $PaCO_2$ and arterial pH. Fraction of inspired oxygen ($FiO_2$) is adjusted to maintain oxygen saturation at 95–100% to prevent secondary brain injury. However, hyperoxia ($PaO_2$ > 300 mmHg) is associated with worse outcomes in TBI patients and should be avoided.

PEEP is included in the lung-protective strategy to recruit more alveoli, improve lung compliance and oxygenation, and avoid derecruitment of alveoli during expiration [49]. However, in patients with impaired cerebral compliance, high PEEP levels may cause further rise in ICP due to direct transmission of increased thoracic pressure, reduced cerebral venous outflow, and decreased cardiac output with consequent cerebral vasodilation [40]. Regardless, a minimum PEEP of 5 $cmH_2O$ should be used to prevent lung injury and is considered safe in brain injury patients [50]. Further, PEEP may be up-titrated preferentially to improve oxygenation provided ICP and CPP are unaffected. Elevating the head of the bed to 30–45° may reduce the impact of increased PEEP on ICP.

Finally, liberation from mechanical ventilation in neurological patients possesses challenges with little data to guide decision-making. The Society of Critical Care Medicine recommends daily spontaneous breathing trials and does not support slow weaning. Daily spontaneous breathing trials should be performed in neurological patients provided there are no contraindications such as $FiO_2$ >40–50%, PEEP >5–8 $cmH_2O$, blood pressure <90 mmHg, vasopressors, neuromuscular blockade, elevated ICP, status epilepticus needing deep sedation, symptomatic cerebral vasospasm, or active neurologic ischemia [41, 48]. The ability to tolerate CPAP for 30 min, with pressure support <5 $cmH_2O$, while maintaining oxygenation and a rapid shallow breathing index (RSBI) of <105, predicts successful extubation. However, this has not been studied in neurologic patients leading to marked variability in practice across NCCUs.

Neurologic patients with depressed consciousness and neuromuscular weakness are likely to fail extubation due to impaired oropharyngeal mechanics, inability to clear secretions, and respiratory fatigue. The ability to tolerate CPAP over a prolonged period in neurologic patients with altered sensorium provides reassurance that the patient is likely to tolerate breathing off the ventilator indefinitely. Thus, although no evidence exists, many centers continue to incorporate prolonged CPAP trials in NCCUs to promote increase in strength, functional residual capacity and NIF as well as to ensure sustenance [40].

Weaning protocols do not ensure ability to clear secretions and airway patency after extubation. Patient arousal and ability to follow commands are often used in medical ICUs as a surrogate for airway clearance and patency. However, inability to follow commands in brain injury is ubiquitous and may be due to focal lesions unrelated to respiratory ability. Therefore, more liberal parameters are ought to be used in NCC patients when assessing possibility of successful extubation. Several studies have demonstrated successful extubation in patients with GCS as low as 4 in the presence of intact cough reflex. Godet et al. demonstrated that, in brain injury, presence of two or more airway reflexes (i.e., cough, gag, or deglutition) in combination with intact visual pursuits resulted in 80% extubation success rates [51]. Therefore, a combination of the patient's mental status, airway reflexes, ability to tolerate prolonged spontaneous breathing trials, amount of secretions, need for deep suctioning, NIF, FVC, and cuff leak test should be used while determining the ability to liberate an NCCU patient from mechanical ventilation. Despite meeting most parameters, approximately 31% brain-injured patients fail extubation. Inability to clear secretions (67%) and stridor (14%) are the most common causes of extubation failure. If failed, tracheostomy should be pursued. A trial assessing the impact of early tracheostomy on outcomes in brain injury patients is ongoing.

### 1.3.6 Optimizing Blood Pressure Control in Neurocritical Care

The brain uses ~20% of systemic oxygen for normal function, making tight regulation of CBF necessary to maintain adequate oxygen delivery. CBF is closely mediated by neural-astrocyte regulation using various vasoactive mediators to meet the high metabolic demand during neuronal activity. By means of cerebral arteriolar dilation and constriction, the CBF is maintained at ~50 mL/100 g of brain tissue/min over a wide range of CPP (~60 to 160 mmHg). CPP is directly linked to the systemic blood pressure (CPP = MAP − ICP) [52]. At CPP levels beyond the upper and lower limits of autoregulation, CBF

has a linear relationship with the MAP. Below the autoregulation threshold (CPP < 60 mmHg), cerebral ischemia ensues leading to increased oxygen extraction, neuronal dysfunction, and ultimately neuronal death. Above the autoregulation threshold (CPP > 160 mmHg), increased permeability and rupture of cerebral arterioles occur leading to vasogenic edema and hemorrhage. Therefore, appropriate blood pressure control to maintain hemodynamic homeostasis is the single most important NCC intervention with variable blood pressure goals depending on underlying disorders (Table 1.5). Recognizing the high variability in CBF across patients, and in the same patient over time, there is great interest in individualizing blood pressure goals by identifying the optimal

**Table 1.5** Blood pressure management in the NCCU

| Condition | Blood pressure goal recommended | Level of recommendation and evidence | Guideline source |
|---|---|---|---|
| *Ischemic stroke* | | | |
| 1. Large hemisphere infarctions without intervention | • MAP >85 mmHg, SBP <220 mmHg (provided no hemorrhagic transformation)<br>• Avoid hypotension<br>• Avoid blood pressure variability | Strong recommendation, low quality of evidence | Neurocritical Care Society guidelines for management of large hemispheric infarctions (2015) |
| 2. Intravenous tpA | • SBP <185 mmHg, DBP <110 mmHg prior to treatment and up to 24 h after | Strong recommendation, moderate level of evidence (non-randomized) | American Heart Association/American Stroke Association guideline for early management of patients with acute ischemic stroke (2018) |
| 3. Intra-arterial mechanical thrombectomy | • SBP <185 mmHg, DBP <110 mmHg prior to treatment and up to 24 h after | Moderate recommendation, moderate quality of evidence (randomized) | |
| *Subarachnoid hemorrhage* | | | |
| 1. Before aneurysm secured | • Treat extreme hypertension, maintain SBP <160 mmHg, MAP <110 mmHg to prevent aneurysm rupture, avoid hypotension | Strong recommendation, low quality of evidence | Neurocritical Care Society guidelines for critical care management of patients following aneurysmal subarachnoid hemorrhage (2011) |
| 2. After aneurysm secured | • Allow autoregulation of blood pressure, allow hypertension, avoid hypotension to prevent vasospasm | Strong recommendation, poor-quality evidence | |
| 3. Delayed cerebral ischemia, symptomatic cerebral vasospasm | • Induce hypertension in a stepwise fashion with assessment of neurologic function to identify optimal MAP goal | | |
| *Intracerebral hemorrhage* | • Lowering SBP to <140 mmHg is safe<br>• The ATACH-2 trial failed to show improvement in outcomes with lowering SBP to below 140, and thus guidelines are likely to change [74] | Strong recommendation, high-quality evidence | American Heart Association Guidelines for management of spontaneous ICH (2015) |
| *Post-cardiac arrest brain injury* | • Avoid hypotension: SBP >90 mmHg and MAP >65 mmHg | Weak recommendation, low quality of evidence (limited data) | American Heart Association guidelines for cardiopulmonary resuscitation (2015) |
| *Traumatic brain injury* | • Age 50–69: maintain SBP >100 mmHg<br>• Age 15–49 or >70: maintain SBP >110 mmHg<br>• Target CPP between 60 and 70 mmHg | Low quality of evidence (class 2 or 3 studies only) | Brain Trauma Foundation TBI guidelines (2017) |

MAP based on continuous noninvasive monitoring of cerebral autoregulation and CBF.

### 1.3.7 Fluid and Electrolyte Management

Fluid resuscitation is important to maintain adequate CBF and oxygenation. The choice of fluid, specifically crystalloids versus colloids, in neurocritical patients remains a dilemma. Multiple studies have shown no or negative impact on outcomes in SAH and TBI patients with synthetic colloids such as pentastarch and gelatin when compared to saline. A trial comparing high-dose albumin (25%) to saline in ischemic stroke patients failed to show improvement in outcomes with albumin and showed higher incidence of pulmonary edema and symptomatic ICH in the albumin group [53]. Subgroup analysis of the TBI patients in the SAFE trial (comparing 4% albumin to saline) found higher mortality in the albumin group [54]. A retrospective study in SAH patients demonstrated a reduced trend toward vasospasm and improved outcomes at 3 months in the albumin group [55], but this needs to be confirmed prospectively. Currently, the European Society of Intensive Care Medicine (ESICM) recommends using crystalloids and suggests against the use of synthetic colloids, albumin, glucose-containing hypotonic solutions, or hypertonic fluids for resuscitation in NCCU patients [56]. While balanced crystalloids have been shown to be associated with reduced incidence of acute kidney injury, renal replacement therapy, and mortality when compared to saline, neurological patients were excluded from these studies due to lower sodium content in balanced crystalloids. While the ESICM working group made no specific recommendation on choice of crystalloids, it might be prudent to use balanced crystalloids in NCC patients without risk for cerebral edema and elevated ICP.

The most important electrolyte in NCC is serum sodium. As previously described, sodium does not cross the blood-brain barrier and thus maintains an osmolar gradient directing flow of intra- and extraneuronal water. Hyponatremia leads to cerebral edema and raises ICP. Hypernatremia also negatively impacts neurocritically ill patients. Severe hypernatremia (>160 mEq/L) is independently associated with increased mortality [57]. The postulated mechanism includes hyperosmolar gradient causing shrinkage of neurons and resultant intraneuronal accumulation of organic osmolytes, amino acids, and methylamines leading to neuronal dysfunction. Hypernatremia is also associated with higher incidence of acute kidney injury in neurologic patients.

Intracranial disorders, in turn, can also lead to impaired sodium balance. Hyponatremia may occur due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting (CSW). Hypernatremia usually occurs due to central diabetes insipidus. We summarize in Table 1.6 common sodium disorders encountered in NCC patients.

Among other electrolyte disorders, hyperchloremic metabolic acidosis has a strong association with acute kidney injury and increased mortality. High chloride levels in renal tubules are sensed by the macula densa resulting in afferent arteriolar constriction and reduction in GFR. Several studies have shown a high incidence of hyperchloremic acidosis in the NCCU due to the use of unbuffered hypertonic saline solutions to treat elevated ICP. Retrospective studies in SAH [58] and ICH [59] patients showed a strong association between hyperchloremia, acute kidney injury, and mortality. All other electrolyte disorders should be aggressively corrected using nurse-led ICU electrolyte replacement protocols. Hypokalemia is often associated with hypertonic saline infusions and fludrocortisone therapy and may precipitate cardiac dysrhythmias. Hypomagnesemia and hypocalcemia should be avoided as these may precipitate seizures. Low serum phosphate levels should be aggressively corrected in fasting patients prior to initiation of feeding to prevent refeeding syndrome.

### 1.3.8 Nutrition and Prophylaxis

Neurocritical illness offsets a hypermetabolic, hypercatabolic state almost immediately. Initiation of enteral nutrition within 48 h in neurosurgical

**Table 1.6** Common alterations of sodium homeostasis in the NCCU

| Parameters | Cerebral salt wasting | SIADH | Central DI |
|---|---|---|---|
| Serum sodium | Low (<135 mEq/L) | Low (<135 mEq/L) | High (>145 mEq/L) |
| Volume status | Severely dehydrated, hypovolemic | Euvolemic or hypervolemic | Dehydrated, hypovolemic |
| Net fluid balance | Markedly negative | Positive | Negative |
| Urine output | Markedly increased (may be >1 L/h) | Normal to lower | Increased (>250 mL/h or >3 L/day) |
| Serum osmolality | High/normal | Low (<280 mOsm/kg) | High |
| Urine osmolality | Normal/high (may be higher than serum) | High (higher than serum, often >300 mOsm/kg) | Markedly low (urine: serum osmolality ratio of <2) |
| Urine sodium | High (>20 mEq/L) | High (>20 mEq/L) | Normal |
| Urine-specific gravity | Normal or high | Normal or high | Low (<1.005) |
| Fluid response | Improves sodium | Further drops sodium | No change in sodium, improves volume status |
| Associated diseases | Subarachnoid hemorrhage | Meningitis, encephalitis, brain tumors, traumatic brain injury, antiepileptic drugs such as carbamazepine and oxcarbazepine | Pituitary adenoma esp. post-resection, craniopharyngioma, brain tumors, pituitary apoplexy, meningitis/encephalitis, severe TBI, large ischemic strokes, intracranial hypertension, impending brain death |
| Treatment | Fluid resuscitation, often replacing 1 mL of urine output with 1 mL of isotonic or hypertonic crystalloids; fludrocortisone to reduce renal sodium losses | Fluid restriction to <1 L, restrict free water intake, loop diuretics, ADH antagonists (tolvaptan, conivaptan); in severe cases hypertonic saline may be used to treat cerebral edema | Mild-moderate DI in awake patient: vasopressin 1 unit SQ<br>Severe DI with no PO intake: replace 1 mL urine output with 1 mL of 1U vasopressin in 1 L ½NS<br>Chronic DI: desmopressin |

patients has been shown to reduce hypercatabolism and is associated with reduced negative nitrogen balance, gut atrophy and infections. In patients with TBI, early initiation of nutrition improved outcomes [60]. However, the study also showed that only 55% of the target caloric goal was achieved in most patients in the NCCU. AHA guidelines for AIS recommend enteral feeding within 7 days of admission after stroke onset as this was associated with an absolute reduction in death by 5.8%. Similarly, the Brain Trauma Foundation guidelines recommend feeding TBI patients within 5–7 days after injury to decrease mortality. Similar recommendations also exist for spinal cord injury patients. Existing ICH and SAH guidelines do not make recommendations on enteral feeding, but recommendations may be extrapolated from other NCC literature.

### 1.3.9 Venous Thrombosis and Gastrointestinal Prophylaxis

Venous thromboembolism (VTE) is extremely common in the NCCU with an incidence ranging from 1–5% in AIS, ICH, and SAH patients to 15–30% in patients with TBI and spine injury and brain tumors. Therefore, initiation of prophylaxis against VTE is necessary, but the benefit has to be weighed against the risk of hemorrhage in brain injury patients. The NCS guidelines [61] recommend mechanical prophylaxis with intermittent venous compression stockings or graded compression stockings upon admission in all neurocritically ill patients. Pharmacological prophylaxis with low molecular weight heparin (LMWH) is preferred over unfractionated heparin (UFH) in

AIS patients and should be initiated upon admission unless patient received r-tpA, intra-arterial mechanical thrombectomy or decompressive craniectomy, in which case initiation should be delayed by 24 h. In patients with ICH, TBI, and SAH, UFH or LMWH should be initiated within 24–48 h provided the hematoma is stable. In brain tumor patients, UFH or LMWH should be initiated upon admission provided there is no hemorrhage on imaging.

Gastrointestinal stress ulcer prophylaxis with a proton pump inhibitor or $H_2$ receptor blocker is indicated in all critically ill patients requiring mechanical ventilation and/or with an ongoing coagulopathy. In addition, neurological patients with elevated ICP are at high risk for stress ulcers and should receive ulcer prophylaxis. Brain tumor patients are often on high-dose corticosteroids for prolonged durations and should also receive ulcer prophylaxis.

All neurologically impaired patients are immobile and are often on opioids for sedation leading to a high incidence of constipation and adynamic ileus which can impair functional recovery and may be associated with ICP elevations. This should be prevented with frequent turning, early mobilization, minimizing opioid use, early nutrition, and a bowel regimen with stool softeners and promotility agents.

## 1.4 Conclusion

In conclusion, NCC has emerged as a distinct discipline over the last several decades. A successful NCCU relies on harmonious collaboration between neurologists, neurosurgeons, intensivists, and specially trained nursing services.

The main focus of NCC is to prevent secondary brain injury. This requires a deep understanding of cerebrovascular and CSF physiology, neuroanatomy, neuropharmacology, internal medicine, critical care, and the interplay between various organ systems and the brain. In addition, intensive neuromonitoring to preempt injury is the hallmark of NCC. While clinical monitoring is the mainstay, multiple monitoring technologies have evolved and are increasingly being used in practice. Supporting other organ systems is as important while preventing secondary brain injury. Needless to say, protecting the brain should be the focus of all critical care and not just limited to the NCCU. It has been increasingly shown that NCC improves outcomes in patients with neurologic injury justifying the rising demand for neurointensivists around the world.

**Key Points**

- The pivotal aspect of NCC involves providing intensive monitoring to critically ill neurological patients.
- It requires the support of specially trained personnel with skills to identify subtle neurologic changes which remain the best markers for worsening injury.
- Management of the neurocritically ill patient begins with ensuring a secured airway, adequate ventilation, and circulation.
- A rapid neurological assessment should be performed to grade the level of consciousness and elucidate the cause and severity of injury in order to identify immediate interventions such as ICP control.
- The main focus of NCC is to prevent secondary brain injury.

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# 2 Fluid Management in Neurointensive Care

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## 2.1 Introduction

The administration of intravenous fluids, which should be considered as drugs, is a vital component in the pharmacological treatment of patients with traumatic brain injury (TBI). Appropriate intravenous fluid therapy plays a vital role in the optimization and maintenance of adequate cerebral perfusion pressure (CPP) and cerebral oxygen delivery. The maintenance of adequate CPP, regardless of the type of TBI suffered, may help reduce post-traumatic cerebral ischaemia or contribute to decreased cerebral oedema [1].

Even short periods of cerebral hypoperfusion may contribute to subsequent brain injury and lead to unfavourable outcomes [2]. The complexity of achieving the best fluid strategy in TBI patients is complicated by the kind of injury, biochemical disturbances and patients' clinical condition and comorbidities. Added to this is the triphasic perturbations in cerebral blood flow (CBF) seen in severe TBI [3]. The hypoperfusion phase is characterized by a decrease of mean CBF to 32.3 ± 1.6 mL/100 g/min and is usually seen during the early phase of the injury [3]. Extremely low CBF (22.5 ± 5.2 mL/100 g/min) has been measured 6 h after TBI, and drastic decrease in CBF (<18 mL/100 g/min) was noted in a third of TBI patients [4]. This early hypoperfusion phase is followed by progressive increases in CBF (hyperaemic phase), reaching a peak flow between 48 and 72 h. The third phase develops between 4 and 14 days, where general vasospasm coupled with persistent post-traumatic cerebral hypometabolism and electrolyte disturbances is observed [3, 5, 6].

Cerebral oedema develops in the early hypoperfusion and hyperaemic phases of CBF which is exacerbated by the simultaneous disruption of the blood-brain barrier (BBB). Increased BBB permeability is a common early complication of TBI, developing within 48 h of the injury. This oedema occurs two- to tenfold higher in pericontusional areas, with rising intracranial pressure (ICP), with disturbances in capillary hydrostatic and oncotic pressures contributing to the problem [6]. Normal physiological conditions dictate that the BBB is permeable only to the smallest non-lipid-soluble

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molecules, as these are non-sinusoidal, non-fenestrated capillaries with endothelial cell membranes that are tightly opposed by zona occludens tight junctions (pore size of <1 nm) [7, 8]. Starling's principle describes the intravascular driving force as a balance between hydrostatic and osmotic pressure gradients. Capillary hydrostatic pressure is dependent on precapillary arteriolar pressure, capillary resistance and postcapillary venous pressure. Capillary resistance is affected by the volume of brain interstitial fluid (BISF) and tissue compliance. Therefore, the fluid flux depends on the net hydraulic and net osmotic forces in the BBB, with pore permeability playing a crucial role. Physiologically, both hydrostatic pressure (the difference between capillary hydrostatic pressure and brain interstitial pressure, a function of the BISF volume and tissue compliance) and osmotic force (the difference between BISF osmotic pressure and blood osmotic pressure) are near zero.

The normal BISF concentration of $K^+$ and $Na^+$ ions ranges from 2.9 to 4 mmol/L and 139 to 146 mmol/L, respectively. Following TBI, extracellular $K^+$ increases rapidly and can reach dangerous levels in excess of 60 mmol/L in BISF [5, 9]. Such large increases in $K^+$ are associated with impaired astrocyte $Na^+/K^+$ATPase pump and $Na^+/K^+/Cl^-$ co-transporter (NKCCl) function. This in turn increases BISF osmolality leading to massive $Na^+$ and water influx and subsequent cytotoxic cerebral oedema, which manifests minutes after acute TBI. The development of cerebral oedema appears to follow various phases. Ionic oedema forms immediately after cytotoxic oedema and results from sodium disturbances in the presence of an intact BBB. Vasogenic oedema, a second phase of cerebral oedema, develops hours after TBI and as a result of plasma protein extravasation. During vasogenic oedema, cerebral micro-vessel permeability breaks down, and non-fenestrated cerebral capillaries behave like fenestrated capillaries, during which both osmotic and hydrostatic pressure gradients affect the formation of oedema [5]. Rapid decreases in plasma tonicity are associated with precapillary vasodilation and significantly intensify water shifts from the intravascular space to BISF [10, 11]. Therefore, administration of hypotonic fluid is strongly contraindicated in patients with TBI.

Many intravenous fluids are often considered relatively isotonic because the sum of their osmotically active components ranges between 275 and 290 mOsm/kg. However, the synthetic fluids available are not ideal plasma equivalents. The crystalloid and synthetic colloid solutions generally used consist mainly of water and electrolytes, buffered by different anions. Plasma, on the other hand, contains proteins, organic acids, phosphates, sulphates and acidic carbonates. These differences explain the need for a multiplication of theoretical "in vitro" osmolality (usually indicated on the solution's packaging or their leaflet) by 0.926 to calculate their real "in vivo" osmolality [12]. Based on this assumption, adequate "in vitro" fluid osmolality should range from 297 to 315 mOsm/kg to ensure their "in vivo" isotonicity.

## 2.2 Traumatic Brain Injury

### 2.2.1 Early Phase of Traumatic Brain Injury

The main goals of fluid therapy in TBI are to restore and maintain adequate cerebral perfusion and cerebral oxygenation and limit fluid extravasation to BISF during the first 24 h. Acute hypoperfusion following TBI may cause cerebral global/regional ischaemia and infarction, further compounding the initial injury. Reflex capillary vasoconstriction decreases capillary pressure ($P_c$), thus influencing transcapillary flow ($Jv$) and fluid extravasation [7, 10, 13]. Also, a rapid increase in BISF tonicity suggests one's choice of intravenous fluid is limited to hypertonic solutions.

Plasma osmolality acutely influences movement of fluid in the brain, and a change by as little as 4–5 mOsm/kg increases the likelihood of cerebral oedema [14]. These subtle changes that influence the movement of fluid in the brain have resulted in ongoing debate about the best fluid choices because many crystalloid solutions are limited by their in vivo tonicity. Several authors have suggested using hypertonic saline (HS) solution in the early phase of TBI [15–18]. HS is

available in 3%, 7.5%, 15% and 23.4% concentrations and can be administrated as boluses or continuous infusion. Both administration strategies reduce ICP; however, boluses may be safer. A bolus of HS increases blood osmolality quickly, creating a driving force across the BBB for the quick mobilization of free water from the BISF. The increase in blood osmolality is associated with hypernatraemia and hyperchloraemia; however, the incidence of hyperchloraemia is significantly lower in patients treated with HS boluses compared to continuous infusion [15].

Numerous clinical and experimental studies have shown that a favourable effect of HS on CBF is associated with a reduction in ICP, or modulation of the neuroinflammatory response [18–20]. HS stimulates the release of atrial natriuretic peptide, which also reduces ICP via regulation of cerebral vascular tone and limitation of cerebral water accumulation [21, 22].

HS may further assist the situation in that microvascular tone and small differences in tonicity between plasma and BISF improve *Jv* and correct fluid movement in peri-traumatic zone [5, 7, 10]. Interestingly, early administration of HS, buffered with lactate, significantly reduces intracranial hypertension and improves post-traumatic cerebral metabolism, thus decreasing the episodes of subsequent raised ICP during the first 48 h after injury [16]. Energy depletion following TBI plays an important role in cerebral injury and has been suggested as a strong predictor of outcome in patients with moderate or severe head injury [23, 24]. Lactate infusion has been shown in experimental models to limit TBI-related disturbances in cerebral metabolism and improve metabolic interaction between astrocytes and neurons [25–27]. Therefore, the use of HS, especially with lactate, as a first-line choice of fluid therapy in early TBI appears well substantiated, particularly in prehospital treatment [28–30]. The main limitation of HS administration is moderate or severe hypernatraemia. Moderate hypernatraemia is defined as a serum sodium concentration higher than 150 mmol/L, while the severe form requires a level higher than 160 mmol/L [31]. Hypernatraemia has been noted in ~37% of TBI patients and has been acknowledged as an independent risk factor for early mortality after severe TBI [31, 32]. For this reason some clinicians prefer mannitol over HS.

Mannitol administration at doses of 0.25 to 1 g/kg body weight is recommended in patients with traumatic brain injury; however, this recommendation is based on low-quality evidence (Level IIB) [33]. Hence, only 45.2% of neurointensivists prefer mannitol, while 54.9% prefer hypertonic saline in the early phase of TBI [34]. Hyperosmolar therapy with mannitol significantly increases the risk of acute kidney injury (AKI), particularly in diabetic, hypovolaemic and chronic kidney disease patients [35–37]. An in vitro study demonstrated the ability of mannitol to induce oxidative stress and inhibit the proliferation of HK-2 cells in a dose- and time-dependent manner, leading to apoptosis and damage to microfilaments in these cells [38]. Prolonged or repeated use of mannitol also predisposes to hyponatraemia, which occurs in more than 10% of patients on the first day of mannitol administration and more than 20% receiving mannitol for 7 days [37, 39]. Therefore, use of mannitol should be guided by plasma osmolality and plasma sodium concentration.

The rate of fluid administration during resuscitation may also affect ICP and outcome. Experimental studies documented that bolus resuscitation with crystalloids or fresh frozen plasma (FFP) increases cerebral oedema and size of injury, in spite of a rapid correction of oxygen saturation [40]. This increase in oedema and injury size was less in animals receiving continuous infusions of fluids, which only slightly affected ICP and seemed safer than rapid infusions. This is an interesting observation, albeit potentially difficult to translate these findings to human polytrauma patients, where fluid resuscitation forms part of a more complex decision tree.

### 2.2.2 24–72 h After Injury

The primary objective of fluid therapy during this period is the maintenance of adequate cerebral perfusion (mean arterial pressure higher than 90 mmHg), plasma osmolality higher than

300 mOsm/kg and euvolaemia. Severe hypovolaemia, massive loss of blood and a positive cumulative fluid balance 5 days post-TBI are all independently associated with a risk of AKI and poor outcome [36, 38, 41, 42]. Zhao et al. showed how a high 5-day cumulative fluid balance (higher than 3.6 L) was associated with significantly higher ICP in comparison to patients with low cumulative fluid balances (0.6–3.6 L) [41]. Noteworthy, a negative fluid balance is also associated with poor outcome. The National Acute Brain Injury Study of Hypothermia documented that a 96-h cumulative negative fluid balance (lower than −594 mL) was independently associated with poor outcomes in patients with TBI [42]. In summary, both fluid volume and type of fluid play an important role in the maintenance of cerebral and extra-cerebral perfusion.

Crystalloid fluids should be used as first-line fluid strategies. Unfortunately, some are hypotonic, thus eliminating them from use in TBI patients. The decision-making process around which crystalloid solution to use should include their osmolality, strong ion difference (SID) and kind of buffer [43]. Tonicity is probably the most important factor determining this often-difficult decision. All hypotonic solutions should be avoided in patients with TBI because even a marginal decrease in blood osmolality of 1 mOsm/L increases the pressure for fluid shifts across the BBB at 19 mmHg. A 3% decrease in plasma osmolality increases brain volume by 3% and reduces intracranial blood and/or CSF by approximately 30% [43–45]. Isotonic balanced solutions contain cations and anions ($Na^+$, $K^+$, $Ca^{++}$, $Mg^{++}$, $Cl^-$) and are buffered by anions including malate, lactate, citrate or acetate. Strong ion difference has been defined as a difference between the sum of $Na^+$, $K^+$, $Ca^{++}$, $Mg^{++}$ and $Cl^-$ [46]. It has been well recognized that normovolaemic haemodilution with a crystalloid having a SID = 24 mEq/L maintains normal metabolic acid-base balance, while crystalloids with SID = 0 mEq/L or 40 mEq/L lead to progressive metabolic acidosis or alkalosis, respectively [47]. Also, the metabolic alkalosis associated with fluids with a SID = 40 mEq/L corresponds with significant deterioration in renal energy status and anaerobic stress [47]. Several studies have also documented significant decreases in glomerular filtration, increased renal oedema and renal vasoconstriction following chloride-rich solution administration [48, 49]. Saline-rich solutions affect coagulation and increase intraoperative blood loss [47, 50, 51]. Acute idiopathic coagulation disorders occur in 59% of patients with TBI and significantly increase mortality, particularly when they develop within the first 24 h of injury [52–55]. Buffers used in some fluids, such as citrate, bind ionized calcium, thus inducing or intensifying coagulation disorders. Balanced solutions that don't contain citrate reduce the occurrence of these problems.

Colloid solutions, such as hydroxyethyl starch or albumin, are not recommended in TBI patients. All colloids increase plasma tonicity and oncotic pressure. This elevated oncotic pressure should theoretically decrease cerebral oedema and improve arterial pressure. A decrease in injured neuronal cells has also been demonstrated in TBI mice treated with colloids [56]. Unfortunately, TBI-related BBB injury increases the extravasation of colloid solutions. Four percent albumin in 24–48 h after severe TBI significantly reduces crystalloid administration; however, it increases the risk of ICH and 28-day mortality [57]. Additionally, hydroxyethyl starch (HES) dilutes coagulation factors such as factors VII and VIII and von Willebrand factor (particularly in patients with blood group 0 [58]) and impairs platelet aggregation leading to coagulation disorders [59, 60]. Colloids are also associated with AKI and an increased need for renal replacement therapy [36, 61]. Other synthetic colloids, such as gelatins, have not been well studied in TBI patients. Anaphylactic reactions following gelatin infusion remain a concern and may limit their usefulness in TBI [62, 63]. Gelatins may also induce ST elevation, increasing the risk of cardiac arrhythmias and sudden cardiac death [64]. It is worth remembering that TBI is associated with different kinds of cardiac arrhythmias and/or ST segment disorders. These may coexist with TBI and are known as heart-brain interactions [65, 66]. The use of gelatin remains controversial in patients with TBI.

### 2.2.3 Late Phase of Traumatic Brain Injury

Cerebral vasospasm and TBI-induced hyponatraemia are the most important complications in the late phase. Inadequate fluid administration may induce and/or intensify cerebral vasospasm, leading to global or focal cerebral ischaemia. Post-traumatic vasospasm has been observed in 19–68% of TBI patients; however, it did not solely depend on the presence of blood in the subarachnoid space [67–69]. The "Triple-H" therapy (hypervolaemia, hypertension and haemodilution) was proposed as a strategy for treating subarachnoid haemorrhage-related (SAH) vasospasm [70]; however, this treatment was detrimental in patients with TBI, particularly hypervolaemia (associated with hypertension). The "hypervolaemia" and "hypertension" components of the "Triple-H" therapy can increase fluid shifts and exacerbate cerebral oedema [71]. Use of calcium channel blockers together with normovolaemia and normotension appeared to be a more physiological way to treat/prevent post-TBI vasospasm; however, a Cochrane Review meta-analysis did not confirm the efficacy of calcium channel blockers in the setting of TBI [72].

## 2.3 Traumatic Brain Injury, Acute Respiratory Distress Syndrome (ARDS) and Acute Kidney Injury

Polytrauma patients present a unique challenge to intensivists. It is frequently difficult to determine the best fluid strategy because of conflicting requirements of different organ systems and compartments. For example, intravenous fluid may be required to maintain CPP and renal perfusion; however, administration of crystalloids may worsen extravascular lung water and cause hypoxemia with difficulty ventilating in cases of ARDS. Careful assessment of volume status is required, with cardiac and neurological monitoring. A decision may be required to prioritize the organ system most at risk and limit injury to others. We feel the complexity of this discussion is beyond the scope of this manuscript, and we have focussed on those situations and conditions which are more closely aligned with neurological injury.

## 2.4 Subarachnoid Haemorrhage

Subarachnoid haemorrhage is associated with a higher occurrence of cerebral vasospasm than other central nervous system surgery, such as sub- or epidural haematoma. Delayed cerebral ischaemia (DCI) following posthaemorrhagic vasospasm leads to poor outcomes and increased risk of death [73, 74]. Appropriate fluid therapy plays a crucial role in the prevention of post-injury vasospasm. Authors have previously supported the importance of euvolaemia and hypertension, as the most important modality in "Triple-H" therapy [75]. Balanced crystalloids seem be the most appropriate and favoured fluid choice in patients with SAH. The administration of 0.9% saline increases the risk of AKI, intensifies the inflammatory response leading to a glycocalyx injury with increased vascular permeability, induces coagulation disorders and impairs gastrointestinal function [76]. Treatment with 0.9% saline in this setting is also associated with a higher fluid balance compared to balanced crystalloids [77]. Use of colloid solutions has also not been recommended in patients with SAH. Colloids appear to increase risk of AKI and worsen coagulation and do not prevent DCI and delayed cerebral infarction [60, 63, 78, 79]. Therefore, the American Heart Association has recommended balanced isotonic crystalloids for intravascular volume restoration (Class IIA, Level of evidence B). The administration of large volume of hypotonic fluids has been contraindicated in patients with SAH [80]. The maintenance of euvolaemia is vital as hypovolaemia intensifies posthaemorrhagic vasospasm and DCI. Hypervolaemia is just as dangerous, causing a fourfold increased risk for DCI and post-injury complications following SAH [81–84]. The importance of attaining euvolaemia is demonstrated by the Japanese SAH PiCCO® group. They recommend strict monitoring of patients, aiming for a global end-diastolic volume index

(GEDI) mean of 822 mL/m$^2$ (680–800 mL/m$^2$) and cardiac index (CI) monitoring to improve outcomes and prevent DCI after SAH [85].

## 2.5 Spinal Cord Injury

Every spinal cord injury has a concomitant sympathetic nerve injury that leads to peripheral vascular dilution. The result is a rapid decrease in blood pressure, a consequence of the mismatch created by the vasodilation and subsequent relative intravascular hypovolaemia. Vasopressors should form the mainstay of treatment; however, precapillary vasodilation increases the $P_c$ and subsequently increases $Jv$ [7, 10]. In patients with efficient cardiac function, mean arterial pressure is maintained by an increased cardiac output, another factor increasing $Jv$. The administration of large quantities of intravenous fluids, particularly hypotonic fluids, may increase fluid extravasation leading to tissue oedema. This pathology also favours rapid redistribution of circulating albumin and insoluble molecules administrated with synthetic colloids, to the extravascular space. Balanced crystalloids seem safer but are not yet proven as there are limited numbers of studies studying the effect of intravenous fluid administration on patient outcome after spinal cord injury. In an animal model, treatment with HS showed a better motor outcome in rats with a spinal cord injury. A reasonable explanation for this could be attenuation of injury-induced spinal cord oedema [86, 87]. Therefore, HS may be a reasonable first-line choice of fluid treatment in patients with spinal cord injury, but further research in this area is required.

## 2.6 Neuroinflammation

Neuroinflammation is characterized by limited entry of inflammatory cells, such as leucocytes, monocytes and lymphocytes. The rate of fluid shifts across the BBB depends on the net rate of solute transport and aquaporin 4 (AQP4) activity. The permeability of the BBB to sodium and chloride is more than 1000-fold lower than in peripheral tissue. Also, the raised expression of AQP4 at the BBB and in ependymal cells lining ventricles results in cytotoxic cerebral oedema [88]. Neuroinflammation is also followed by an increase in proinflammatory cytokines which causes BBB and cerebral microcirculation dysfunction, leading to elevated AQP4 expression and subsequently perivascular oedema [89–91]. This is followed by an acute breakdown in the BBB, with a high activity of vascular endothelial growth factor (VEGF) and elevated bradykinin and histamine levels, which in turn increase microvascular permeability by opening tight junctions and/or creating small transitory gaps (100–400 nm) [92, 93]. This raised BBB permeability, together with acute neuroinflammation, predisposes to neurons, pericytes and astrocytes to oedema. Increases in mast cells and leucocytes in turn elevate BISF oncotic pressure. Also, precapillary vasodilatation following bradykinin release increases $P_c$ and so further increases $Jv$ [7, 10]. Inadequate fluid administration may intensify this cytotoxic oedema, and hypotonic fluids should be avoided. Albumin and/or synthetic substances in the BISF activate microglia and astrocytes to release proinflammatory cytokines, thus intensifying the neuroinflammatory response [94, 95]. Therefore, synthetic colloids and albumin should also be avoided. HS appears to be the best fluid choice in patients with neuroinflammatory processes. Administration of HS suppresses proinflammatory mediators in activated microglia and downregulates increased Na-K-Cl co-transporter 1 (NKCC-1) expression in the cerebral cortex astrocytes, as well as TNF-α and IL-1β release from inflammatory-activated microglia [96, 97]. The Na-K-Cl co-transporter system plays an important role in the accumulation of intracellular water, and its upregulation in the BBB via phosphorylation contributes to increase vascular permeability and subsequent astrocyte/cerebral oedema [5, 98, 99]. HS also reduces cerebral oedema through restoring the BBB integrity following reduction of VEGF expression and tight junction proteins such as zona occludens 1 and claudin-5 [20–22, 100].

Adverse effects of balanced crystalloid administration have been not well documented in

patients treated for neuroinflammation. Crystalloids are safe and widely used for fluid resuscitation in such patients. Unfortunately, acute neuroinflammation increases the risk of intracerebral haemorrhage via neutrophil-downregulated tissue plasminogen activator and activation of matrix metalloproteinase-9 [101, 102]. As previously discussed, certain crystalloids are buffered by citrate, which may affect coagulation and increase the likelihood of intracranial haemorrhage. Therefore, citrate-buffered crystalloids should be avoided in patients with neuroinflammation, but further research is required in this area.

## 2.7 TBI-Related Electrolyte Disturbances

### 2.7.1 Hyponatraemia

Hyponatraemia is a frequent complication following various types of TBI, spinal cord injury, central nervous system infection and neurosurgery [59, 103–105]. It is commonly defined as a serum sodium concentration lower than 135 mEq/L and is classified according to sodium concentration: mild being a serum $Na^+$ 134–131 mEq/L, moderate 130–125 mEq/L and severe with serum $Na^+$ <125 mEq/L. Hyponatraemia has been reported in 16.8–50% of patients and increases hospital mortality by 16–28% [59, 103, 106, 107]. Two principal types of hyponatraemia commonly encountered are (1) cerebral salt wasting (CSW) and (2) syndrome of inappropriate antidiuretic hormone secretion (SIADH) [108, 109].

Clinical distinction between CSW and SIADH is practically impossible without invasive monitoring techniques and diagnostic criteria. These criteria are based on serum biomarkers, antidiuretic hormone, atrial natriuretic peptide, plasma urea and urine analysis, but are not sensitive in distinguishing the aetiology of hyponatremia (Class III evidence) [110, 111]. Hyponatraemia is classified into two subtypes: hypotonic (hypovolaemic, euvolaemic or hypervolaemic) which corresponds to low plasma tonicity and isotonic or hypertonic, which results from extravasation of osmotically active fluids, such as mannitol [112]. Hypovolaemic hypotonic hyponatraemia frequently occurs in patients treated with hypotonic fluids and loop diuretics [113, 114]. Therefore, all hypotonic fluids should be avoided. Regardless of aetiology, treatment of hyponatremia forces a treatment strategy. Discernment of the correct volume status plays a prominent role in adequate treatment. Current evidence recommends a continuous infusion of 3% HS for the initial treatment of hyponatraemia [115]. However, the rate of its infusion largely depends on the severity and character of the hyponatraemia [59, 103–106, 111, 115]. Sodium deficit can be supplemented relatively quickly in patients who have a sudden and rapid development of hyponatremia, while in chronic cases the sodium supplementation should occur over a longer period with frequent monitoring of serum sodium concentration. Patients with TBI complicated by severe hypovolaemic hyponatraemia require strict and controlled sodium supplementation to increase serum $Na^+$ concentrations at rate of approximately 0.5–1 mmol/L/h, but not more than 12 mmol/L increase over 24 h. Strict monitoring and control of haemodynamic parameters should be guided by using stroke volume variation (SVV), cardiac index (CI) as well as plasma and urine osmolality [43, 114, 115]. Additionally, glucocorticoids, such as hydrocortisone, can be used to reduce renal sodium extraction. Allowing a natriuresis with appropriate sodium and fluid supplementation is a well-established and effective therapy in patients with TBI-induced hyponatraemia.

### 2.7.2 Hypernatraemia

Hypernatraemia is defined as a plasma $Na^+$ concentration >150 mEq/L and is frequently observed in TBI patients. It may develop in patients treated with hyperosmolar therapy (mannitol and/or hypertonic saline), hypovolaemia, diabetes insipidus and hypodipsia [17, 31, 32, 116–119]. It can be divided into three categories: mild hypernatraemia with a plasma sodium concentration 150–155 mmol/L, moderate hypernatraemia 155–160 mmol/L and

severe hypernatraemia with sodium >160 mmol/L [117]. Several authors have speculated that the severity of hypernatraemia is related to the amount of water lacking. A cumulative negative fluid balance may provide clues to this condition, with severe hypernatraemia developing in patients with a negative fluid balance more than 35 mL/kg body weight per day [117].

Hypernatraemia develops in 24–65% of patients with severe TBI and is an independent risk factor for mortality. The risk of mortality depends on the severity of hypernatraemia and ranges between 32 and 66% in ICU patients [31, 32, 117, 118]. Severe hypernatraemia is the main risk factor for death in TBI patients, whereas mild and moderate hypernatraemia are only independent risk factors for death in these patients [117]. Treatment of hypernatraemia depends on its ethology and predisposing factors. Hypernatraemia is largely managed by determining patients' volume status and then choosing the appropriate fluid strategy. Hypovolaemic patients should be resuscitated with crystalloids regardless of serum sodium concentrations. Balanced crystalloids appear to be the fluids of choice in hypernatraemic patients; however, Muhsin and Mount have suggested normal saline in these patients [119]. Infusions of normal saline tend to lead to hyperchloraemic metabolic acidosis, which may be avoided when using balanced crystalloids. In 2000, Adrogue and Madias proposed two formulae to calculate water deficit in hypernatraemic patients. Water deficit should be determined as total body water (TBW) × (plasma [Na+]/140 − 1) [120]. "Fluid administration to treat hypernatraemia should be performed with haemodynamic monitoring and should focus on supplementation of the water deficit and subsequent reduction of hypotonic fluid losses.

### 2.7.3 Hypokalaemia

Hypokalaemia is another condition frequently encountered in TBI patients. It is frequently seen following a forced diuresis or hyperosmotic treatment, or after the administration of large volumes of saline solution, or in association with a saline-induced hyperchloraemic acidosis [48, 76]. Hypokalaemia is associated with hypomagnesemia, which in turn may be a risk factor for cardiac arrhythmias (including ventricular fibrillation) and sudden cardiac death. Correction of hypokalaemia is achieved through intravenous supplementation of potassium and should be accompanied by magnesium if concomitant hypomagnesemia is identified. The use of balanced solutions should theoretically limit the risk of hypokalaemia; however, some authors have not confirmed this benefit [48, 76, 121]. This may be due to a low (<5 mEq/L) potassium concentration, which is further diluted by hypokalaemic serum. Secondly, balanced crystalloids do not mobilize potassium from the intracellular space. Thirdly, urinary loss of potassium is higher after balanced crystalloid infusions when compared to saline, possibly due to the adverse effects of saline on renal function. In summary, potassium should be supplemented in all TBI patients receiving large volumes of fluids.

## 2.8 Conclusions

Choosing the best fluid management strategy in the neurointensive care setting is a complex and challenging process**.** The complexity of this decision-making process is confounded by an array of pathological injuries, pathophysiological pathways that develop and alter with time and without an ideal plasma substitute. A good understanding of underlying cerebral and vascular physiology is required, as well as a thorough knowledge of available intravenous fluids which should be treated as drugs. There is still much research required in this field, in particular how choices of different fluid strategies influence survival and cognitive outcome.

**Key Points**

- The inappropriate administration of intravenous fluid may cause pathological interstitial fluid distribution and elimination.
- This may adversely affect perivascular fluid balance and brain interstitial fluid composition, finally leading to cerebral and/or spinal cord oedema and cellular injury.
- Fluid composition and tonicity are crucial when considering which intravenous solution to use in the treatment of neurologic conditions, particularly cerebral trauma.
- Generally, hypotonic fluids and synthetic colloids should be avoided.
- Both cumulative negative and positive fluid balance within the first week are associated with worse outcomes.
- The use of saline solutions should be guided by serum electrolyte concentrations.

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# Part II

# Intensive Care Management

# Myasthenia Gravis in the ICU

3

Maxwell S. Damian

## 3.1 Introduction to Myasthenia Gravis

### 3.1.1 Epidemiology and Clinical Presentation

Myasthenia gravis (MG) is an autoimmune condition characterized by muscle fatigability on exertion and fluctuating weakness [1]. Its prevalence varies from 1 to 40/100,000 and seems to be increasing, with a bimodal age distribution, most often in females younger than 40 years and males aged over 60 years. 85–90% of patients with generalized MG harbor antibodies to the nicotinic acetylcholine receptor (AchR) [2], which originate from the thymus in the first decades of life. Half of MG cases manifest with fatiguing weakness of the extraocular muscles, and ca. 20% of all cases remains restricted to these (i.e., "ocular MG"). Purely ocular patients have a lower proportion of antibody positivity (30–50%). In the majority, fatigability will generalize to other muscles, which may include weakness of neck muscles causing head drop, dysphagia and chewing problems and dysarthria, as well as limb weakness and shortness of breath. Generally speaking, onset of myasthenia gravis in middle age has less severe manifestations, but there is a lower probability of full remission; exacerbations ("myasthenic crises") in the elderly have higher mortality than in younger patients. Ultimate quality of life is largely determined by the development of fixed or refractory diplopia and weakness and the secondary effects of immunosuppressive therapy, which may include recurrent infections, osteoporosis, cataract, or malignancy [3]. About 10% of patients with MG have a lymphoepithelial thymoma [4], and patients with malignant thymoma may be the most difficult to manage, particularly where the tumor has spread beyond the capsule.

MuSK antibody-positive MG is a clinically as well as immunologically distinct variant of autoimmune MG: 80% of patients are female with a peak incidence of 40 years, older than anti-AChR antibody-positive females but younger than anti-AChR antibody-positive males, and with a predilection for certain ethnic groups [5]. The course is often acute or subacute and rapidly progressive, affecting the facial, oropharyngeal, and respiratory more than limb muscles at onset. Neurophysiological testing and responses to treatment may be distinct (see below).

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### 3.1.2 Pathophysiology

AchR antibodies reduce the number of functional postsynaptic receptors at the muscle cell membrane, resulting in impaired responsiveness



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of the neuromuscular junction requiring a higher percentage to be occupied by acetylcholine. If all receptors are occupied either by antibodies or by acetylcholine, the transmission will be blocked, and a decrement in action potential amplitude results, as fewer muscle cells contract. Secondary degeneration of the postsynaptic membrane follows [6]. The majority of so-called seronegative cases have antibodies against muscle-specific kinase (MuSK) or LRP4 protein, which are involved in AchR clustering in the active zones of the muscle cell membrane [7, 8].

Seventy percent have lymphoid follicular hyperplasia, especially patients aged younger than 60 years and HLA-DR3-positive females. Stimulated T lymphocytes and thymic B cells from MG patients produce AchR antibodies in excess compared with control patients and peripheral B cells. Possible immunologic mechanisms initiating MG in the thymus include the fact that thymic myoid cells share epitopes with the AChR and are located close to mature lymphocytes and dendritic cells; persistence of the embryonic gamma subunit within the thymus may diminish self-tolerance, and dendritic cells expressing HLA-DR may play a role in AChR antigen presentation. The myoid and dendritic cells could provide both an antigen and a mechanism for autosensitization to the AChR [9].

### 3.1.3 Diagnosis of MG

Diagnostic testing in myasthenia gravis starts with the clinical examination looking for fatigability, for instance, with 90 s upgaze and with lateral gaze, 60 s head raise from the flat, 90 s arm abduction, and 90 s leg flexion and knee extension. The Tensilon test (2 mg and then 8 mg intravenous edrophonium under ECG control) is seldom needed, and the potential severe side effects (bradycardia) have largely consigned it to medical history. Ophthalmologists will perform the "ice pack test" to observe the transient improvement of neuromuscular transmission through external cold application to a ptotic eyelid, but this is an unspecific phenomenon observed in other neuromuscular disorders. Proof of fatiguing is essential to avoid confounding other neuromuscular disorders featuring ophthalmoplegia, such as mitochondrial disease, oculopharyngeal muscular dystrophy, or some congenital myopathies.

Stimulated EMG (3/s repetitive stimulation trains of 6) shows more than 10% decrement of the compound muscle action potential, sometimes followed by post-exercise facilitation (Fig. 3.1). Single fiber EMG reveals increased variability of the time interval for transmission through intermittent transmission blocking, so-called "jitter" (Fig. 3.2). A positive antibody test

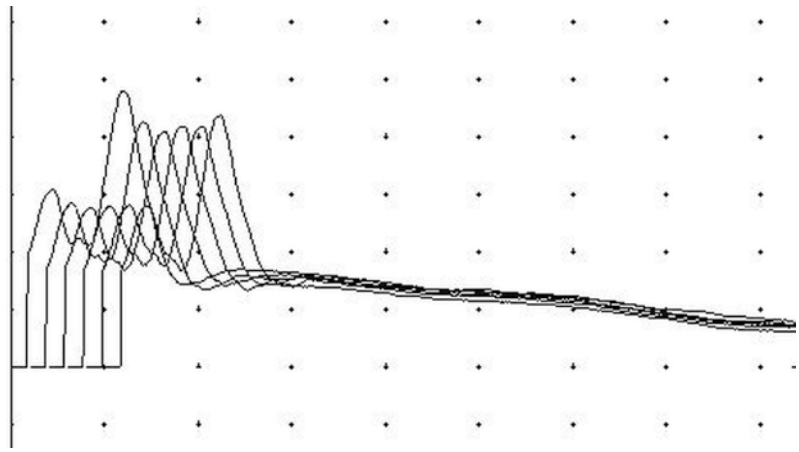

**Fig. 3.1** 3Hz repetitive nerve stimulation of the right nasalis muscle in a 74-year-old man with facial and oropharyngeal weakness showing >30% maximum amplitude decrement (Courtesy Dr. L. Wijesejera, Department of Clinical Neurophysiology, Ipswich Hospital)

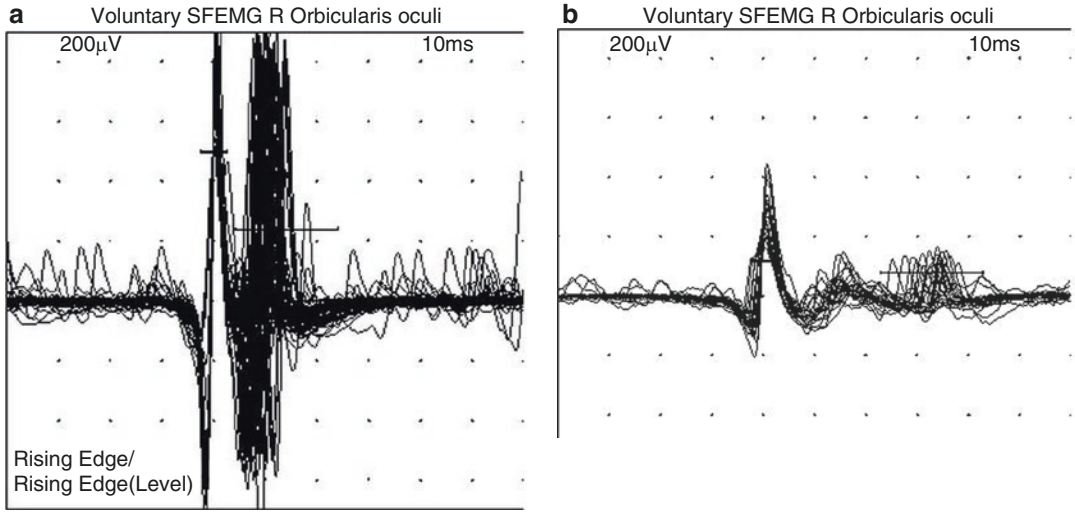


**Fig. 3.2** (**a, b**) Voluntary "single fiber" jitter studies of the same patient: right orbicularis oculi performed with concentric needle electrode showing increased jitter and impulse blocking in most muscle fiber pairs recorded

confirms the diagnosis, and "clustered" antibody tests may be AchR antibody positive in cases seemingly seronegative in the standard assay; the majority of the rest have either anti-MuSK or anti-LRP4 antibodies. Anti-striational antibodies, which include anti-titin, anti-ryanodine receptor, and anti-Kv1.4 antibodies, are associated with thymoma [10] and should prompt a tumor search, particularly if found in a patient where rescue treatments provide only short respite.

### 3.1.4 Other Neuromuscular Junction Syndromes

The Lambert-Eaton myasthenic syndrome (LEMS) is a presynaptic myasthenic syndrome most often caused by antibodies against voltage-gaited calcium channels (VGCC) in the nerve ending [11]. The antibodies interfere with calcium influx following an action potential and thus reduce acetylcholine release, causing fatiguing weakness most often in the legs, less frequently in the arms and cranial muscles, and rarely affecting respiration. Sixty percent of adult cases are found to harbor a neoplasm within the next 3 years, whereas younger onset female cases are unlikely to be paraneoplastic. Paraneoplastic LEMS is often associated with other antibodies (anti-GAD ABs, antimuscarinic and nicotinic AchR-ABs, antithyroid and anti-SOX1 antibodies) and clinically with dysautonomia. Contrary to postsynaptic MG, LEMS is electrophysiologically characterized by an incremental response to high-frequency (10–20/s) repetitive stimulation. The treatment is also different in that LEMS tends to respond better to 3,4-diaminopyridine, a calcium open channel blocker, than it does to pyridostigmine (see below). Immunomodulatory treatments are however identical to MG.

Botulism is by contrast a toxic presynaptic disorder caused by the toxin of *Clostridium botulinum* [12]. Most cases occur after ingestion of anaerobic foods, or by wounds infected by *Clostridium botulinum*; the toxin inhibits acetylcholine exocytosis by proteolyzing SNARE proteins such as VAMP, SNAP-25, or syntaxin, depending on the type of botulinum toxin (A, B, E). Annually, approximately 1000 cases are recorded worldwide, presenting with weakness and dysphagia associated with prominent auto-

nomic features. Treatment comprises early antitoxin, clearance of the gut or wound, and supportive for a prolonged period; mortality is 5%.

Congenital myasthenic syndromes are caused by inherited defects of the neuromuscular junction, mainly presenting in childhood with extraocular muscle involvement and proximal limb weakness [13]. Some forms such as cholinesterase acetyltransferase (ChAT) deficiency or Rapsyn mutations are associated with episodic respiratory arrest, and patients may require home apnea monitors. Respiratory arrest becomes less frequent in adolescence and disappears before adulthood. Anticholinesterase drugs help some cases but may exacerbate others; other drugs used include 3,4-diaminopyridine, ephedrine, salbutamol, and selective serotonin reuptake inhibitors. ICU admission is rarely required in adult life. Diagnosis is best established by genetic analysis.

### 3.1.5 General Principles of Treatment of MG

Defects of neuromuscular transmission can be improved by a number of strategies: by increasing acetylcholine at the endplate with cholinesterase inhibitors such as pyridostigmine (Mestinon®); by removing the source of antibody production surgically with thymectomy; by removing antibodies from the circulation through plasma exchange or immunoadsorption; by modulating immune response and inactivating antibodies through IVIg treatment; and by generally suppressing the immune system through steroids or long-term "steroid-sparing" drugs such as azathioprine, mycophenolate, cyclosporine, rituximab, or tacrolimus. Each treatment therefore can have its own advantages and drawbacks: pyridostigmine will ultimately lose effect if antibodies persist; thymectomy will work best early in the course before germinating centers spread antibody production outside the thymus; plasma exchange and IVIg have only a short-term effect and are expensive; steroids carry multiple long-term side effects; and steroid-sparing drugs have a delayed onset of benefit, often high cost (rituximab), and have potential for opportunistic infection and malignancy with long-term use. A number of excellent evidence-based guidelines for general management of MG provide the clinician with detailed recommendations [14, 15].

In practice, *early management* starts with pyridostigmine starting at 30 mg tds for immediate effect, titrating up to 60 mg 6× daily. Pyridostigmine is an oral cholinesterase inhibitor effective in the neuromuscular junction used as the initial treatment for MG is 30 mg tds; each dose is effective for 4–5 h so often 4–6 doses are needed (Fig. 3.3).

More than 360 mg daily is seldom helpful, and very high doses may cause "cholinergic crisis." Gastrointestinal side effects such as cramps commonly occur and are controlled with additional propantheline15 mg qds. Hypersecretion may be a problem with respiratory weakness and can improve with glycopyrrolate. Patients unable to swallow may need IV preparations such as pyridostigmine IV (1 mg IV is equivalent to 15–30 mg oral) or neostigmine i.m. (1 mg equivalent to 60 mg pyridostigmine p.o.). Pyridostigmine will lose effect if continued without immune treatment.

*Early immunosuppression* starts with prednisolone, beginning at 10 mg, daily or every other day, increasing by 10 mg every fourth dose, and stopping at significant clinical improvement or at 50 mg daily or 100 mg every other day. The full dose is maintained for ca. 6 months and then tapered by 5 mg per month, and the rate is slowed when down to 20 mg per day. Concomitant medication should be calcium/Vit D3 substitution and bisphosphonate plus a proton pump inhibitor. Steroid treatment must be incremental: there is well-documented deterioration with high doses of steroids, especially in the elderly, with bulbar or severe symptoms [16]. There is also experimental evidence that higher doses of steroids abolish anticholinesterase support of the neuromuscular junction and halving the dose reinstitutes the anticholinesterase effect [17].

*Thymectomy* is indicated in generalized MG with AchR antibodies, within the first years of illness. All patients need a CT chest looking for thymoma, which occurs in 10% and may be infiltrative. Thymectomy was introduced in the 1930s [18], but the effect was controversial for decades;


**Fig. 3.3** Shortness of breath in an MG patient dependent on pyridostigmine dosage intervals: dip in the vital capacity prior to the morning dose

the long-standing debate was finally resolved in 2016 through a long-running multicenter trial [19] which compared 3-year outcomes showing a clinically relevant benefit of transsternal extended thymectomy in patients between 18 and 65 years of age with generalized, AchR antibody-positive, nonthymomatous MG and a disease duration of <5 years. Video-assisted "keyhole" procedures are less invasive, but may not remove thymic tissue as thoroughly.

*Long-term immunomodulation* will often start with azathioprine [20], used from the outset in generalized myasthenia after checking thiopurine methyltransferase levels to avoid severe bone marrow depression. It is considered safe in pregnancy. The target dose is 2–3 mg/kg/day; azathioprine takes 12–18 months to be effective. Other immunosuppressants are used if azathioprine is unsuccessful, or not tolerated. Mycophenolate mofetil (dose 1 g bd) is gaining popularity, as it is often better tolerated and probably effective with less delay. Alternatively, ciclosporin 2–3 mg/kg or tacrolimus 50 mcg/kg also takes effect relatively quickly. Rituximab is becoming popular for severe cases.

*Rescue treatments* for severe generalized myasthenia include plasma exchanges (PLEX) or intravenous immunoglobulins (IVIg) when other treatment is unsuccessful, or when deterioration is too quick to await the effect of conventional drugs (Fig. 3.4) [21]. Their overall effect is comparable, but PLEX generally needs inpatient admission and a central venous access and carries risks of infection, coagulopathy, and air embolism; IVIg seems less invasive than PLEX, but its effect may be slower; it may cause migraine headaches and can have severe side effects in the elderly or debilitated patient.

Apart from managing the immune process, great attention should be given to avoiding


**Fig. 3.4** Regular respiratory monitoring may establish a need for plasma exchanges: deterioration of respiratory function in a 23-year-old patient despite high-dose steroid treatment, pyridostigmine 360 mg/day. The first three exchanges achieved an unstable improvement; the second course of two exchanges achieved stable remission. Rituximab had been started but had not yet taken effect

medications that affect function of the neuromuscular junction. Many drugs can have a negative effect on MG. Table 3.1 gives a list of some of the commonest known [22], but it is not exhaustive, and it is prudent to check every newly prescribed drug. Newer immune modulatory drugs such as immune checkpoint inhibitors may also induce myasthenia.

### 3.1.6 Management of the Unstable MG Patient

In the unstable patient, bedside respiratory monitoring is key [23]. Although not technically difficult, it is sadly not done satisfactorily in the vast majority of hospitals, and, instead, too much reliance is placed on blood gas analyses or, even worse, oxygen saturation, which only becomes abnormal in advanced neuromuscular failure. Staff need to be aware of the clinical features of developing respiratory failure and document clinical indicators such as inability to lie flat, failure to complete a sentence without breath, use of auxiliary respiratory muscles, decreasing ability to count loud in one breath, or paradoxical abdominal movement. Medical and nursing staff dealing with neuromuscular patients need to be instructed how to perform the bedside lung function tests reliably and need to know the pitfalls in testing, for instance, from unsatisfactory posture, failure to cooperate, or inadequate mouth and nasopharyngeal seal. A range of parameters should be tested, as this allows equivocal results to be judged better and because focal muscle involvement may only severely affect certain parameters.

A failure of diaphragmatic function will affect vital capacity and reduce values lying flat in particular; intercostal muscles are important particularly for expiration and airway clearance, whereas the diaphragm is the strongest inspiratory muscle.

**Table 3.1** Drugs to be used with caution in myasthenia gravis: "the 14 A's"

| | |
|---|---|
| *A*CTH and corticosteroids | Prednisone |
| *A*nalgesics | Narcotics |
| *A*nesthetics, local | Cocaine, procaine, lidocaine, bupivacaine, prilocaine |
| *A*ntacids or laxatives containing magnesium | Maalox, Mylanta |
| *A*ntiarrhythmics | Quinidine, lidocaine, procainamide |
| *A*ntibiotics | Aminoglycosides, quinolones, telithromycin, azithromycin, erythromycin, clindamycin, ampicillin, imipenem, vancomycin, metronidazole |
| *A*nticonvulsants | Phenytoin |
| *A*ntihypertensives | Beta-blockers, calcium channel blockers |
| *A*ntimanics | Lithium salts |
| *A*ntipsychotics | Chlorpromazine |
| *A*ntirheumatic | Chloroquine |
| *A*rthritis agents | Penicillamine-induced myasthenia gravis |
| *All neuromuscular blocking agents* | |
| *A*ntimalarials | Chloroquine, hydroxychloroquine |

**Table 3.2** Monitoring of respiratory function in determining admission to the intensive care unit (ICU)

| Parameter | Normal value | Critical value for ICU and/or intubation |
|---|---|---|
| Vital capacity | 40–70 mL/kg | 15–20 mL/kg |
| Peak inspiratory Pressure | Male: >−90 cm $H_2O$ Female: >−70 cm $H_2O$ | −30 to −40 cm $H_2O$ |
| Peak expiratory Pressure | Male: >100 cm $H_2O$ Female: >90 cm $H_2O$ | 40 cm $H_2O$ |
| Cough | Male: >330 L/min Female: >280 L/min | Peak cough flow >160 L/min or mouth or PEF >60 L/min at tube needed for safe extubation |

The "20/30/40" rule is a simple way to assess the potential need for monitoring in the ICU, originally in Guillain-Barré syndrome but which can also be applied to MG (Table 3.2) [24].

## 3.2 Management of MG in the ICU

*Myasthenic crisis* is the leading cause for ICU admission in MG, occurring in 10–60% of MG patients. Crisis is often understood as MG complicated by respiratory failure or oropharyngeal weakness requiring intubation and/or mechanical ventilation for more than 24 h. Patients with overdose of cholinergic drugs may present with massive secretions and diarrhea, but this rarely leads to respiratory weakness. Usually the need for ventilatory support follows weakness of respiratory muscles, but mechanical ventilation also may become necessary because of airway collapse from oropharyngeal muscle weakness, stridor from vocal cord weakness (rare), or the inability to clear secretions. Recurrent myasthenic crisis points toward an individual predisposition or compliance problems.

Viral or bacterial infection may precipitate crisis in half of cases, and other causes include aspiration, reduction of the pyridostigmine dose, or incautious initiation of high-dose IV corticosteroids. Other factors are surgical procedures (particularly major thoracic or abdominal surgery), pregnancy, exposure to drugs, or even emotional stress.

Ideally, a deteriorating patient will be admitted to an experienced unit where regular monitoring of fatigability, respiratory function, cough, and swallowing will allow the clinician outside the ICU to recognize impending myasthenic crisis early and ward off full crisis through rescue treatments. A number of factors can make respiratory failure difficult to recognize, foremost, its variability.

In the ICU, priority is given to securing airways; and the patient should be intubated if in doubt. Apart from treating infection and rehydration, medications that impair neuromuscular transmission should be avoided, such as beta-blockers given for tachycardia. Patients may have

been overdosed with cholinesterase inhibitors and may have excessive salivation and sweating, abdominal cramps, and urinary urgency. Pyridostigmine can be discontinued initially during ventilation and reintroduced gradually for weaning. In a ventilated patient, it is feasible to start steroids in high doses such as 1 g IV and then 100 mg oral. Thymectomy has a significant effect on outcome, but as its benefit only becomes significant after months, it is not commonly performed while the patient is unstable. The situation may be different if there is an occult thymoma, and that must be considered with recurrent or refractory crises. Patients with MuSK antibody-positive myasthenia gravis have prominent oropharyngeal problems and a much less successful response to acetylcholine esterase inhibitors; therefore, when they deteriorate, early PLEX and escalation of immunosuppressive treatment are advised, for instance, to second-line steroid-sparing agents such as rituximab or tacrolimus. Anti-striational antibodies and a severe course should prompt a repeat of diagnostic testing for thymoma, even if previously negative; anti-Kv1.4 has also been associated with myocarditis [25].

The mortality rate for myasthenic crisis has declined from a nearly always fatal outcome in the 1920s to less than 5% in the twenty-first century as a result of timely treatment [26, 27]. However, data from selected centers may not reflect real life: mortality in UK ICUs was found to be 8.7% overall, and acute hospital mortality after an ICU stay from myasthenic crisis reaches 22% [27]. Deaths can be attributed to delayed treatment and unrecognized complications, belated admission to the ICU (suggesting shortcomings of ward-based monitoring), and inappropriate transfer from ICU to the general ward, where monitoring may not take into account that fatigability can develop rapidly in a patient who hours before seemed safe [28]. Regrettably recurrent crises may be refused for readmission; however, recurrent crises are not predictive of outcome, and "futility" can never be an argument to deny re-intubation. There must a strategy for adequate long-term immunosuppression as repeated rescue treatment with IVIg and PLEX will seldom achieve lasting stability.

Initial noninvasive BiPAP via mask may avoid intubation if oropharyngeal function is preserved or reduce ventilator days [29]. Tracheostomy should not be performed early, as a rapid recovery is possible. It is important to reintroduce cholinesterase inhibitors before extubation trials are initiated. Before attempting to wean from the ventilator, in addition to satisfactory treatment of the myasthenic symptoms, there should be no major pulmonary problem or difficulty handling secretions. Weaning can be initiated once VC reaches 25 mL/kg and the patient achieves spontaneous tidal volumes of 10–12 mL/kg. Secretion volume, whether the patient is comfortable with a T-piece trial, and a completely normal chest X-ray have some predictive value for successful extubation. PI max exceeding –50 cm $H_2O$ and VC improvement by 4 mL/kg from pre-intubation to pre-extubation are associated with successful extubation, but, nevertheless, repeated extubation failure is common [30]. Weaning methods can include BiPaP with daily small decreases in positive pressure support or intermittent mandatory ventilation with gradual reduction in the mandatory frequency; further research is needed to evaluate novel weaning techniques such as neurally adjusted ventilatory assist (NAVA) [31] in neuromuscular disease.

Perioperative management must be well planned; patients should be stabilized as well as possible prior to surgery, for which preoperative IVIg or PLEX are useful. The specialist clinic should provide a preoperative neurological status. Customary medications should be taken with as little interruption as possible, by giving pyridostigmine via nasogastric tube or intravenously. Prednisolone should remain unchanged but for major surgery hydrocortisone can be given as perioperative stress cover, for example, 50 mg hydrocortisone at induction and postoperatively 25 mg three times daily. Sugammadex can reverse vecuronium-induced neuromuscular blockade. Postoperative VCs should be monitored 8-hourly, or more often if clinically indicated, and any weakness or reduced mobility needs to be precisely documented.

The effect of pregnancy on myasthenia is unpredictable, and myasthenia worsens in about one third of pregnant patients. Respiratory function may deteriorate when thoracic expansion is impaired in advanced pregnancy. Prolonged labor may worsen fatigability, and postpartum exacerbations may also occur. Pyridostigmine, steroids, and azathioprine are probably safe in pregnancy; PLEX as rescue therapy is probably safe. Perinatal management requires joint management between the neuromuscular clinic to monitor for deterioration of MG and the high-risk obstetrics clinic. Antibodies are transferred through the placenta in the second half of pregnancy, and 20–50% of children experience transient neonatal myasthenia. Weakness of swallow, suck, breathing, and limbs may develop hours after birth and last for days, in some cases requiring respiratory support but almost always with complete resolution. Rarely, arthrogryposis has been described in children of myasthenic mothers.

**Key Points**

- The diagnosis of MG is based on evidence of muscle fatiguing and confirmed by the presence of acetylcholine receptor antibodies.
- Treatment of MG includes support of neuromuscular transmission, immunomodulation, and avoidance of detrimental medications.
- Close systematic monitoring of respiratory and oropharyngeal function is key to recognizing unstable patients developing myasthenic crisis.
- Deterioration can be rapid.
- Rescue treatments include IV immunoglobulins and plasma exchanges.
- Intubation and mechanical ventilation may be short, but there is a high risk of extubation failure.

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# 4 Critical Care Management of Guillain-Barré Syndrome

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## 4.1 Introduction

Guillain-Barré syndrome (GBS), also called acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is an inflammatory disorder affecting the peripheral nervous system that is characterized by acute or subacute onset and typically monophasic course of the disease. Some patients with this disorder need hospitalization to an intensive care unit (ICU). Among neuromuscular disorders, only several ones require monitoring and treatment at ICUs, namely, GBS, amyotrophic lateral sclerosis, and acute myasthenia gravis. Management of these patients in ICU normally includes specific therapy, vital signs' monitoring, treatment of systemic complications, as well as the elimination of autonomic nervous system disorders [1–5].

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GBS is considered the most common cause of inflammatory polyneuropathies, the annual frequency of which is estimated as 1–3 cases per 100,000 people. GBS might develop at any age (from 2 months to 95 years); however, there is a tendency of the predominance of male patients aged 15–35 and 50–75 years among those who develop this disorder. The risk of this disease in females reduces during pregnancy and increases after the delivery [6, 7].

The pathogenesis of GBS is based on the autoimmune damage of the myelin sheath of the peripheral nerves. Despite the fact that only sporadic cases of this disease are reported, about two-thirds of patients have a history of infections 1–4 weeks prior to the development of neurological symptoms. These infections are most often caused by viruses (cytomegalovirus, Epstein-Barr, HIV, enteroviruses, herpes simplex, hepatitis A and C viruses) but also may be of bacterial origin (*Mycoplasma* or *Campylobacter jejuni*) and are respiratory or gastrointestinal (mainly diarrhea) in 40% and 20% of cases, respectively [8–10]. Zika virus has also been shown to be a possible trigger [11]. GBS might be associated with surgical procedures or vaccination. However, one-third of patients have no prior history of infections or any other relevant factors [12–15]. *C. jejuni* infection is the most common one and can be found in 25–50% of patients [16]. It is often associated with the motor form of GBS, more severe course, and the positive result of the test for antibodies to GM1 and GD1a gangliosides [17–20]. Anti-GM1 antibodies and antibodies to other



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gangliosides are observed in 20–40% of GBS patients. Gangliosides are glycosphingolipids that can primarily be found in the nervous system, particularly in neuronal axons. There are several subtypes of gangliosides, for example, GM1, GM2, GM3, GD1a, GD1b, GT1b, and GQ1b [21]. Positive results of the test for these antibodies are generally associated with a poorer outcome [18].

Thus, AIDP is a rapidly progressing post-infection disorder manifested with muscle weakness in the extremities, involvement of cranial nerves accompanied by reduction, and, subsequently, lack of deep tendon reflexes. Other symptoms include specific changes in the cerebrospinal fluid and electroneuromyography findings [22]. Muscle weakness is symmetrical (in some cases, slight asymmetry may be observed during the disease onset) and develops within 5–10 days. Increase in muscle weakness stops in 2, 3, and 4 weeks after the disease onset in 50%, 80%, and 90% of patients, respectively. This is followed by a period of the plateau. There is no special biological marker for the GBS diagnosis; however, such invasive diagnostic procedures as electrodiagnostic testing and lumbar puncture usually help in making this diagnosis [20]. About one-fourth of patients require mechanical ventilation and may develop autonomous system disorders; many of them need admission to critical or intensive care units [1, 20].

## 4.2 History of Guillain-Barré syndrome

The disease was described for the first time by Octave Laundry in 1859 [23]. Later, in 1916, Guillain, Barré, and Strohl reported two cases of acute ascending weakness associated with good prognosis in respect of recovery [24]. The term "Guillain-Barré syndrome" was suggested by Draganescu and Claudian [25]. The first diagnostic criteria were developed in 1960 by Osler and Sidell [26]. After an epidemic of GBS in the USA following the use of swine flu vaccines, the National Institute of Neurological and Communicative Disorders and Stroke suggested new criteria for the disease, which were revised in 1990 by Asbury and Cornblath [27, 28] and became widely used by both investigators and clinical practitioners. In 2011, the new "Brighton criteria" were published [29–31].

## 4.3 Clinical Variants

Clinical variants of AIDP depend on the type of fibers that are damaged. It is possible to destroy the only motor nerve fibers, or just sensory, as well as mixed (motor and sensory) fibers, involving cranial nerves or autonomic fibers. And also, the type of damage (demyelination) or axonal injury is essential (Table 4.1).

Other, rarer variants have also been described (acute pharyngeal weakness, paraparetic GBS (1–7%), facial diplegia and distal limb paresthesia (1–2%), pure cranial nerves, acute ophthalmoparesis (1%), etc.) [32–34]. Diagnosis of a typical GBS usually does not cause difficulties, but in some patients, the diagnosis can be more complicated (constant asymmetry of weakness or dysfunction of the bladder or intestine at the beginning, etc.) [44].

## 4.4 Clinical Features

The most common manifestation of GBS is bilateral muscle weakness (Table 4.2) [28, 31, 35]. The disease generally starts in the lower limbs and is ascending. The patients experience difficulties climbing the stairs and raising from a chair. At the early stages of the disease, there are no sensory disturbances. However, some patients demonstrate mild paresthesia prior to the palsy development. Reflexes may be decreased or normal at the beginning of the disease, and they disappear afterward. In some cases, however, there may be hyperreflexia [45]. Fifty percent of patients experience pain, and in 50% of cases, facial and pharyngeal muscle weakness may be the first manifestation of GBS [46]. Involvement of the phrenic nerve and development of weakness are also possible. Weakness is generally more pronounced in the lower limbs compared to the upper limbs [20].

Patients may have progression of weakness over the course of 4 weeks (sometimes 2 weeks or

**Table 4.1** Clinical variants of GBS

| Clinical variants | Clinical features |
|---|---|
| Typical clinical GBS (acute inflammatory demyelinating polyneuropathy—AIDP) (71–90% of cases) [28, 32–34] | Progressive course of the disease, symmetric muscle weakness, absence of deep tendon reflexes |
| Acute motor axonal neuropathy (AMAN) (3% of cases) [32–36] | Tendon reflexes may be preserved; sensory nerves do not suffer; faster progression, antibodies to the gangliosides GM1, GD1a, GalNac-GD1a, and GD1b are present |
| Acute motor and sensory axonal neuropathy—AMSAN (<1% of cases) [32–36] | A more severe form of AMAN, both sensory and motor fibers are affected |
| Miller Fisher syndrome (MFS) (5–17% of GBS cases) [32–34, 37, 38] | Ophthalmoplegia, ataxia, and areflexia with no weakness, antibodies to GQ1b are present in 85–90% of patients with MFS |
| Bickerstaff's brainstem encephalitis (BBE) is a variant of MFS (1–10% of MFS cases) [32–34, 39] | Confusion of consciousness, paradoxical hyperreflexia, ataxia, and ophthalmoparesis associated with anti-GQ1b antibodies |
| Pharyngeal-cervical-brachial variant (2–5% of cases) [32–34, 40, 41] | The acute weakness of the oropharyngeal, neck, and shoulder muscles with swallowing dysfunction |
| Acute pandysautonomia (<1% of cases) [32–34, 42, 43] | Dizziness, vomiting, diarrhea, abdominal pain<br>Orthostatic hypotension, urinary retention, pupillary abnormalities, violation of heart rhythm and sweating, salivation, and lacrimation<br>Decrease or absence of tendon reflexes |
| Pure sensory GBS (1% of cases) [32–34, 42] | Ataxia, reflexes are absent, and there may be minor motor involvement, association with antibodies to GD1b |

**Table 4.2** Summary of Guillain-Barré syndrome [14, 16, 28, 30, 31]

- Progressive weakness in lower limbs and/or upper limbs
- Areflexia (or decreased tendon reflexes)

and

- Progressive phase lasts days to 4 weeks (often 2 weeks)
- Symmetrical weakness
- Mild sensory symptoms (not present in acute motor axonal neuropathy)
- Cranial nerve involvement
- Autonomic dysfunction
- Pain (common)
- Albuminocytological dissociation of CSF
- Typical electrodiagnostic features

up to 6 weeks after onset). During the progressive phase, 20–30% of patients develop respiratory failure and need ventilation at an intensive care unit (ICU) [20, 31].

According to the data obtained by Willison et al. [20] and Hughes et al. [47], there may be deterioration of the condition of 25% of patients during or after the immunoglobulin administration or plasma exchange. Therefore, a conclusion was made that the patients' condition without this therapy would have been worse and that this fact could not be considered resistance to treatment [20, 47].

The severity of clinical manifestations and the duration of the disease may vary greatly among patients: some patients experience mild weakness and spontaneous recovery, while the others develop severe tetraplegia with respiratory disorders that require mechanical ventilation, no signs of recovery within several months. However, almost all patients demonstrate improvement after some time, while it can be the reason for severe disability in very rare cases [48].

About one-third of GBS patients require mechanical ventilation [48]. In two-thirds of AIDP cases, autonomous system disturbances develop, which are especially frequent in mechanically ventilated patients. More than 50% of patients develop sinus tachycardia [5]. Other symptoms of autonomic dysfunction may include bradycardia (mostly observed in intubated patients), orthostatic hypotension (as well as associated syncopal episodes), BP fluctuations (most often hypertension, less often hypotension), and sweating disorders (despite their high frequency, the patients usually do not complain of these disorders). About 10–20% of patients

develop transient pelvic floor disorders (often urinary retention, sometimes urinary incontinence) due to dysfunction of the sphincter muscles [5, 48, 49].

Additional tests used in patients with suspected GBS include lumbar puncture with cerebrospinal fluid analysis (cell counts and protein levels) and the electrophysiology studies. However, it should be taken into account that the findings of these investigations may be within the normal ranges in the early stage of the disease. CSF examination allows to rule out other potential causes of progressive weakness (HIV, CMV, Lyme, sarcoid, carcinomatous, or lymphomatous polyradiculoneuropathy) [5, 20, 50]. The most important finding for the diagnosis of GBS is increased protein level (>0.55 g/L), which develops within 1 week from the disease onset and reaches its peak on Weeks 3–4. During the first 2 days, 85% of patients demonstrate normal protein levels; by the end of Week 1, an increase in protein levels is observed in two-thirds of patients; and at Week 2, this is a typical finding in 80% of patients. The phenomenon of combined normal cell count and increased protein concentration is known as cytoalbuminologic dissociation and is typical for patients with Guillain-Barré syndrome [5, 20, 50].

Neurophysiological testing helps confirm the diagnosis GBS; suggests different clinical variants, AIDP, AMAN, and AMSAN; and also determines the type of damage, demyelination or axonal damage. In some cases, the electrodiagnostic test helps to establish a prognosis [51–53]. For the diagnosis it is necessary to study at least four motor nerves, not less than three sensory nerves, and the presence of F-wave and H-reflexes. Demyelination is characterized by prolonged distal motor latency, reduced nerve conduction velocity, prolonged F-wave latency, increased temporal dispersion, and conduction blocks [20].

The GBS Classification Group indicates that the diagnosis of GBS, MFS, and their variants can be established clinically in most patients. Existing diagnostic criteria are rigid and often depend on laboratory data. Electrophysiological testing and analysis of cerebrospinal fluid in the onset of the disease do not always confirm this diagnosis. The albuminocytological dissociation of CSF is absent in the first week of symptoms in more than half of patients with GBS, and in approximately 40% of patients, electrophysiological studies conducted during the first week can offer diagnosis of neuropathy without the manifestation of criteria for one of the specific electrophysiological variants [32].

## 4.5 Differential Diagnosis

The differential diagnosis of Guillain-Barré syndrome (GBS) includes other polyneuropathies with acute onset (e.g., acute intermittent porphyria, toxic neuropathies, vasculitic neuropathy, and others), chronic inflammatory demyelinating polyneuropathy (CIDP), and spinal cord diseases (spinal cord vascular disease and others), disorders of neuromuscular transmissions (Fig. 4.1) [20, 54–56].

The red flags or signs that make one doubt the diagnosis include high cell count (>50 cells/μL) in CSF, severe respiratory failure accompanied by mild or no weakness in the limbs, pronounced sensory disturbances accompanied by no weakness in the limbs at the disease onset, bladder or bowel dysfunction at early stages of the disease, fever at the disease onset, segmental sensory disorders, and persistent asymmetry of weakness or its slow progression [20, 44, 54–56].

Apart from acute transverse myelitis, the differential diagnosis of GBS should include myasthenic crisis (in this case, medical history data, presence of transient ptosis, or other oculomotor disorders, the severity of which depends on physical activity, should be taken into account) or botulism (the typical signs of which include dilated pupils with no light reaction, constipation, and the development of neurological symptoms within 12–36 h after the intake of contaminated products). The development of facial nerve palsy, including facial diplegia, may occur in patients with neuroborreliosis. Other diseases with symptoms similar to those of GBS

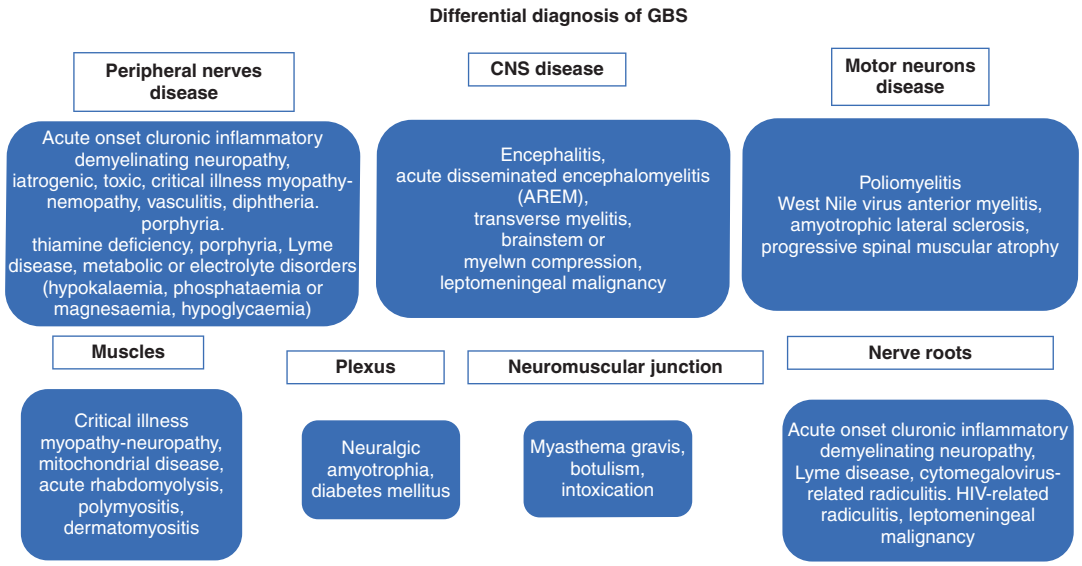


**Fig. 4.1** Differential diagnosis of Guillain-Barre syndrome (GBS)

include polyneuropathies of different origin (related to vasculitis, porphyria, paraneoplastic syndromes), acute polymyositis, acute steroid myopathy, rare cases of heavy metal or organophosphate poisoning, and hypophosphatemia (parenteral nutrition, abstinence syndrome in patients with alcohol abuse, and some other conditions may provoke the development of quadriplegia characterized by hyporeflexia and rapid regression after restoration of phosphate levels). Critically ill patients with sepsis and multiorgan failure may develop axonal polyneuropathy (critical illness polyneuropathy) [20, 44, 54–56].

## 4.6 Respiratory Failure

In a study by Hughes, it shown that about 30% of patients with AIDP need endotracheal intubation for mechanical ventilation (MV) when they enter the intensive care unit (ICU) [22]. At present, the importance of clinical, immunological, biochemical, and neurophysiological criteria for the prediction of GBS is actively being studied in the world [4, 48, 57–59]. Studies have shown that clinical prognostic factors that require intubation and MV in critical care are inability to walk, inability to raise the head, decreased vital capacity (VC), delay in hospitalization for less than 7 days, and high level of liver enzymes [60].

The need for MV in this disease can vary significantly in different patients—from a few days, months to a year or more. It is considered that the need for tracheostomy occurs when the expected duration of ventilation is more than 14 days. Both delayed and early tracheostomy can lead to undesirable consequences: in the first case, an increased risk of infectious complications (e.g., pneumonia associated with the ventilator) and, in the second case, an unjustified risk of complications in patients with rapid recovery [61–63]. It should be noted that the appointment of specific therapy led to an acceleration of functional recovery and a reduction in the timing of MV.

In a study by Fourrier et al. [60], it was shown that, in patients with GBS, long-term MV can be predicted with a functional marker: the lack of foot flexion ability at the end of immunotherapy was significantly associated with MV lasting more than 15 days. The results of EMG evaluation confirmed the sensitivity of this simple marker. François Fourier suggests using this marker to address the issue of the need for tracheostomy after the completion of immunotherapy [60, 64–66].

## 4.7 Treatment

The acute phase of GBS (even mild cases) should be considered an emergent condition since decompensation with the development of severe respiratory failure requiring mechanical ventilation may develop within several hours. Therefore, these patients should be urgently hospitalized.

Treatment of Guillain-Barré syndrome can be conventionally divided into supportive care, which is aimed at preventing or managing complications, monitoring of respiratory function, cardiac and hemodynamic monitoring (autonomic dysfunction), prophylaxis for deep vein thrombosis, management of possible bladder and bowel dysfunction, pain management, early initiation of physiotherapy and rehabilitation, psychosocial support, and specific therapy, including the use of intravenous immunoglobulins and plasmapheresis [5, 20, 44, 47, 67, 68].

Plasmapheresis was suggested as a method of GBS treatment in 1978, and its positive effects were subsequently demonstrated in randomized clinical trials [69, 70]. Since 1988, intravenous immunoglobulin has been used for treatment of this disease [71]. In 1992, the first randomized clinical study demonstrated similar efficacy of both these therapeutic methods [72].

## 4.8 Intravenous Immunoglobulin (IVIg) and Plasma Exchange (PE)

The main issues related to the use of intravenous immunoglobulin that concerned clinical practitioners were whether its effect was comparable to that of plasmapheresis, whether addition of corticosteroids was more effective in respect of GBS treatment, and what the optimal dose of immunoglobulin was [67, 68].

Table 4.3 contains a summary of the recommendations of the European Academy of Neurology (EFNS) guidelines and the American Academy of Neurology (AAN) guidelines for the treatment of GBS.

Management of patients who worsen or fail to improve after being treated with IVIg or PE is

**Table 4.3** Summary of the recommendations of the European Academy of Neurology (EFNS) guidelines and the American Academy of Neurology (AAN) guidelines [67, 68]

| EFNS guidelines for the use of intravenous immunoglobulin in the treatment of neurological diseases (2008) | Evidence-based guidelines: intravenous immunoglobulin in the treatment of neuromuscular disorders (AAN) (2012) |
|---|---|
| The first line of therapy may include treatment with immunoglobulin (0.4 g/kg/day for 5 days) or plasmapheresis, which are equally effective (Level A) | Plasmapheresis should be used within 4 weeks from the disease onset (*Level A*, *Class II*) |
| IVIg has fewer side effects than plasma exchange (PE), which would favor IVIG over PE treatment (*Level B*) | PE is recommended for ambulant patients within 2 weeks of the onset of neuropathic symptoms (*Level B*, *Class II*) |
| IVIg treatment after PE, as a standard combination, does not produce significant extra benefit and cannot be recommended (*Level B*) | If PE started within 2 weeks of onset, the effects of PE and IVIg in patients requiring walking aids are equal (*Level B*, *Class I*) |
| Combining high-dose intravenous methylprednisolone with IVIg may have a minor short-term benefit (*Level C*) | IVIg is recommended for non-ambulant patients within 4 weeks of the onset of neuropathic symptoms (*Level B*, *Class II*) |
| Patients who improve after IVIg and then relapse should preferentially be retreated with a second course of IVIg (*good practice point*) | If started within 2 weeks of onset, IVIg has comparable efficacy to PE in patients requiring walking aids (*Level B*, *Class I*) |
| In patients who seem to be unresponsive to the first course of IVIg, a second course may be tried, but evidence supporting such a strategy is lacking (*good practice point*) | IVIg is recommended for non-ambulant patients within 2 weeks of onset of neuropathic symptoms (*Level A*, *Class II*) |
| No recommendations can be given as to whether mildly affected GBS patients or patients with Miller Fisher syndrome should be treated with IVIg | Sequential treatment with PE followed by IVIg does not have a greater effect than either treatment given alone (*Level A*, *Class I*) |

unknown. It is common practice to retreat patients with IVIg (2 g/kg in 2–5 days) or PE. There is some indication that relapses occurring after 9 weeks may indicate that the patient had acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP) [73–75].

Despite a great variety of clinical forms of GBS, the qualitative and quantitative characteristics of recovery after the use of either of two modern methods of treatment of this disease—plasmapheresis or immune therapy—are similar. In some cases, in 8 weeks after initial improvement as a result of plasmapheresis sessions or immune therapy, the patient's condition may deteriorate again. This phenomenon can be explained by continuous production of abnormal antibodies and can easily be eliminated with a repeated treatment course. This repeated course may improve the patient's condition again, although no data on randomized clinical studies are available so far [20, 44, 73, 75].

*Corticosteroids*: the results obtained over the past years have demonstrated no response to therapy with corticosteroids in patients with GBS. A special study (meta-analysis), which summarized the results of six randomized trials of corticosteroids, has put a final point in this issue [76, 77]. Its major conclusion was as follows: recovery by the end of the first month of the disease was similar in patients treated with corticosteroids or placebo; however, it was worse in patients treated with hormones by the end of the first year.

Plasmapheresis is used in patients demonstrating increase in the severity of neurological symptoms in patients who need mechanical ventilation, those who cannot walk more than 5 m with support or assistance, or those who can get out of bed and slowly walk more than meters on their own. The optimal volume of plasmapheresis is not known. In most cases, five sessions of plasma exchange are applied using at least 2–3 L of plasma depending on body weight per session for 2 weeks. This therapy should be initiated within the first 4 weeks from the disease onset [78].

The number of complications associated with plasma exchange is higher than that of immunoglobulin use. This fact, along with convenient route of administration and high availability of the product in developed countries, has made the immunoglobulin a more preferable type of treatment in many centers. One of the restrictions of this therapy is its high cost, so in a number of clinics (especially in low-income countries), plasma exchange is still used [20, 44, 76–86].

**Summary**

1. Treatment of GBS must be started as soon as possible.
2. Treatment with plasma exchange or intravenous immunoglobulin hastens recovery from GBS.
3. Plasmapheresis and intravenous immunoglobulin are equally effective in patients with advanced GBS symptoms.
4. Plasmapheresis may carry a higher risk of side effects and is more difficult to administer.
5. Combining the two treatments is not recommended.
6. Corticosteroid treatment is not recommended.

## 4.9 Supportive Care

Despite progress in immunotherapy, GBS remains a severe pathology with an unpredictable outcome. This statement is based on statistical data. The mortality rate ranges between 4% and 15%, and some 20% patients have residual disability [87–90]. Complications of infection and sepsis are the major causes of mortality. Cardiac arrhythmia is the cause of 20%–30% of deaths in patients with GBS. Lethal outcomes predominantly develop in patients who need mechanical ventilation (MV), which is a considerable risk factor of morbidity and mortality. Nearly 20%–30% of patients with GBS have respiratory insufficiency (RI) and require MV [48, 62, 89, 91, 92], and 78% of these patients need ventilation longer than 3 weeks.

Time from onset to admission of less than 1 week, bulbar paresis, facial and neck weakness, and Medical Research Council sum score are

strong risk factors associated with respiratory failure [22, 57, 59]. Lack of foot flexion ability at the end of immune therapy is a strong predictor of prolonged MV and tracheostomy [60]. Muscle weakness, dysphagia, and pneumonia are possible causes of RI. In some cases only one of these causal factors is present, but other patients might have all these causes of RI simultaneously. The major problem in evaluating the respiratory function of a patient with GBS is that the standard approach assesses almost predominantly muscle weakness. The "20/30/40 rule" is a classic assessment tool for making a decision on trachea intubation and the commencement of MV [48]. According to the rule, the patient should be intubated if forced vital capacity is less than 20 ml/kg body weight, maximum inspiratory pressure is less than −30 cm $H_2O$, and maximum expiratory pressure is less than 40 cm $H_2O$. This approach does not consider the severity of dysphagia and pneumonia. The Burdenko respiratory insufficiency scale might support objective decision-making in difficult clinical situations (Chap. 8, Table 4.2).

Noninvasive MV should be avoided in patients with GBS, because it does not improve outcomes and can be dangerous. Trachea intubation is the method of choice for airway management. The timing of tracheostomy is still a controversial issue. The generally accepted timing for tracheostomy is 14 days of MV. That is a quite reasonable tactic, which makes it possible to avoid unnecessary operations and probable complications, including life-threatening sequels. However, on the other hand, such an approach leads to patient discomfort, increases sedation load and the risk of laryngeal injury, and impedes oral hygiene and upper airway suction. Depth of experience makes percutaneous dilation tracheostomy a safe operation [93]. In recent years there has been a clear trend toward early tracheostomy in many groups of critically ill patients, even in those who usually have a shorter duration of MV among GBS patients [94–96].

Severity of muscular weakness and RI are strongly correlated with autonomic disturbances. Cardiac arrhythmias and extreme hypertension or hypotension occur in approximately 20% of patients with GBS [97, 98]. Bradycardia can be extremely severe, which might require a cardiac pacemaker [3, 99]. Endotracheal suction can provoke these changes. A reduction in variation in heart rate predicted subsequent dysautonomia. A dynamic ileus and dysfunction of bronchial mucosa are other important autonomic disturbances in GBS [2, 100, 101].

Different types of sensory disturbances occur in the majority of cases of GBS. Pain develops in one-third to two-thirds of patients and should be managed adequately and in a timely manner. Acetaminophen and nonsteroid anti-inflammatory drugs are the medications of first choice; however, patients with GBS frequently need opioids. Other drugs, such as gabapentin, carbamazepine, and tricyclic antidepressants, may also be required. Excessive use of opioids is associated with bowel hypomotility, which exacerbates ileus [5, 102].

Prolonged immobilization, muscle weakness, and complications of infection are strong risk factors for the development of deep vein thrombosis (DVT) [7]. All patients should be given subcutaneous fractionated or unfractionated heparin and stockings [5, 102].

## 4.10 Conclusion

The prognosis of GBS is generally considered favorable. The outcome of GBS has varied widely in published series, with mortality rates ranging between 1 and 18% [103]. Mortality in ventilated patients is usually higher and ranges from 20 to 38.3% in a number of studies [104, 105]. Factors that affect mortality are age (>40 or >50 years), rate of progression, sensory disorders, need for ventilation, bulbar dysfunction, dysautonomia, sepsis, and pulmonary complications [106–109].

In general, the mortality rate of even well-treated patients is about 4%, up to 20% of patients can walk unaided after 4 weeks, and only 60% regain full motor strength after 1 year; 14% of patients still have severe disability after a year. The presence of positive antibodies to gangliosides may indicate a poor recovery and be a predictive factor [106–109].

**Key Points**

- Guillain-Barré syndrome (GBS), also called acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is an inflammatory disorder affecting the peripheral nervous system that is characterized by acute or subacute onset and typically monophasic course of the disease. The most common manifestation of GBS is bilateral muscle weakness.
- The disease generally starts in the lower limbs and is ascending. Reflexes may be decreased or normal at the beginning of the disease, and they disappear afterward.
- The phenomenon of combined normal cell count and increased protein concentration is known as cytoalbuminologic dissociation and is typical for patients with Guillain-Barré syndrome.
- Electrodiagnostic testing and CSF analysis are often used for diagnosis, but inconclusive in the early stages of the disease.
- Clinical variants of GBS are typical clinical GBS, acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), Miller Fisher syndrome (MFS), pharyngeal-cervical-brachial variant, acute pandysautonomia, pure sensory GBS, and others.
- Plasma exchange and intravenous immunoglobulin and IVIg are equally effective in patients with advanced GBS symptoms.

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# 5 Intensive Care Management of the Neuromuscular Patient

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## 5.1 Introduction

Clinically, neuromuscular conditions are diseases of the nervous system that affect the motor neuron unit between the anterior horn cells and the muscle. This group of diseases classically affects lower motor neuronal body which could be in the cranial nerve nuclei or spinal cord, the corresponding axon including its multiple branches, and the neuromuscular junction. Patients can have symptoms due to affection of any part of the motor neuron unit thus making this group of diseases quite heterogenous. Patients presenting acutely can have a range of symptoms. While some may require observation only, others could have life-threatening complications. Occasionally, these conditions can have an acute presentation that necessitates admission to an intensive care unit. Patients suffering from acute non-traumatic neuromuscular weakness typically present with difficulties in protecting their airway with or without symptoms of respiratory distress. Certain neuromuscular diseases can also lead to dysfunction of the autonomic nervous system which can lead to circulatory collapse, while others can be due to a consequence of prolonged critical illness. When respiratory symptoms do develop, these patients often require ventilation support with the use of invasive or noninvasive devices.

## 5.2 Clinical Presentations and Localization of Neuromuscular Disorders (NMD)

The two crucial steps in the diagnosis and management of neuromuscular diseases are:

1. Identifying the anatomic localization of the site of the lesion that is producing symptomology
2. Determining the etiology of the lesion

A systematic approach to localization is to place the lesion within the nervous system. Disease can occur in the central nervous system (CNS), containing the brain and spinal cord, or peripheral nervous system (PNS). The CNS includes the cerebral motor cortex, corticospinal tracts, and spinal cord, and the PNS includes

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spinal nerves, nerve roots, nerve branches, neuromuscular junctions (NMJ), and muscles [1]. CNS and PNS lesions should be identifiable from a detailed neurologic examination. The distribution of motor weakness, presence of sensory involvement, presence or absence of deep tendon reflexes, and pain are all important in localizing the lesion in the nervous system. These features are listed for neuromuscular diseases that are commonly encountered in critical care (Table 5.1). The focus of the rest of this chapter will be to discuss neuromuscular diseases of the PNS in greater detail.

## 5.3 Sites of Neuromuscular Disease

- *CNS*—diseases affecting the brain and spinal cord result in upper motor neuron (UMN) impairment. These include trauma, infections like abscesses, inflammatory diseases like multiple sclerosis or acute disseminated encephalomyelitis (ADEM), tumors, degenerative diseases, vascular disease like stroke, toxicities like carbon monoxide poisoning, genetic diseases like leukodystrophies, and metabolic diseases like vitamin deficiencies. Appropriate imaging studies of the CNS and PNS based on the suspected site like computed tomography (CT), magnetic resonance imaging (MRI), or plain radiographs and perhaps a cerebrospinal fluid (CSF) examination may be necessary to identify the primary disease.
- *Anterior horn cells*—diseases affecting anterior horn cells include degenerative diseases like amyotrophic lateral sclerosis (ALS) and familial spinal atrophy, infections like poliomyelitis and West Nile virus as well as toxins like lead poisoning. Patient age, exposure history, family history, time course of disease, laboratory tests, nerve conduction studies, and CSF examination can help differentiate between these diseases.
- *Spinal nerve roots*—diseases causing acute radiculopathies include trauma resulting in spinal disk herniation, infections like Lyme disease and varicella zoster virus, inflammatory diseases like acute inflammatory demyelinating polyradiculoneuropathy (AIDP; Guillain-Barré syndrome), neoplasms including lymphoma or multiple myeloma, as well as vascular diseases like arteriovenous malformations and vasculitis.
- *Peripheral spinal nerves and branches*—diseases can affect a single nerve, for instance, as a sequelae of nerve compression as in carpal tunnel syndrome, or multiple nerves. Mononeuropathy multiplex, an ischemic disease affecting multiple nerves, can occur as a result of diabetes mellitus (DM) or vasculitis. A symmetric polyneuropathy with weakness and sensory symptoms has a wide variety of causes, ranging from common such as DM, critical illness, HIV, and alcohol abuse, less common such as vitamin B12 deficiency and Lyme disease, to rare such as porphyria and Charcot-Marie-Tooth disease. Symmetric polyneuropathy often occurs as an adverse effect of medication or as a manifestation of systemic disease. The characteristics (axonal or demyelinating) and rate of progression of disease can help differentiate between causes.
- *Neuromuscular junction (NMJ)*—diseases of neuromuscular transmission that affect the presynaptic junction can interfere with acetylcholine (ACh) release as in botulism or affect voltage-gated presynaptic calcium channels as in Lambert-Eaton syndrome. Other less common presynaptic diseases include congenital myasthenic syndromes, severe hypermagnesemia, and tick paralysis. Diseases that affect the postsynaptic junction include the generation of anti-acetylcholine receptor antibodies in myasthenia gravis and inhibition of acetylcholinesterase by organophosphate poisoning.
- *Muscles*—diseases of the muscle have a wide variety of causes, including inflammatory disorders such as critical illness and polymyositis, infections such as influenza, endocrinopathies such as hypothyroidism, metabolic myopathies such as hypokalemia, drugs and toxins such as corticosteroids or statins, and the various causes of rhabdomyolysis. The specific diagnosis may be suspected from the history and course of disease. The presence of features of a systemic

**Table 5.1.** Symptoms and physical examination findings in neuromuscular disorders that may be encountered in the ICU

| Localization | | Disease | Diagnostic category | Clinical features | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Motor | | Sensory | Reflexes | Neuropathic pain present |
| | | | | Distribution | Symmetric | | | |
| CNS | Cerebral motor cortex<br>CS tracts | *Brain abscess or tumor* | Infectious or neoplastic | UMN | No | No[a] | Increased | No |
| CNS | Cerebral motor cortex<br>CS tracts | *Leukodystrophy* | Genetic | UMN | No | No[a] | Increased | No |
| CNS | CS tracts<br>Anterior horn hells | Amyotrophic lateral sclerosis | Inflammatory | UMN and LMN. Begins focally. Spares bladder | No; often presents as asymmetric limb weakness | No | Increased | No |
| PNS | Peripheral nerve root | *Acute lumbosacral radiculopathy* | Infectious or inflammatory or trauma or neoplastic | LMN. focal in nerve(s) distribution(s) | No | Yes | Decreased in nerve distribution | Yes |
| PNS | Peripheral nerve branch | *Mononeuritis multiplex* | Vascular, metabolic, endocrine | LMN. Focal in 2 or more nerve(s) distribution(s) | No | +/− | Decreased | Yes |
| PNS | Peripheral nerve and roots | *Guillain-Barré Syndrome* | Inflammatory | LMN. Diffuse; Ascending paralysis | Relative symmetry | Yes | Decreased | Yes |
| PNS | Peripheral nerve | *Peripheral neuropathy* | Infectious, Inflammatory, Endocrine | LMN. Diffuse | Yes | Yes | Decreased | Yes |
| PNS | NMJ | *Myasthenia Gravis* | Genetic, Inflammatory | Diffuse; prominent corticobulbar weakness | Yes | No | Normal | No |
| PNS | NMJ | *Eaton-Lambert syndrome* | Neoplastic, inflammatory | Diffuse; begins in proximal muscles | Yes | No | Normal | No |
| PNS | NMJ | *Botulism* | Infectious | Diffuse; descending paralysis | Yes | No | Normal | No |
| PNS | Muscle | *Exogenous steroids* | Inflammatory | Diffuse; begins in proximal muscles | Yes | No | Normal | No |

*CNS* central nervous system, *CS* corticospinal, *ICU* intensive care unit, *PNS* peripheral nervous system, *UMN* upper motor neuron

[a]Sensory involvement is present if lesion involves cerebral sensory cortex

illness such as systemic lupus erythematosus may be indicative of myositis. Medication, alcohol, or substance abuse may be a clue to drug-induced myopathy. History of endocrinopathies such as thyroid dysfunction could be a clue to diagnosis. A history of recurrent episodes of exertion-related hematuria and weakness could suggest a metabolic myopathy.

*Distribution of motor muscle weakness as a guide to localization of lesion*—Determining the pattern of weakness is diagnostically important and can localize the lesion to the CNS or PNS. Weakness of both CNS and PNS can be broadly classified as diffuse, involving all muscle groups in varying extents or focal, involving specific distributions of the brain, nerve, or muscle. Diffuse muscle weakness can involve muscles in a symmetric pattern or asymmetric pattern. Symmetric weakness can cause proximal or distal loss of muscle strength. As such, in patients with diffuse weakness, the physician should determine whether the loss of function is proximal or distal while obtaining patient history by asking which physical activities muscle weakness limits as well as by conducting a focused neurologic examination testing specific muscle group strength against resistance.

Proximal muscle weakness involves the axial muscle groups, deltoids, and hip flexors. If the patient has difficulty lifting their head off the bed (neck flexors), rising from a seated position (quadriceps), or brushing his or her hair (deltoids), the weakness is proximal. Proximal muscle weakness is typically seen in the various myopathies, certain muscular dystrophies, and myasthenia gravis.

Distal muscle weakness is characterized by decreased grip strength, weakness of wrist flexion or extension, decreased plantar flexion strength, and foot drop. If the patient has difficulty walking on their heels (tibialis anterior, extensor hallucis longus) and toes (gastrocnemius/soleus muscles) or buttoning their shirt with their hands (intrinsic muscles), the muscle weakness is distal. Distal symmetric weakness can be a characteristic of early motor neuron disease or peripheral neuropathy.

*Determining etiology of lesion*—Once the neuromuscular site of the lesion has been localized, the etiology of disorders at each site can be categorized as trauma, infectious, inflammatory, neoplastic, degenerative, vascular, toxic, or metabolic in origin (see above sites of neuromuscular disease for examples). Once anatomic localization is made, it is pieced together with patient history to generate differential diagnoses.

## 5.4 Clinical Investigations

### 5.4.1 Laboratory Tests

Basic laboratory tests can be useful in diagnosis of patients with neuromuscular weakness. Diseases that damage striated muscle fibers result in leakage of intracellular enzymes into the blood, where they become measurable by serum tests. These include creatine kinase [2, 3], myoglobin, aldolase, transaminases, and lactic acid dehydrogenase [4, 5]. The presence of myoglobin in urinalysis can be a useful marker of muscle diseases. Myoglobin is an iron-protein compound present in the sarcoplasm of striated skeletal and cardiac muscle fibers, containing a red pigment that gives muscle its characteristic color. Muscle destruction regardless of cause therefore releases myoglobin, which due to its small size is filtered freely through the renal glomeruli and appears in the urine, a phenomenon referred to as "myoglobinuria" [5]. Specific autoantibody tests such as anti-acetylcholine receptor antibodies (AChR-Ab), muscle-specific tyrosine kinase (MuSK-Ab), and voltage-gated potassium channel antibodies (VGKC-Ab) can help identify specific NMJ diseases. Moreover, detection of antibodies against extractable nuclear antigens such as anti-Ro/SSA, anti-La/SSB, anti-Sm, and anti-RNP and myositis-associated antigens such as anti-histidyl-t-RNA synthase (anti-Jo-1) can be suggestive of an inflammatory myopathy or associated connective tissue disease [6].

### 5.4.2 Electrodiagnostic Testing

Electrophysiologic studies such as nerve conduction studies (NCS) and electromyography (EMG) are useful when the location of the lesion responsible for weakness is suspected to be in

the PNS, i.e., spinal nerves, NMJ, or muscle. Our goal in the next few paragraphs is to discuss the importance of these studies in the diagnosis of neuromuscular disease. Details of NCS and EMG interpretation are beyond the scope of this chapter.

Most often, NCS, which are obtained using surface electrodes, is followed by EMG. NCS includes studies of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs), which collectively provide valuable information about the integrity of motor and sensory nerve fibers. Analysis of amplitudes and latencies of CMAPs and SNAPs allows localization of the problem to axon, myelin sheath, nerve root, or branches.

EMG involves insertion of a needle with a recording electrode into muscle and observing its electrical waveforms at rest and with activation. Analysis of the waveforms allows evaluation of the integrity and function of motor units which comprises anterior horn cells, nerve axon, terminal nerve branches, and muscle fibers innervated by these branches. Collectively, NCS and EMG can be useful to localize peripheral weakness, identify characteristic features that narrow differential diagnoses, and identify affected muscles for biopsy [7]. They can differentiate between neuropathic and myopathic disease (Fig. 5.1) as well as identify defects in presynaptic or postsynaptic transmission, but the yield of these studies is higher when the electromyographer has an idea of clinically weak muscles and an idea of the differential diagnoses based on history and examination [8]. When clinically appropriate, certain specialized nerve conduction techniques can be employed, such as repetitive nerve stimulation and single fiber EMG for suspected disorders of neuromuscular transmission [6] as well as short or long exercise testing for suspected non-dystrophic myotonias and periodic paralysis [9].

The first step in performing an EMG is to assess for the presence of abnormal spontaneous activity while the muscle is at rest. Following electrode insertion into normal muscle at rest, a brief burst of electrical activity typically occurs lasting 300 ms or less, followed by electrical silence [10]. Neuropathic disorders exhibit abnormal spontaneous activity at rest, including fibrillations and positive sharp waves, which arise from spontaneous firing of individual muscle after denervation. In general, muscle is electrically silent in myopathies, but it is important to note that spontaneous activity may occur in certain myopathies due to irritability of the muscle membranes. This occurs particularly in inflammatory, necrotic, or certain congenital myopathies as well as muscular dystrophies [11].

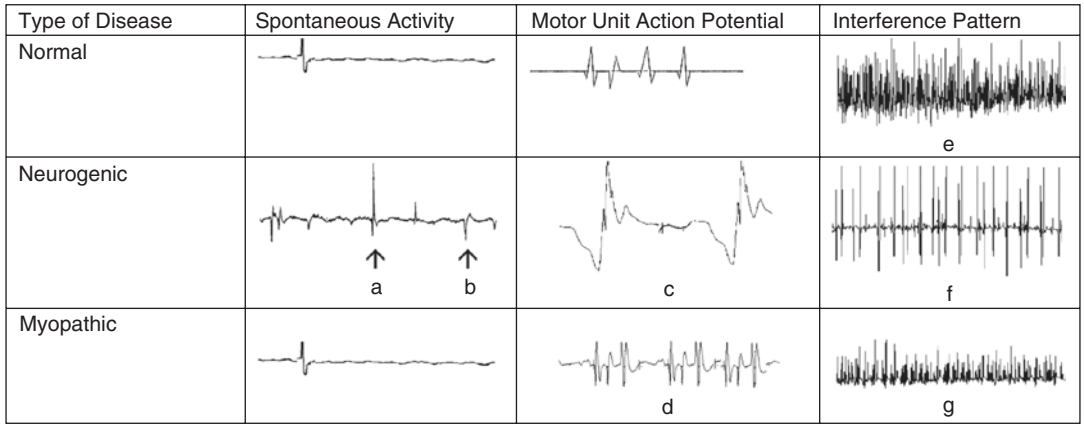


**Fig. 5.1** Characteristic electromyography (EMG) features in neuropathic and myopathic types of neuromuscular disease. (1) Spontaneous activity at rest: (**a**) fibrillations, (**b**) positive sharp waves. (2) Motor unit potentials: (**c**) giant polyphasic units and reduced recruitment, (**d**) small units and increased recruitment. (3) Interference pattern: (**e**) full, (**f**) reduced units, (**g**) reduced amplitude, normal number of units

Following assessment of spontaneous activity at rest, muscle is activated minimally so that motor unit action potential (MUAP) morphology including amplitude, duration, and waveform can be assessed, and the muscle power is increased so that recruitment pattern can be assessed. Recruitment is the firing pattern of additional motor units and the rate at which they are activated as the patient increases power of contractions. Recruitment testing is often challenging in the intensive care unit setting (ICU) if patients lack awareness or are unable to participate in incrementally increasing their power of contractions.

In general, neuropathic disorders affect the number of voluntary motor units. When fewer voluntary motor units are available for muscle contraction, muscle recruitment is reduced, and increased effort results in rapid firing of a reduced number of motor units. Since the remaining motor units are larger than normal, the total amplitude of the MUAP and the interference pattern is increased [8]. Myopathic disorders reduce the number of functioning muscle fibers; therefore the force generated by each motor unit is reduced, resulting in MUAPs with lower amplitudes and shorter durations. To generate the same force, more motor units are recruited and motor unit firing rate increases. These differences become more apparent with increased force. Of note, these morphologic changes are not entirely specific as MUAPs with low amplitudes, and short durations can also be seen in early reinnervation after neurogenic injury. The general EMG differences between neuropathic and myopathic disorders are outlined in Fig. 5.1, but one must note there are exceptions to this simplified table. Given nuances and overlap in electrophysiologic findings, it is important to remember that electrophysiology is only part of the clinical investigation and must be interpreted in the appropriate clinical context to determine disease pattern or arrive at the correct diagnosis.

If a muscle biopsy is required for diagnosis, EMG can help to guide the biopsy site by detecting subclinical abnormalities, especially if the patient does not have any weakness on examination or only has weakness in muscles that are not typically biopsied, like the iliopsoas. It is important to only study one side of the patient if a biopsy is planned, so the biopsy can be done on the contralateral side as needle artifacts may affect muscle biopsy interpretation.

### 5.4.3 Imaging Studies

Neuroimaging such as plain radiographs, CT, or MRI can be useful in ruling out focal mass lesions such as tumors, abscesses, bulging disks, and traumatic axonal injury in the CNS or PNS accounting for neuromuscular weakness. Moreover, MRI and ultrasound are increasingly being used to detect and characterize skeletal muscle abnormalities [12]. Like EMG, skeletal muscle MRI can be used to identify targets for muscle biopsy, especially when muscles are not clinically weak, are difficult to test, or appear normal on EMG. MRI signal abnormalities lack specificity, but certain findings can be suggestive of specific conditions, for instance, edema can suggest inflammatory myopathy and fatty infiltration can suggest an underlying disease process causing chronic muscle injury. Location and appearance of muscles that are affected can also help to narrow down the differential diagnosis. For example, atrophy and edema involving the vastus lateralis and medialis with relative sparing of the rectus femoris can help to distinguish inclusion body myositis from other myopathies [13]. If a muscle biopsy is necessary for diagnosis, MRI of the muscles not only helps to identify the optimal site for biopsy but has been shown to reduce overall cost [14]. A modality gaining popularity is ultrasound, as it is noninvasive and inexpensive and provides an assessment of muscle thickness, abnormal movements (e.g., fasciculations), and infiltration by fibrotic tissue or fat, but it lacks the imaging detail offered by MRI.

### 5.4.4 Muscle Biopsy

Diagnosis of a myopathy can be made using patient history and physical examination in conjunction with laboratory tests, electrophysiology, imaging, and sometimes genetic testing. In challenging cases, a muscle biopsy is required to make or confirm a diagnosis and remains the gold standard.

In patients with proximal muscle weakness, elevated CK, a myopathic EMG, or abnormal skeletal muscle MRI without a definite diagnosis, a muscle biopsy is strongly considered as it has a highly positive diagnostic outcome. In the absence of these findings, patients should be counseled that the yield of a muscle biopsy is low [15].

Common proximal biopsy sites include deltoid, biceps brachii, triceps brachii, and quadriceps, and common distal biopsy sites include forearm extensors, gastrocnemius, and tibialis anterior, but other muscles are considered based on the clinical scenarios. There are two approaches in performing a muscle biopsy, the open and percutaneous approach, and each approach has its own advantages and disadvantages. Open biopsy allows larger sampling offering the opportunity for more extensive testing due to a larger sample size, but by its open nature is more invasive. The percutaneous approach is less invasive as it involves the use of a needle with a hollow core to obtain multiple small samples; however, the samples are smaller and testing is often limited. Muscle biopsy is done on muscles that have mild to moderate weakness; muscles that are severely weak are usually of a low diagnostic yield, as they often show end-stage pathologic changes that cannot distinguish between various myopathies or even severe neurogenic atrophy.

Once the biopsied tissue reaches the pathology laboratory, pieces are flash frozen in isopentane and cooled in liquid nitrogen. Various stains are then performed on these frozen sections and used for routine histochemistries, Western blots to evaluate specific proteins, enzymology to evaluate lipid or glycogen storage diseases, and genetic testing for diseases such as mitochondrial diseases. Some of the stains include hematoxylin and eosin (H&E) staining that displays muscle architecture, a modified Gomori trichrome stain for examining structural changes, ATPase staining for visualization of fiber type-specific atrophy, and periodic acid-Schiff staining for evaluation of glycogen content. In certain cases, such as to confirm inclusion body myositis, additional specimens are placed in formalin and glutaraldehyde solution and further analyzed under electron microscopy [16].

### 5.4.5 Genetic Testing

Specific defects can be identified by Western blot or molecular analysis of mutations. Genetic testing is becoming increasingly useful in confirmation and categorization of patients with heritable diseases such as mitochondrial myopathies and muscular dystrophies [17]. When genetic defects are strongly suspected, it is advisable to obtain genetic testing prior to performing a muscle biopsy. Western blotting is useful in differentiating an enzymatic production defect from a kinetic defect. Molecular analysis of specific mutations can confirm an enzymatic deficiency detected in biochemical assay of lymphocytes, fibroblasts, or muscle tissue [17]. If single gene sequencing has failed or it is unlikely to provide a diagnosis, large-scale molecular diagnostic testing (i.e. next-generation sequencing) can be considered, especially if it is available at a low cost.

## 5.5 Neuromuscular Diseases Commonly Encountered in the ICU

### 5.5.1 Critical Illness Polyneuropathy and Myopathy

#### 5.5.1.1 Background

Recognition that critically ill patients frequently develop new neuromuscular dysfunction was not widespread until the final decade of the twentieth century. In 1984, a series of five patients were noticed to develop flaccid paralysis with areflexia and difficulty in weaning from the ventilator at the peak of their sepsis and multiple organ dysfunction with neurophysiology indicating development of a new axonal sensorimotor polyneuropathy [18]. In 1992, persistent paralysis was observed following long-term neuromuscular blockade but attributed to higher plasma levels of vecuronium metabolites and impaired renal function [19]. Another study reported severe weakness in two critically ill asthmatic patients treated with high-dose steroids and non-depolarizing blocking agents, in whom muscle biopsy demonstrated depletion of thick myosin filaments; they called this acute quadriplegic

myopathy and reported their clinical course over several months [20]. Many of these reports did not include detailed neurologic examination or electrophysiological testing, limiting definitive diagnosis at the time. In 1994, in 23 out of 24 critically ill comatose patients with quadriparesis or quadriplegia and diminished deep tendon reflexes (DTR), a landmark study demonstrated evidence of neuropathy, myopathy, or both based on electrophysiology [21].

As this entity was becoming more widely recognized, people began referring to this condition by several names including acute quadriplegic myopathy, acute necrotizing myopathy of intensive care, thick filament myopathy, acute corticosteroid myopathy, acute hydrocortisone myopathy, acute myopathy in severe asthma, and acute corticosteroid and pancuronium-associated myopathy, critical care myopathy, and acute myopathy of intensive care [22]. Physicians were beginning to recognize that these patients may in fact have motor recovery upon recovering from their concurrent critical illness, and the term critical illness polyneuropathy and myopathy (CINM) was coined [23].

CINM presents in critically ill patients with generalized flaccid paralysis with decreased or absent DTR and failure to wean from the ventilator. Weakness can be from an axonal polyneuropathy (critical illness polyneuropathy—CIP), a myopathy (critical illness myopathy—CIM), or both [21]. Numerous survivors of critical illness suffer from weakness and long-term disability for months to years after discharge from hospital [23, 24]. Diagnosis of CINM is challenging in the ICU due to pre-existing disorders, other active conditions during the stay contributing to muscle weakness, and patient's clinical condition precluding careful neurologic examination. Moreover, many times in the ICU when patients are critically ill, the focus becomes patient survival, and less attention is paid to the gradually progressive neuromuscular weakness from CINM in the background. CINM is a major contributor of ICU-acquired weakness, resulting in chronic disability in survivors of critical illness, and intensivists should be familiar with its diagnosis and clinical course.

#### 5.5.1.2 Epidemiology

A lack of consistent nomenclature, variation in patient population, diagnostic criteria used, and timing of assessment have been a barrier to determining exact incidence of CINM [23, 25]. Reported incidence of CINM is estimated to be as high as 25.3% of patients that are mechanically ventilated for 7 or more days [26], 60% of patients with acute respiratory distress syndrome (ARDS) [27], 50–84% of mechanically ventilated ICU patients with sepsis and multiorgan failure [28, 29], and 95–100% of mechanically ventilated patients with sepsis and coma [21, 30].

#### 5.5.1.3 Risk Factors and Pathophysiology

Systemic inflammatory response syndrome (SIRS), sepsis, sepsis with mechanical ventilation [26], and multiorgan failure appear to consistently be risk factors for CINM [28, 29, 31–33]. Diaphragmatic weakness, a prominent feature in CINM, has been observed to rapidly develop during mechanical ventilation and is significantly related to the duration of ventilator support [34]. A high catabolic state from systemic inflammation likely contributes to early diaphragmatic weakness in these patients. The strong occurrence of CINM with sepsis and MODS suggests that there are likely shared metabolic, cellular, and microcirculatory pathophysiological mechanisms. Sepsis results in ischemic hypoxia due to widespread impairment in microcirculation [35] as well as impaired mitochondrial function resulting in reduced adenosine triphosphate (ATP) production [36, 37]. Excitable tissue like peripheral nerves and muscle are probably damaged as a result of this microcirculatory failure, resulting in distal axonopathy [38]. In patients with CIP, the expression of E-selectin, a marker of endothelial activation, is increased in vascular endothelium [39]. This could result in increased leukocyte adhesion, local cytokine production, increased microvascular permeability, and endoneurial edema, which could be further worsened by hypoalbuminemia and hyperglycemia. In addition, decreased nutrient supply, increased demand, and decreased clearance of toxic substances and tissue edema can ultimately terminate

in bioenergetic failure, neuronal injury, and axonal degeneration. Pathologically in CIN, there is axonal degeneration without inflammation.

Other risk factors for CINM include prolonged ICU stay [40–42], hyperglycemia [40], hypoalbuminemia [40], duration of vasopressor and catecholamine support [41], hyperosmolarity [42], parenteral nutrition [42], and neurologic failure [25, 42]. This data is conflicting for nondepolarizing neuromuscular blockers (NMB) and steroids. High corticosteroid levels are thought to increase expression of ubiquitin, leading to increased proteolytic activity [43]. NMBs have been identified as risk factor [25, 42], but a large study showed that early administration of cisatracurium improved 90-day ARDS patient survival and increased the time off the ventilator without increasing muscle weakness [44]. This finding could be explained by either, the intermediate-effect duration of cisatracurium, or the fact that cisatracurium was only used for 48 hours in the study. It is postulated that nondepolarizing NMBs cause muscle weakness by upregulation of acetylcholine receptors with fetal-type receptors that are less responsive to acetylcholine, presynaptic inhibition of exocytosis of acetylcholine, and potentiation of muscle damage by corticosteroids [45].

Immobility and muscle inactivity acts as a potent stimulus of the ubiquitin-proteasome pathway of proteolysis in skeletal muscle, increasing muscle wasting [46] during critical illness. Denervation from coexisting CINM may make the muscle more susceptible. Muscle biopsy in CIM shows loss of thick myosin (thick) filaments, fiber-type atrophy, and/or necrosis [20, 47]. Whether the different pathologies represent a spectrum of severity of the same disease or completely different entities is unsettled.

#### 5.5.1.4 Clinical Presentation

CINM is most often diagnosed when sedation is weaned or sepsis and encephalopathy improve in a mechanically ventilated patient, revealing a profound generalized weakness that cannot be explained by coexisting neurologic disease, metabolic disturbances, increased metabolic demand, nutritional disorders, profound anemia, or delirium. In a patient who is alert, muscle strength can be tested in functional limb muscle groups with the Medical Research Council (MRC) scale. Neurologic exam reveals normal cranial nerves with generalized flaccid quadriparesis or quadriplegia, often worse distally, usually in conjunction with failure to wean from the ventilator. Hyporeflexia, areflexia, and muscle atrophy can be seen in CIP, though reflexes are usually preserved or hypoactive in CIM. Distal sensory loss to pain, temperature, and vibration may be observed in alert patients [48] but is not always reported or amenable to testing [49]. When noxious stimulus is applied, one may observe facial grimacing but reduced or absent movement of the limbs. Sensation is normal in CIM if neuropathy does not coexist, but testing is often limited by coexisting encephalopathy [46]. Electrodiagnostic studies can therefore be key to diagnosis, though a high index of clinical suspicion is prerequisite.

#### 5.5.1.5 Diagnosis

CIP is a distal sensory-motor axonal polyneuropathy affecting limb and respiratory muscles, sparing cranial nerves [21]. Muscle weakness in the limbs is symmetric and worse distally than proximally. Diagnostic criteria exist for CIP and CIM and are outlined in Table 5.2. A high index of clinical suspicion must exist if patient develops new neuromuscular weakness after survival of critical illness, SIRS, sepsis, and/or MODS. Alternative causes for neuromuscular weakness in the ICU must be considered and, if possible, excluded based on history and examination (refer to Table 5.1). Laboratory studies can help to exclude mimics, including muscle enzymes such as CK. Depending on clinical suspicion, imaging of the brain and spinal cord may be appropriate to exclude other disease of the CNS and PNS such as tumors, infections, and disk diseases. Cerebrospinal fluid findings are not often reported in CIP. Lumbar puncture is indicated principally if there is clinical suspicion of CNS or PNS infection.

Electrophysiologic testing and muscle biopsy can help confirm CIM or CIP and help to distinguish them from each other as well as other

**Table 5.2** Diagnostic criteria for critical illness polyneuropathy (CIP) and critical illness myopathy (CIM)

| CIP[a] | CIM[b] |
|---|---|
| The patient is critically ill (with SIRS, sepsis, and MODS) | SNAP amplitudes >80% of the lower limit of normal |
| Difficulty weaning patient from ventilator after nonneuromuscular causes such as heart and lung disease have been excluded | Needle EMG with short-duration, low-amplitude MUPs with early or normal full recruitment, with or without fibrillation potentials |
| Possible limb weakness | Absence of a decremental response on repetitive nerve stimulation |
| Electrophysiologic evidence of axonal motor and sensory polyneuropathy | Muscle histopathologic findings of myopathy with myosin loss |
| | CMAP amplitudes <80% of the lower limit of normal in two or more nerves without conduction block |
| | Elevated serum creatine kinase (CK) |
| | Demonstration of muscle inexcitability |

[a]These diagnostic criteria are now well established, originally created by Bolton [38]. Other acute axonal polyneuropathies should be excluded

[b]For a definite diagnosis of CIM, patients should have all of the first five features

disorders of nerve, NMJ, and muscle. Nerve conduction studies may be difficult to perform and interpret due to multiple artifacts, extremities may be cool and difficult to warm, and they may be confounded by tissue edema. EMG may not be useful when patients are not awake or unable to contract muscles to command. Nonetheless, they are usually diagnostic [38].

Nerve conduction studies in CIP show decreased CMAP and SNAP amplitudes with normal or mildly reduced conduction velocities and normal CMAP durations. The abnormalities are usually length-dependent. NCS findings are generally present by day 14 of critical illness, but low amplitudes may be noted within a week and as early as 72 h after onset of sepsis [49]. Needle EMG studies in CIP may show fibrillation potentials and positive sharp waves in a multifocal pattern generally after 2 weeks but have been reported as early as 7 days after initiation of mechanical ventilation [33]. Muscle biopsy in CIP shows evidence of acute denervation of muscle with atrophy of both type 1 and type 2 fibers and grouped atrophy as recovery occurs. Nerve biopsy is rarely indicated but if done will show signs of axonal neuropathy [21].

In patients with CIM, the CMAP is also of low amplitude, but unlike CIP, CMAP duration is prolonged due to slowing of muscle fiber conduction velocity and reduced excitability of the sarcolemma membrane. These changes occur within 2 weeks of critical illness [50]. SNAPs are normal in CIM, unless there is coexistent CIP. Voluntary muscle activity may be difficult to study in poorly cooperative patients, but when performed, reduced recruitment is seen in CIP, and small polyphasic motor unit potentials are seen in myopathy, helping to differentiate CIP from CIM.

Muscle biopsy in CIM shows selective loss of myosin and varying degrees of muscle necrosis directly proportional to disease severity [21, 51]. During recovery in CIM, electrophysiological studies show a rise in CMAP amplitude, normal CMAP duration as well as loss of fibrillation potentials, and/or positive sharp waves from muscle. There is a wide variance in electrophysiology based on severity of disease. In severe CIPM where CIP and CIM coexist, CMAP and SNAP amplitudes are considerably reduced, and muscle biopsy shows substantial, generalized necrosis. Although muscle and nerve biopsies may be diagnostic, they often only change management if they demonstrate an alternative diagnosis that is treatable, for instance, an inflammatory myopathy or demyelinating or vasculitic neuropathy. If the clinical index of suspicion is high for CINM, a biopsy is likely not warranted.

Additional electrodiagnostic studies that may be useful in diagnosis include phrenic nerve stimulation and diaphragmatic EMG, but many electromyographers do not have necessary experience with them to be confident in their performance or interpretation. Phrenic nerve stimulation in the neck with surface recording over the diaphragm shows a normal response in patients with pulmonary causes of respiratory failure but a low amplitude or absent response in patients with neuromuscular respiratory weakness. Needle EMG of the diaphragm can be done in patients without severe chronic obstructive pulmonary disease (COPD), ileus, or coagulopathy and may

diagnose denervation or myopathy affecting the diaphragm [52].

#### 5.5.1.6 Management

Since no specific therapy that decreases incidence or severity of CINM has been found, management has been largely supportive [53]. Treatment of hyperglycemia, early physical rehabilitation, and minimization of sedation have been demonstrated to improve short-term and long-term functional outcomes, increase ventilator-free days, and reduce delirium [54]. Of the factors that may contribute to the development of CINM, many—like the response to sepsis and the incidence of multiorgan failure—are related to the severity of the presenting critical illness and are not easily modifiable. It remains to be demonstrated whether the reduced use of corticosteroids or neuromuscular blocking agents will result in a decreased incidence of CIM. Intensive insulin therapy to maintain strict normoglycemia was shown to reduce the incidence of critical illness polyneuropathy by 49% in a single-center study [41], but this practice has been shown to increase mortality in patients who are critically ill [55]. Therefore, control of sustained hyperglycemia is reasonable, but aggressive insulin protocols and any hypoglycemic episodes should be avoided [55]. Patients with neuropathy are more prone to pressure palsies, and, thus, great care must be taken in positioning and support to avoid this complication. Neurotoxic medications should also be avoided. In patients that are unable to participate in active strengthening exercises, early physical therapy should be directed toward prevention of muscle atrophy and contractures, as studies have shown that repeated daily passive mobilization prevents muscle atrophy observed by serial muscle biopsies [56]. Early rehabilitation in the ICU requires a cultural shift and a strong commitment from a multidisciplinary team but improves functional outcome [54].

#### 5.5.1.7 Prognosis

There is no comprehensive study on prognosis in CINM. Mortality is high early in the course and is related to the underlying critical illness [34]. Patients with CINM who survive the acute illness and who begin to recover strength are likely to continue to recover over the weeks to months that follow, and it is sufficient to monitor improvement with clinical assessment of strength. Patients with severe CINM have slow and often incomplete recovery, and nearly a third of patients with CINM do not recover spontaneous ventilation or independent walking [25]. Patients with CINM who fail to show clinical improvement in strength can be evaluated with repeat electrophysiologic testing. Patients with evidence of severe axonal loss, with small or absent responses to nerve stimulation and abundant positive waves and fibrillations on needle EMG, will recover slowly if at all and are likely to have residual deficits—sometimes severe [40, 48]. The task of regenerating severely damaged axons appears more daunting than regenerating muscle [21], but recent evidence suggests CIM to predict a better functional recovery at both time of discharge and 1 year follow-up [57].

#### 5.5.1.8 Future Directions

A good understanding of the pathophysiology of CINM is necessary to be able to develop goal-directed interventions, and recent discoveries make this a realistic possibility in the future. Skeletal muscle regeneration is reliant on stem (satellite); this is supported by human evidence that shows that decreased satellite cell content impedes muscle growth and results in protracted muscle wasting [58]. Emerging evidence shows that impairment of satellite cells leads to inefficient muscle regeneration and engrafting mesenchymal stem cells restores metabolic and mitochondrial function of satellite cells, improving muscle strength in a mice model [59]. An experimental ICU porcine model study that reproduced ICU conditions such as sedation, long-term mechanical ventilation, and muscle unloading showed that mechanical silencing is a dominant factor triggering the preferential loss of myosin and muscle atrophy in a period of within 6 h to 14 days [60]. In a later study, the same authors attempted to identify gene signatures and molecular pathways that regulate mechanical activation of skeletal muscle affected in the ICU; they found that mechanical silencing triggers genes that regulate mitochondrial dynamics and mitophagy as well as ubiquitin

ligases Fbxo31 and SMART, which are all reversed by passive mechanical loading [61]. This may explain the beneficial effects of early mobilization and physical therapy in CINM. CINM continues to be an area of active research and discovery, and it is our hope that we will have better understanding and be able to tailor therapy accordingly in the future.

## 5.5.2 Myasthenia Gravis

### 5.5.2.1 Background

Myasthenia gravis (MG) is the most common autoimmune disorder of the NMJ. It is caused by autoantibodies against receptors located in postsynaptic cleft, which affects neuromuscular synaptic transmission [62]. The first documented case of MG in literature was in a Native American, Chief Opechankanough, who died in 1664 [63, 64]. However, the autoimmune nature of the disease was established in 1973 when first antibodies to acetylcholine receptor (AchR) were identified [65]. Since then, there has been major progress in understanding the pathophysiology of the disease and introduction of multiple treatment options which has led to improvement in outcome and mortality of the patients with MG.

### 5.5.2.2 Epidemiology

The incidence of MG incidence varies from 0.25 to 2.0 per one million people with prevalence of 15–179 per one million people worldwide of which 10% are in pediatric population [62, 66, 67]. It has a bimodal distribution with early-onset disease seen in second and third decades of life with a female predominance and late-onset disease which is seen in sixth to eighth decade of life and has a male predominance [68].

### 5.5.2.3 Pathophysiology

The NMJ consists of the terminal branch of the motor axon, synaptic cleft and postsynaptic muscle fibers. When a wave of depolarization reaches the terminal branch of an axon at NMJ, it causes calcium channels located in the membrane of the axon to open and an influx of calcium follows. This increase in intracellular calcium mobilizes the vesicles containing acetylcholine to move closer to the membrane and subsequently release acetylcholine into synaptic cleft. When the released acetylcholine binds to its receptor on muscle fibers, it causes a small and focal depolarization of the membrane called miniature endplate potential (MEPP). The summation of these MEPPs eventually exceeds the depolarization threshold of the muscle fiber, resulting in muscle contraction.

MG is an autoimmune disorder with autoantibodies against receptors at NMJ. Three major receptors have been identified that are affected by autoantibodies resulting in muscle weakness as the main clinical symptom of MG. In this section, we will review these three receptors, the autoantibodies and their role in NMJ and muscular weakness.

Acetylcholine receptor is a nicotinic receptor located on the postsynaptic muscle fiber membrane of skeletal muscles. This receptor is made of five homologous subunits that are arranged in a circular fashion around a central pore [69]. The α1 subunit which is called the main immunogenic region (MIR) is the main target for AchR autoantibodies [70]. They are detected in 85–90% of generalized MG and 40–70% of ocular MG patients [71]. AchR antibodies are of IgG1 and IgG3 subclass of antibodies [72] that disrupt the process of neuromuscular transport/contraction by three primary mechanisms: (1) attach to MIR and directly inhibit AchR; (2) activate complement, causing lysis of the postsynaptic membrane, changing synaptic configuration and subsequently destruction of the acetylcholine receptors located in this area [73, 74]; and (3) induction of AchR endocytosis and lysosomal destruction by autoantibody-mediated cross-linking of AchR, which decreases the number of available functioning Ach receptors at the surface of muscle fibers [75, 76].

Muscle-specific tyrosine kinase receptor (MuSK) was first identified in 2001 [77]. This receptor has an important role in clustering of postsynaptic AchR in NMJ through agrin, which results in spatial arrangement of AchR required for proper function of NMJ [78]. Autoantibodies against MuSK are of the IgG4 subclass and

directly inhibit MuSK receptors at NMJ with no activation of complement as part of autoimmune process which explains no loss of AchR or complement deposition as seen in AchR antibody-positive patients [79]. Of note, MuSK-MG has a marked female predominance and 40% of patients with generalized, acetylcholine receptor antibody (AChR-Ab)-negative MG had MuSK-MG [62]. Lipoprotein-related protein 4 (LRP4), identified in 2011, is a membrane protein, which is also responsible for clustering of AchR though agrin-LRP4 interaction. LRP4 autoantibodies are positive in 9% of patients who are negative for both AchR and MuSK antibodies [80].

#### 5.5.2.4 Clinical Presentation

The hallmark of MG is muscle weakness that varies throughout the day and that worsens with exercise and improves with rest. The majority of patients (about 80%) have generalized MG, but in 20% of cases, the muscle weakness can be limited to ocular muscles such as the levator palpebrae, and this subtype is known as ocular MG [81]. This muscle weakness is asymmetric and results in double vision and ptosis, which can be transient or fluctuate throughout the day. Nearly 50–80% of patients who primarily present with symptoms limited to ocular muscles develop systemic MG within 2 years of initial presentation (secondary generalized MG); therefore, it is reasonable to postpone the diagnosis of ocular MG for 2 years after initial presentation given the high rate of developing SGMG [82–84].

Pattern of muscular weakness in patients who are found to be positive for MuSK antibody is usually different from what is seen in patients who are AchR positive. In comparison with AchR-positive MG patients, there is a female predominance in MuSK-positive myasthenia patients with a younger age of onset, mostly less than 60 years of age [85]. These patients most often present with bulbar weakness associated with tongue and facial atrophy, neck and shoulder weakness, and respiratory failure secondary to respiratory muscle weakness without ocular involvement. However, they can also present with similar symptoms indiscernible to AchR-positive patients [72]. Myasthenic crisis is defined as respiratory failure secondary to muscular weakness. Around 20% of patients with myasthenia will experience one episode of crisis throughout their disease course, and it may be their initial presenting symptom that leads to the diagnosis of MG [86, 87].

#### 5.5.2.5 Diagnosis

Diagnosis of MG is made based on a combination of history, typical physical examination findings, serologic testing and electrophysiologic studies. Bedside testing such as the edrophonium ("Tensilon") test have high sensitivity but have fallen out of favor due to low specificity and high interpreter variability.

Nerve Conduction Studies (NCS) and Electromyography (EMG)

Sensory and NCS studies in MG patient are generally normal but may show low CMAP amplitudes in muscles that demonstrate severe weakness. Slow repetitive nerve stimulation (RNS) with 2–3 Hz is a specialized test that has over 80% sensitivity in generalized MG [88]. RNS evaluates the safety factor which is the number of acetylcholine receptors on the post synaptic junction that is required to form an adequate endplate potential causing membrane depolarization and muscle contraction. In MG, there are not enough acetylcholine receptors available, and the safety factor is decreased. A decrement of more than 10% in CMAP amplitude is seen after slow repetitive stimulation and is more pronounced between the first and second stimuli. RNS usually is done on distal muscles first, but if the results are negative, proximal muscles like trapezius or nasalis muscles and in cases of ocular myasthenia, the orbicularis oculi muscle should be tested. It is important to remember that RNS should not be performed near a pacemaker or indwelling central venous catheter, and all anticholinergic medications should to be discontinued for 12 h prior to edrophonium testing [8].

On EMG of MG patients, the most significant finding is moment-to-moment variation in the amplitude of MUAP, which requires studying one single MUAP over a period of time. The changes in the MUAP amplitude have the same meaning as the decrements in RNS [8]. Single fiber EMG is the gold standard for

diagnosis of NMJ disorders which shows increased jitter in MUAPs. However, since it is a technically difficult procedure, it is reserved for when there is high suspicion for the disease and RNS is negative [8].

#### 5.5.2.6 Trial of Cholinesterase Inhibitor

The administration of edrophonium, a cholinesterase inhibitor is described here for historical reasons but the drug is no longer available in the United States and many other countries. Edrophonium is a short-acting (5–10 min) cholinesterase inhibitor with fast onset (30–45 seconds). A positive test for MG is characterized by by rapid improvement of symptoms upon administration. This test should only be used in patients with ocular myasthenia or patient with general myasthenia who have a pronounced ptosis or ophthalmoparesis in whom the improvement of symptoms can easily be evaluated. It has a sensitivity of 80–90% but is not specific to MG.

The test begins with the administration of 2 mg of edrophonium intravenously followed by 2 mg every 60 s, up to total of 10 mg. This slow incremental dosing will ensure that patients get enough medication to improve their symptoms while avoiding cholinergic side effects as much as possible. However, patients can still develop cholinergic side effects including bradycardia, bronchospasm, gastrointestinal cramping, and increased salivation. Atropine should be available for immediate intravenous administration if side effects occur. This test should be avoided in elderly patient and those with cardiac abnormalities such as bradycardia or conduction blocks or bronchospasm [89].

#### 5.5.2.7 Ice Pack Test

The ice pack test is performed in patients whom edrophonium testing is contraindicated. It has 80% sensitivity and can be done at bedside or in the office. It is only useful in patients with ptosis and cannot be used in patients with ophthalmoparesis since those muscles are located deeper and cannot be sufficiently cooled by ice packs. The test is performed by placing the ice pack on the eye with ptosis for 2 min followed by immediate evaluation of the degree of improvement in ptosis [90, 91].

#### 5.5.2.8 Management

Significant decrease in MG mortality in recent decades is likely attributable to advancements in both ICU care as well as in immunomodulatory therapies such as intravenous immunoglobulin (IVIG) and plasma exchange (PLEX). MG treatment options can be divided in three categories: symptomatic therapy, chronic immunosuppressive therapy, and rapid immunomodulating therapy.

The first category of treatment options is symptomatic therapy. The most commonly used medication used for symptomatic relief is pyridostigmine, which is an acetylcholinesterase inhibitor. Cholinergic side effects of this medication are the main reason for noncompliance in patients. Diarrhea can be a major issue in elderly patients who have underlying problems with sphincter control. Loperamide can help alleviate diarrhea without affecting NMJ [92]. Patients with MuSK autoantibody do not respond as well to usual doses of pyridostigmine and require higher doses, which increases the systemic side effects of the medication [93]. However the side effects of the medication are seen at doses higher than 300 mg/day. If pyridostigmine bromide cannot be tolerated secondary to GI side effects, ambenonium chloride can be used as a replacement [94].

The second category of treatment options is chronic immunosuppressive therapy. There are multiple medications in this category, but the two mostly used agents as first-line therapy are corticosteroids and azathioprine, a steroid-sparing immunosuppressant. Second-line agents are reserved for patients with poor response to initial therapy. These include, cyclosporine A, methotrexate, mycophenolate mofetil, and tacrolimus.

Corticosteroids can improve symptoms in 70–80% of patients within 4–8 weeks, and there are different regimen to choose from, including intravenous methylprednisolone (MP) and oral prednisone:

- Intravenous MP: Dosing can vary between 500 mg and 2 g daily for 3–5 days followed by an oral prednisone taper [95, 96]. Administration of such high-dose steroids can lead to a transient worsening of myasthenia symptoms and in some cases a myasthenia crisis.

For this reason, this treatment is reserved for patients with myasthenia crisis and in combination with other acute phase treatments, like IVIG and plasmapheresis. It is important to remember that steroids can cause peptic ulcers and osteoporosis among other side effects like HTN and psychosis, which makes it crucial for all these patients to be treated with calcium (1000–1500 mg/day) and vitamin D (400–800 IE/day) as well as proton-pump inhibitors (PPI) or H2 blockers for prevention of osteoporosis and peptic ulcers, respectively [94].

- Oral prednisone: 10–20 mg as initial dose, with weekly increase by 5 mg/day until patient's symptoms improve or stabilize [97]. The disadvantage of this regimen is the slow speed of recovery compare to higher doses of steroids; however, it prevents transient worsening of muscle weakness and clinical symptoms upon initiation of therapy [94].
- Oral prednisone: Initial dose of 1–1.5 mg/day/kg bodyweight in conjunction with a steroid-sparing immunosuppressant. Dose can later be decreased by 5 mg/day every 4 weeks when clinical symptoms improve with goal to completely discontinue steroids. This regimen can result in rapid recovery and resolution of symptoms; however, about 10% of patients will experience transient decline and worsening of muscle weakness with initiation of therapy [98, 99].

Steroid-sparing immunosuppressants include:

- Azathioprine (AZA): is the first-line agent in this group for treatment of MG [100]. AZA derivative, 6-mercaptopurine, acts by prohibiting activation and proliferation of B cells and T cells in the body leading to its immunosuppressant effect. The starting dose is 2–3 mg/day/kg, which can later be decreased to as low as 1 mg/day/kg bodyweight if the patient's clinical symptoms have been stabilized or remission has been achieved. Treatment effects of AZA will be seen months after initiation of therapy [101]. AZA in combination with steroids can lead to lower doses of steroids required, more effective treatments, and less side effects [102] although in 10–20% of patients who are resistant to therapy, higher doses of steroids may be required despite use of AZA. AZA treatment should not be abruptly discontinued since it can cause recurrence of MG symptoms and at times MG crisis [103, 104]. Side effects seen in patients treated with AZA are increased MCV, reversible lymphopenia, nausea, vomiting, and diarrhea [105]. At times, AZA dose can be decreased by 25% with addition allopurinol that prevents AZA metabolization and hence decreases the myelotoxic side effects of AZA [94].
- Ciclosporin a (CSA): has been proven to be effective in treatment of MG in one placebo-controlled trial [106]. The initial dose is 3–4 mg/day/kg in two single doses and in conjunction with steroids. This dose can later be reduced to 2–2.5 mg/day/kg as the patient's disease stabilizes. Ciclosporin compared to AZA has a more rapid clinical affect, usually within 4–6 weeks, but it also has worst side effect profile with myelosuppression, opportunistic infections, and nephrotoxicity leading to hyperkalemia. It can decrease seizure threshold and cause reversible posterior leukoencephalopathy syndrome [94].
- Methotrexate (MTX): causes its immunosuppressant effects by lowering the proliferation of lymphocytes through preventing the production of DNA, RNA, and proteins. Based on a recent clinical trial published in 2011 done by Heckmann J et al., MTX had equivalent effect in steroid-sparing properties when compared to AZA in a span of 2 years [107]. Hence MTX at doses 7.5–25 mg/week can be used as a second-line agent for MG treatment. Patient should also be prescribed folic acid supplements in conjunction with MTX [108]. Hepatotoxicity, anemia, leukopenia, nausea, vomiting, abdominal pain, renal failure, and acute pneumonitis are some of the side effects of MTX.
- Mycophenolate mofetil (MMF): has been shown to improve clinical symptoms of MG when used in doses of 1500–2000 mg/day [109–111]. Although there were two studies that did not show any superiority to prednisone [112] and no steroid-sparing benefit in 9 months

[113], it was thought that a 9-month follow-up period was not long enough to evaluate the efficacy of MMF since the clinical effects of the medication take a long time to be seen.

- Tacrolimus (TCM): like ciclosporin A, works by inhibiting calcineurin and lymphocyte activation. However, it is 10–100 times stronger than CSA and causes the same side effects. It has been shown that TCM in doses of 3–5 mg/day can be beneficial for treatment of patients with MG [114–117]. In one cohort study of 79 patients with MG, the effects of TCM was compared to the combination of CSA and prednisone which showed symptom stabilization and decreasing levels of AchR antibodies [118, 119]. Drug's blood level should be monitored for nephrotoxicity and neurotoxicity side effects.
- Rituximab: is an antiCD20 monoclonal antibody, which causes immunosuppression by decreasing the number B lymphocytes in circulation. A recent metanalysis, published in 2015, looking at 15 studies and 168 patients, showed a response rate of 83.9% to rituximab. The patients in these studies were either positive for AchR antibodies or MuSK antibodies or were negative for both of these antibodies. The rituximab dose used in these 15 studies was also different. This metanalysis showed that patients with positive MuSK antibodies had a better response to rituximab treatment compared to the rest of the patients [120]. This was thought to be secondary to the fact that IgG4 antibodies in MuSK-positive patient were made by CD20+ plasma cells in blood that are more affected by rituximab [121, 122].
- Cyclophosphamide (CPP): can be used in cases of severe MG that has not responded to standard treatments or those who require frequent plasmapheresis or immunoadsorption [123]. It can be administered as pulse therapy with 500 mg/m$^2$ body surface area every 4 weeks [124] or immunoablative therapy with 50 mg/day/kg for 4 consecutive days [123, 125]. The latter dose should be followed by GCSF or stem cell transplantation [125, 126].

The third category of treatment options, rapid immunotherapy such as intravenous immunoglobulin (IVIG) and plasmapheresis/plasma exchange (PLEX), is the main category of therapies to treat myasthenic crises. They are rapid in onset but short-acting, only lasting up to a few weeks. They are also used as bridge therapies to slower-acting immunosuppressive therapies, preoperative optimization prior to thymectomies, treatment in patients who have contraindications for other immunosuppressant therapies or refractory MG patients who have failed standard immunosuppressive therapies. IVIG is pooled immunoglobulin from donors. Mechanism for IVIG in MG is unclear. IVIG can be administered as 0.4 g/day/kg in 5 days or 1 g/day/kg in 2 days [127, 128]. IVIG has been shown to be as effective as plasmapheresis in resolution of MG crisis and to decrease the time required for mechanical ventilation [129]. Side effects of IVIG include headache, hypertension, pulmonary edema, heart failure exacerbation secondary to volume overload, thrombotic and thromboembolic events like venous thrombosis, strokes and myocardial infarctions, infections, aseptic meningitis, and anaphylactic reaction especially in patients with IgA deficiency [130].

Therapeutic PLEX directly removes AChR antibodies from circulating blood and clinical improvement with plasmapheresis roughly correlates with the reduction in antibody levels. It is usually 5-8 treatments that are administered every other day [131]. With each treatment human albumin is used as a substitute, and in patients who have IgG levels of less than 150 mg/dl, polyvalent IgG is administered. It is important to remember that with plasmapheresis, coagulation factors are also depleted; therefore careful attention to signs of bleeding or use of concomitant anticoagulation drugs is prudent [132]. Studies have shown similar efficacy between plasma exchange and IVIG [133–136]. All newly diagnosed MG patients must undergo CT chest or MRI for thymoma screening.

Ten to fifteen percent of AchR antibody-positive patients are found to have a thymoma on CT chest [137, 138]. In this group of patients, thymectomy is indicated mainly to treat the tumor

and prevent local invasion but also to help with myasthenia symptoms. Of patients with positive AchR antibody and no thymoma on the CT or MRI, 60–70% have hyperplasia [137, 138]. A MG treatment trial published in 2016 randomized 126 patients with generalized MG, positive AchR antibody and disease duration of less than 5 years to thymectomy, and alternate-day prednisone alone over 3 years. Patients who underwent a thymectomy had lower quantitative MG score, lower requirements for alternate-day prednisone, lower requirements for immunosuppression, lower rates of MG exacerbation and hospitalization, and higher improvement in clinical status, indicative of beneficial clinical outcome in non-thymomatous patients who underwent thymectomy [139].

The Association of British Neurologists guidelines for the management of MG recommends thymectomy for patients less than 45 years of age and positive AchR antibodies as long as the disease is well controlled prior to operation and surgery is being done by an experienced surgeon in a facility that works closely with neurologists experienced in MG. This procedure can result in remission, prevention of generalization of ocular myasthenia, and decrease corticosteroid dose required to control the disease [140]. Thymic pathologies are rare in patients with MuSK-positive antibodies [141–144], and only a few of the patients improve clinically after thymectomies [85, 145].

### 5.5.3 Guillain-Barré Syndrome (GBS)

#### 5.5.3.1 Background

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy that is caused by antibodies against antigens situated on neurons which leads to destruction of myelin, axons, or both.

#### 5.5.3.2 Epidemiology

In Europe and North America, GBS incidence is between 0.8 and 1.9 per 100,000 people per year, with a mild degree of male predominance [146]. Incidence increases with age up to 2.7 per 100,000 people per year in patients older than age 80 [147]. GBS is responsible for over 6000 hospital admission per year in the United States (US) [148]. Increased geographic incidence rates that have been published are likely related to increased rates of preceding infections in those areas [149]. Miller Fisher, a variant of GBS, made up 5% of the cases in Western Europe with higher rates seen in Japan and Taiwan [150].

#### 5.5.3.3 Pathogenesis

There is a proven relationship between GBS and infections by *Campylobacter jejuni*, *Cytomegalovirus*, *Epstein-Barr virus*, *Influenza A*, hepatitis A/B/E, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and most recently Zika virus [151–154]. Pathogenesis is thought to be due to molecular mimicry, i.e., an immune response to a preceding infection that cross reacts with peripheral nerve components, causing the immune system to attack peripheral nerves and their spinal roots [155–157]. The nature of the microbial agent that causes the preceding infection has a role in clinical phenotype and patient's outcome [158, 159].

GBS is a heterogenous disorder with many variant forms, and each form has distinct clinical presentations, pathophysiology, electrophysiologic findings, and pathology. The three main variants are a purely demyelinating form, known as acute inflammatory demyelinating polyneuropathy (AIDP) accounting for over 90% of the cases of GBS in the United States and Europe [160]; a purely axonal form, known as acute motor axonal neuropathy (AMAN); and acute motor and sensory axonal neuropathy (AMSAN).

In AMAN, ganglioside antigens located on the axonal membrane (axolemma) are attacked by antibodies of IgG1 and IgG3 subclass, which are produced in response to an infection. The main two antigens in this category are GM1 and GD1a [161]. The binding of these antigens and antibodies activates complement with subsequent attraction of macrophages to the area, which leads to destruction of axolemma at nerve terminals and nodes of Ranvier causing conduction block in involved neurons [162]. GQ1b is another ganglioside antigen, mainly located in motor

neurons of extraocular muscles. Antibodies to this antigen can cause one of the variants of GBS known as Miller Fisher syndrome [163, 164]. *Campylobacter jejuni* is the most common infection preceding GBS, found in 25–50% of patients with AMAN [154, 165].

The mechanism for AIDP is less clear, because of larger number of presumed factors (bacterial and viral infections) that stimulate the immune system and yet to be identified antibodies that attack the neuronal antigens [155]. There have been small studies that indicated immune responses from B cell and T cell to compact myelin proteins (P0, P2, and PMP22) [166].

#### 5.5.3.4 Clinical Presentation

Hallmark of this disease is rapidly progressive, fairly symmetric, bilateral ascending weakness.

Patients often experience paresthesia in limbs distally with associated severe back pain and a tight band feeling around their torso. These symptoms usually appear 1–2 weeks after the presumed infection [167]. As the disease progresses, paresthesia spreads to all limbs, and 1–2 days later, patients develop proximal muscle weakness usually in the legs, described as difficulty standing up from a sitting position or climbing up stairs. Weakness continues to progress and involve upper extremities and, in 50% of cases, involve facial and bulbar muscles which can lead to respiratory failure [168]. Patients can develop profound dysautonomias that can be a cause of mortality during their hospital course. They include labile blood pressures with or without triggers, cardiac arrhythmias with severe bradycardias, Takotsubo cardiomyopathy, adynamic ileus and bladder dysfunction [169–172]. Symptoms reach their peak in 2–4 weak from the initial presentation [167]. Dysautonomia usually resolves prior to improvement in muscle weakness.

Patients with the Miller Fisher variant present with primary involvement of oculomotor muscles, causing ophthalmoplegia, facial and bulbar weakness. They also have associated ataxia, and as in patients with GBS, these patients have decrease or loss of DTR [173]. Secondary to muscular weakness, patients can develop acute respiratory failure. Approximately 20–30% of GBS patients end up requiring mechanical ventilation [167].

#### 5.5.3.5 Diagnosis

There are only few other diseases that can be considered in differential diagnosis of GBS with its hallmark ascending paralysis. Transvers myelitis, botulism, MG, severe hypokalemia, and heavy metal intoxication should be considered when patients present with acute muscle weakness. If during physical exam, findings not typically associated with GBS are present (i.e. hyperreflexia or pyramidal signs), a spinal cord MRI should be considered to rule out an alternative cause of symptoms.

CSF analysis often shows an elevated protein with a normal white blood cell count, a finding known as albuminocytologic dissociation. It's important to remember that patients may have a normal protein level and white count if the study is done when muscle weakness is mild. If CSF profile shows elevated levels of white blood cell, infectious or inflammatory diseases like HIV, Lyme, and sarcoidosis should be considered [168].

#### 5.5.3.6 NCS/EMG

NCS in GBS can support the diagnosis and help differentiate between axonal and demyelinating variants of GBS. Early in the course, NCS can be normal. The most prominent abnormalities are seen typically about 2 weeks into the course of the disease [160]. In early stages of AIDP, the most common findings are F wave abnormalities, decrease in CMAP, and conduction block, which is the most sensitive parameter [174]. In demyelinating form of GBS, findings are increased F wave latency, prolonged distal motor latency, conduction block, and temporal dispersion, while sensory nerve potentials are normal [175]. In axonal forms, NCS shows decreased motor or sensory amplitudes based on the nerves involved. If it is a mixed motor and sensory form, a decrease in both amplitudes will be seen. At times, there may be a transient conduction block, secondary to involvement of nodes of Ranvier in these neurons [176]. This transient conduction block can cause confusion in differentiating between demyelinating form and

axonal form; however since it is reversible in the axonal variant, repeating NCS later in the course of the disease can help differentiate the two [177].

EMG shows decreased recruitment, presence of fibrillation, positive sharp waves, and polyphasic motor unit action potentials (MUAPs) at different times during the course of the disease. Fibrillations are more prominent between weeks 6 and 10 and MUAPs between week 9 and 15 after the onset of symptoms [178].

#### 5.5.3.7 Treatment

All patients who are diagnosed with GBS should be closely monitored as deterioration from muscle weakness can occur rapidly. If signs of respiratory failure, rapidly progressive weakness, or severe autonomic dysfunction are present, an admission to ICU is warranted for cardiopulmonary and hemodynamic monitoring and support. Immunotherapy with IVIG or PLEX should be initiated as soon as the diagnosis is suspected, and the performance of diagnostic tests should not delay treatment [179].

Two effective disease-modifying treatments that exist for GBS are PLEX and IVIG, and treatment should be initiated with one of these modalities as soon as possible as they hasten recovery. PLEX works by removing antibodies from systemic circulation. It is performed every other day for five courses, and as discussed in the MG section, plasma is substituted with albumin 5% after each treatment [180]. It has been shown to increase muscle strength and reduce the need for mechanical ventilation [181, 182]. IVIG is pooled IgG that is administered at 0.4 g/kg per day infusion for 5 days. It is as effective as PLEX in treatment of GBS [179], and there is some evidence that it may have fewer complications compared to PLEX [183, 184].

IVIG and PLEX have been shown to be equally effective in treatment of GBS, and the decision on using one or the other is dependent on patient's comorbidities, contraindications, and availability of the treatment [185]. Administration of IVIG and PLEX together has not been shown to be beneficial in treatment of GBS [184]. Corticosteroids have limited to no effect on GBS patients in both acute phase of disease and for long-term outcomes [186].

#### 5.5.3.8 Preventative Measures

Patients with GBS have limited mobility secondary to neuromuscular weakness and spend most of their time immobilized in their bed or chair, which increases their risk of deep venous thromboses (DVT). Therefore, it is crucial for these patients to be placed on intermittent pneumatic compression devices and thromboprophylaxis such as subcutaneous heparin if they do not have contraindications. Pulmonary embolism should be ruled out if patient develops an acute decline in their respiratory status [185]. In patients with corticobulbar weakness, swallowing evaluation should be performed prior to initiation a diet to avoid aspiration.

#### 5.5.3.9 Prognosis and Outcome

The outcome and prognosis of patients with GBS depends on their clinical phenotype. In the purely demyelinating type, remyelination is possible. However, in patients with the purely axonal type, axonal regeneration may not be possible if there is extensive damage to the axon, and even when there is any possibility of regeneration, it is very slow. For this reason, patients with AMAN have longer recovery periods.

Older age, rapid onset, severe muscle weakness on presentation, preceding diarrheal illness, and need for ventilatory support are predictive of poorer recovery from GBS [154, 187, 188]. A patient recovery scoring system, Erasmus GBS Outcome Scale (EGOS), is used to predict patient's ability to ambulate 6 months after GBS onset. The score is performed 2 weeks after admission [189]. EGOS looks at three patient characteristics: age >40 years old, history of diarrhea or *C. jejuni* infection in the past 4 weeks, and severe disability at the nadir of the disease.

Approximately 20% of patients with GBS will not be able to walk without assistance at 6 months, and most patients continue to experience fatigue and pain [190, 191]. Mortality rate has been estimated at 3–7% [165, 192] in North America and Europe. As deterioration can happen

quickly in both the early and later courses of disease, prolonged monitoring of patients until they have demonstrated stability is recommended [192, 193].

### 5.5.4 Respiratory Failure in Neuromuscular Disorders

Various neuromuscular diseases can produce severe weakness of respiratory muscles and result in ventilatory failure. This can be acute or be a sudden exacerbation of chronic progressive neuromuscular disease [194]. Patients with neuromuscular respiratory failure without a known diagnosis prior to admission have poorer outcomes, and those whose diagnosis remains unknown at discharge have the highest disability [195]. Therefore, even though these cases often represent a diagnostic challenge in the ICU, evaluation and timely diagnosis of their neuromuscular weakness is essential.

There are four groups of muscles that are primarily involved in ventilation and respiratory efforts:

1. Bulbar muscles: Responsible for maintaining the airway open and assisting with clearing secretions
2. Diaphragm: The main respiratory muscle responsible for 70% of respiratory function at rest; innervated by phrenic nerve from C3 to C5
3. Accessory inspiratory muscles: These consist of external intercostal, scalene, and sternocleidomastoid muscles, which take over more responsibility when there is increased work of breathing
4. Expiratory muscles: These consist of internal intercostal and abdominal wall muscles which help with forced expiration.

#### 5.5.4.1 History and Physical Exam

When a patient presents with acute neuromuscular respiratory failure, a detailed history and a careful neurologic exam are warranted to help establish the underlying cause of respiratory failure. Patients and their families should be asked about any recent infections, surgeries, changes in medications, new or developing symptoms (diplopia, difficulty swallowing, or changes in their voice), and a prior history of similar symptoms or prior hospital administration for respiratory failure requiring mechanical ventilations. The onset of symptoms, the pattern of muscular weakness, and the speed at which they progress are crucial in predicting the need for mechanical ventilation.

On physical exam, dyspnea, tachypnea, tachycardia, staccato speech (inability to finish a sentence in one breath), diaphoresis, use of accessory muscles, weak cough, and, most important of all, paradoxical breathing are signs of impending respiratory failure and should be closely monitored [196]. Patients with neck flexion weakness usually have associated diaphragmatic weakness. Vital capacity can be evaluated by asking the patient to count from 1 to 20 in one single breath. Facial muscles, gag and cough reflex, and tongue strength should be checked which helps evaluate patient's ability to maintain airway and manage secretions. In all patients with neuromuscular weakness, a general exam including vital signs and a heart, lung, and abdominal exam is necessary to evaluate for signs of dysautonomia, cardiopulmonary instability, abdominal distension and/or paradoxical breathing.

#### 5.5.4.2 Workup of Respiratory Failure

After a detailed history and physical exam, patients should be worked up for reversible underlying causes of respiratory failure. All patients with signs of impending respiratory failure should be admitted to an ICU for close monitoring with continuous pulse oximetry. Chest X-ray (CXR) is necessary to identify underlying pulmonary diseases like pneumonia or pulmonary edema which can trigger respiratory failure or worsen respiratory function. Arterial blood gas (ABG) can provide information regarding oxygenation and ventilation by measuring $PaO_2$ and $PaCO_2$, respectively. Worsening of respiratory failure and need for invasive ventilation should be monitored by bedside assessment of forced vital capacity (FVC), maximum inspiratory

pressure (MIP)/negative inspiratory force (NIF), and maximum expiratory pressure (MEP). FVC of less than 20 ml/kg or a 30% decline or more over 24 h and MIP of less than −30 cm $H_2O$ or MEP of less than 40 cm $H_2O$ are indicators of impending respiratory failure requiring intubation [197]. However, one must remember that these tests are effort dependent, can be falsely low if patient is fatigued, and requires that patient receive proper instructions prior to their performance. Moreover, in patients with facial muscle weakness, providing a good seal around the spirometer can be difficult and result in erroneous measurements. It is preferred that these measurements are taken in the same body position every time since FVC and MIP are higher when the patient is in upright position compared to supine position. A decrease of more than 20% in FVC from upright to supine position is indicative of diaphragm weakness.

#### 5.5.4.3 Respiratory Support and Ventilation

The pattern of respiratory failure seen in NMDs is restrictive. Primarily patients develop microatelectasis at the base of the lungs due to muscular weakness resulting in tachypnea and subsequently respiratory alkalosis. As patients become more fatigued, they develop alveolar hypoventilation, which is evident by continued and worsening tachypnea, normal $PCO_2$, and slightly low levels of $PaO_2$ on ABG. In later stage of respiratory failure with worsening muscular weakness and increasing fatigue, alveoli start to collapse resulting in severe hypoxemia and hypercapnia [194]. These signs and symptoms should alert the physicians to an impending respiratory failure and consideration of mechanical ventilatory support.

Modes of ventilation support can be divided into noninvasive ventilation (NIV) such as CPAP and BiPAP or invasive ventilation, i.e., intubation. Noninvasive modes of ventilation can be beneficial in acute setting in ICU or ED or in late stages of progressive NMDs as seen in ALS. It is of utmost importance that patient's cardiopulmonary comorbidities, mental status, and secretion are evaluated prior to administration of NIV.

Noninvasive ventilation includes continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP). Both can be used in patients with NMDs. CPAP provides a continuous positive pressure, which helps maintaining the airway and alveoli open; however, CPAP is not as helpful in patients with respiratory muscle fatigue. BiPAP is a great option for patients with respiratory failure secondary to neuromuscular weakness, since it provides positive airway pressure during inspiration and expiration with oxygen flow that helps improve oxygenation and ventilation [198]. It is important to keep in mind that patients with neuromuscular weakness mostly breathe through their mouth so the mask used in noninvasive ventilation should cover both the nose and mouth [194]. One caveat to use of noninvasive mode of ventilation is in patients with bulbar weakness that may be having difficulty in managing their secretions—using positive airway pressure can increase their chances of aspiration.

In patients who present with a MG crisis, NIV can be used as the primary attempt to stabilize patients and has been shown to decrease the length of stay in ICU and rate of intubation in this group. NIV should be initiated as soon as there are signs of respiratory failure and before patient becomes hypercapnic which increases the chances of NIV failure [199, 200]. NIV can also be considered as a rescue therapy in post-extubation patients who are showing increased work of breathing and possible need for reintubation [201].

In MG patients who present with impending respiratory failure or require intubation, acetylcholinesterase inhibitors should be discontinued to rule out cholinergic crisis as a possible cause of weakness and respiratory failure. This also helps to decrease salivation in patients who have difficulty managing their secretions. These medications can be restarted after patients' symptoms improve or after extubation [185].

In patient who require intubation, as their symptoms improve, spontaneous breathing trials are recommended, and it is preferred to monitor them for 24 h on PSV prior to extubation to ensure they do not fatigue. Their cough strength

should be considered as it is indicative of their ability to maintain their airway open and manage their secretions. Age of over 50 years old, low peak FVC values in the first week, and elevated bicarbonate level at baseline are predictive factors of longer time on mechanical ventilation [86].

Patients with Guillain-Barré syndrome (GBS) who develop respiratory failure as a result of muscular weakness usually continue to worsen as the disease reaches its nadir followed by a prolonged recovery period. Therefore NIV is usually not helpful, and they will require emergent intubation [202]. It is important to remember that these patients develop dysautonomia as part of the disease pathology that can cause labile blood pressure, cardiac arrhythmias, bradycardia, and conduction blocks in response to medication administered during an emergent intubation. It is crucial to closely monitor signs and symptoms of respiratory failure, severe bulbar weakness or rapidly progressive muscular weakness, and consider elective intubation [202]. NIV in patients with GBS can be used in post-extubation period when patients have recovered from their acute phase and are showing enough improvement in muscle strength to be considered appropriate for extubation [201].

Other diseases that can benefit from NIV are progressive NMDs like ALS and muscular dystrophies, when an acute illness causes a sudden decompensation in their respiratory function. If it is determined that underlying disease progression is unlikely and, despite their neuromuscular weakness, they did not require interventions prior to their acute illness, they could benefit from NIV [203, 204].

## 5.6 Anesthetic Considerations in Patients with Neuromuscular Disorders

Anesthetic management of patients with NMDs poses a challenge to the provider given its relatively low incidence, variable pharmacologic response, and presence of multiple coexistent diseases. General anesthesia can exacerbate respiratory and cardiovascular symptoms due to a marked sensitivity to anesthetic drugs. Furthermore, succinylcholine and halogenated volatile agents can trigger life-threatening reactions, such as severe hyperkalemia, rhabdomyolysis, and malignant hyperthermia. In addition, during acute illness, surgery, or ICU admission, patients with neuromuscular diseases are exposed to high levels of physiologic stress response which can exacerbate symptomatology. Cardiac and pulmonary complications represent the major cause of perioperative complications, being respiratory insufficiency the leading cause of death among patients with NMDs [205].

### 5.6.1 Preoperative Assessment

A thorough history and physical examination is a key component of the preoperative evaluation of patients with NMDs. A detailed neurologic examination is essential to confirm the diagnosis and to determine presence of bulbar dysfunction and peripheral and autonomic neuropathy [206]. Patients and family must be made aware of potential risks and complications associated with anesthetic procedures during the intraoperative and postoperative periods.

#### 5.6.1.1 Preoperative Pulmonary Evaluation

Respiratory involvement varies significantly between patients with NMDs [207]. Inspiratory force reduction results in pulmonary disease with a restrictive pattern, with a progressive reduction of forced vital capacity [208]. Hypoventilation, atelectasis, hypoxia, and inability to clear airway secretions can be seen with more advanced inspiratory muscle disease. Inability to swallow can be seen with bulbar involvement, which is especially high in patients with ALS and MG [209, 210]. Detailed preoperative evaluation is recommended in patients with advanced disease to assess the risk of respiratory complications and the need for perioperative optimization [211–213]. In addition to medical history and physical examination, preoperative workup should include CXR, ABG, and pulmonary function tests (PFTs) when

feasible [211–213]. When PFTs are abnormal, NIV and manual or mechanically assisted cough techniques may be indicated. NIV is recommended in patients with Duchenne muscular dystrophy with FVC <50% [214].

In addition to the regular preoperative airway evaluation, careful assessment for macroglossia, mandible ankylosis, atrophy of masseter muscles, and limited cervical spine range of motion must be performed [215, 216]. Providers should follow the current guidelines for management of difficult airway when encountered with these findings.

#### 5.6.1.2 Cardiac Preoperative Evaluation

Cardiac evaluation is another key component of patients with NMDs, as they can manifest with myocardial failure, arrhythmias, and autonomic dysfunction leading to inability to modify cardiac output in response to surgical stress and currently used anesthetics. Patients with evidence of nocturnal hypoxia can present with right ventricular dysfunction resultant from pulmonary hypertension [215]. Moreover, relative immobility of patients with NMDs may predispose development of deep venous thrombosis and pulmonary embolism perioperatively. Workup should include electrocardiogram (ECG) and serial echocardiograms in all patients when possible to assess fractional shortening and left ventricular ejection fraction [217–219]. Characteristic ECG findings related to fibrous replacement of the myocardium include tall right precordial R and Q waves in leads I, aVL, $V_5$, and $V_6$ [220]. 24 h Holter testing should be considered when there is suspicion for arrhythmias [218, 219].

#### 5.6.1.3 Miscellaneous Preoperative Anesthetic Considerations

Patients with NMDs are at increased risk of intraoperative positioning injuries related to chronic contractures and skeletal deformities. These can be prevented with careful padding and positioning of extremities, head, and torso. When possible, nutritional status should be optimized before surgery to favor adequate wound healing [211, 212]. Premedication should be given carefully as there is an increased sensitivity to narcotics and benzodiazepines, leading to sleep apnea and hypoventilation [216]. Perioperative stress dose steroid administration should be considered in NMD patients that take steroids chronically.

In addition to the standard American Society of Anesthesiologists (ASA) monitors, an arterial line should be placed when there is suspicion or evidence of cardiac compromise. Careful temperature monitoring is crucial as NMDs patients are predispose to hypothermia [206] and/or hyperthermia which can trigger disease flares. Intravenous access can be challenging, and ultrasound-guided techniques should be used when possible to limit unnecessary discomfort [221].

### 5.6.2 Intraoperative Management

The anesthetic concerns for specific NMDs are summarized in Table 5.3. In general, the severity of the disease tends to correlate with the incidence of intraoperative complications. In patients with compromised respiratory function, regional anesthesia should be favored over general anesthesia (GA). If regional anesthesia is not an option, GA must be administered avoiding depolarizing neuromuscular blockers and halogenated agents. The cytoskeleton of the muscle membrane is abnormal in patients with NMDs, and life-threatening amounts of intracellular potassium can be released after exposure to succinylcholine and volatile agents. Total intravenous anesthesia based on short-acting opioids, propofol, and dexmedetomidine should be a first-line option, considering their cardiac depressant effects.

In most patients with NMDs, nondepolarizing neuromuscular blockers may show prolonged duration of blockade. Therefore, there is a strong recommendation to avoid its use intraoperatively whenever possible [222, 223]. If the use of neuromuscular blockers is needed, smaller doses should be titrated to effect using train-of-four monitoring [216, 224]. Rapid sequence induction can be performed safely with high-dose

**Table 5.3** Anesthetic considerations in patients with neuromuscular disease

| Disease | Pathophysiology | Volatile agents | DNMBs (succinylcholine) | NDNMBs | Regional anesthesia | TIVA | Opioids | Other anesthetic considerations |
|---|---|---|---|---|---|---|---|---|
| *Neuromuscular junction disease* | | | | | | | | |
| Myasthenia gravis | Antibodies against postsynaptic membrane of the NMJ | Safe | Increase dose due to resistance | Avoid or lower dose due to increased sensitivity | Allowed | Allowed | ↓ | Use of rocuronium with sugammadex is recommended<br>Epidural analgesia can be used during pregnancy<br>Poor response to anticholinesterases |
| Eaton-Lambert syndrome | Antibodies directed against presynaptic voltage-gated calcium channels | Safe | Lower dose due to increased sensitivity | Avoid or lower dose due to increased sensitivity | Allowed | Allowed | ↓ | Autonomic dysfunction<br>Paraneoplastic syndromes<br>3,4-Diaminopyridine should be continued until the day of surgery |
| *Peripheral neuropathy* | | | | | | | | |
| Guillain-Barré syndrome | Antibodies to gangliosides in peripheral nerves | Safe | Avoid | Avoid or lower dose | Allowed | Allowed | ↓ | Severe dysautonomia can be present<br>Mechanical ventilation may be needed post-op |
| Familial dysautonomia (Riley-Day syndrome) | Deficiency of dopamine-β-hydroxylase | Safe | Avoid | Avoid or lower dose | Allowed | Allowed | ↓ | Excessive oral secretions, pneumonia, poor response to hypercarbia/hypoxia, decreased gag reflex |
| Porphyrias | Disorder of heme synthesis | Probably safe | Safe | Probably safe | Allowed | Allowed | Safe | Acute crisis affect CNS and PNS via direct neuronal damage, demyelination<br>Avoid barbiturates and etomidate |
| Charcot-Marie-Tooth disease | Peripheral neuromuscular denervation | Safe | Avoid | Avoid or lower dose due to increased sensitivity | Allowed | Allowed | ↓ | Vocal cord paresis and cardiac conduction abnormalities can be present |

| Disease | Pathophysiology | Volatile agents | DNMBs (succinylcholine) | NDNMBs | Regional anesthesia | TIVA | Opioids | Other anesthetic considerations |
|---|---|---|---|---|---|---|---|---|
| *Myopathy* | | | | | | | | |
| Duchenne muscular dystrophy | X-linked recessive disorder absence of dystrophin | Avoid | Avoid | Avoid or lower dose due to increased sensitivity | Allowed | Allowed | ↓ | Cardiac dysfunction (MVP)<br>Smooth muscle and platelets dysfunction<br>Kyphoscoliosis<br>Marked CK elevation<br>Post-op respiratory failure |
| Becker muscular dystrophy and other progressive muscular dystrophies | Dystrophin deficiency | Avoid | Avoid | Avoid or lower dose due to increased sensitivity | Allowed | Allowed | ↓ | Avoid AChE<br>Sugammadex should be considered |
| *Myelopathy* | | | | | | | | |
| Amyotrophic lateral sclerosis | Degenerative disease involving the corticospinal tract and anterior horn cells. Etiology unclear | Safe | Avoid | Avoid or lower dose due to increased sensitivity | Allowed | Allowed | ↓ | Succinylcholine-induced hyperkalemia<br>Autonomic dysfunction<br>Neuraxial anesthesia has been safely used |
| Multiple sclerosis | Autoimmune response to myelin | Safe | Avoid | Decreased sensitivity | Allowed | Epidural anesthesia has been used safely<br>Spinal anesthesia may exacerbate disease | ↓ | Avoid stress and hyperthermia |

**Table 5.3** (continued)

| Disease | Pathophysiology | Volatile agents | DNMBs (succinylcholine) | NDNMBs | Regional anesthesia | TIVA | Opioids | Other anesthetic considerations |
|---|---|---|---|---|---|---|---|---|
| *Periodic paralysis: skeletal muscle ion channelopathies* | | | | | | | | |
| Hypokalemic | Calcium channel defect | Safe | Avoid | Avoid or lower dose due to increased sensitivity | Allowed | Probably safe | Safe | Precipitating factors<br>• Hypothermia<br>• Carbohydrate load<br>• Strenuous exercise<br>• Stress<br>monitor for dysrhythmias<br>maintain normal potassium |
| Hyperkalemic | Sodium channel defect | Safe | Avoid | Avoid or lower dose due to increased sensitivity | Allowed | Probably safe | Safe | Precipitating factors<br>• Rest after exercise<br>• Potassium infusions<br>• Metabolic acidosis<br>• Hypothermia<br>avoid carbohydrate depletion |
| *Skeletal muscle disease* | | | | | | | | |
| Central core disease | Anomaly ryanodine receptor | Avoid | Avoid | Increased sensitivity | Allowed | Probably safe | ↓ | Kyphoscoliosis |
| Mitochondrial myopathies | Affection of oxidative phosphorylation | Low MAC probably safe | Avoid | Avoid or lower dose due to increased sensitivity | Allowed | Ketamine is recommended | ↓ | Total AV block can occur<br>Strict glucose control<br>Avoid stress<br>Respiratory failure can occur |

*DNMBs* depolarizing neuromuscular blockers, *NDMBBs* nondepolarizing neuromuscular blockers, *TIVA* total intravenous anesthesia

rocuronium, which can be quickly reversed with the now FDA-approved sugammadex [225, 226].

The use of regional anesthesia offers a significant advantage in patients at risk for postoperative respiratory complications [214, 217]. On the other hand, it has some potential risks especially in patients with pre-existing peripheral neuropathy who are at increased risk of suffering from permanent neurologic damage from inadvertent nerve puncture, local anesthetic, and vasopressors use. However, evidence suggests that the use of ultrasound-guided nerve blocks significantly reduced amount of local anesthetic and major vascular complications [227].

### 5.6.3 Postoperative ICU Management

Hypoventilation is a major postoperative risk in patients with NMDs. Therefore, careful titration of analgesia is crucial in preventing depressed respiratory function [213, 228]. Narcotics should be administered in conjunction with preemptive analgesia (acetaminophen, NSAIDs, gabapentin, clonidine, etc.) to reduce opioid requirements [229, 230]. Also, peripheral nerve blocks and wound infiltration with local anesthetics should be used when possible to achieve adequate analgesia without the need of excessive opioid administration.

Postoperative extubation success should be individualized based on preoperative pulmonary function [213]. Extubation to NIV should be considered for patients with a baseline FVC less than 50% of predicted. Postoperative use of assisted cough techniques such as mechanical insufflators/exsufflator must be considered for any patient with preoperative maximum expiratory force (MEP) <60 cm $H_2O$ [228]. If excessive oral secretions are a concern, extubation should be delayed in order to decrease the risk of aspiration and reintubation [231].

In conclusion, NMDs represent a heterogeneous spectrum of challenges for the anesthesiologist and intensivist. A thorough preoperative evaluation and a detailed knowledge of individual diseases are vital for safe anesthetic management.

## 5.7 Conclusion

Most patients with neuromuscular disorders are diagnosed and treated in the outpatient clinic; however a small but significant subset of these patients can present with a rapidly advancing muscle weakness which can be a life-threatening emergency. The most significant compromise occurs in respiratory function needing mechanical ventilation although monitoring of cardiac function, hemodynamics, and bulbar function is also sometimes warranted. A thorough history and physical examination along with prudent intensive care management has the potential to mitigate morbidity and mortality. With the increased availability of therapies such as immunoglobulins, plasma exchange, steroid-sparing agents, immunomodulatory therapy, as well as specialized care in neurointensive care units, physicians today have a range of therapies to offer.

**Key Points**

- Neuromuscular conditions are diseases of the nervous system that affect the motor neuron unit between the anterior horn cells and the muscle.
- Anesthetic management of patients with NMDs poses a challenge to the provider given its relatively low incidence, variable pharmacologic response, and presence of multiple coexistent diseases.
- General anesthesia can exacerbate respiratory and cardiovascular symptoms due to a marked sensitivity to anesthetic drugs.
- Hypoventilation is a major postoperative risk in patients with NMDs.
- With the increased availability of therapies such as immunoglobulins, plasma exchange, steroid-sparing agents, immunomodulatory therapy, as well as specialized care in neurocritical care units, physicians today have a range of therapies to offer.

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# 6 Neuromuscular Weakness in the ICU

Marc-Alain Babi

## 6.1 Introduction

Critical illness muscular and nerve weakness is a common occurrence among patients who are critically ill or are admitted to intensive care units. Weakness is frequently observed in patients with multiple organ failure and severe systemic disease and may also be associated with treatments administered in the intensive care unit. Neuromuscular weakness in the ICU is most often due to critical illness myopathy, critical illness polyneuropathy, or a combination of both. Some authors apply the term "intensive care unit-acquired weakness" for patients who are admitted to intensive care units with systemic disease and subsequently develop clinically detected weakness but no other clear explanation of their weakness other than their primary critical care illness [1]. This chapter reviews the neuromuscular weaknesses commonly encountered in the intensive care unit.

## 6.2 Critical Care Illness Myopathy

Critical illness myopathy is the most common form of intensive care unit-acquired neuromuscular disorder [2–4]. It is observed in 10–25% of patients who are on vasopressor therapies or prolonged mechanical ventilations beyond 1-week duration [3, 4].

### 6.2.1 Histology

The major histopathological finding in critical illness myopathy is that of selective myosin loss in muscular fibers, as well as lack of reactivity to myosin ATPase in non-necrotic fibers [5, 6]. In addition, there is selective atrophy of type 2 fibers over type 1 fibers. Additionally, there is myofibrillar disorganization and abnormal basophilic stippling on hematoxylin and eosin staining, and some necrosis may also be observed [5–7].

### 6.2.2 Pathogenesis

Several processes have been identified to be involved in the development of critical illness myopathy. For example, there is evidence of upregulation of calpain, resulting in muscle fiber apoptosis [7]. In addition, activation of the ubiquitin-degradation system accelerates this process. There is also upregulation of serum amyloid A1 protein and activation of the growth-factor beta/mitogen-activated protein kinase [5–8]. The end result is muscular fiber apoptosis and myosin fiber loss. Oxidative stress is also thought to play an important role in the pathogenesis of critical illness myopathy [6–8]. This is demonstrated by

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the finding of reduced nitric oxide synthase isoform NOS1 in patients affected by critical illness myopathy [6–9]. NOS1 loss is thought to eventually lead to muscular fiber lack of excitability through reduction of nitric oxide release at the muscular membrane level [10]. In addition, a link of steroid-muscular interaction has been suggested [9]. Histopathological models have shown a link between glucocorticosteroid exposure and denervation, leading to mRNA depletion in myosin fibers and in turn muscular atrophy [10, 11]. Sepsis is also a well-established cause of critical illness myopathy. It is thought that sepsis alters muscle sodium channel properties, leading to reduced sodium channel and in turn leading to muscle inexcitability [11]. This similar model is established with the use of neuromuscular junction blockade medication, in turn leading to a similarly observed phenomenon [1, 11].

### 6.2.3 Differential Diagnosis

There is a broad differential diagnosis of acute generalized weakness in patients admitted to intensive care unit or who are critically ill. Generally speaking, the following list of acute generalized weakness in the ICU should be considered when evaluating patients with generalized weakness [1, 6–12]:

- Brain and brainstem disorders: neurotrauma, ischemic stroke, hemorrhagic stroke, infection of the central nervous system, brain abscess, central pontine myelinolysis, demyelinating and inflammatory disorders of the CNS
- Spinal cord disease: spinal cord trauma, spinal cord compression, non-traumatic compressive myelopathies, compressive myelopathies, immune-mediated myelopathies (i.e., neuromyelitis optica, transverse myelitis), infective myelopathies (i.e., HIV myelopathy, West Nile-related myelopathy), vascular disorders (i.e., spinal arteriovenous malformation, spinal cord infarction)
- Anterior horn cell disorders of the spinal cord: motor neuron disease, acute post-asthmatic amyotrophy, diabetic amyotrophy, poliomyelitis
- Polyradiculopathies and neuropathies: Guillain-Barré syndrome, lymphoma-related neuropathy, carcinomatosis, HIV-associated neuropathy, porphyric neuropathy, vasculitis neuropathy, lymphoma-related neuropathy, critical illness neuropathy, diphtheric neuropathy, nutritional-related neuropathies, paraneoplastic-neuropathies
- Neuromuscular junction disorder: myasthenia gravis, Lambert-Eaton myasthenia gravis, congenital myasthenic disorder, botulism, neuromuscular blockade medication, tick paralysis, exogenous toxins (i.e., snake bites)
- Muscular disorders: rhabdomyolysis, disuse myopathy, malignancy-related cachexia, infectious and inflammatory myopathies, mitochondrial myopathies, critical illness myopathy, myotonic dystrophy, Duchenne muscular dystrophy, adult-onset acid maltase deficiency

### 6.2.4 Epidemiology and Risk Factor

Neuromuscular weakness related to critical illness myopathy (or neuropathy) is a fairly common occurrence among patients admitted to intensive care units. Epidemiological studies report an incidence of 10–40% of CIM/CIP in patients who are mechanically ventilated in the intensive care unit for over a week [12–15].

Risk factors for the development of critical illness myopathy include the use of intravenous glucocorticosteroids in the intensive care setting, use of various types of paralytic agents, higher illness severity index, hyperglycemia, hyperthyroidism, and prolonged immobility [16–23].

## 6.3 Diagnosis and Evaluation

### 6.3.1 Evaluation

The essential step in evaluating a patient with possible critical illness myopathy is by obtaining a thorough medical and history evaluation. It is essential to review the prehospital functional status and prehospitalization medical comorbidities

(in particular coexisting neuromuscular disorders). Subsequently, a thorough analysis of the time course of the neurological symptoms, in conjunction with the acquired systemic disorders, is essential. Identifying potential risk factors associated with critical illness myopathy such as sepsis, multiple organ failure, high index severity of illness, hyperglycemia, and exposure to glucocorticosteroids or neuromuscular agents is also key.

A thorough physical examination is also essential. In critical illness myopathy, there is evidence of diffuse muscular weakness throughout affecting both proximal and distal segments, but with minimal sensory involvements. In addition, deep tendon reflexes are typically present or mildly affected. However, physical examination may be hindered in critically ill patients, particularly when obtunded, ventilated, or comatose. Muscle strength testing can be scored by the Medical Research Council (MRC) scale which ranges from 0 (no contraction observed) to 5 (full strength) [17–20].

### 6.3.2 Laboratory Evaluation

Laboratory testing is neither sensitive nor specific for the confirmation of critical illness myopathy. However, it is reasonable to obtain laboratory studies in select patients with critical illness weakness. Commonly obtained laboratory testing includes:

- Serum creatinine kinase: Usually, an elevation of serum creatinine kinase is observed in patients with critical illness myopathy and may support this diagnosis. However, this lab is neither sensitive nor specific, and its absence does not rule out this diagnosis [20].
- A comprehensive metabolic panel including electrolytes, magnesium, calcium, phosphorus, renal panel, liver function tests, total bilirubin, and ammonia. Glycosylated hemoglobin (hemoglobin A1c) and thyroid function panel.
- Inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate.
- Infectious etiologies such as hepatitis panel, human immunodeficiency virus, and tuberculosis (in select cases).
- Lumbar puncture and cerebrospinal fluid analysis in select cases, particularly if an infectious or inflammatory cause of acute generalized weakness is thought. In critical illness myopathy, the CSF is expected to be normal, whereas abnormal CSF values may point to alternative diagnoses or a concurrent additional disease process.
- Muscle biopsy: This is seldom required, but may need to be pursued if an alternative diagnosis is considered. Muscle biopsy findings in critical illness myopathy are discussed under "histopathology."

### 6.3.3 Neuroimaging

Neuroimaging is seldom required for the diagnosis of critical illness myopathy, but may be pursued if an alternative diagnosis is suggested. This may be particularly needed if suspicion for a central nervous system lesion is thought. In the latter, magnetic resonance imaging (MRI) of the brain may be required.

### 6.3.4 Electrodiagnostic Testing

Serial electrodiagnostic testing is helpful in predicting and assessing the development of critical illness myopathy. In addition, electrodiagnostic testing with nerve conduction studies (NCS), electromyography (EMG), and repetitive nerve stimulation (RNS) may help assess the severity of disease, reliably confirm the diagnosis of CIM, or hint toward an alternative diagnosis.

Nonetheless, the important limitation of electrodiagnostic testing is the potential lack of availability in some centers, the lack of ability of patient to fully cooperate or participate, especially those with severe critical illness.

Some of the findings on electrodiagnostic testing finding in critical illness myopathy includes reduction (>25%) in motor amplitude (compound muscle action potential) which some authors

consider as the most useful benchmark to diagnose critical illness myopathy [23–26]. In addition, there is frequent broadening (prolonged duration) of the compound muscle action potential. Sensory responses are often normal or minimally altered in comparison to motor findings, unless there is a coexisting chronic polyneuropathy or concurrent critical illness polyneuropathy [24–26]. Needle examination often reveals myopathy findings, characterized by fibrillation potential activity, early recruitment, decreased amplitude, and frequent polyphasic discharges [24–28].

### 6.3.5 Management

Treatment of critical illness myopathy is directed toward the treatment of the primary disease process, management of secondary compilations, and early muscular strength rehabilitation [27, 28]. Avoidance of neuromuscular blockade agents, minimizing sedation, and early mobilization are all key principles in the management of critical illness myopathy [28]. In addition, it is suggested to discontinue glucocorticosteroids in patients who develop critical illness myopathy, unless their benefit far outweighs the risk of prolonged muscular weakness [28–31].

Some experts have reported that intensive insulin therapy (i.e., blood glucose target of 4.4–6.1 mmol/L) may lower the incidence of critical illness myopathy and may even hasten their recovery. However, these are limited studies, with shortcoming in their methodologies and sample size [29–32]. In additions, studies have shown that intensive insulin therapy in the intensive care unit is associated with frequent hypoglycemic events and in turn increased morbidity and mortality compared to conventional insulin treatment [33–37].

### 6.3.6 Prognosis

Neuromuscular weakness, in particular critical illness myopathy, is thought to often occur in the context of patients who survive critical illness. This includes a continuum spectrum of a syndrome characterized by prolonged impairment in cognition, decline in mental and physical function, and global generalized weakness. This is best known as post-intensive care syndrome (PICS) [38–41].

Nonetheless, critical illness myopathy is usually reversible, with resolution over weeks to months. However, it is directly associated to an increase in length of stay in the ICU. However, and in general, critical illness myopathy is more favorable than critical illness neuropathy, or when co-occurring with critical illness polyneuropathy. Small-scale epidemiological studies have shown that most affected patients with critical illness myopathy do recover on the long run [42, 43].

## 6.4 Other Neuromuscular Diseases in the ICU

### 6.4.1 Critical Illness Polyneuropathy

Critical illness polyneuropathy refers to a neuromuscular condition characterized by acute sensory and motor axonal injury in the context of acute critical illness in the intensive care unit [44]. It was first described clinically in the 1970s and has since been widely recognized [44–46]. The exact pathogenesis of critical illness polyneuropathy is not known, but some studies and animal models have demonstrated injury at the level of microcirculation of distal nerves, leading to sensory and motor nerve injury and in turn axonal degeneration with sparring of the myelin and neuromuscular junction [44–47]. Critical illness polyneuropathy often accompanies severe illness, in particular sepsis, multiple organ failure, and prolonged immobility [45]. However, many patients who have critical illness polyneuropathy also have concurrent critical illness myopathy. This combined term has been coined “Critical illness polyneuromyopathy.” Electrodiagnostic findings in critical illness polyneuropathy include findings consistent with generalized axonal polyneuropathy [25]. This is characterized by the decrease in motor and sensory amplitudes on

nerve conduction studies. Subsequently, fibrillation potential may eventually develop on needle electromyography (EMG). Demyelination is not seen in critical illness polyneuropathy, and its presence should prompt the clinician to evaluate alternative diagnoses [25, 47]. Laboratory evaluation is similar to critical illness myopathy, and examination findings reveal diffuse generalized weakness with sensory involvement and severely decreased or absent deep tendon reflexes [47]. Recovery from critical illness polyneuropathy tends to be worse than critical illness myopathy [37–40]. Clinical recovery may take months to years, and electrodiagnostic studies may take years to normalize [40]. In addition, patients with severe critical illness polyneuropathy may remain quadriplegic [39, 40].

### 6.4.2 Guillain-Barré Syndrome

Guillain-Barré syndrome refers to an acute immune-mediated polyradiculoneuropathy and is classified under the eponym Guillain-Barré syndrome. It is thought to occur at an incidence of 1–2 cases per 100,000 patients per year [48–50]. Its incidence in isolation in patients admitted to critical care units with another primary systemic disease is however unknown but likely to be underrepresented or mislabeled under "critical illness neuropathy" since the latter share common clinical and electrodiagnostic features. The cardinal features of GBS is that of acute progressive symmetric motor and sensory neuromuscular weakness associated by absent or severely decreased deep tendon reflexes. Onset of symptoms is typically days to week, and the weakness may vary from mild generalized weakness to total flaccid tetra-/quadriparesis requiring full mechanical ventilatory support [49, 50]. Electrodiagnostic findings may include demyelinating findings such as increased distal motor latency, increased F-wave latency, conduction blocks, and decreased motor nerve conduction velocity or axonal findings such as decreased motor and/or sensory amplitudes [51]. Combination of both axonal and demyelinating features and/or sensory/motor involvement can also be observed. Treatment includes supportive care and management of secondary complications (such as respiratory failure, autonomic dysfunction, bladder and bowel care, and cardiovascular support) as well as disease-modifying agent with either plasma exchange therapy or intravenous immunoglobulin therapy [51–53].

### 6.4.3 Cachectic Myopathy

Cachectic myopathy refers to a subset of critical illness myopathy that is observed in certain critically ill patients. In these patients, there is a predominant proximal pattern of muscular weakness with evidence of muscle atrophy and wasting. This disorder is thought to occur as a result of increased catabolism related to critical illness as well as disuse atrophy [47, 54]. Electrodiagnostic findings include myopathic changes with or without fibrillation potentials. Histopathological findings include prominent type 2 fiber atrophy [54]. Cachectic myopathy is a diagnosis of exclusion, and alternative diagnoses should be first explored.

## 6.5 Summary

In summary, neuromuscular weakness frequently develop in patients who are critically ill. The most common neuromuscular weakness in the intensive care unit is critical illness myopathy followed by critical illness polyneuropathy or combination of both. Risk factors include severity of illness, sepsis, multiple organ failure, and the use of certain medications such as neuromuscular blockade agents or glucocorticosteroids. The diagnosis of neuromuscular weakness in the intensive care unit is established by a thorough history and physical evaluation of the patient, electrodiagnostic findings, and laboratory work-up aimed at excluding masquerading diseases. Treatment of critical illness myopathy and neuropathy is supportive and primarily aimed at treating the primary disease and addressing secondary complications.

**Key Points**

- Become familiar with the differential diagnosis of generalized weakness in the intensive care unit
- Recognize the pathophysiology, evaluation, and management of critical illness myopathy
- Become familiar with other neuromuscular diseases commonly encountered in the intensive care unit

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# 7 Intensive Care Management of Status Epilepticus

Stephane Legriel

## 7.1 Introduction

Status epilepticus (SE) is a major medical emergency associating a heterogeneous set of electroclinical presentations, within which convulsive SE is the most common and serious form [1, 2]. In the short term, 20% of patients with convulsive SE die during their ICU stay [3, 4]. When seizure activity proves to be refractory, the mortality rate reaches 40% and is up to 65% in cases of progression to nonconvulsive SE with coma. Moreover, half the survivors after convulsive SE requiring ICU management demonstrate functional impairments at day 90 [3, 5]. The age of the patient, longer seizure duration, cerebral insult as the cause of SE, consciousness impairment at presentation, and refractory convulsive SE have been identified as independent predictors of poor outcome [5–7]. Thus, management of SE in the ICU requires knowledge of definitions and classification of status epilepticus types, a clear understanding of pathophysiology and related-complications—but also practical modalities of symptomatic and etiological treatments—and, finally, conditions of EEG monitoring.

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## 7.2 Definitions

SE is defined as 5 min or more of continuous seizure activity (clinical and/or electrographic), or recurrent seizure activity without returning to baseline between seizures [1].

Refractory SE (RSE) is defined by persistent seizures that are resistant to first-line anticonvulsant therapy (benzodiazepines) and second-line ("classic") anticonvulsant therapy, such as valproate, phenytoin/fosphenytoin, phenobarbital, or levetiracetam [1, 8].

Superrefractory SE is defined as persistent or recurrent SE 24 h or more after anesthesia induction, including cases occurring at reduction or withdrawal of the anesthetics [9, 10].

## 7.3 Pathophysiology

The mechanisms involved in the genesis and persistence of seizures involve neuronal hyperexcitability, mainly mediated by glutamate, inducing hyperexcitation and hyperexpression of *N*-methyl-D-aspartate receptors (NMDA) exceeding the neuroinhibitory capacities mediated by the gamma-aminobutyric acid (GABA) system [2, 11]. The persistence of seizures beyond the fifth minute, a period of convulsion beyond which a seizure rarely spontaneously stops [12], corresponds to the concept of impeding status epilepticus [2]. This also corresponds to the time at which



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SE treatment should be started [1]. After 30 min of seizure activity, SE is considered as established [2]. Numerous experimental and clinical data show that SE is then self-maintained, characterized by a phenomenon of pharmacology resistance to anticonvulsants, and associated with the occurrence of neuronal damages [13, 14]. When seizure activity is not controlled, SE becomes subtle and is then characterized by discrete motor clinical manifestations, ultimately disappearing and then leaving the patient in an apparent isolated comatose state we call "NCSE with coma." It is considered that there is a continuum between these three pathophysiological concepts of status epilepticus [15].

Pathophysiological mechanisms leading to neuronal damages after SE may be schematically attributed to the direct (central) and indirect (systemic) effects of status epilepticus [16]. The description of central effects of SE is based on theories of excitotoxicity and inflammation. The excitotoxicity theory is linked to the activation of NMDA receptors, which leads to intraneuronal calcium entry and results in mitochondrial dysfunction, and activation of proteases, lipases, endonucleases, caspases, and NO synthase, which leads to cellular morphological alteration as well as to the release of free radicals and finally to neuronal necrosis [17]. Intracellular calcium entry also results in the activation of early genes that rapidly lead to apoptosis. The increase in glutamate release is also responsible for the activation of alpha-amino-3-hydroxy-5-méthylisoazol-4-propionate (AMPA) receptors, gating to an intracellular sodium entry and then leading to neuronal osmotic lysis [18]. The theory of inflammation is characterized by local inflammatory phenomena combining astrocytic activation and microglial proliferation. This activation of gliosis is the consequence of ionic movements and the production of proinflammatory cytokines (TNF alfa, IL6) related to neuronal death. Thus, induced alterations are then responsible for the constitution of aberrant circuits that are responsible for the hyperexcitability and hypersynchrony that perpetuate seizure activity [18].

Finally, systemic complications of SE also contribute to neuronal loss [16, 19–21]. Indeed, after an initial phase of physiological adaptation to an increased seizure-induced metabolism demand, several adaptive mechanisms are exceeded, which contributes to the worsening of neuronal loss. Thus, hypoxemia [16], hypoglycemia [22, 23], hyperthermia [24, 25], lactic metabolic acidosis, loss of self-regulation of cerebral blood flow associated with increased intracranial pressure and cerebral edema, and blood arterial hypotension secondary to the insufficiency of the endogenous adrenergic activity [26] will be at the origin of a cerebral hypoxemia, which in this context is becoming deleterious. At the same time, we observe the occurrence of organ failures that may progress to a multi-organ failure syndrome and ultimately to death [4, 5, 19, 20]. The general consensus holds that 60 min is the time beyond which neuronal injury develops after SE. Consequently, management of SE in the ICU should consider the whole spectrum of these potential complications and control SE within 60 min.

## 7.4 Classification

According to the 2015 ILAE Task Force on Classification of status epilepticus, we distinguish between SE with prominent motor symptoms, which is usually easy to recognize on clinical grounds, and SE without prominent motor symptoms (also called nonconvulsive SE, or NCSE), in which the symptoms may be minimal or negative, making the role of EEG much more important (Fig. 7.1) [27].

SE with prominent motor symptoms represents the easiest form to recognize. Depending on the type of abnormal movements presented by the patient, we describe convulsive SE (CSE) in cases of tonic-clonic seizures, which should be distinguished from other forms such as myoclonic SE, focal motor SE, tonic SE, and hyperkinetic SE.

NCSE with coma can be encountered in 14–20% of cases and corresponds to the ultimate progression of CSE that has been untreated or insufficiently treated [13, 15, 28]. It can be characterized by a

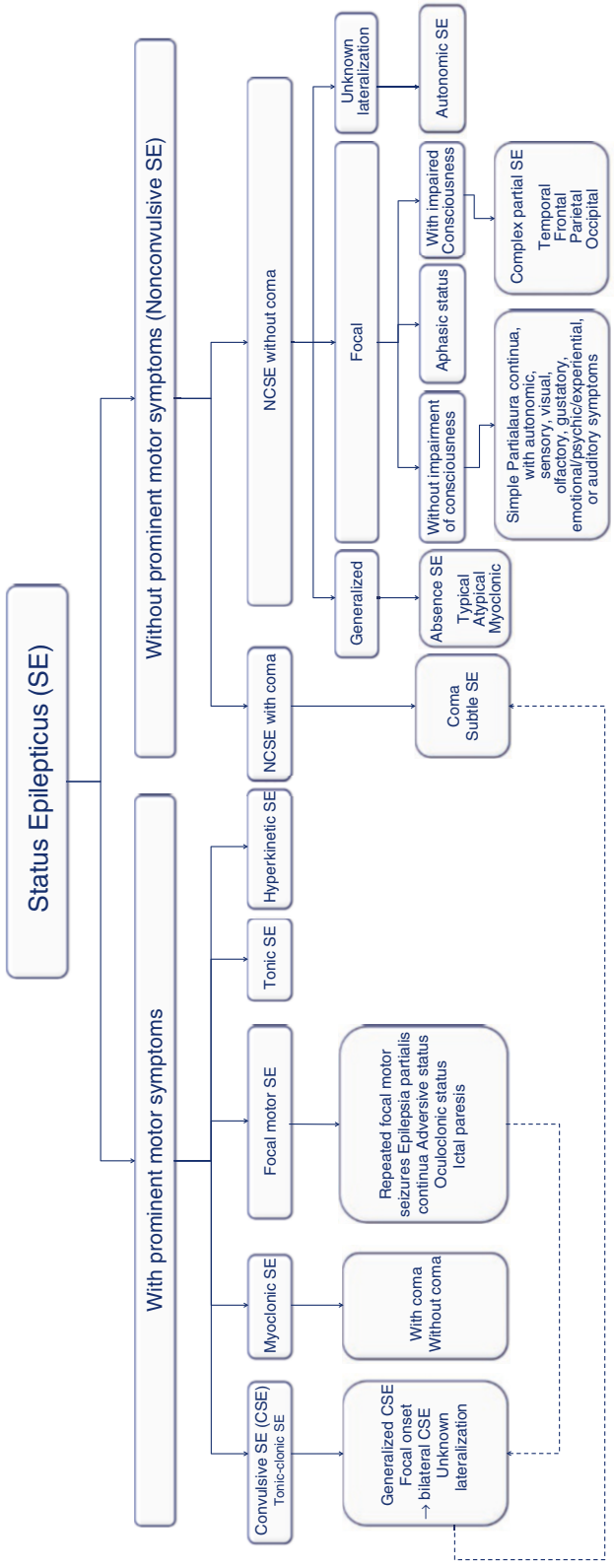


**Fig. 7.1** Classification of status epilepticus according to the 2015 ILAE Task Force on Classification of status epilepticus. SE denotes status epilepticus

comatose state sometimes accompanied by subtle motor clinical manifestations limited to the distal territories (thumb and/or big toe) and to the face (palpebral clades), or simple eye revulsions with brief tonic axial contractions. Maximally they take a purely nonconvulsive, electrographic or "pure" electrical form, where only the electroencephalogram can be used to diagnose it. The classification of other forms of NCSE depends on generalized or non-generalized nature of electroencephalographic seizure activity. Absence SE is generalized, whereas focal NCSE corresponds to aphasic, simple, partial, or complex NCSE. Another form is autonomic SE, regardless of lateralization of electroencephalographic seizure activity.

## 7.5 Diagnosis

### 7.5.1 Positive Diagnosis

Diagnostic strategy of SE with prominent motor symptoms does not require an EEG, except for myoclonic seizures in particular cases (e.g., drug intoxication, postanoxic status epilepticus), to differentiate SE from encephalopathy [1].

EEG confirmation is mandatory in all forms of NCSE [1]. Salzburg EEG criteria may help to diagnose NCSE [29]. Indeed, NCSE is considered as certain in the presence of epileptiform discharges >2.5 cycles/s. NCSE may also be considered as certain in cases of epileptiform discharges ≤2.5 cycles/s if associated with typical spatiotemporal evolution, or with subtle clinical ictal manifestations, or even both electroencephalographic and clinical improvement after anticonvulsants. NCSE is considered as possible in the presence of epileptiform discharges ≤2.5 cycles/s and no EEG and clinical improvement after anticonvulsants [29].

### 7.5.2 Differential Diagnosis

CSE may be confounded with different abnormal motor activity manifestations such as tetany, neuroleptic malignant syndrome, chills, drug-induced myoclonus, decerebration posturing, hemiballism, and athetosis. NCSE also requires a particular attention, as it sometimes may be attributed to mental disturbances including major depression or even psychosis psychosensory disorders. Psychogenic nonepileptic status (Pseudo-SE) is another important differential diagnosis of SE in ICU patients [30]. It should be recognized in the presence of motor or behavioral manifestations mimicking SE in the absence of identifiable electrical seizure activity or documented brain lesions [31]. Its incidence in patients with previous epilepsy is nearly 15%. Patients with pseudo-SE are also more likely to be associated with antecedent sexual abuse. The best distinctive features for differentiating pseudo-SE from SE that have been identified are eye opening and closing. Whereas open eyes is the rule during epileptic seizures, the eyes are closed in most pseudo-epileptic seizures [32].

Diagnostic errors can also be related to the electroencephalogram monitoring. It may consist of recording artifacts linked to the EEG technique (e.g., chest stimulations, oscillating water condensation in ventilator circuits, or even motors purring of continuous hemofiltration machines). Moreover, EEG patterns can be attributed erroneously to NCSE. This concerns almost exclusively periodic or pseudo-periodic paroxysmal activities whose main differential diagnosis is encephalopathy. The epileptic nature of these paroxysmal patterns should be considered as related to an epileptic nature only if associated with combination of a suggestive context and both clinical and electrical responses to treatment [33–36].

## 7.6 Management

Management of SE in the ICU concurrently combines symptomatic general measures and antiepileptic treatment appropriate for the electrical and clinical pattern in the patient initiated on an emergency basis. Investigations to identify and correct the cause of SE itself should be performed simultaneously. The use of continuous EEG monitoring is an important part of the management of SE.

### 7.6.1 General Measures

Intensive care management of SE requires to ensure the necessary general measures commonly taken in the ICU. Hemodynamic stability should be warranted in order to ensure adapted cerebral blood flow. Patients with RSE often necessitate catecholamines because of the anesthetic agents used that can induce hypotension and/or heart failure. Similarly, upper airway protection should be ensured. Therefore, even if the main management objective is seizure resolution with full recovery and then an isolated initial phase of coma have to be tolerated, endotracheal intubation may be required. In these cases, rapid sequence induction can be used associating etomidate, ketamine, propofol, or sodium thiopental with succinylcholine or rocuronium if there is evidence of hyperkalemia. Special attention should be paid to the fact that seizures may transiently be masked by neuromuscular agents used. Hypoglycemia, if any, should be corrected. And if glucose is administrated, 100 mg of thiamine should be also given in cases where vitamin B1 deficiency is suspected.

Hyperthermia, respiratory acidosis, and/or metabolic disturbances including acute renal failure and rhabdomyolysis should be promptly corrected. Patients should be routinely evaluated for aspiration pneumonia and various injuries (e.g., head injury, shoulder dislocation).

Aspiration pneumonia may complicate the initial consciousness disorders. Patients should be evaluated for injuries such as head injury and shoulder dislocation.

### 7.6.2 Anticonvulsant Strategies

Anticonvulsants should be administered with progressive therapeutic escalations (Fig. 7.2), considering the type of SE and response to prior treatments, with the final objective to definitively control clinical and electrical seizure activity in less than 60 min from the onset of SE [1].

#### 7.6.2.1 First-Line Treatments: Emergent Initial Therapy

Intravenous lorazepam and intramuscular midazolam are the first-line treatments for generalized convulsive SE [37]. Alternatively, intravenous clonazepam or diazepam can be given [38]. If the seizure persists, a second injection can be given 10 min later. It is important to note that clonazepam and diazepam may be given through the intrarectal route and that midazolam has also been administered by the intranasal and buccal routes, which is potentially useful in adult patients in whom venous access is difficult.

#### 7.6.2.2 Second-Line Treatments: Urgent Control Therapy

Several "classic" antiepileptic drugs are available for the second-line treatment of SE, but the data and expert opinion differ about which agent is the most effective [13]. Thus, the choice should be guided by the spectrum of antiepileptic activity, contraindications, and expected side effects. In patients with previously known epilepsy who have been on an antiepileptic treatment before admission, it is preferred to provide an intravenous bolus of this anticonvulsant before initiating an additional agent [1]. In patients with de novo SE, based on the evidence, phenytoin/fosphenytoin would theoretically be the agents of choice but should be used with caution in patients with cardiovascular comorbidities. Valproate is another interesting therapeutic option that may be preferred in cases of primary generalized epilepsy. Valproate is contraindicated in pregnancy and in cases of liver impairment. Patients should be monitored for evidence of hyperammonemia encephalopathy, particularly when consciousness remains abnormal after initiation of the drug. Phenobarbital is an alternative that may cause hemodynamic instability and central or respiratory depression with rapid infusions. Levetiracetam and lacosamide would be some interesting alternatives to be considered but are not supported by evidence [39–41]. If used, lower maintenance doses of levetiracetam and lacosamide should be considered in patients with reduced renal function. Lacosamide may also be used with caution in patients with cardiovascular comorbidities.

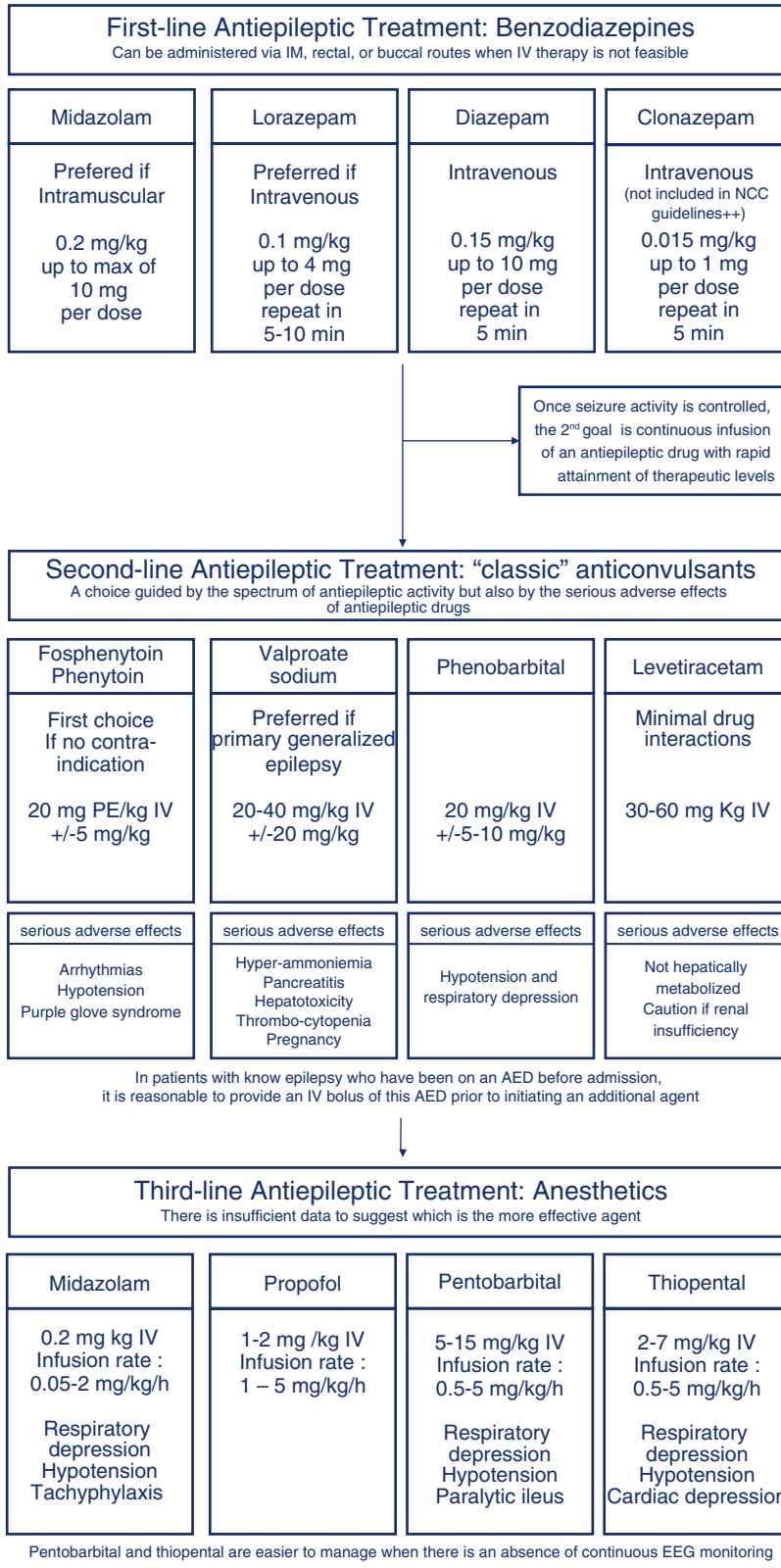


**Fig. 7.2** Status epilepticus anticonvulsant options according to treatment refractoriness

#### 7.6.2.3 Third-Line Treatments: Refractory Status Epilepticus

Several anesthetic agents may be used for the treatment of RSE, namely, propofol, midazolam, or sodium thiopental/pentobarbital [1, 8, 42]. There are insufficient available data to prefer one of these anesthetics over another. The pharmacokinetic and pharmacodynamic properties of sodium thiopental/pentobarbital indicate a high probability of drug accumulation of these agents that should not be considered as a first anesthetic choice. Conversely, for the same pharmacological reasons, pentobarbital and thiopental are easier to manage when there is an absence of continuous EEG monitoring [43].

Nevertheless, a weight-based loading dose of chosen anesthetic agent should be given followed by additional dose titration at 3–5-min intervals under EEG monitoring keeping in mind the objective of burst-suppression pattern or seizure-suppression pattern. In case of suppression-burst pattern, it has been suggested that a suppression of 5–10 s may be sufficient.

Once this objective is obtained, a continuous infusion is given to ensure the seizure-/burst-suppression pattern for 12–24 h. Additional boluses may be given in cases of seizure recurrences or if the burst-/seizure-suppression pattern is lost and then continuous-infusion dose increased consequently. Finally, treatment-discontinuation modalities of anesthetic agent vary according to their associated pharmacokinetic and pharmacodynamic properties. Thus, a 20% reduction is appropriate with propofol, whereas a 50% reduction every 3 h can be recommended with midazolam. Given their high half-life values, sodium thiopental/pentobarbital can be completely stopped in one go [42]. In case of particular refractoriness, slower withdrawal of anesthetic agent should be considered. Adjuvant anticonvulsant therapies may also be considered [42, 44]. Importantly, one or two long-acting antiepileptic agents should be given simultaneously with the anesthetic agent and be continued after anesthesia withdrawal. Figure 7.2 illustrated status epilepticus anticonvulsant therapeutic options according to treatment refractoriness.

#### 7.6.2.4 Fourth-Line Treatments: Superrefractory Status Epilepticus

Superrefractory SE management is based on a multimodal strategy associating the use of anesthesia, antiepileptic drugs, and adjuvant therapies (Fig. 7.3). Anesthesia may be used for 24 additional hours and up to 5–7 days in case of further recurrences. Polytherapy of antiepileptic drugs should be used in tandem with the anesthesia. There is no drug superiority, but drugs without a predominant GABAergic effect may be preferred. No more than three antiepileptic drugs at high doses should be used, and making frequent changes in drug regimens is not recommended [45]. Adjuvant therapies may be required in particularly superrefractory cases. In these cases, ketogenic diet, ketamine, volatile anesthetics such as isoflurane and desflurane, and mild therapeutic hypothermia (32–35 °C) may be considered. Steroids and immunotherapy may be suggested in suspected immune-mediated status epilepticus [9, 10].

#### 7.6.2.5 Treatment Goals and Management Particularities According to the Type of SE

Immediate treatment goals in patients with CSE are cessation of the clinical seizure activity and prevention of progression to NCSE with coma. In NCSE with and without coma, the goal of treatment is resolution of the critical EEG patterns, accompanied with a return of the patient's clinical status to normal. According to current recommendations, the immediate treatment objective in patients with RSE is seizure control or prompt generation of a burst-suppression pattern. Generalized CSE and complex partial SE are associated with neuronal damage, high mortality, and morbidity rates supporting the use of an aggressive treatment strategy [46]. Similarly, NCSE with coma is particularly resistant to treatments and carries a high mortality rate, suggesting an aggressive treatment strategy as in RSE [13, 15]. In complex partial SE, RSE should be defined as failure after the use of two second-line therapies. Finally, absence SE and focal motor

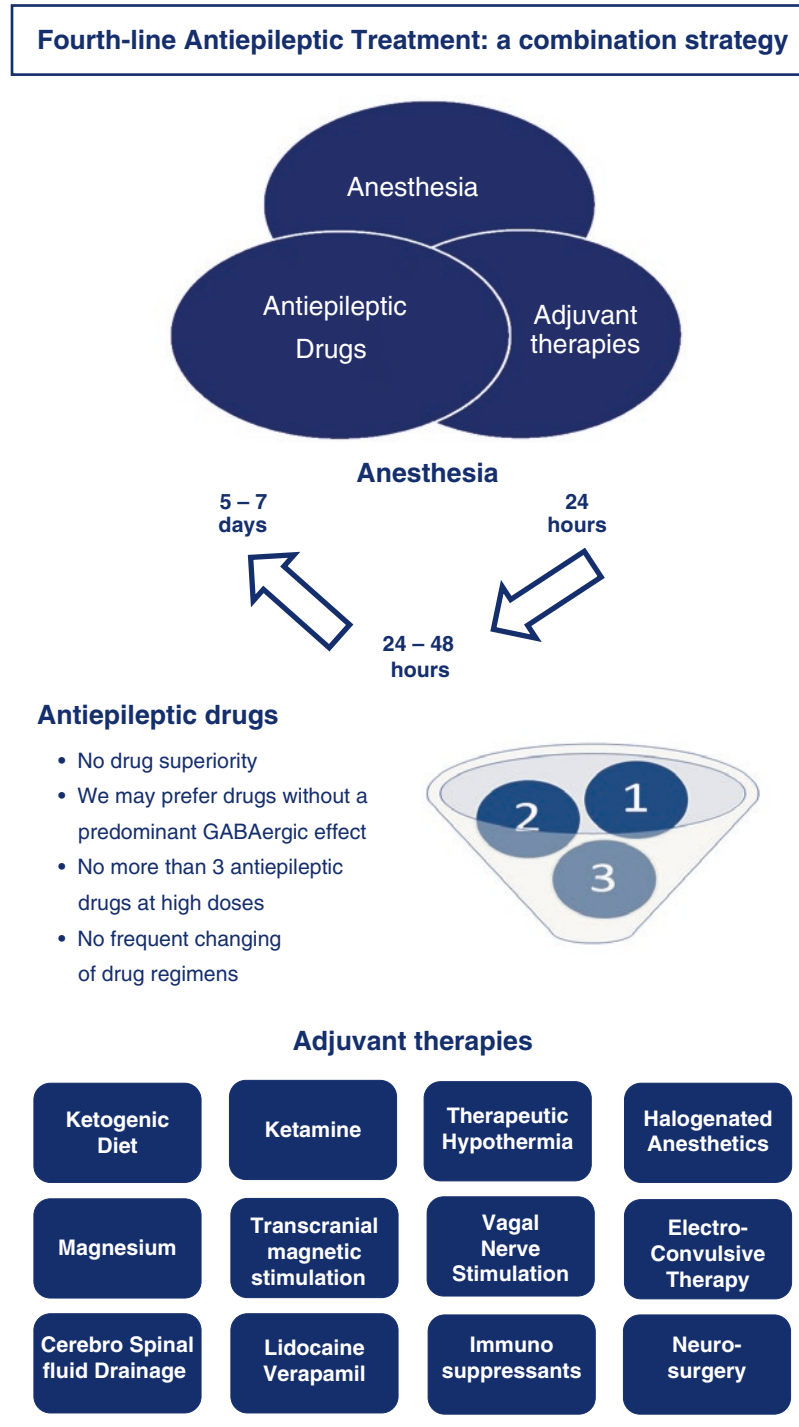


**Fig. 7.3** Management of superrefractory status epilepticus

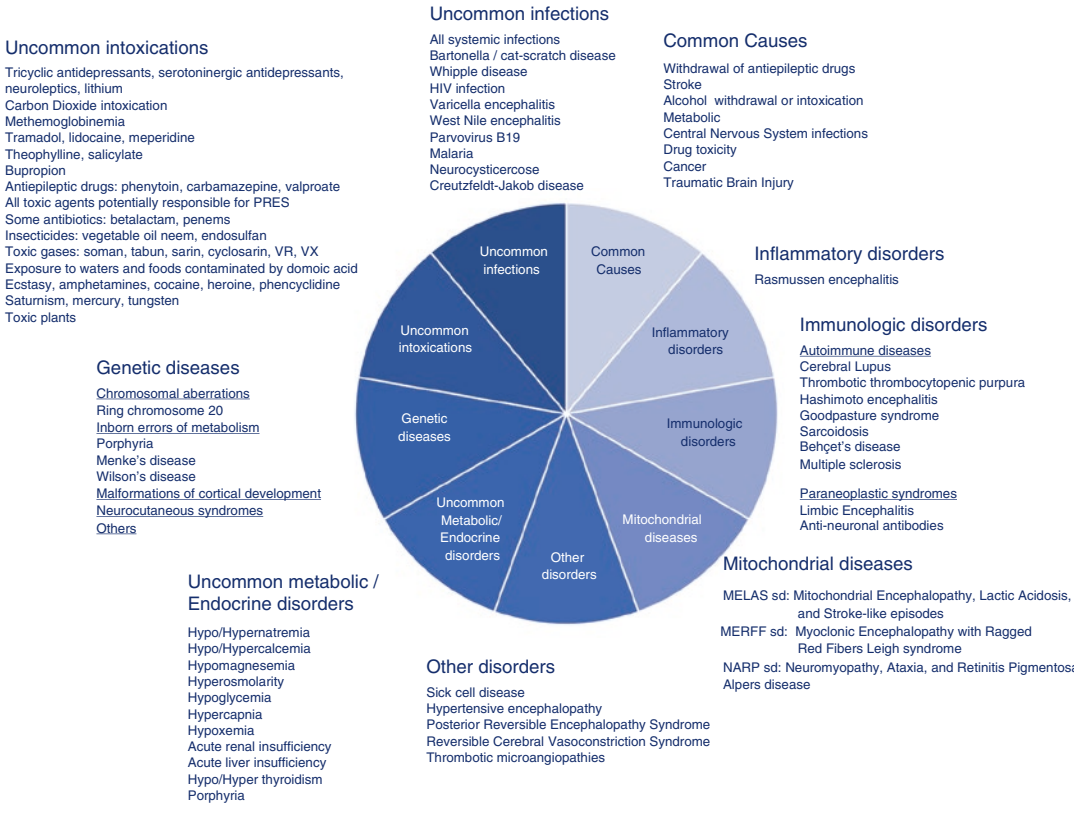


**Fig. 7.4** Etiological spectrum of status epilepticus

SE without consciousness impairment may be controlled after a benzodiazepine alone and may require several treatment lines before being considered as refractory [46].

### 7.6.3 Etiological Investigations

Etiological investigations should be conducted simultaneously to general and specific measures taken for intensive care unit management of SE. A complete initial clinical examination should be performed and associated with the realization of diagnostic tests in direction of the first diagnostic hypothesis.

The main causes are summarized in Fig. 7.4. Withdrawal of antiepileptic drugs is the most common cause of SE in patients with a previous history of epilepsy indicating the systematic evaluation for subtherapeutic anticonvulsants in the epileptic population. In patients with de novo status epilepticus, the main causes are dominated by acute and remote stroke, acute metabolic disorders, drug toxicity, alcohol-related issues, central nervous system infections, and cancer.

Brain imaging (brain scan without and with contrast or brain MRI) is ideally performed as soon as patient's admission to facilitate management of bleeding lesions that would require neurosurgical intervention. A blood assay should be performed looking for glycemic (hypoglycemia or hyperglycemia) or metabolic disorders (e.g., hypocalcemia, hyponatremia, high uremia, hypomagnesemia, hypoxemia, carbon monoxide, hypercapnia). The search for rare metabolic disorders (porphyria, thyroid dysfunction) may be considered if the etiologic diagnosis remains unknown. Investigations for drug toxicity can be based on the search for toxic substances (cocaine, amphetamines, tricyclic/serotonergic antidepressants) based on the context [47] or for a iatrogenic cause (antibiotic overdose, etc.). Leukoencephalopathy

or reversible cerebral vasoconstriction syndrome may be one of the possible manifestations of toxic causes, most of the time in association with hypertensive encephalopathy. In the presence of fever or meningeal stiffness and in those whose identifying etiology remains negative, a lumbar puncture will also be systematically performed. In immunocompromised patients, cerebrospinal fluid should performed more systematically and analyzed in detail (pressure, glucose, protein, cell counts, smear, standard bacteriological cultures, cultures for slow-growing microorganisms, India ink, mycological cultures, *Cryptococcus* antigens, viral PCR and cultures, BAAR test, and PCR and cultures for the tubercle bacillus). Blood specimens are usually taken for further tests to identify the suspected microorganisms (blood cultures, *Aspergillus* antigen, *Cryptococcus* antigen, viral PCR and cultures, HIV serology, and p24 antigen). Other investigations may include tests for slow-growing organisms in respiratory tract specimens, sputum tests for the tubercle bacillus, and urinary cytology and cultures. Lumbar puncture may be repeated up to three times to improve the diagnostic yield if neoplastic meningitis is suspected. In undetermined cases, we should look for autoimmune diseases including paraneoplastic syndromes that may explain status occurrence. Finally, the cause may remain unknown in about 20% of cases.

### 7.6.4 Continuous EEG Monitoring

Continuous EEG is an indispensable tool for the management of SE in the ICU. It allows for achievement of two major objectives: to diagnose the progression to subtle SE after CSE and to assess efficacy of therapy for SE, refractory SE, or superrefractory SE [36, 48]. Indeed, guidelines tell us that continuous EEG monitoring should be initiated within 1 h of SE onset if ongoing seizures are suspected. Moreover, the duration of continuous EEG in comatose patients should be at least 48 h to evaluate NCSE [48]. The limitations on its use are mainly based on the difficulties of access to interpretation. The ease of setting up and managing continuous EEG recording, as well as telemedicine solutions that allow near-simultaneous off-site interpretation, should help to overcome these difficulties. The use of continuous EEG monitoring would improve the management and monitoring of patients with status epilepticus. In the absence of availability of this technique, a conventional EEG should be systematically performed and repeated as necessary.

## 7.7 Conclusions

SE management in the ICU requires prompt initiation of symptomatic and anticonvulsant treatments and a broad and thorough etiological investigation. NCSE with coma and other NCSE types are difficult to identify, and their diagnosis is necessarily based on the realization of an electroencephalogram. Many diagnostic pitfalls exist, dominated by the pseudo-SE that must be systematically evoked. Undeniable therapeutic progress has been made in recent years, making it possible to propose different therapeutic strategies according to the type of SE encountered and its degree of severity. Refractory and superrefractory SE are the subject of a particularly aggressive treatment to reduce the mortality associated with them. In all cases, continuous EEG is the ideal monitoring technique for patients with status epilepticus.

**Key Points**

- Status epilepticus (SE) is a major medical emergency associating a heterogeneous set of electro-clinical presentations.
- NCSE with coma can be encountered in 14–20% of cases and corresponds to the ultimate progression of CSE that has been untreated or insufficiently treated.
- EEG confirmation is mandatory in all forms of NCSE.
- Anticonvulsants should be administered with progressive therapeutic escalations considering the type of SE and response to prior treatments, with the final objective to definitively control clinical and electrical seizure activity in less than 60 min from the onset of SE.
- Continuous EEG is an indispensable tool for the management of SE in the ICU.

**Conflicts of Interest** I have no conflicts of interest to declare.

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# 8 Intensive Care Management of Stroke

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## 8.1 Introduction

Ischemic stroke is a social problem and a strong challenge to both healthcare system and providers. Nearly, 12 million cases of ischemic stroke are registered worldwide annually [1, 2]. Ischemic stroke is a predominant kind of vascular brain injury. Outcomes of ischemic stroke are usually much better in comparison to hemorrhagic stroke, and results of treatment have been considerably improved during last decades due to progress in intensive care, endovascular technologies, and implementation of aggressive neurosurgical approach [3]. However, mortality and rate of invalidation are still high, especially in some groups of patients with ischemic stroke, for example, in cases with malignant stroke, when almost 90% have unfavorable outcomes [4].

Pathophysiologically, ischemic stroke presents infarct of the brain due to arterial thrombosis and further events, developing in the core zone, penumbra, and surrounding tissues. Intensive care management of stroke is based on the understanding of pathophysiological mechanisms. Therefore, following treatment directions will be discussed below: (a) recanalization, (b) prevention of thrombosis enlargement and early recurrent stroke, and (c) intensive care and management of complications.

## 8.2 Recanalization

Recanalization is the cornerstone of intensive care management of stroke, and it should be performed as early as possible [5–8]. Shortening of time between stroke onset and recanalization significantly improves outcomes. Recanalization is achieved with intravenous thrombolysis and endovascular treatment. Stroke onset 3–4.5 h, absence of contraindications for recombinant tissue plasminogen activator (rt-PA), and blood pressure less than 185/110 mmHg are strong indications for intravenous thrombolysis. Thrombolysis in Cerebral Infarction (TICI) scale reflects visual success of the treatment on angiograms, where TICI 2a is partial recanalization, TICI 2b is near complete recanalization,

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and TICI 3 is complete recanalization. TICI 2b and TICI 3 are being perceived as a successful result [9].

Zeumer et al. first reported successful recanalization of basilar artery occlusion after intra-arterial administration of streptokinase in 1983 [10]. A number of experimental studies of 1980s led to establishing safe and effective regimens of intravenous thrombolytic therapy. Thus, the biggest randomized clinical trials of 1990s concerning intravenous thrombolytic therapy of acute stroke were based on intravenous administration of recombinant tissue plasminogen activator (rt-PA). The dosage of rt-PA was reduced from 1.1 mg/kg in ECASS I to 0.9 mg/kg in all other trials without loss of its efficacy.

Results of ECASS I were published in 1995. It was randomized as 1.1 mg/kg of rt-PA vs placebo in 511 patients [11]. Outcomes in thrombolytics group were significantly better; however, 30-day mortality was equal. National Institute of Neurological Disorders and Stroke Trial (NINDS trial) showed 50% higher probability of good outcome in 3 months after stroke onset comparing to the control group [12]. In this trial, randomization was between groups of 0.9 mg/kg of rt-PA and placebo in 624 patients. NINDS trial established safe 3-h therapeutic window for intravenous thrombolysis in acute stroke. ECASS II study, whose results were reported in 1998, contained an attempt to enlarge therapeutic window up to 6 h in randomization between groups of rt-PA 0.9 mg/kg and placebo in 800 patients [13]. The rates of hemorrhagic complications were significantly higher in treatment group, and therapeutic window remained unchanged after this study. In 2008, ECASS III study demonstrated safe enlargement of therapeutic window for 0.9 mg/kg intravenous administration of rt-PA up to 4.5 h [14]. IST—III study accounted 3035 patients, 1617 of which were older than 80, and there were no significant differences in outcomes [15].

Comparing guidelines for early management of patients with acute ischemic stroke from the American Heart Association/American Stroke Association (AHA/ASA), published in 2013 and in 2015, shows liberalization of rt-PA use [16, 17]. History of ischemic or hemorrhagic stroke, and gastrointestinal or gastrourinary bleeding in anamnesis are no longer contraindications for rt-PA use. These changes were based on the experience of rt-PA safety in patients with complicated anamnesis. Seizures at onset with postictal neurologic impairment, hypoglycemia at the presentation, and the severity of stroke are no longer contraindication for intravenous thrombolysis according to recent guidelines. These changes are very interesting. Previous position was based on the concept that thrombolysis in stroke mimics leads to complications. However, recent studies demonstrated safety of thrombolysis in patients with stroke-like symptoms, and worsening outcomes in patients with stroke, whose symptoms were incorrectly interpreted as stroke mimics, and thrombolysis was avoided [18]. NIHSS 4 or less is not a guarantee of favorable outcomes, and some patients even with minimal NIHSS can have poor outcomes [19–21]. The matter is that the NIHSS predominantly assesses anterior circulation, and the scale can miss some kinds of posterior circulation infarction. Moreover, NIHSS at presentation cannot exclude patient's deterioration.

Besides CT data regarding volume of brain infarct, and laboratory data regarding hemostasis abnormalities, like platelet count, international normalized ratio (INR), prothrombin time (PT), and anamnesis data of use of heparin or new oral anticoagulants (NOA), were removed from recent AHA/ASA guidelines in comparison to 2013 edition. Age greater than 77 years is no longer contraindication for rt-PA use, because intravenous thrombolysis has showed benefit in elderly patients, in spite of increased risk of intracranial hemorrhage in comparison to younger groups [16, 17]. In accordance with recent guidelines, uncontrolled arterial hypertension is still a contraindication for intravenous thrombolysis; however, there are in the literature some examples of successful off-label rt-PA use in patients with blood pressure, exceeding 200/110 mmHg [22].

The only permitted drug for intravenous thrombolysis in patients with stroke rt-PA is Alteplase, which was approved in North America in 1996 and in Europe in 2002. Alteplase is

administrated via peripheral IV line. Before thrombolysis, two peripheral IV lines should be placed. Central vein and arterial catheterization as well, as placement of nasogastric tubes and urinal catheters is strictly prohibited. These manipulations should be postponed for, at least, 2–4 h after thrombolysis. Dose of Alteplase is 0.9 mg/kg of actual body mass, not to exceed 90 mg. The initial 10% of the dose is injected during 1 min, and the remaining 90% is infused over 1 h. Use of both anticoagulants and antiplatelet drugs starts in 24 h after thrombolysis, and this approach distinguishes cerebral thrombolysis from other kinds of systemic thrombolysis.

Alteplase is not without side effects and complications. Most dangerous of them are intracranial hemorrhage and angioedema with following airway obstruction. Uncontrolled arterial hypertension, volume of infarction area, and age are strong risk factors of intracranial hemorrhage during and immediately after intravenous thrombolysis. In the case with suspicion to intracranial hemorrhage, Alteplase infusion is stopped, and emergent CT is indicated with the following neurosurgical consultation. Management of hemostasis is a difficult issue, and mainstream of treatment is the use of cryoprecipitate or fibrinogen concentrate with or without platelet transfusion. Conventional laboratory tests include fibrinogen, prothrombin time (PT), and complete blood count. However, such global method of hemostasis investigation as rotational thromboelastometry (ROTEM) is a much more precise method. Analysis of maximum clot firmness in FibTEM and ExTEM (FibTEM-MCF, ExTEM-MCF) allows to make a correct decision regarding the use of fibrinogen donators and platelets [23, 24].

Angioedema after Alteplase use represents a type of anaphylactoid reaction, which develops much more rarely in comparison to the rates of anaphylaxis after streptokinase administration [25, 26]. Angioedema during Alteplase infusion develops in 0.02–1.9% of patients (Fig. 8.1) [27–29]. Interestingly, angioedema appears more frequently in cases with cerebral thrombolysis in comparison to other kinds of systemic thrombolysis. The cause of angioedema is complement and kinin cascades activation [30]. There are several important clinical issues that deserve discussion. First, angioedema can rapidly lead to upper airway obstruction, and hypoxia, which is a strong factor of secondary brain injury in patients with cerebral catastrophe. Second, cases with stroke frequently have dysphagia and consciousness alterations, and even mild upper airways obstruction can rapidly decompensate patient's condition. Third, management of airways in cases with angioedema and intravenous thrombolysis is an extremely difficult challenge, because both laryngoscopy during tracheal intubation and emergent cricothyrotomy would be complicated with bleeding in the upper airways. Therefore, timely tracheal intubation is the only safe and effective decision in stroke patients with angioedema.

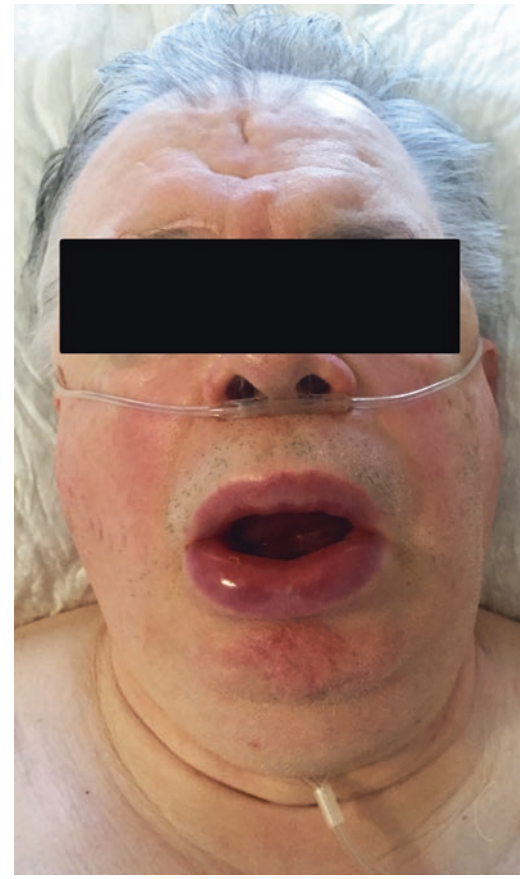

**Fig. 8.1** Angioedema after rt-PA use

Despite the approved efficiency of rt-PA, the outcomes after intravenous thrombolysis in patients with large vessel occlusion (LVO: intracranial segment of internal carotid artery (ICA), proximal segment (M1) of middle cerebral artery (MCA), vertebral artery (VA), and basilar artery (BA)) still remain poor, and recanalization does not exceed 40% in this cohort [31–34]. Outcomes are strongly linked with recanalization, and endovascular treatment is an important option for recanalization.

Real renaissance of endovascular treatment for acute stroke therapy started only in 2015 with technological development of mechanical thrombectomy. However, first generation of thrombextractors did not show any benefits in comparison to systemic thrombolytic therapy. Moreover, in 2013 three trials showed poorer results of mechanical thrombectomy in comparison to systemic thrombolysis: SYNTHESIS [35], MR RESCUE [36], and IMS-III [37]. Second generation of clot retrievers was a game changer. On March 3, 2008, Dr. Hans Henkes in Stuttgart performed first thrombectomy with intracranial self-expandable stent Solitaire, a device originally engineered as assistance for brain aneurysms coiling. It was the start of stent-retrievers era in the treatment of stroke. This safe and effective method is widely spread around the globe. Several prospective randomized trials were ended and reported in 2015. Published in January 2015, MR CLEAN study, or Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands, randomized 233 patients with endovascular thrombectomy and standard therapy vs 267 patients with standard intravenous thrombolytic therapy [38]. Patients with stroke in anterior circulation were included, 90% of them received rt-PA intravenously in both groups. Stent retriever was used in 97% of endovascular procedures. Results showed significant prevalence of favorable outcomes in endovascular group.

ESCAPE trial, or Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke, compared also endovascular and standard treatment randomized groups of 165 and 150 patients with anterior circulation stroke; however, therapeutic window for thrombectomy was as large as 12 h [39]. Patients with big core or poor collaterals on CTA were excluded. The study was stopped earlier than planned. Results were reported on February 2015 with better outcomes in endovascular arm compared to standard. EXTEND-IA, or Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection, trial was also stopped in advance after randomization of 70 patients due to clinical success of an endovascular arm [40]. This study was designed for patients with stroke in anterior circulation with core of brain infarction <70 ml and timing to start endovascular treatment within 6 h since symptoms onset. Trial showed better outcomes in endovascular arm in comparison to medical treatment. Similar results were achieved in industry—sponsored SWIFT PRIME, or SOLITAIRE FR with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke trial [41]. Another industry funded trial, REVASCAT, or Endovascular Revascularization with Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 h, with extended therapeutic window for thrombectomy, showed twice superiority of an endovascular method regarding outcomes without significant difference in safety [42]. In June 2015, American Heart Association published special focused update to the guidelines concerning inclusion of endovascular therapy in the early stroke management, based on the data of the randomized controlled trials published earlier in 2015 [43].

Despite the recent success of stent retrievers, it is not the exclusive type of devices for intracranial thrombectomy. Contact aspiration technique, mostly conducted by Penumbra with its catheters and aspiration system, also appeared to be safe and effective. Lapergue et al. reported slight superiority of thrombaspiration in a prospective nonrandomized trial whose results were published in June 2016 [44]. However, randomized controlled trial ASTER (Direct Aspiration First Pass Technique for Thrombectomy Revascularization of Large Vessel Occlusion in Acute Ischemic Stroke) did not

show any significant difference in recanalization rates between ADAPT and stentretreiver groups with rates of achievement of TICI 2b–3 85.4% and 83.1%, respectively [45]. In practice, most cath labs use both methods for acute stroke therapy and often combine them. Distal access catheters, like Sofia by Microvention or Fargo by Balt, appeared to be suitable for aspiration simultaneously with stentreiver thrombectomy.

In January 2018, Society of Neurointerventional Surgery (SNIS) published a standard for neuroendovascular management of stroke and summarized some important statements [46]. Successful mechanical thrombectomy, as defined by TICI grade 2b/3 reperfusion, should be an angiographic goal to be achieved. Despite the fact that intravenous thrombolysis is insufficiently effective in LVO, there is no evidence for harm from IV rt-PA administration. Because of the possibility of benefit and the lack of clear evidence of harm, candidacy for thrombectomy should not preclude patients, receiving full-dose IV rt-PA. In agreement with AHA guidelines, patients who meet the criteria for on-label use of IV rt-PA should receive it, irrespective of whether endovascular treatments are being considered or not [47, 48]. The role of intra-arterial thrombolysis remains unclear. There is no evidence of its effectiveness.

The type of anesthesia for performing mechanical thrombectomy is an important question. Randomized controlled trial Sedation vs Intubation for Endovascular Stroke TreAtment (SIESTA) and meta-analysis did not find significant differences between sedation and general anesthesia [46, 49]. Moreover, another recent randomized trial AnStroke (Anesthesia During Stroke) resulted with equal percentage of good outcomes at 3 months between sedation and general anesthesia groups [50]. Thus, both types of anesthesia are acceptable and may be individualized on the basis of patient's condition or stroke team habits.

Recently published DAWN trial showed the possibility of safety and effectiveness of endovascular treatment far beyond 6-h window [51]. It is a prospective randomized multicenter trial, focused on patients with severe clinical condition, relatively small core of brain infarction, and stroke onset between 6 and 24 h. One arm received standard care and the other arm combination of standard care and thrombectomy with Trevo device. Infarct volume was assessed with the use of DWI MRI or perfusion CT and was measured with the use of automated software (RAPID, iSchemaView). Results showed impressive difference with significantly better outcomes in the combined therapy arm. One month later, New England Journal of Medicine published the results of NIH funded DEFUSE-3 randomized trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) [52]. This trial compared endovascular treatment within 6–16-h therapeutic window vs standard medical therapy. Patient's selection was based on CTP data and included those with volume of brain infarction less than 70 ml and a ratio of ischemic tissue on perfusion imaging to infarct volume 1.8 or more. Any thrombectomy device could be used. Results showed superiority of endovascular treatment not only in terms of good outcomes but also in mortality rate.

Therefore, state-of-the-art strategy of recanalization in patients with stroke comprises intravenous thrombolysis with immediately following mechanical thromboectomy with stent retriever devices in eligible for this procedure candidate. All manipulations are required to be performed as fast as possible without any time delay; however, the most recent data show safety and effectiveness of aggressive recanalization, performed during first 24 h of acute ischemic stroke.

## 8.3 Prevention of Thrombosis Enlargement and Early Recurrent Stroke

Stroke is an arterial thrombosis, and thus all patients obligatorily require antiaggregants. Adequate antiplatelet therapy prevents thrombosis enlargement and early recurrent stroke. There are some possible clinical scenarios, and therapeutic tactics is different from case to case (Table 8.1).

**Table 8.1** Clinical scenarios of antiaggregants administration

| | No antiaggregants before stroke | Antiaggregants before stroke |
|---|---|---|
| No intravenous thrombolysis | A: Immediately antiaggregants | B: Continue antiaggregants |
| Intravenous thrombolysis | C: Antiaggregants in 24 h after thrombolysis | D: Discontinue antiaggregants and resume in 24 h after thrombolysis |
| Endovascular mechanical thromboectomy | E: Antiaggregants perioperatively | F: Antiaggregants perioperatively |

*Clinical Scenario A: No Antiaggregants Before Stroke, No Intravenous Thrombolysis* Patient should receive antiplatelet therapy immediately. This recommendation is based on the two large RCTs, and demonstrated significant reduction of morbidity and mortality due to administration of antiplatelet agents within 2 days after stroke [53, 54]. Despite the 48 h, mentioned in trials as a time of antiplatelet therapy beginning, antiaggregants should be given as early after stroke onset as possible in cases with missed intravenous thrombolysis. Choice of aspirin, COX-1 inhibitor, as a first line of antiplatelet therapy is still a commonly accepted approach. Monotherapy with clopidogrel, P2Y12 receptor inhibitor, is hypothetically possible, but did not demonstrate any benefit in comparison to aspirin [55]. Ticagrelor, another P2Y12 receptor inhibitor, works without metabolic activation. Comparison of aspirin and ticagrelol showed some nonsignificant benefit of ticagrelor, for example, in preventing stroke, myocardial infarction, and death within 3 months (Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes trial (SOCRATES)) [56]. This trial focused on non-severe stroke, and therefore further studies are needed for drawing any definite conclusions regarding comparison of aspirin and ticagrelor. Eptifibatide, glycoprotein IIb/IIIa inhibitor, is a promising antiplatelet agent, and the results of ongoing studies are forthcoming.

Dual antiplatelet therapy in patients with stroke is the controversial issue. Pathophysiologically, benefit of dual therapy can be explained with several arguments. First, different antiaggregants inhibit different pathways of platelets activation. Second, rate of nonresponders to COX and P2Y12 receptor inhibitors is not low in the population, and sometimes that is not easy to timely verify this phenomenon [57]. The most investigated and cited combination of antiaggregants is aspirin and clopidogrel. Moreover, this regimen demonstrated significant benefit in comparison to monotherapy in RCTs and meta-analysis (Clopidogrel plus Aspirin for Infarct Reduction in patients with acute stroke/TIA with large artery stenosis and microembolic signal (CLAIR), Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS)) [58, 59]. However, some important remarks have to be made. All above-mentioned studies, that showed benefit of dual antiplatelet therapy over monotherapy, had involved patients with TIA, or mild stroke. There are no trials that included patients with severe stroke, and thus we cannot extrapolate demonstrated evidence to severe stroke. The next extremely important remark, limited enthusiasm of administration of dual antiplatelet therapy in severe stroke, is the strong necessity of co-administration of anticoagulants. Low molecular weight heparin (LMWH) is not indicated for treatment of cerebral infarction, but anticoagulants are strongly recommended for the prevention of thromboembolic complications [16, 17]. Simultaneous use of dual antiplatelet therapy and LWMH in patients with stroke is very risky and dangerous, because even combination of aspirin and LWMH increases the rate of intracranial hemorrhage [60]. Therefore, in patients with severe stroke antiaggregant therapy should be presented to monotherapy with aspirin.

*Clinical Scenario B: Antiaggregants Before Stroke, No Intravenous Thrombolysis* Antiplatelet therapy should be continued. There are two main questions that should be answered before antiaggregant administration. First, if patient received antiplatelet monotherapy before stroke, should this therapy be continued, or should it be changed

to another antiaggregant? There is no any evidence, which could be used as a basis for the answer to this question. Hypothetically, it would be reasonable to perform aggregometry [61]. Second, if patient received antiplatelet dual therapy before stroke, should this therapy be continued, or should it be switched to monotherapy? It is also a disputable issue. In severe stroke, it is reasonable to switch to the monotherapy, as we discussed above. Aggregometry can help to choose the antiplatelet agent, which should be cancelled, and which should be kept. Further antiaggregant and anticoagulant therapy has to be managed under ROTEM [24].

*Clinical Scenario C: No Antiaggregants Before Stroke, and Intravenous Thrombolysis* In accordance to recent guidelines, antiplatelet agent should be started not earlier than in 24 h after intravenous thrombolysis and only after controlled CT. In severe stroke, LMWH should be co-administrated for prevention of thromboembolic events also, at least, in 24 h after thrombolysis [16, 17].

*Clinical Scenario D: Antiaggregants Before Stroke, and Intravenous Thrombolysis* Similar to the previous scenario, antiaggregants can be begun on the next day and after CT only. Tactics regarding the choice of antiplatelet agent is similar to scenario B.

*Clinical Scenario E: No Antiaggregants Before Stroke, Endovascular Mechanical Thromboectomy* If intravenous thrombolysis was missed, antiplatelet therapy is administrated perioperatively. Aspirin should be started as early as possible, before endovascular thromboectomy, and should be continued postoperatively [16, 17]. Indications can appear for intraoperative use of glycoprotein IIb/IIIa inhibitors. An indication for postoperative dual antiplatelet therapy is controversial and very risky in severe stroke.

*Clinical Scenario F: Antiaggregants Before Stroke, Endovascular Mechanical Thromboectomy* If intravenous thrombolysis was missed, antiplatelet therapy is administrated perioperatively. It is reasonable to stop dual antiaggregant therapy, and to begin monotherapy with choice like in scenario B. Intraoperatively, surgeon can face with the necessity of glycoprotein IIb/IIIa inhibitors. Postoperatively, antiaggregant monotherapy is continued under control of ROTEM. Intravenous thrombolysis, performed before endovascular therapy, is a strong contraindication for perioperative use of antiplatelet agents in both scenario E and F.

## 8.4 Intensive Care and Management of Complications

### 8.4.1 Blood Pressure Management

The majority of patients with stroke have arterial hypertension during acute stage of illness [62]. Rapid decrease of blood pressure is not indicated, and this can be dangerous, because the curve of cerebral autoregulation shifts to the right in most cases with stroke. This means that elevated level of blood pressure is required for adequate cerebral blood flow, especially in penumbra. Permissive hypertension is a commonly accepted practice. In cases without intravenous thrombolysis, or endovascular treatment blood pressure should not be lowered until 220/120 mmHg. As it was discussed above, blood pressure should be less than 180/105 after recanalization for the minimization of the risk of intracranial hemorrhage.

Arterial hypotension develops much more rarely in the acute stage of the stroke in comparison to the rate of arterial hypertension; however, decreased blood pressure is much more dangerous for the injured brain, and especially, for the penumbra zone [63]. Therefore, arterial hypotension should be corrected immediately. The target value of blood pressure for patient with stroke is a disputable question. According to the pathophysiology of the stroke, blood pressure should be maintained at the high level of patient's habitual blood pressure, or a little bit higher [16, 17]. Crystalloids compose the basis of volume resuscitation, whose aim is achievement and maintenance of euvolemia. Solution of 25% albumin can be also successfully used for the volume resuscitation. Simultaneously with volume effects, high dose of albumin demonstrates neuroprotective effects [64]. If arterial

hypotension persists, infusion of sympathomimetics starts without delay. Alpha-sympathomimetics are preferable, and norepinephrine is the sympathomimetic of choice. Beta-sympathomimetics should be avoided, especially in patients with cardioembolic type of stroke, because of high risk of cardiac rhythm abnormalities.

### 8.4.2 Airways Management

Patients in coma with the absence of protective reflexes due to severe dysphagia, and with hypoxic or hypercarbic respiratory failure are intubated immediately, because all these conditions represent absolute and classical indications for tracheal intubation and mechanical ventilation. There are some specific neurological indications for tracheal intubation: signs of increased intracranial pressure, infarct size >2/3 of MCA territory, and midline shift with compression of basal cisterns [65, 66]. In clinical practice, the spectrum of conditions between normal breathing and absolute indications for intubation and mechanical ventilation is extremely wide, and making decision regarding intubation is almost totally a subjective process. Today, there are no commonly accepted scales, which would objectify this making decision.

Previously, my group created Burdenko Respiratory Insufficiency Scale (BRIS: Table 8.2) [67]. The scale evaluates mental status with Richmond agitation sedation scale (RASS); swallowing, cough, and airway patency with previously reported protocols [68], and $pO_2/FiO_2$ index. Scoring is increased by 1 point with obesity because it has negative impact on the respiratory function [69]. Minimal total score is 0 (healthy person), maximal total score is 12 in a patient with normal weight, and 13 in an obese patient. BRIS parts begin with a normal criterion and ends with absolute indication for the intubation and mechanical ventilation. Therefore, patient must be intubated and ventilated immediately, if there is BRIS scoring 4 in any part of the scale ("Mental status", or "Swallowing, cough, and airway patency", or "Index $pO_2/FiO_2$"), or BRIS score of 5 or more as a sum. A BRIS score of 3 or less means that the patient can breathe spontaneously. A BRIS score of 4 as sum points of all three parts of BRIS is still a gray zone.

### 8.4.3 Deep Venous Thrombosis Prophylaxis

Stroke is a prothrombotic state, and larger half of patients with stroke have such risk factors, which considerably increase the risk of thromboembolic complications, such as hemiparesis and immobilization. Therefore, deep venous thrombosis prophylaxis should be performed in all cases, and needs intensive care. Prophylaxis can be started at least in 24 h and after brain CT, confirmed absence of bleeding, in cases with intravenous thrombolysis, and immediately after patient's admission and brain CT, if patient missed intravenous thrombolysis. Heparins either

**Table 8.2** Burdenko Respiratory Insufficiency Scale (BRIS)

| | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 |
|---|---|---|---|---|---|
| Mental status | RASS 0 or consciousness | RASS −1/+1 or hypersomnia | RASS −2/+2 or obtundation | RASS −3−4/+3+4 or stupor | RASS −5 or coma |
| Swallowing, cough, and airway patency | Independent swallowing. Effective cough. Normal airway patency | Independent swallowing. Ineffective cough. Normal airway patency | Slight aspiration of liquids. Effective cough. Normal airway patency | Aspiration for 2 or more food constituents. Ineffective cough. Normal airway patency | Aspiration for 2 or more food constituents. Ineffective cough. Impaired airway patency |
| Index $pO_2/FiO_2$ | >300 | 250–300 | 220–250 | 200–220 | <200 |

*Scoring is increased by 1 in patients with obesity (body mass index > 30)*
*RASS* Richmond agitation sedation scale

unfractionated or LMWH can be used for prophylaxis; however, LMWH are more effective in comparison to unfractionated heparin in preventing deep venous thrombosis [70].

It is difficult to choose correct dose of LMWH, because conventional hemostatic tests do not reflect influence of LMWH to hemostasis. The gold standard for this purpose is Anti-Xa-activity [71]. However, this test does not assess antiaggregants' influence on hemostasis, and has limited accuracy in cases with multi-organ dysfunction and sepsis. Therefore, ROTEM is a preferable laboratory method for choosing adequate dose of LMWH in cases with severe stroke, because different parameters of this test are influenced with both anticoagulants and antiaggregants [23].

### 8.4.4 Malignant Cerebral Infarction

W. Hacke and coauthors coined the term "malignant cerebral infarction" (MCI) in 1996 [72]. MCI is a space-occupying brain edema, developed in patients with ICA or MCA occlusion on the third-to-fifth day after stroke onset. CT and MRI show infarct of, at least, 1/2 of the MCA territory with midline shift and basal cisterns effacement. MCI is the most difficult and severe type of stroke with extremely high morbidity and mortality. Notwithstanding comprehensive patient management with timely use of state-of-the-art methods of recanalization and advanced intensive care give the chance for functional independence to 40–45% of patients with MCI in MCA territory, and to 22–45% of patients with thrombosis of BA [73].

MCI is a unique neurocritical care condition. There is no any other pathology, which would have brain herniation with nearly normal intracranial pressure [74]. This phenomenon is explained with Monro–Kellie doctrine, which postulates that increased volume of brain edema compensates with decreased volume of blood in case of LVO. Therefore, MCI is the only state when routine monitoring of intracranial pressure is not indicated, and when decision-making regarding decompressive hemicraniectomy is solely based on the clinical picture and CT data [74]. Decompressive hemicraniectomy with durotomy decreases mortality, and improves functional outcomes if it performs during 45 h after neurological deterioration. This statement is based on several RCTs [75–78]. For routine clinical practice, this means that decompressive hemicraniectomy should be performed in every patient with MCI regardless of the age, damage of dominant hemisphere, level of consciousness after deterioration, instability of blood pressure, and severity of patient's condition.

In MCI, temperature management is recommended in two regimens: induced normothermia in case of fever, and induced normo- or hypothermia in case of resistant intracranial hypertension after decompressive hemicraniectomy. Prophylactic induced normo- or hypothermia did not show benefit to outcomes [16, 17]. Hypothetically, that is an illogical fact, because decompressive hemicraniectomy and temperature management are most effective maneuvers for intracranial pressure reduction, and their effectiveness is comparable [79–81]. Commonly accepted explanation of the absence of approved efficacy of temperature management is wide spectrum of possible complications of induced hypothermia, which can worsen outcomes [82]. However, decompressive hemicraniectomy has also a lot of possible complications, including fatal [83]. At the same time, there is precise protocol of decompressive hemicraniectomy with description of all details of surgical technique. As a result, effective brain decompression is achieved. Surgical protocol is standardized and implemented into routine clinical practice [84]. Diametrically opposite situation existed with temperature management. Today, there is no single standardized temperature management protocol in MCI, which would be based on RCT. It is difficult to create design and perform high-quality RCT, because temperature management has a lot of details and nuances. We believe that standardized temperature management started in perioperative period of decompressive hemicraniectomy and continued during relatively long period, enough for brain edema dissolving would prove its effectiveness and benefit for outcomes. Further studies are strongly desirable.

## 8.5 Conclusion

Management of stroke is a hard teamwork, when well-organized cooperation between neurologist, intensive care specialist, and neurosurgeon increases the chance of survival and functional independence. Timely performed recanalization, correct prevention of recurrent early thrombosis, and adequate intensive care are obligatory conditions for patient's recovery.

**Key Points**

- Recanalization is the cornerstone of stroke management, and it should be performed as early as possible, because shortening of time between stroke onset and recanalization significantly improves outcomes. Recanalization is achieved with intravenous thrombolysis and endovascular treatment.
- Stroke is an arterial thrombosis, and thus all patients obligatorily require antiaggregants. Dual antiplatelet therapy with aspirin and clopidogrel is reasonable in selected subpopulations.
- Permissive arterial hypertension is a commonly accepted practice, because rapid decrease of blood pressure can be detrimental. Arterial hypotension is dangerous for the injured brain, and it should be corrected immediately.
- Malignant cerebral infarction is a unique neurocritical care condition, and requires decompressive hemicraniectomy with durotomy. Timely and adequate surgery improves outcomes in patients with malignant cerebral infarction.
- Hemostasis management is a real challenge for intensivists, because critically ill patients with stroke receive antiaggregants and anticoagulants. Traditional methods of hemostasis assessment frequently miss dangerous abnormalities. Global method of hemostasis investigation, such as rotational thromboelastometry (ROTEM) or thromboelastography (TEG), can be useful in intricate clinical situations.

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# 9 Intensive Care Management of Meningitis and Encephalitis

Archana Hinduja, Areej Tariq, and Sarah Adriance

## 9.1 Introduction

Meningitis and encephalitis are neurologic emergencies that are associated with significant morbidity and mortality. Meningitis is an inflammatory disease of the leptomeninges and subarachnoid space, while encephalitis is inflammation of the brain parenchyma. The diagnosis of both these conditions is challenging due to its diversity in clinical manifestations and epidemiological features. Although both are pathologically distinct syndromes, there is an extensive clinical overlap between both entities. Due to major overlap in clinical features and treatment decisions, the term "meningoencephalitis" (ME) is frequently used to define this broad spectrum.

Meningitis is characterized by fever, neck rigidity, and altered mental status. Encephalitis is characterized by fever, headaches, altered sensorium, and cerebral dysfunction like seizures and focal neurological deficits. Serious complications like impaired sensorium, hemodynamic instability, and respiratory compromise from these infections require monitoring in the intensive care unit. Although both community and healthcare-associated infections are well-identified causes of ME, there is increasing recognition of noninfectious causes and autoimmune causes. Management strategies in these patients should be targeted toward the offending agent and neurological and systemic complications.

## 9.2 Epidemiology

Following the introduction of conjugate vaccines, a dramatic shift in the epidemiology of community-acquired bacterial meningitis has occurred [1]. Over the past 10–20 years, the incidence has decreased to 0.7–0.9 per 100,000 persons each year in the USA, Finland, and the Netherlands. However, meningitis remains a significant health burden worldwide with the highest rates in sub-Saharan Africa at 10–40 per 100,000 persons each year. *Streptococcus pneumoniae* is the leading causative pathogen globally, and the second is *Neisseria meningitidis*. Infection with pathogens with serotypes not covered by available vaccines presents the biggest challenge of disease control at this

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time. The third most common pathogen is *Listeria monocytogenes*, which mostly affects neonates and the elderly. The occurrence of listerial meningitis is more frequent in patients taking immunosuppressive medications, alcoholics, and those with diabetes mellitus. Meningitis secondary to *Haemophilus influenzae* type b has decreased greatly secondary to the widespread success of the vaccine. Cases observed in adults at this time are largely due to non-b serotypes or non-typable strains. Notably, there is a rise in zoonotic pathogens causing meningitis in regions of the world such as Southeast Asia.

As with bacterial meningitis, fungal meningitis is at its highest in sub-Saharan Africa, where resources are limited and coinfection with HIV is common [2]. *Cryptococcus* meningitis is more common in adult patients in this region than any other pathogen. It is estimated that 220,000 cases occur annually around the world and close to 181,000 deaths each year.

The epidemiology of encephalitis is not as well defined when compared to bacterial meningitis. In general, the disease carries a significant morbidity and poor functional outcomes. Worldwide an incidence of 1 in 10,000 persons per year is estimated [3]. When an etiology can be determined, which occurs approximately 50% of the time, the majority of cases involve a viral infection. The leading global causes are herpes simplex virus (HSV) and varicella zoster virus (VZV). Other notable infectious causes are enteroviruses and West Nile virus [3]. An autoimmune etiology of encephalitis is increasingly being recognized given detection methods of autoantibodies and accounts for approximately 20% of all encephalitis cases. Besides, there is no significant difference between the prevalence of autoimmune encephalitis when compared to infectious encephalitis. The incidence has increased over time, which may partly be from increased recognition of autoantibody-positive cases. Among patients admitted to the intensive care unit (ICU), antibodies to the *N*-methyl-D-aspartate receptor (NMDAR) and leucine-rich glioma-inactivated-1 protein (LGI1) of the voltage-gated potassium channel complex are frequently observed.

## 9.3 Definition

### 9.3.1 Meningitis

The classic triad of fever, neck stiffness, and altered mental status is observed in less than 50% of patients with bacterial meningitis and thus requires a high index of suspicion by the providers to make a diagnosis [4]. Headache and photophobia are common features in patients with meningitis. Almost all patients present with at least two of the four symptoms, which includes headache, fever, neck stiffness, and altered mental status. Examination of the cerebrospinal fluid (CSF) is crucial for establishing a diagnosis of meningitis.

### 9.3.2 Encephalitis

Encephalitis is an inflammation of the brain parenchyma that arises from penetration of blood-brain barrier or overlying meninges. Clinical manifestations include fever, headaches, altered mental status, and features of cerebral dysfunction like seizures and focal deficits. The diagnostic criteria for encephalitis proposed by the International Encephalitis Consortium are [5]:

Major criterion (required)

- Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 h with no altered cause identified.

Minor criteria (2 required for possible encephalitis; ≥3 required for probable or confirmed encephalitis)

- Documented fever ≥38 °C (100.4 °F) within the 72 h before and after presentation
- New onset of focal neurological findings
- Cerebrospinal fluid white blood cell count ≥5/mm$^3$
- Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is new from prior studies or appears acute in onset
- Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause

## 9.4 Infections Causes

Overall, the two foremost causes of infectious meningitis and encephalitis are bacterial and viral in nature. Bacterial cases are considered a neurologic emergency, but all patients suspected of having meningitis or encephalitis should be treated with urgency given the fact that a bacterial diagnosis may not be confirmed initially [6]. Bacterial causes are commonly described by two major subgroups, community-acquired and healthcare-associated, which are differentiated by the environment of infection acquisition. This differentiation changes the anticipated pathogens and empiric antimicrobial treatment employed. Anticipated pathogens according to age and/or patient group for community-acquired bacterial meningitis and healthcare-associated infections are provided in Table 9.1. Healthcare-associated infections are distinct from a clinical presentation perspective and pathogens involved. Common organisms observed in these scenarios include *Staphylococcus*, *Propionibacterium acnes*, and gram-negative organisms *like Pseudomonas* and *Acinetobacter.*

Fungus and parasites may also cause meningitis or encephalitis, although more rarely encountered overall. Untreated, these infections are usually fatal. Immunocompromised patients are at much higher risk. The most common fungal pathogen is *Cryptococcus.* Other pathogens include *Histoplasma*, *Blastomyces*, *Candida*, and *Coccidioides.*

## 9.5 Immunocompromised

Immunocompromised individuals are a challenging population for several reasons. These include atypical presentation of various diseases, increased risk of infection by uncommon and novel agents, and a high morbidity and mortality for the specific cause. Besides they have relatively benign CSF profiles, making this diagnosis is challenging. There is increased incidence of HSV and VZV CNS infections among patients on immunosuppressive and immunomodulatory therapies [7]. Balamuthia mandrillaris, a free-living amoeba, causes granulomatous encephalitis predominantly in the immunocompromised patients [7]. In patients that received organ transplantation, besides donor-related infections, HHV (human herpes virus)-6 and BK virus are possible causes of encephalitis [7]. Due to the presence of atypical pathogens, atypical presentations, potential for multiple concurrent pathogens in these patients, and next-generation sequencing of the CSF play a huge role in identifying the offending pathogen [7].

## 9.6 Noninfectious Causes

Noninfectious meningitis presents with symptoms similar to patients with infectious meningitis, although clinical signs and symptoms may be more chronic in nature (e.g., present for at least 4 weeks in duration). In noninfectious meningitis, severity

**Table 9.1** Empiric antimicrobial treatment for meningitis or encephalitis

| Patient group | Etiologies | Antibiotics[a] |
|---|---|---|
| Age ≥1 month and not immunosuppressed<br>Basilar skull fracture | *Streptococcus pneumoniae*<br>*Neisseria meningitidis* | Vancomycin 15–20 mg/kg IV q8-12h and ceftriaxone 2g q12h |
| Age >50<br>Immunosuppressed | *Streptococcus pneumoniae*<br>*Listeria monocytogenes*<br>Gram-negative bacilli | Vancomycin 15–20 mg/kg IV q8-12h and ceftriaxone 2g IV q12h and ampicillin 2g IV q4h |
| Healthcare-associated meningitis<br>Penetrating trauma<br>Post-neurosurgery | *Staphylococci*<br>Aerobic gram negatives including *Pseudomonas aeruginosa*<br>*Propionibacterium acnes* | Vancomycin 15–20 mg/kg IV q8-12h<br>Cefepime 2 gm IV q8h |
| Meningitis with severe beta-lactam allergy | | Vancomycin 15–20 mg/kg IV q8-12h<br>Levofloxacin 750 mg IV q24h<br>Add TMP/SMX 5 mg/kg q8h if age > 50 or immunosuppressed |
| Encephalitis | | Acyclovir 10 mg/kg IV q8h |

[a]Dosing for adult patients with normal renal function

and acuity can vary. Causes include leptomeningeal metastases, inflammatory disorders (systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, primary central nervous system angiitis, and sarcoidosis), medications, Mollaret's meningitis, brain injury, and neurosurgery. Specific medications that have been associated with noninfectious meningitis include nonsteroidal anti-inflammatory drugs (NSAIDs), trimethoprim-sulfamethoxazole, intravenous immune globulin, azathioprine, cyclosporine, carbamazepine, and isoniazid. Treatment strategy is largely supportive and generally involves management of the causative disorder and cessation of an offending drug if applicable. In a patient who is critically ill, early management should still include broad-spectrum antimicrobials until life-threatening, acute bacterial meningitis or encephalitis is ruled out.

## 9.7 Autoimmune Causes

Autoimmune encephalitis is increasingly an important etiology of new-onset altered mental status, which frequently requires intensive care. The classical presentation described involves a subacute, progressive decrease in mental status that may fluctuate and involve altered cognition. This however may only described in 25% of patients prior to ICU presentation. A frequent presentation that should raise suspicion is status epilepticus [8]. When encountered, the clinician should anticipate immunotherapy and a lengthy hospital admission.

Diagnostic criteria for possible autoimmune encephalitis:

Diagnosis is made when all three criteria have been met

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. At least one of the following:
   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytsis (white blood cell count of more than five cells per $mm^3$)
3. Reasonable exclusion of alternative causes

Diagnostic criteria for definitive autoimmune limbic encephalitis:

Diagnosis can be made when all four definitive criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes
3. At least one of the following:
   - CSF pleocytosis (white blood cell count of more than five cells per $mm^3$)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes

Various alternative etiologies that need to be excluded include CNS infections, septic encephalopathy, metabolic encephalopathy, drug toxicity, cerebrovascular disease, neoplastic disorders, epileptic disorders, Creutzfeldt-Jakob disease, autoimmune disorders, and mitochondrial diseases.

## 9.8 Clinical Features of Meningoencephalitis

Common features of meningitis include fever, headache, neck stiffness, and nuchal rigidity. These patients may present as malaise, fever, irritability, and vomiting or have a fulminant presentation. The course is often acute in patients with bacterial meningitis, and the classical triad of fever, headache/nuchal rigidity, and altered mental status is not always present, but most patients have high fever and severe diffuse headache which is easily distinguishable from regular headache [4]. In the community-acquired meningitis, fever is present at presentation in 95%, nuchal rigidity in 88%, headache in 87%, and lethargy and confusion in 78% of patients [9]. Older patients with diabetes mellitus or cardiopulmonary diseases and immunocompromised may manifest with

confusion, lethargy, and obtundation in the absence of fever or other meningeal signs. Neisseria meningitides infection may manifest with petechial rash and purpura. Although bacterial meningitis spares other organs, sepsis and multiple organ involvement can ensue, especially if meningitis is sequela of systemic infections.

Viral meningitis presents similar to bacterial meningitis however follows a less severe and more self-limited course. Viral encephalitis is a more severe disease that can be distinguished from meningitis on the basis of absence of normal cerebral function. Viral infection can either present as aseptic meningitis or encephalitis. Patients with encephalitis have a variable presentation depending on the etiology. Common features include headache, seizures, lethargy, and personality or behavioral changes. Other features include neck stiffness, irritability, focal deficits, and coma [10]. Seizures are most commonly seen with viral and autoimmune or antibody-associated encephalitis. The occurrence of seizures is variable, with highest incidence of 85% seen with Japanese encephalitis or Murray Valley encephalitis and 10% of West Nile virus encephalitis. West Nile virus is particularly known to cause both paralysis and sensory loss and cranial neuropathies that interfere with swallowing and laryngeal functions. Patients with fungal meningitis have a more indolent presentation of their symptoms and common in the immunocompromised patients. Autoimmune encephalitis can present with variable symptoms like typical limbic encephalitis or complex neuropsychiatric syndromes with psychosis, seizure, memory deficits, chorea, or coma. Women and children are commonly affected.

Tuberculous meningitis frequently presents with headache, confusion and cranial nerve signs, coma, seizures, and hemiparesis. It progresses through three discernible stages with prodromal phase lasting 2–3 weeks characterized by headache low-grade fever and personality change. Meningitic phase follows this, with neurologic manifestations of meningismus, vomiting, confusion, lethargy, and cranial nerve/long tract signs. Paralysis is the third and most fulminant of the three phases, because it rapidly progresses to coma, seizures, and death within 5–8 weeks of onset in untreated patients.

## 9.9 Diagnostic Tests in Patients with Meningitis and Encephalitis

CSF examination is the cornerstone of diagnosis, but significant concerns are present in performing a lumbar puncture in patients with cerebral edema and hydrocephalus due to risk of herniation (Table 9.2). A non-contrast computed tomography (CT) should be obtained before a spinal tap in immunocompromised patients or adults with focal neurological signs, seizures, obtundation, and papilledema [11]. Early clues to the potential pathogen are obtained by the differentials and gram stain on the CSF. Besides routine analysis, various antibodies, polymerase chain reaction testing, and cultures of various pathogens assist in establishing a diagnosis. Besides, this blood cultures, serologies, magnetic resonance imaging (MRI) of the brain, and electroencephalography assist in evaluating the etiology and course (Table 9.3).

**Table 9.2** CSF analysis in patients with meningoencephalitis

| | Appearance | Opening pressure (cm H2O) | WBC count (cells/mm$^3$) | Glucose % of serum levels | Protein (mg/dl) |
|---|---|---|---|---|---|
| Normal | Clear | 10–20 | 0–5 | >60 | <45 |
| Bacterial | Clear/cloudy or purulent | >25 | >100 (>90% PMN) | <40 | >50 |
| Viral | Clear | Normal or elevated | 10–1000 (lymphocytic predominance) | >60 | >50 |
| Fungal | Clear/cloudy | Elevated | 10–500 | Low | Elevated |
| Tuberculosis | Clear/opaque | Elevated | 50–5000 (PMN in early stages) | Low | Elevated |

**Table 9.3** Common diagnostic tests for initial evaluation in meningitis and encephalitis

| Routine studies |
|---|
| CSF |
| Opening pressure, leucocyte count with differential, erythrocyte count, protein, glucose |
| Gram stain and bacterial culture |
| HSV-1/2 PCR (consider HSV CSF IgG and IgM in addition) |
| VZV PCR (consider VZV CSF IgG and IgM in addition) |
| Enterovirus PCR |
| Cryptococcal antigen and/or India ink staining |
| Oligoclonal bands and IgG index |
| Venereal disease research laboratory |
| Serum |
| Routine blood cultures |
| HIV serology (consider RNA) |
| Treponemal testing (rapid plasma regain, specific treponemal test) |
| Hold acute serum and collect convalescent serum 10–14 days for paired antibody testing |
| Imaging |
| Neuroimaging (MRI preferred to CT, if available) |
| Chest imaging (chest X-ray or CT) |
| Neurophysiology |
| Electroencephalogram |
| Conditional studies |
| Immunocompromised, CMV PCR; HHV6/7 PCR; WNV, PCR serology; *Listeria*, culture; *Toxoplasma gondii*, serology; MTB, chest X-ray; PPD, serology; fungal infections, culture, biopsy, other methods |
| Autoimmune antibodies |
| NMDAR, AMPAR, GABA-A, GABA-A, D2R, GlyR, LG1, CASPR2, DPPX, Ma2, Hu, Yo, amphiphysin, GAD |
| Evaluation for systemic malignancy |

## 9.10 Biomarkers

Few controlled studies in ICU patients have examined biomarkers to determine the need for initiation or duration of antibiotic therapy. The role of biomarkers in management of meningitis is less studied; however due to practical problems in discriminating bacterial and viral/aseptic meningitis because of overlapping CSF parameters and nondistinctive physical examination, the use of biomarkers in diagnosis and progress of disease is becoming more popular among ICU physicians. Significant ones that have been identified in the literature include:

1 Lactate
Meta-analyses on CSF lactate concluded that it is a reliable biomarker for differentiating BM from aseptic meningitis, with a sensitivity of 0.93 (95% CI, 0.89–0.96) and specificity of 0.96 (95% CI, 0.93–0.98) [12]. Cutoff CSF lactate levels of ≥3.5 mmoles/L were used. In patients who had received antibiotics, the sensitivity was lower 0.49 (95% CI, 0.23–0.75), which limited the application of CFS lactate as a biomarker in a subset of patients.

2 Procalcitonin
The sensitivity of CSF procalcitonin (PCT, a polypeptide of 116 amino acids) as a marker in the diagnosis of ME has demonstrated mixed results. Although earlier studies reported a sensitivity of 99% and specificity of 83%, follow up cross-sectional studies failed to replicate these results [13]. However, when used in combination with other markers, it was a reasonable marker to exclude the diagnosis of bacterial meningitis. Among patients with ME, CSF-PCT levels are significantly higher ($P < 0.01$) in patients with bacterial meningitis than other etiologies, including those that received empiric antibiotic treatment and thus may be assist in case of diagnostic dilemma [14].

3 Heparin-binding protein
CSF HBP level > 20 ng/mL was 100% sensitive and 99.2% specific for bacterial meningitis and thus may be used to differentiate from other causes of CNS infections [15].

## 9.11 Management in the ICU

Central nervous system infections are emergent conditions, and the initial suspicion and management should be initiated in the emergency department. About 25% of patients with ME are admitted to the ICU [16]. Patients with ME admitted to the ICU frequently require admission for management of their neurological complications or for medical complications and occasionally a combination of factors. The immediate goal on presentation to the ICU is to ensure patient safety simultaneously undertaking efficient and effective measures to effectively

diagnose and manage patients with suspected ME. The clinical needs of patients with ME are complex and require a multidisciplinary team. Assessing the ABCs is the essential first step. Patients with reduced level of consciousness from seizures, cerebral edema, metabolic encephalopathy, or systemic conditions like pneumonia may result in failure to protect the airway, hypoxia, or hypercarbia that may necessitate intubation and mechanical ventilation. Coma followed by inability to protect airway, seizures, and respiratory failure are common sequela that result in most of these patients thus warranting an ICU admission. Coma may result from involvement of the reticular activating system (RAS) either by direct effects of the virus or from raised ICP and cerebral edema. Patients with various specific encephalitis like anti-NMDAR encephalitis and HSV encephalitis may have impaired autonomic dysfunction and require hemodynamic stability.

## 9.12 Risk Factors for Admission to the ICU

Various factors that are associated with admission to the ICU in patients with ME include seizures, status epilepticus, altered mental status (Glasgow Coma Score—GCS < 8), and respiratory failure [17–19]. Various factors that are associated with need for respiratory support are a high SOFA score, low GCS, raised ICP, and thrombocytopenia [19]. Major concerns in these patients include raised ICP and mass effect, direct and global inflammation or infection of the brain, and systemic issues that affect the cerebral function (i.e., fever, hypoglycemia, electrolyte abnormality, systemic infections, hypoxia, and hypercarbia).

## 9.13 Management of the Offending Etiology

Bacterial meningitis was nearly a fatal disease before the advent of antimicrobial agents, with a case fatality rate of >70%. This was markedly been reduced from timely use of antimicrobials. Instituting early antimicrobial therapy cannot be overstated when managing a patient suspected of having meningitis or encephalitis [6, 20–22]. Increased mortality and worsened neurological outcome can occur with delayed initiation of antibiotics [23]. Therapy should not be delayed for CSF sampling or results of other diagnostic work-up. Suggested routine treatment recommendations for adult patients with suspected meningitis or encephalitis are detailed in Table 9.1. In general, dose adjustments for most antimicrobials for treatment of CNS infection are required in the setting of renal insufficiency and can be addressed once initial doses have been administered. De-escalation of broad-spectrum antimicrobials should occur once culture data become available. Consultation with infectious diseases should be considered. Duration of therapy varies depending on organism and is based on guidelines [6, 20–22]. For most community-acquired pathogens, treatment for 7–14 days is adequate with the exception of *Listeria monocytogenes* and group B streptococcus in which a 14–21-day course is recommended. Enterobacteriaceae and other gram-negatives such as *Pseudomonas aeruginosa*, which are more commonly encountered in healthcare-associated infections, are generally treated for 3 weeks. Patients in whom systemic therapy fails, intrathecal administration of antibiotics may be considered after discussion with multidisciplinary team. Besides antibiotics, empiric antiviral therapy with acyclovir is initiated in patients with suspected viral ME until the cultures or serology is negative.

However, empiric antifungal therapy is not routinely initiated in every patient with suspected meningitis or encephalitis. Once a fungal pathogen is suspected, the empiric therapy of choice is amphotericin B 5 mg/kg IV every 24 h. Duration of therapy is not well defined for fungal CNS infection, but in general it is treated for longer than bacterial or viral infections. An infectious diseases specialist should be consulted. In patients with tuberculous meningitis, therapy is done with four drugs (rifampin, isoniazid, pyrazinamide, and ethambutol) administered daily for

2 months, which is followed by prolonged continuation phase with two drugs (isoniazid and rifampin) given over 7–10 months. Glucocorticoids are warranted in cases of rapid deterioration, encephalitis, and patients with advancing hydrocephalus or tuberculoma patients with significant mass effect.

In patients with autoimmune encephalitis, anti-NMDAR encephalitis has become a model for treatment strategy in many types of autoimmune encephalitis [24]. Treatment typically involves methylprednisolone 1 gm intravenous daily for 5 days and/or IVIg 0.4 gm/kg/day for 5 days. In unresponsive cases, other intravenous therapies such as rituximab or cyclophosphamide are more commonly used. Available literature supports the prompt initiation of immunotherapy to impact clinical improvement and quick escalation of therapy in patients who do not improve. Recovery with autoimmune encephalitis is expected to be slow, and many cases have a tendency to relapse. A thorough systemic work-up to exclude underlying malignancy should be performed for long-term resolution.

## 9.14 Corticosteroids Therapy in Meningitis

Animal models of bacterial meningitis have demonstrated bacterial lysis induced by antibiotics leads to inflammation in the subarachnoid space, which might be a predominant factor contributing to the morbidity and fatality. Attenuation of inflammatory response may play a role in reduction of various pathophysiological consequences from bacterial meningitis such as cerebral edema, elevated intracranial pressure, cerebral vasculitis, and neuronal damage. Based on these observations, several clinical trials on use of steroids in meningitis have been undertaken. Dexamethasone, a glucocorticosteroid with anti-inflammatory and immunosuppressive properties, has an excellent CSF penetration. In children with *Haemophilus influenzae* meningitis, a decrease in CSF inflammatory response and the incidence of deafness from treatment with cefotaxime plus dexamethasone compared to cefotaxime alone have been observed [25]. In adults with pneumococcal meningitis, early treatment with steroids has been associated with decreased mortality and unfavorable outcome [26]. However, subsequent studies have demonstrated conflicting results, which range from mortality benefit to benefit in confirmed bacterial meningitis only and lack of mortality benefit [26–29]. Early administration of steroids is crucial since various studies have shown lack of benefit in patients from low-income countries, where they tend to present late in their disease course [27, 30]. Several guidelines have recommended the routine use of adjuvant steroids in patients with pneumococcal meningitis [6, 31]. In patients with meningococcal meningitis, adjunctive steroids were not associated with increased risk of adverse events [32]. In HIV-associated cryptococcal meningitis, adjunctive steroid use did not reduce mortality but was associated with more adverse events and disability [33]. In tuberculous meningitis, adjunctive use of steroids has a significant mortality benefit on short-term analysis [34]. However, when disabling neurological deficit alone or combined outcome of death or disabling residual neurological deficit was analyzed, only a few trials showed benefit from steroids use [34, 35]. The survival benefit from steroids was observed only on short-term follow-up and not long-term follow-up in grade 1 disease [34–36]. There is insufficient data on mortality benefit in patients with tuberculous meningitis that are HIV-positive [34, 35].

## 9.15 Management of Neurological Complications

Despite advances in antimicrobial therapy, the US Centers for Disease Control and Prevention population-based surveillance between 1998 and 2007 demonstrated a decline in case fatality rate of 1.4% from bacterial meningitis that was statistically insignificant ($p = 0.05$). Death in patients with ME is caused by cerebral edema, cerebral infarction leading to herniation and brainstem compression, sepsis, and coagulopathy. The management of common neurological complications encountered in these patients is described.

## 9.16 Raised Intracranial Pressure

Raised ICP leading to herniation and compression of the brainstem is a frequent cause of death from meningitis. Raised ICP has been reported in approximately 50% of patients with encephalitis and 90% of severe cases of bacterial meningitis. Cerebral edema in patients with ME is multifactorial in etiology (cytotoxic, vasogenic, and interstitial), and the severity depends on the offending agent. CNS inflammation, cerebral edema, and impaired autoregulation all contribute to the development of raised ICP. Despite the fact that elevated intracranial pressure and subsequent death is a well-known complication of meningitis, no specific guidelines targeting management of ICP in these patients are outlined. Acute reduction or alteration in the levels of consciousness is an emergent neurological issue. Concerns for ICP abnormalities could be suspected by prompt bedside assessment and immediate imaging of the brain. However, in patients with encephalitis, altered mental status might be from global or brainstem dysfunction or raised ICP. A routine head CT might be insufficient to exclude raised ICP in all cases. Several studies have demonstrated a failure to identify cerebral edema on CT in patients with meningitis [37]. Studies have demonstrated a lack of significant correlation between various signs of elevated ICP on head CT with elevated ICP upon objective measurement in patients with bacterial meningitis [38]. Lower mean cerebral perfusion pressure (CPP) in these patients has been associated with adverse outcome ($p = 0.005$) [38]. Cerebral herniation following lumbar puncture has been reported despite a normal CT [39]. Patients with a meningitis that have a GCS $\leq 8$ have a significantly high mortality rates compared to those with a GCS $\geq 12$, which is consistent with the fact that elevated ICP is highly prevalent in patients with lower GCS score [9]. Therefore in patients with meningitis who are stupors or comatose, despite a normal CT, raised ICP should be suspected. Besides, ICP may vary considerably throughout the disease course, and ICP monitoring has been associated with improved outcomes.

Initial targets of raised ICP that include assisted mechanical ventilation, maintaining a normal oxygenation ($O_2$ saturation of >90%), hyperventilation to $pCO_2$ of 30 ± 5 mmHg (as a temporary measure), mean arterial pressure of at least 60 mmHg, adequate analgesia, and sedation are reasonable. For mass effect from cerebral edema or raised ICP, osmotherapy with hypertonic saline or mannitol may be used. Caution should be taken to avoid dehydration from mannitol. Hypertonic saline is advantageous especially in patients with hyponatremia, which is commonly observed in patients with meningitis. Glycerol had minimal or no effect on death in patients with bacterial meningitis (RR = 1.09, 95% CI 0.89–1.33) or on combined death and functional outcome (RR = 1.04, 95% CI 0.86–1.25) [40]. An aggressive approach in neurointensive care to control ICP control has translated to good outcomes in adults with severe bacterial meningitis. All patients received routine care in the ICU with mechanical ventilation, sedation, antibiotics, and steroids [41]. Additional treatment of ICP included drainage of the cerebrospinal fluid using external ventricular drain, osmotherapy, hyperventilation, external cooling, methylprednisolone, and deep barbiturate sedation with a target ICP <20 mmHg and a cerebral perfusion pressure of >50 mmHg. A significant reduction in 2-month mortality (10% versus 30%, $p < 0.05$) and improvement in overall clinical outcome using GOS (Glasgow outcome score) at 2–6 months (54% versus 32%, $p < 0.05$) were observed from intensive therapy compared to controls. Optimal control of ICP alone might be insufficient in improving clinical outcomes. In a prospective open-label randomized controlled trial that compared CPP-targeted therapy (CPP $\geq$ 60 mmHg) to ICP-targeted therapy (ICP < 20 mmHg), there was a significant decrease in 90-day mortality (18.2% versus 38.2%, $p = 0.020$) and 90-day disability (37.8% versus 70.6%, $p = 0.004$) in favor of the CPP-targeted therapy [42]. Alternatively, CSF diversion using a lumbar drain with the standard therapy has shown reduction in mortality despite a greater clinical severity in these patients (0% versus 15.4%, $p = 0.0001$) [43]. In persistent cases, a ventriculoperitoneal (VP) shunt may be placed. In certain

cases, multimodal monitoring has guided in decisions to undertake a decompressive craniectomy for management of refractory ICP that resulted in good outcome [44]. Thus in patients with ME with GCS $\leq 8$, ICP monitoring may be considered with stepwise management of ICP and CPP.

## 9.17 Hydrocephalus

Hydrocephalus is a common complication of meningitis and is associated with high fatality rates and poor outcomes. It has been observed in 3–5% of cases with complicating community-acquired bacterial meningitis, but roughly 30–80% of patients with tuberculous and cryptococcal meningitis developed hydrocephalus [45]. Both impairment of CSF absorption and excessive production contribute to the development of obstructive and communicating hydrocephalus. Communicating hydrocephalus in these patients is reflective of failure of CSF absorption by the arachnoid granulation due to severe infection and obstructive hydrocephalus results from blockage of CSF by exudate at the ventricular pathways. Hydrocephalus may be observed on presentation or develop during the course of their illness, thus requiring frequent surveillance for its development or progression. The manifestations are non-specific ranging from headache to nausea or vomiting, altered sensorium, coma, and raised ICP. Medical management should be the first line of therapy, which includes administration of steroids, osmotherapy, diuretics like acetazolamide, and furosemide to reduce CSF production. Early surgical measures in patients with persistent hydrocephalus and raised ICP by diverting CSF (eg., EVD, lumbar drain) may be performed. In ongoing cases of hydrocephalus or coma, these may be transitioned to a VP shunt or ventriculoatrial shunt [46]. The timing of placement of VP shunts in these patients is highly controversial. In certain etiologies like tuberculosis, a direct VP shunt may be placed as the initial invasive measure [47]. Endoscopic third ventriculostomy may be formed alternatively to avoid insertion of foreign body [46]. The placement of VP shunt may not improve altered sensorium in all cases although it may result in improvement in hydrocephalus. Altered sensorium in these patients is multifactorial and cannot be attributed to the presence of hydrocephalus. Outcomes in patients that required VP shunts is highly dependent on the clinical severity, with HIV-infected individuals having a worse prognosis compared to HIV uninfected patients [48].

## 9.18 Seizures

Seizures and status epilepticus are a common presentation of ME and are observed in 15–55% of patients admitted with ME [4, 9, 16, 17]. Seizures are a risk factor associated with admission to the ICU and poor outcome [16, 17]. These could be convulsive or nonconvulsive seizures. Rapid control of seizures is crucial for several reasons (1) to control systemic complications, that include rhabdomyolysis, lactic acidosis, aspiration pneumonia, (2) limit additional neurological damage and (3) ongoing seizures are difficult to control over time. Although the incidence of nonconvulsive status epilepticus is high with encephalitis, there is lack of evidence that supports prophylactic use of antiepileptic drugs. The initial drug of choice is intravenous lorazepam with simultaneous assessment of the airway performed. The second-line antiepileptic agent should begin even though the seizures were aborted by lorazepam, to prevent relapse of seizures. Because rapid administration is preferred, intravenous preparations are preferred. These include phenytoin, fosphenytoin, valproate, and levetiracetam. It is not uncommon for patients with encephalitis to progress to refractory status epilepticus that requires a third-line agent with anesthetic properties like midazolam, propofol, barbiturates, and ketamine with a goal to eradicate seizures. Continuous electroencephalographic (EEG) monitoring is required to optimize the antiepileptic drug therapy while minimizing the duration of drug exposure. The optimal degree of suppression to target is highly controversial. The typical targets used in practice include suppression of clinical and electrographic seizures or burst suppression pattern on EEG monitoring for 24 h followed by taper over the

next 24–48 h while monitoring for recurrence of seizure activity. As the use of aggressive measures increases, so does the supportive care due to potential complications of hypotension, loss of protective airway reflexes, and systemic complications like sepsis and pneumonia. Besides, caution must be executed for the development of various adverse events like propofol infusion syndrome and acidosis from their use.

## 9.19 Strokes

Stroke is a common complication in patients with ME and is associated with high mortality and long-term sequel among survivors. These are observed in 15–50% of patients with ME [49]. These are commonly of the ischemic type, affecting the basal ganglia. Several mechanisms of infarctions in patients with ME that have been proposed include vasculitis, vasculopathy, vasospasm, activation of coagulation cascade, and diffuse intravascular coagulation [50]. Various risk factors associated with cerebral infarction include worsening inflammation, high erythrocyte sedimentation rate, low GCS, low CSF white cell count, hydrocephalus, smoking, meningeal inflammation and basal exudates on imaging. Imaging of the cerebral vasculature in patients may reveal either normal narrowing or occlusion of the intracranial vessels. The use of aspirin in patients with tuberculosis resulted in an insignificant reduction in strokes but a significant reduction in 3-month mortality. While majority of the strokes occur during the acute phase, delayed cerebral thrombosis, a rare fatal phenomenon, is observed in 1% of patients. Autopsy has showed thrombosis of the penetrating arteries supplying the thalamus and brainstem, indicative of immunological process targeting the blood vessels. Various proposed mechanisms include CSF analysis that was indicative of persistent or recurrent inflammation without ongoing bacterial infection or from sustained coagulation and platelet aggregation.

Although arterial infarcts are common, cerebral venous infarction is a rare complication in patients with ME.

## 9.20 Outcome

Patients that are admitted to the ICU with ME have a substantial morbidity and mortality. Despite admission to the ICU, good outcome (modified Rankin Scale = 0–3) has been observed in 60% of patients [8, 17]. The mortality rate in patients with community-acquired bacterial meningitis is about 20–25% but is noticeably high in pneumococcal meningitis than other types [4, 9]. Factors associated with poor outcomes in patients with meningitis include old age, presence of otitis or sinusitis, absence of rash, absence of fever, low admission GCS, tachycardia, positive blood culture, elevated erythrocyte sedimentation rate, thrombocytopenia, low CSF white cell count, and seizures within the first 24 h [4, 9, 18]. Treatment with steroids before initiation of antibiotics in bacterial meningitis has reduced the rates of unfavorable outcomes [4, 26].

In general, the mortality rate from encephalitis in large population-based studies is about 6%, but this could be as high as 19% in large tertiary care centers [16, 51]. Factors associated with mortality and poor outcome from encephalitis include immunocompromised state, HIV/AIDS or cancer, coma, cerebral edema, status epilepticus, thrombocytopenia, endotracheal intubation with ventilator support, aspiration pneumonia, lower body temperature, elevated CSF protein levels, and delayed ICU admission [16, 51, 52]. In contrast, the development of seizures or focal neurological deficits was not associated with clinical outcomes [10]. There is conflicting data on etiology of encephalitis and outcomes in these patients [10, 16]. Long-term follow-up of patients with encephalitis of unknown etiology revealed persistent neurological deficits and cognitive problems in approximately half of those that survived [53]. Normal EEG is an independent predictor of survival and thus may be used in conjunction with clinical and diagnostic information as a prognostication tool in these patients [54]. Patients that survive hospitalization may have seizures, focal deficits, and cranial nerve deficits and require neurorehabilitation. Besides, neuropsychological examinations revealed that one third of patients have cognitive deficits and require cognitive therapy.

## 9.21 Conclusions

Neurointensive care frequently involves patients with a suspected or confirmed case of meningitis or encephalitis. These disease states can be devastating neurologically. Empiric therapy should be initiated early and must appropriately cover the most anticipated pathogens to optimize a favorable outcome. Antimicrobial therapy is started without delay for diagnostic work-up and de-escalated or discontinued based on available data. Management of complications from meningitis and encephalitis is frequent in the intensive care setting, and the clinician should be prepared to encounter these in the course of care.

**Key Points**

- About 25% of patients with meningoencephalitis require care in the neurointensive care unit.
- Risk factors of admission to the intensive care unit include seizures, status epilepticus, altered mental status, and respiratory failure.
- Major neurological concerns encountered in these patients include elevated intracranial pressure, hydrocephalus, and seizures including status epilepticus and strokes.
- Patients admitted to the intensive care unit have a substantial morbidity and mortality.

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# Critical Care Management of Subarachnoid Hemorrhage

10

Christopher E. Dukatz and Ines P. Koerner

## 10.1 Epidemiology and Diagnosis

Subarachnoid hemorrhage (SAH) causes significant morbidity and mortality. Roughly 1 in 10,000 adults suffers SAH caused by a ruptured cerebral aneurysm (aneurysmal SAH, aSAH) every year. Fifteen percent will die before reaching the hospital and another 20% in the hospital. A large number of survivors of SAH suffer at least moderate long-term disability, and only 50% recover sufficiently to return to work in their profession [1]. Poor outcome relates to early brain injury associated with the ictus as well as a plethora of delayed complications, including hydrocephalus, vasospasm, and delayed cerebral ischemia (DCI). Many of these complications can be ameliorated when diagnosed and treated early, which is why patients after subarachnoid hemorrhage should be monitored in intensive care units with experts treating this disease.

While trauma represents the most common cause of blood in the subarachnoid space, the etiology of non-traumatic SAH is dominated by aneurysmal rupture in 80% of presentations. Other etiologies include arteriovenous malformations (AVMs), amyloid angiopathy, vasculitis, and toxic and inflammatory vasculopathies. This chapter focuses on the treatment of aneurysmal subarachnoid hemorrhage, as these patients are at highest risk for developing complications and pose the most challenges to the treatment team.

Presentation is varied, although most cases share a sudden onset, with the majority of patients describing acute onset of severe headache, frequently characterized as the "worst headache of my life." This is often associated with nausea, vomiting, neck pain, and brief loss of consciousness. More severe cases present with profound reduction of level of alertness, up to coma, and a variety of focal deficits.

As aneurysms of the cerebral arteries are acquired malformations that likely develop in response to chronic vascular injury, risk factors include increasing age, hypertension, tobacco use, alcohol abuse, and use of sympathomimetic drugs. There also appears to be a genetic component, as women carry increased risk, as do individuals with a family history of aneurysmal SAH in first-degree relatives and those affected by polycystic kidney disease and connective tissue diseases such as Ehlers-Danlos syndrome.

The initial study when SAH is suspected should be a non-contrast computed tomography (CT) of the brain, which has close to 100%

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sensitivity to detect SAH when completed within 6 h of onset of headache on a modern CT scanner and interpreted by skilled radiologist [2]. MRI including gradient recovery echo sequences has even higher sensitivity and can be helpful in unclear situations. Typical distributions of subarachnoid blood on CT scan include spread to the basal cisterns and major fissures and within the ventricles. False-negative CTs do occur, particularly when presentation is delayed. Lumbar puncture with spectrophotometric evaluation of cerebrospinal fluid (CSF) for xanthochromia remains standard of care for evaluation of patients with negative or equivocal CT scans [3]. Xanthochromia indicates the presence of hemoglobin breakdown products (mostly bilirubin and oxyhemoglobin), which is caused by the degeneration of red blood cells and develops within 4–6 h after the ictus. Once the diagnosis of SAH is confirmed, CT angiography (CTA) or digital subtraction angiography (DSA) can identify the underlying aneurysm. DSA remains the most sensitive study and has the advantage that coil embolization of amendable aneurysms can be performed during the initial angiography. CT angiography can be used alternatively if DSA is not immediately available.

## 10.2 Initial Management

Initial evaluation and management should focus on airway and hemodynamic stability. Patients who are unable to protect their airway should be intubated before CT imaging. Severe hypertension should be treated, as it may increase the risk of rebleeding [4]. Most commonly, a systolic blood pressure of less than 160 mmHg is targeted while avoiding hypotension. Short-acting intravenous agents should be used for blood pressure control, such as labetalol (5–20 mg) or hydralazine (5–20 mg). Nicardipine infusion (5–10 mg/h) is helpful to control refractory hypertension.

Severity of the initial injury and amount of blood present on initial CT scan are the most reliable predictors of neurologic complications and outcome after SAH. All patients should therefore be scored after initial stabilization. Hunt and Hess scale, World Federation of Neurological Surgeons (WFNS) scale, and Fisher Scale are the most commonly used scales (Table 10.1). Higher scores correlate with more severe injury and higher risk of poor outcome. The WFNS scale uses more objective measures and is thus preferable to the older Hunt and Hess scale.

**Table 10.1** SAH grading scales

| World Federation of Neurological Surgeons scale | | | Hunt and Hess scale | | Fisher scale | | |
|---|---|---|---|---|---|---|---|
| Grade | Glasgow Coma Score | Motor deficit | Grade | Neurologic findings | Grade | Subarachnoid blood on CT | Intraparenchymal/ intraventricular blood on CT |
| 1 | 15 | Absent | 1 | Mild headache, nuchal rigidity | 1 | Absent | Absent |
| 2 | 13–14 | Absent | 2 | Moderate or severe headache, no deficit other than cranial nerve palsy | 2 | <1 mm thick diffuse layer | Absent |
| 3 | 13–14 | Present | 3 | Drowsiness, confusion, mild focal deficit | 3 | >1 mm thick diffuse layer or localized clots | Absent |
| 4 | 7–12 | Absent or present | 4 | Stupor, hemiparesis | 4 | Any | Present |
| 5 | 3–6 | Absent or present | 5 | Coma | | | |

Patients with aSAH benefit from close collaboration between medical teams, including neurointensivists, neuroanesthesiologists, neurosurgeons and neuroradiologists, to facilitate prompt diagnosis, early securing of the aneurysm using the most appropriate method for the patient, and early recognition of complication to facilitate appropriate medical or interventional management. Patients should be transferred to a high-volume center that has diagnostic capabilities (CTA and DSA) and vascular neurosurgeons as well as interventional neuroradiologists as early as possible after initial stabilization and should be admitted to a dedicated intensive care unit. Outcomes are better for aSAH patients treated in high-volume centers that see >35 cases per year [5].

## 10.3 Treatment of Unsecured Aneurysms

Rebleeding risk is highest in the first 24–48 h after ictus [6]. Aneurysms should thus be secured as early as possible within the first 72 h. Both microvascular clipping and endovascular coil embolization are available to secure aneurysms. The International Subarachnoid Aneurysm Trial (ISAT) found that for aneurysms deemed appropriate for both clipping and coiling, coiling was associated with a lower complication rate and higher rates of independent survival both at short-term (1 year) and long-term (10 years) follow-up [7, 8]. Certain characteristics of aneurysm, such as a broad neck, location on the middle cerebral artery (MCA), or association with large intraparenchymal clot, make them more amenable to surgical clipping, while aneurysms of the basilar tip are preferentially coiled. Older patients with comorbidities and those with high-grade SAH may benefit from the lower complication rate associated with coiling. The appropriate treatment modality for an individual patient should be selected after multidisciplinary discussion involving the neurosurgeon, neurointerventionalist, and neurointensivist.

## 10.4 Management in the Intensive Care Unit

Patients with SAH are critically ill and prone to a variety of both early and delayed medical and neurologic complications, which benefit from monitoring and treatment in a dedicated, multidisciplinary, and collaborative intensive care unit. SAH is often associated with a profound systemic inflammatory response (SIRS), which may be triggered by early brain injury from the acute increase in intracranial pressure upon aneurysm rupture. An inflammatory cascade is initiated, which contributes to disruption of the blood-brain barrier, cerebral edema, and disturbed autoregulation, increases circulating catecholamines and inflammatory mediators, and may exacerbate delayed cerebral ischemia. SIRS after aSAH is associated with increased complications and poor outcome.

## 10.5 Early Complications

*Rebleeding* Aneurysm rebleeding is associated with high mortality and is a risk factor for poor functional recovery. The risk is highest in the initial 24 h after symptom onset [6]. Rebleeding risk increases with longer time to definitive aneurysm treatment, severity of initial hemorrhage (loss of consciousness, poor neurological status at admission, need for external ventricular drain placement), previous sentinel headaches, persistent hypertension, and larger aneurysm size [4, 9–13]. Early definitive treatment of the aneurysm is the best way to prevent rebleeding. Definitive blood pressure goals to reduce the risk of rebleeding remain poorly defined. A goal systolic blood pressure <160 mmHg is a reasonable target. Short-acting, titratable infusions or intermittent bolus dose medications are recommended in the acute phase. Invasive hemodynamic monitoring via arterial cannulation is indicated while titrating medications but should not delay initiation of therapy. Goals of therapy should balance the risk of rebleeding with maintenance of cerebral perfusion pressure (CPP) in patients with elevated intracranial pressure (ICP).

If securing the aneurysm must be delayed for any reason, it is reasonable to consider a limited course (<72 h) of antifibrinolytics (epsilon aminocaproic acid or tranexamic acid) to stabilize the thrombus, unless medical contraindications exist [14]. Delayed (>48 h after ictus) or prolonged (>3 days) use of antifibrinolytic therapy increases risk of thromboembolic complications without offering additional benefit, as rebleeding risk drops after the first days, and should thus be avoided.

*Hydrocephalus* Acute hydrocephalus occurs in up to 30% of aSAH patients, usually within the first few days [15]. Patients become symptomatic with signs of increased ICP, including nausea and decreased level of consciousness. Symptomatic patients should undergo urgent non-contrast head CT and, if ventriculomegaly is present, have an external ventricular drain (EVD) inserted without delay to provide CSF diversion. Up to 20% of patients after aSAH will develop chronic hydrocephalus and require placement of a permanent shunt [16, 17].

*Seizures* Seizures or seizure-like activity is seen frequently in the acute phase of aSAH, especially with intraparenchymal hemorrhage and MCA aneurysms. However, the incidence of long-term epilepsy after SAH is low [18, 19]. As acute seizures increase rebleeding risk, it is reasonable to provide a short-term (e.g., 1 week) course of antiepileptics to patients deemed at high risk for seizure or who presented with ictal seizure [20]. While no large randomized controlled trials are available to guide choice of antiepileptic agent [21], small studies suggest that levetiracetam is associated with fewer complications and possibly better outcome than phenytoin [22–24]. Nonconvulsive seizures (NCS) are common in patients with high-grade aSAH and associated with poor outcome independent of treatment [25–27]. EEG monitoring can be used to detect NCS in comatose patients.

*Neurogenic Stressed Myocardium* Signs of cardiac stress are frequently seen in the early days after aSAH and include a wide range of symptoms from EKG changes such as QT prolongation and ST changes, over-arrhythmias, and cardiac enzyme elevation all the way to reduced ejection fraction and cardiogenic shock. This syndrome of neurogenic stressed myocardium (NSM) is linked to early catecholamine surge and may be caused by injury to the central autonomic network in the medulla and hypothalamus with a resulting sympathetic hyperactivation that leads to myocyte contraction, ATP depletion, and cell death [28, 29]. NSM is characterized by ST changes and wall motion abnormalities that do not follow a vascular distribution, as well as relatively low troponin levels, which help differentiate NSM from acute coronary syndrome. Typical regional wall motion abnormalities in NMS affect the left ventricle in a global pattern, often with apical predominance and apical ballooning similar to stress-induced Takotsubo cardiomyopathy [29, 30]. In rare cases when suspicion for acute coronary syndrome remains even after echocardiography, cardiac perfusion imaging can be helpful to detect or exclude transmural myocardial ischemia. The presence of NSM after aSAH is associated with vasospasm, DCI, and poor outcome, likely because it is a marker of the severity of initial injury [31, 32]. It is important to be aware of NSM to limit unnecessary invasive workup for coronary disease in patients with typical EKG changes and to institute appropriate pharmacological support for patients who develop cardiac dysfunction leading to hypotension (i.e., inotropes to support left ventricular function over vasoconstrictors). Treatment of NSM is supportive, including inotropic support as needed. While subendocardial petechial hemorrhage and contraction band necrosis with focal myocyte death surrounding sympathetic nerve terminals can be present on autopsy, myocardial infarction is absent, and full recovery of cardiac function with complete resolution of symptoms can be expected within weeks [29, 30].

*Neurogenic Pulmonary Edema* Flash pulmonary edema without cardiac dysfunction can occur after neurologic insults, including aSAH. It is characterized by rapid onset (within minutes to hours) of hypoxic respiratory failure, classically

associated with bilateral pulmonary edema on chest X-ray. Neurogenic pulmonary edema (NPE) has been linked to acute intracranial pressure increase and insults to trigger zones in medulla or hypothalamus, similar to NSM. NPE is short-lived, and resolution typically occurs within 48–72 h. Longer duration of respiratory failure should raise suspicion for non-neurogenic causes, such as acute respiratory distress syndrome (ARDS), aspiration, pneumonia, or cardiogenic pulmonary edema [33–35]. Treatment of NPE is supportive and should include lung-protective ventilation strategies with positive end-expiratory pressure (PEEP) and low tidal volumes.

## 10.6 Late Complications

### 10.6.1 Delayed Cerebral Ischemia

Delayed cerebral ischemia (DCI) is a common and feared detrimental complication after aSAH, affecting a third of patients. It is defined as any focal or global neurologic deterioration that lasts longer than an hour without an obvious alternative cause [36]. DCI can lead to cerebral infarction, disability, and death and is a main driver of poor functional outcome after aSAH [37].

DCI has traditionally been attributed to vasospasm, a narrowing of the larger intracerebral vessels that appears in 70% of aSAH patients between 4 and 14 days after ictus. The assumption is that vasospasm can become severe enough to compromise local cerebral perfusion and cause ischemia. However, there is a dissonance between the occurrences of vasospasm in 70% and DCI in 30% of patients after aSAH. DCI can present in the absence of vasospasm on DSA. More importantly, drugs such as clazosentan reduce vasospasm but do not improve outcome after aSAH, whereas nimodipine improves outcome without affecting vasospasm [38], supporting that vasospasm is likely not the only cause of DCI and that not all vasospasm leads to DCI [39]. Alternative causes of DCI include cortical spreading depolarizations [40], a depolarization wave in the gray matter that results in EEG depression and can cause spreading vasoconstriction and ischemia [41]; microthrombosis of small vessels, which is seen in areas of ischemia on autopsy [42]; and microvascular constriction. DCI is more common in younger patients, in smokers, and in those with higher WNFS and Fisher scores. Early brain injury, global cerebral edema, NPE, and NMS all are associated with the development of DCI [43].

*Diagnosis and Monitoring* DCI is a clinical diagnosis and requires frequent neurologic examination. Most practitioners assess neurologic status every hour, while some suggest that patients at low risk for DCI can safely be assessed less frequently (i.e., every 2–4 h) [39]. The gold standard for diagnosis of vasospasm is digital subtraction angiography (DSA). Given the invasive nature of DSA, however, it is poorly suited for daily screening. Daily monitoring of blood flow velocities in the large intracerebral vessels using noninvasive transcranial Doppler ultrasonography (TCD) provides an estimate of vessel dimension and can be helpful in predicting vasospasm and recognizing it early. The correlation of TCD velocities with vasospasm is best established for the middle cerebral artery (MCA) territory. Mean flow velocities (MFV) of > 200 cm/s are usually seen as evidence of vasospasm, while MFV < 120 cm/s make vasospasm unlikely. The Lindegaard ratio divides MFV in the MCA by MFV in the extracranial carotid artery, which is not affected by vasospasm, thus controlling for increases in MFV that are caused by elevated cardiac output. A Lindegaard ratio of > 3 suggests vasospasm. In the hands of experienced operators, the sensitivity of MFV elevation for vasospasm and its negative predictive value are high, making TCDs a good screening tool to detect patients at low risk for DCI, who may be eligible for early transfer from the ICU. Unfortunately, specificity of TCDs is low [44]. Some practitioners use CT angiography and CT perfusion studies to identify vasospasm and brain tissue at risk of ischemia, which correlates with DCI [45]. However, these studies cause significant additional exposure to contrast dye and radiation and should not be used for routine screening.

It is especially challenging to detect DCI in patients with high-grade aSAH, who do not have a reliable neurologic exam that can be followed. Multimodal monitoring, including continuous EEG and monitoring of intracranial pressure and arterial blood pressure, holds some promise for prediction and early detection of DCI in this population. Early studies suggest that the electroencephalographic alpha/delta ratio may predict DCI [46, 47], whereas the cerebral pressure reactivity index (calculated as a correlation coefficient between arterial blood pressure and intracranial pressure) may indicate a compromised cerebral autoregulation and predict poor prognosis [48, 49]. These monitoring techniques should currently be used within research protocols to obtain more definitive data.

The duration of monitoring in the ICU can be individualized. Many programs will watch all patients after aSAH in the ICU throughout the phase of high vasospasm risk (14 days) and perform a second DSA before discharge to confirm successful occlusion of the aneurysm and absence of additional aneurysms and exclude significant vasospasm. Others recommend that those at low risk for DCI (age > 65 years, WFNS grades 1–3, Fisher grades 1–2) and without evidence of vasospasm by TCD velocities and CT perfusion imaging can be considered for transfer from the ICU as soon as 5–7 days after the SAH [39].

*Prevention* Prevention and treatment of vasospasm and DCI are among the most challenging tasks in critical care after aSAH. Despite a multitude of promising preclinical studies, few pharmacological interventions have proven to be beneficial in clinical trials. The calcium channel blocker nimodipine given enterally (60 mg every 4 h) or intravenously (1–3 mg/h, not available in the USA) improves outcome after aSAH without affecting vasospasm [50]. The rho-kinase inhibitor fasudil (available only in Asia) may have some benefit as well [51]. Unfortunately, large randomized trials have failed to confirm promising results from pilot studies for several other drugs. There is no evidence of improved outcome in patients receiving magnesium (IMASH [52]), statins (STASH [53]), or the endothelin receptor antagonist clazosentan (CONSCIOUS-2 [54]).

Patients with decreased intravascular volume have a higher risk to experience DCI and cerebral infarctions. However, prophylactic hypervolemic therapy does not improve outcome while increasing cardiopulmonary complications [55]. Current best practice is to maintain euvolemia in all patients with aSAH, which is frequently done by close monitoring of fluid intake/output and replacement of any excessive fluid loss. Beyond maintaining an even fluid balance, no single best method for determining volume status and defining euvolemia has been established. Most practitioners rely on a combination of fluid balance, daily weights, and various invasive and noninvasive measures of preload and fluid responsiveness, including pulmonary wedge pressure, global end-diastolic volume measured by transpulmonary thermodilution, and echocardiographic measures of preload such as left ventricular end-diastolic volume and pressure and dynamic changes in vena cava diameter. Dye and isotope dilution studies, if available, provide highly reliable measures of circulating blood volume and can be useful to establish euvolemia in complex clinical situations [56–59].

*Treatment* Rescue measures should be initiated once signs of DCI occur. Triple-H therapy consisting of induced hypertension, hypervolemia, and hemodilution, used to be the mainstay of rescue therapy for DCI. However, only induced hypertension actually augments cerebral blood flow, whereas the other components do not. Triple-H therapy is therefore no longer recommended and has been abandoned in favor of induced hypertension [55]. Most practitioners will use vasopressors such as norepinephrine to increase mean arterial blood pressure (MAP) in a stepwise fashion (20–30%) until symptoms improve or MAP of 120–130 mmHg is reached. No single vasopressor is clearly superior. Blood pressure should be monitored continuously by arterial line. Unfortunately, the first randomized trial to investigate whether induced hypertension can improve outcome (HIMALAIA) was recently stopped early due to slow enrollment and was unable to show a clear benefit of blood pressure augmentation for functional outcome [60]. In the

absence of more definitive studies, blood pressure augmentation remains the best medical treatment option available for DCI.

Patients who do not rapidly improve after hypertension is induced should be referred for urgent DSA and possible balloon or pharmacological angioplasty of large vessel vasospasm. Several different vasodilator drugs, including nicardipine, verapamil, and milrinone, have been used for super-selective intra-arterial infusion to relieve cerebral vasospasm. Vasodilatory effects are short-lived, and no large controlled trials have investigated whether angioplasty improves outcome after aSAH. In the absence of alternative treatment options, balloon or pharmacological angioplasty should be considered when medical therapy fails to improve DCI [61].

### 10.6.2 Hyponatremia

Hyponatremia is very common after aSAH and may be associated with worse outcome [62]. It can be caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or by cerebral salt wasting. While SIADH usually presents with euvolemia or hypervolemia and cerebral salt wasting with hypovolemia/volume contraction, urine and serum osmolarity and sodium concentrations are similar in both conditions. The two disorders can be difficult to distinguish in the clinical setting where patients routinely receive intravenous fluids [63, 64]. Moreover, both conditions can coexist in the same patient, leading to fluid and salt loss aggravated by disproportional water retention. Fluid restriction, the treatment of choice for SIADH, can be detrimental when applied to an individual with cerebral salt wasting, as it will worsen hypovolemia and can exacerbate vasospasm and DCI. It should therefore not be used in patients with aSAH. Similarly, the vaptans (vasopressin receptor antagonists), which are used to treat chronic SIADH [65], can force significant diuresis and cause hypovolemia and should be used only with very careful monitoring, if at all. In contrast, infusion of hypertonic saline can be safely used to replace sodium and fluid in cerebral salt wasting, or force appropriate diuresis in SIADH, correcting hyponatremia in both conditions [66]. Fludrocortisone can be given additionally to increase sodium and water retention, although it may be most effective when initiated before cerebral salt wasting begins [67].

### 10.6.3 Anemia

Anemia develops frequently after aSAH, caused by inflammatory suppression of erythropoietin, iatrogenic blood loss from frequent lab draws, and red blood cell dilution from aggressive fluid treatment. While the presence of anemia associates with injury severity and poor outcome after aSAH, it is unclear if transfusion, which itself is associated with complications, can improve outcome. A high transfusion threshold (maintaining hemoglobin levels above 9–10 g/dL) is recommended to optimize cerebral oxygen delivery in patients with vasospasm and DCI [68–70].

## 10.7 Thromboprophylaxis

As SAH patients are often immobilized for a prolonged time and have a high inflammatory state, they are at high risk for venous thromboembolic disease (VTE). Mechanical means of thromboprophylaxis such as sequential compression devices should always be used. Pharmacological prophylaxis appears safe once the aneurysm is secured, even in the presence of an external ventricular drain [71, 72].

## 10.8 Mobilization

Early mobilization is recommended for critically ill patients, as it reduces ventilator days and delirium and hastens return to functional independence [73]. Patients after aSAH have traditionally been subjected to prolonged bedrest out of concern that mobilization may increase the risk of rebleeding and compromise cerebral blood flow and exacerbate vasospasm-associated ischemia.

It is reasonable to prescribe bedrest until the aneurysm is secured to minimize straining and the risk of rebleeding. However, early mobilization once the aneurysm is secured appears safe and may preferentially benefit patients with higher-grade bleeds [74]. An individualized approach should be used when patients have vasospasm to avoid orthostatic changes that may compromise cerebral blood flow.

## 10.9 Guidelines

The American Heart Association [75] and European Stroke Organisation [76] have published fairly recent guidelines for the management of patients with SAH, which include the critical care phase. Similarly, the Neurocritical Care Society published a consensus statement with recommendations for critical care management of SAH [77]. This chapter generally follows these recommendations. When regional/local recommendations deviate, we recommend the reader to use their best judgment to decide which approach is the best fit for their patients' individual circumstances.

**Key Points**

- Initial evaluation and management of patients with suspected aneurysmal subarachnoid hemorrhage (aSAH) should focus on airway and hemodynamic stability. Patients who are unable to protect their airway should be intubated before CT imaging. Severe hypertension should be treated, as it may increase the risk of rebleeding.
- Rebleeding risk from a ruptured aneurysm is highest in the first 24–48 h after ictus. Aneurysms should thus be secured as early as possible within the first 72 h.
- Acute hydrocephalus is a frequent early complication after aSAH. Patients who develop signs of increased ICP should have an external ventricular drain (EVD) inserted if ventriculomegaly is present on non-contrast head CT.
- Signs of cardiac stress are frequently seen in the early days after aSAH. This syndrome of neurogenic stressed myocardium (NSM) is linked to early catecholamine surge and often correlates with severity of the SAH. Treatment of NSM is supportive, including inotropic support as needed.
- Prevention and treatment of vasospasm and delayed cerebral ischemia (DCI) are among the most challenging tasks in critical care after aSAH. The calcium channel blocker nimodipine improves outcome after aSAH without affecting vasospasm. Current best practice is to maintain euvolemia in all patients with aSAH. Induced hypertension, using vasopressors to increase blood pressure until symptoms improve, is the initial treatment of choice for DCI. Patients who do not rapidly improve after hypertension is induced should be referred for urgent balloon or pharmacological angioplasty of large vessel vasospasm.

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# 11 Intensive Care Management of Head-Injured Patient

Serge C. Thal

## 11.1 Introduction

Traumatic brain injury (TBI) is the most common cause of trauma-related death and disability in industrialized countries [1]. Following primary injury subsequent mechanisms like cerebral inflammation, apoptosis and malperfusion lead to progression of secondary brain damage [2]. After initial treatment in the emergency room and operating theater, severely injured patients may require intensive care treatment. Therefore, TBI patients should be transferred directly to a neurosurgical center to avoid delay and to prevent secondary transfer associated with worsening of outcome [3]. Depending on the initial presentation (Glasgow Coma Scale (GCS), severity of TBI, and concomitating injuries), typical indications for admission to the intensive care unit (ICU) are severe TBI (initial GCS <9, focal lesion in CT scan), need for ventilation, sedation, or invasive ICP monitoring.

## 11.2 Causes of Poor Outcome

Treatment has improved substantially in the last 60 years and resulted in a reduction in TBI-associated mortality [4]. This is mostly related to advances in general ICU treatment algorithms and special treatment guidelines, e.g., by the Brain Trauma Foundation (see update 2017 [5]), who defined management standards for TBI patients to limit secondary brain damage. Most recent analyses of patient outcomes failed to demonstrate substantial improvement in outcome in level I trauma centers [6], which indicates that new and more effort has to be put into improvement of TBI care. Although underlying mechanisms of secondary brain damage are well studied and treated in experimental studies, this knowledge has not yet been successfully transferred to clinical settings [7]. This is in part related to the highly variable clinical presentation of TBI with differences in trauma mechanism, type and extent of brain lesions (e.g., focal, diffuse), and presence of additional organ injuries. To achieve optimal outcome, key principles of care are therefore focusing on the individual normal physiology ("5 normos"): normotension, normoxia, normocapnia, normothermia, and normoglycemia. In TBI patients special attention needs to be put on cerebral perfusion and cerebral oxygenation. To maintain and monitor cerebral perfusion, the cerebral perfusion pressure (CPP) was defined as surrogate parameter, which is calculated as the difference between mean arterial pressure and intracranial pressure. Until recently, the focus was to maintain CPP between 60 and 70 mmHg and to keep intracranial pressure (ICP) below 20 mmHg. Unfortunately, measures to reduce ICP may have deleterious side effects, because they can cause

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cerebral vasoconstriction or arterial hypotension thereby reducing brain perfusion and putting brain tissue at risk for insufficient oxygenation. Focusing on ICP only by, e.g., craniectomy failed to improve outcome [8]. Recently, a phase II randomized controlled trial (RCT) with a combined strategy focusing on both ICP and brain tissue oxygen levels indicated reduced mortality and better outcome compared to ICP control only [9].

In addition, TBI patients frequently show several non-neurological and neurological complications during the course of ICU treatment (Table 11.1). Non-neurological complications even outnumber neurological complications and play a prominent role in later phases of ICU stay [10].

**Table 11.1** Non-neurological and neurological complication after TBI

| Non-neurological complication | Neurological complication |
|---|---|
| Pulmonary infections, ARDS | Seizures |
| Delirium | Ischemic stroke |
| Decubitus | Hydrocephalus |
| Thrombosis, pulmonary embolism | Intracranial bleeding |
| Acute kidney failure or dysregulation (diabetes insipidus, SIADH) | |
| Wound infections | |
| Myocardial infarction | |
| Coagulopathy | |

## 11.3 Intracranial Pressure and Regulation of Cerebral Perfusion

The oxygen requirement of the brain is dependent on the metabolic state. To meet the demand, oxygen is supplied via the bloodstream, which is dependent on oxygenation in the lung, hemoglobin level, cardiac output, and cerebral perfusion. Arterial oxygen saturation, hemoglobin level, and cardiac output are monitored by routine ICU equipment, whereas cerebral oxygen requirement, supply, and perfusion are difficult to determine. In order to overcome this limitation, CPP is calculated and maintained at defined levels. A key determinant for CPP is the ICP, which represents the pressure within the skull and displays the pressure required to allow intracranial blood circulation. As a result of TBI, bleeding or swelling of the brain may result in the evolution of a mass, which displaces the other contents of the head. The correlation between intracerebral volume and pressure is known as the Monro–Kellie doctrine (Fig. 11.1). Small masses are easily compensated by space occupied by cerebrospinal fluid or venous blood. If this compensation reserve is exhausted, little further increases in mass volume result in rapid elevation of ICP. In normal situations, ICP does not change substantially, where in

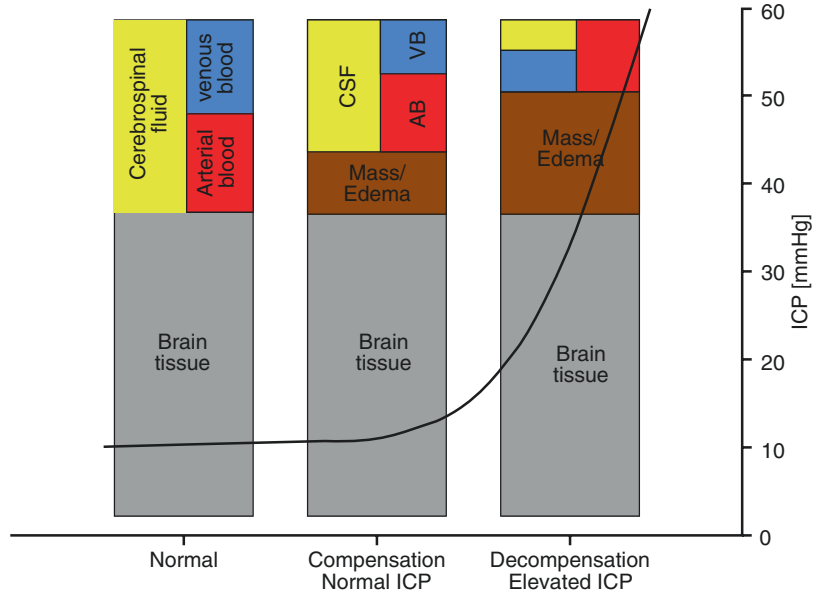


**Fig. 11.1** Monro–Kellie doctrine

**Table 11.2** Factors influencing intracranial pressure (ICP)

| Factors reducing ICP | Factors increasing ICP |
|---|---|
| • Reduction of intracranial liquor volume (external ventricular drainage)<br>• Reduction of brain tissue volume<br>Osmodiuretics<br>Corticosteroids<br>Hypertonic saline<br>• Reduction of intracranial blood volume<br>Position of the head (elevation)<br>Reduction of cerebral perfusion (arterial $pCO_2\Downarrow$, $pO_2\Downarrow$, hypnotics)<br>Evacuation of intracranial hematoma<br>Hypothermia<br>• Decompressive craniectomy | • Drugs causing: Histamine liberation, cerebral vasodilation, cerebral metabolism⇑<br>• Central venous pressure<br>Limitation of venous return<br>Transmission of central venous pressure to intracranial veins<br>• Positive end expiratory pressure (PEEP)<br>No clear data, generally believed to be save: 10–15 cm $H_2O$<br>• Fever (increase of metabolism and CBF) |

pathological conditions with no or very limited compensatory capacity small volume changes demonstrate substantial ICP rise. In general, ICP is influenced by various factors (see Table 11.2). Unfortunately, several interventions to reduce ICP, e.g., hyperventilation, are associated with an increased risk for local hypoperfusion.

In the healthy brain, cerebral perfusion is not influenced by change of blood pressure in a range between 50 and 150 mmHg mean arterial blood pressure. This phenomenon is called cerebral autoregulation and is an essential foundation for a constant blood supply of the brain (Fig. 11.2). Cerebral autoregulation is changed or completely abrogated in pathological brain conditions. Different approaches were therefore developed to determine the individual state of autoregulation. The principle behind these techniques is a correlation analysis between blood pressure and parameters of cerebral perfusion or oxygenation (e.g., Doppler flux, cerebral oximetry, ICP, etc.). Lack of correlation indicates intact autoregulation, whereas strong correlation between blood pressure and, e.g., ICP shows abrogated cerebral autoregulation. The combination of CPP measurement and correlation analysis was helpful to determine an optimal CPP level. Unfortunately, values are not similar between all patients and institutions, as demonstrated in a recent retrospective analysis [11]. In addition, brain vasculature shows vasorelaxation with high arterial $pCO_2$ values, with low arterial $pO_2$ values; release of vasoactive substances such as lactate, prostaglandin E, nitric oxide, or adenosine; or increased interstitial $K^+$ levels. Importantly and in contrast,

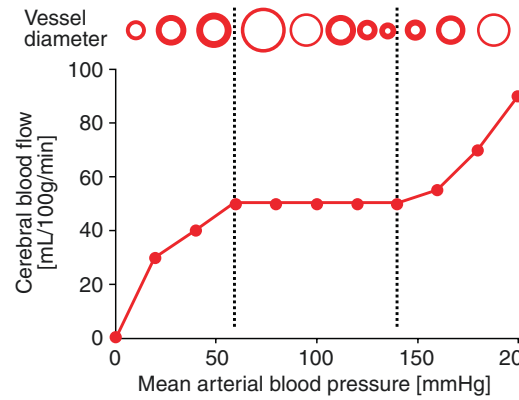


**Fig. 11.2** Cerebral autoregulation

reduction in arterial $pCO_2$ levels (hyperventilation) is the most powerful determinant for vasoconstriction of cerebral arteries. In addition, vasoconstrictors such as norepinephrine cause generalized vasoconstriction including brain vessels.

## 11.4 Critical Care Treatment of the Head-Injured Patient

### 11.4.1 Cerebral Hemodynamics and Intracranial Hypertension

The primary goal of the treatment is to maintain a sufficient oxygen supply for the brain. To maintain best cerebral oxygen supply, target CPP limits are defined in most ICUs. To determine CPP it is required to measure both mean arterial blood pressure (MAP) and ICP.

Therefore, the placement of an ICP probe should be considered early in the decision process. Although ICP probes by themselves may present a risk for tissue damage or infections, current data suggest that information from ICP monitoring helps to reduce mortality of patients with severe TBI [5]. However, this view was challenged by a randomized controlled trial performed in high-volume trauma centers in Bolivia and Ecuador investigating the impact of ICP monitoring-guided therapy compared to non-ICP monitoring-guided management and demonstrating no superiority of ICP monitoring compared with care based on imaging and clinical examination [12]. Therefore, it is not monitoring per se that affects outcomes, rather the quality of management and monitoring as a tool to direct treatment. However, focusing on ICP only by all means may also increase the risk for patients to experience cerebral ischemia. In fact, while being powerful to reduce elevated ICP, these measures can also, on the other hand, increase the risk for pneumonia, drop MAP or result in cerebral vasoconstriction (Table 11.3) [13]. To limit side effects, drops in blood pressure (vasopressors, inotropics) or cerebral oxygenation (Table 11.4) need to be treated immediately.

**Table 11.3** Side effects of ICP control

| Side effects of interventions |
|---|
| • Sedation and ventilation<br>Ventilator associated pneumonia, delirium |
| • ICP probe/external ventricular drainage<br>Infections |
| • Hyperosmolar therapy<br>Volume overload, electrolyte disbalance |
| • Hyperventilation, hypocarbia<br>Cerebral vasoconstriction, ischemia |
| • Decompressive craniectomy<br>Secondary hematoma, bleeding, hydrocephalus |
| • Hypothermia/metabolic suppression<br>Arterial hypotension, coagulopathy, pneumonia |
| • Barbiturate sedation<br>Arterial hypotension, pneumonia |

**Table 11.4** Measures to increase cerebral oxygenation

| Factors increasing brain oxygen levels |
|---|
| • Correct mechanical cause<br>Head position |
| • Increase supply (oxygen delivery)<br>Increase blood pressure<br>Normalize $pCO_2$ to physiologic level<br>Increase $FiO_2$<br>Increase hematocrit<br>Increase cardiac output |
| • Decrease demand (cerebral metabolism)<br>Increase anesthetic depth<br>Decrease body temperature |

The second parameter of CPP, the MAP, is also by itself an important factor for survival and represents the available pressure to allow perfusion of all organs. Current trauma guidelines therefore recommend to maintaining systolic blood pressure (SBP) at ≥100 mmHg for patients 50–69 years of age or at ≥110 mm Hg or above for patients with the age of 15–49 or over 70 to decrease mortality and improve outcomes [5].

Due to individual differences and limited clinical data, the lower and upper limits of CCP are in constant debate. In the last years, the view on CPP has changed. The current 4th guideline of the Brain Trauma Foundation (BTF) recommends a range between 60 and 70 mmHg based on two clinical studies suggesting a favorable outcome [14, 15]. However, a study from 1999 demonstrated more complications with CCP target above 70 mmHg [16]. Interestingly, determining a general optimal CCP by means of autoregulation analysis in TBI patients by different institutions resulted in highly different numbers [11]. It is therefore debatable if CPP targets should be individualized by personalized analysis of the cerebral autoregulation to determine the optimal CPP level in single patients at different time points. The principal idea is to avoid hypoperfusion by adjusting the CPP to the optimal autoregulated level and to avoid hyperperfusion or vasogenic brain edema formation by preventing high CPP levels in patients with abrogated autoregulation. To determine a tailored blood pressure and CPP range based on individualized limits of autoregulation, MAP needs to be correlated online with intracranial pressure, cerebral perfusion, or measures of cerebral oxygenation using, e.g., cerebral oximetry (NIRS, $rSO_2$), brain tissue $O_2$ levels ($ptO_2$), or jugular venous oxygen saturation. So far, no prospective data is available demonstrating the superiority of an individualized CPP-based treatment compared to maintaining generalized CPP targets.

### 11.4.2 Interventions to Prevent, Treat, and Aggressively Treat ICP Increase

The basis of intervention in most neuroICUs is the continuous monitoring of the patients to guide treatment decisions. The most prominent parameters are the intracranial pressure and blood pressure. Unfortunately, there is no clear evidence from literature to give a level 1 recommendation on when and whom to place an ICP probe or intraventricular drainage. The current 4th BTF guideline gives only a level 2B recommendation to place an ICP monitoring based on data demonstrating reduced in-house or 2-week mortality [17]. Originally (3rd BTF guideline) and current clinical practice is to monitor ICP in patients with severe TBI and abnormal CT findings (hematomas, contusions, swelling, herniation, or compressed basal cisterns) or in patients with severe TBI, normal CT scan, and two or more features including age above 40, unilateral or bilateral motor posturing, or systolic blood pressure (BP) <90 mmHg. In general, ICP monitoring is placed for better care and to guide basic interventions to prevent ICP increase in all TBI patients requiring sedation and therefore not allowing continuous clinical examination of neurological function. The principal steps in patients with severe TBI are [13] (I) basic treatment to prevent rise in ICP by sedation, intubation with normocapnic ventilation, and avoidance of pyrexia; (II) hyperosmolar therapy and cerebrospinal fluid (CSF) drainage to treat rise in ICP; and (III) metabolic suppression, hypothermia, decompressive craniectomy, and hypocapnia to treat persistent and severe rise in ICP. Importantly, all these strategies have side effects and put the patients at beforehand described risks (Table 11.3).

### 11.4.3 Level I: Basic Treatment

In addition to the three basic interventions (sedation, normocapnic ventilation, avoidance of pyrexia) to control ICP, 25° to 30° elevation of the head is routinely performed based on clinical experience. However, a recent Cochrane analysis did not show strong evidence for the efficacy of this intervention [18]. Future studies are required to determine if and when different backrest positions affect outcome. Prophylactic cooling has been investigated in several experimental and clinical studies to reduce cerebral metabolism and to protect the brain from secondary brain damage. Unfortunately, prophylactic use within the first 48 h after injury showed conflicting results in clinical trials. The body of evidence for beneficial effects is rather low due to various methodological limitations, low sample size, missing impact on mortality, and no clear influence on neurofunctional outcome. Due to side effects of hypothermia, the use of cooling is limited to therapy-refractory ICP increase.

### 11.4.4 Level II: Hyperosmolar Therapy and CSF Drainage

ICP levels of 22 mmHg and above are level 2B trigger thresholds for therapeutic interventions. However, it remains unclear which extend and duration in ICP increase, e.g., during wake-up phases, should be tolerated. Also, the speed required to successfully limit brain damage by escalating measures to treat rise in ICP is not clear. First-line intervention is the intravenous hyperosmolar therapy, which has become routine in the management of intracranial hypertension and herniation syndromes. Mannitol and hypertonic saline are routinely employed as hyperosmolar agents for ICP reduction. The selection of a specific substance is mostly dependent on the patients' needs, as both agents reduce intracranial pressure to a great extent by increasing plasma osmolarity, increasing the osmotic gradient between the brain and blood, shifting water from the brain tissue to the bloodstream, expansion of plasma volume and reduction of blood viscosity, and increasing MAP and thereby improving microcirculation. The use of mannitol, however, is limited by the decreased efficacy after repeated administration and rebound phenomenon (for review see [19]). Recent meta-analyses have identified hypertonic saline as the

favorable substance compared with mannitol due to a reduced rebound rate and less kidney injury [20–22]. To improve the effect of hypertonic saline in patients with intracranial hypertension, bolus 20% NaCl and continuous infusion with serum $Na^+$ target increase by 5 mmol/l up to 155 mmol/l for a minimum duration of 24 h were investigated in a retrospective analysis and in pooled data from the Corti-TC, BI-VILI, ATLANREA trials [23–25]. In the pooled data set, continuous NaCl treatment was associated with improved 90-day survival [25].

External ventricular drainage (EVD) in a closed position allows for monitoring of ICP, while the open EVD allows the drainage of cerebrospinal fluid. In severely traumatized patients, a continuous drainage of CSF can be used to prevent sudden increases in ICP [26, 27]. The current 4th BTF guideline gives a level 3 recommendation for a continuous drainage zeroed at the midbrain for more effective drainage than intermittent use. Furthermore, they give a level III recommendation to lower ICP in patients with an initial GCS <6 during the first 12 h after injury [28]. However, continuous drainage and monitoring ICP via frequently performed catheter closures for ICP assessment may mask a significant amount of ICP increases above thresholds. Therefore, the trend goes to an EVD with an integrated ICP probe, e.g., an air-pouch-based ICP probe, for simultaneous CSF drainage and ICP assessment [29] or new systems using an integrated system with a roller pump and pressure probe to allow continuous ICP measurement and CSF drainage (defined levels and amount).

### 11.4.5 Level III: Metabolic Suppression, Hypothermia, Decompressive Craniectomy, and Hypocapnia

Basic technique to facilitate intensive care treatment but also to limit mobility and cerebral metabolism is the proper sedation and analgesia. Despite several experimental data on neuroprotective and neurotoxic effects of different sedation strategies in TBI models, limited data is available from clinical trials. Most data are on the impact of sedation on intracranial pressure and cerebral perfusion, demonstrating the safety of most anesthetics in patients with normal ICP. In clinical settings it is well-known that patients with TBI, especially young male patients, require multimodal sedation paradigms with multiple substances and that standard sedation strategies are often insufficient (e.g., propofol and sufentanil only). The effects of a mixture combining propofol with benzodiazepines, α-agonist, and ketamine on the damaged brain tissue remain unclear. Sedation with volatile anesthetics may present as an alternative. One reason for the lack of outcome studies on sedation with volatile anesthetics in brain-injured patients may be the concern that volatile anesthetics may raise intracranial pressure and reduce cerebral perfusion pressure by their vasodilative properties. However, clinical studies investigating this topic demonstrated sufficient sedation depth without relevant increase in ICP [30] and even improved regional cerebral blood flow in comparison to propofol [31]. A recent study demonstrated cases of marked ICP increases and MAP drops with sevoflurane sedation [32]. However, this may be attributed to a marked reduction in mean arterial blood pressure leading to malperfusion and consecutive vasodilation. Important for the use of volatile anesthetics in TBI patients is therefore the continuous control of arterial pressure and $pCO_2$ monitoring.

A quite popular strategy to quickly reduce cerebral metabolism and consecutively ICP is the use of barbiturates. Unfortunately, the use of barbiturates is associated with drop in blood pressure and an increased risk for the early onset of pneumonia, which again is associated with a worsening of secondary brain injuries [33]. Moreover, barbiturate coma therapy for ICP treatment has been associated with refractory hypokalemia [34]. The current 4th BTF guideline gives a level 3 recommendation for a high-dose barbiturate administration only to control elevated ICP refractory to maximum standard medical and surgical treatment and only in combination with control of hemodynamic stability. Propofol may present as a new alternative to classical barbiturates, because a

comparison of thiopental sodium (bolus 2 mg/kg and maintenance 2 mg/kg/h) with propofol (bolus 0.5 mg/kg and maintenance 20 μg/kg/h) found comparable effects on ICP reduction and no significant differences in mean CPP, $SpO_2$, and arterial blood pressure [35].

As mentioned above, the use of cooling is limited to therapy refractory ICP increase. Still, there is uncertainty about the proper timing and duration as well as the lack of evidence of benefit in long-term clinical outcomes. Although a recent retrospective study demonstrated that therapeutic hypothermia was effective for lowering ICP after decompressive craniectomy and reduced mortality in the ICU [36], the Eurotherm Trial using titrated hypothermia as the primary intervention to reduce elevated ICP demonstrated harmful effects in patients with a lower severity of injury and no clear benefits in patients with a higher severity of injury [37]. The investigators conclude that therapeutic hypothermia should not be used after TBI, for neuroprotection or to reduce ICP. Again a combination of hypothermia with monitoring of brain tissue partial pressure of oxygen can help guide the course of therapeutic hypothermia by detecting local malperfusion [38].

The current 4th BTF guideline gives a level 2A recommendation for a large frontotemporoparietal decompressive craniectomy for reduced mortality and improved neurologic outcomes in patients with severe TBI. The DECRA trial demonstrated that early large bifrontotemporoparietal decompressive craniectomy failed to improve outcome and was associated with more unfavorable outcomes although it decreased ICP and the length of stay in the ICU [8]. In the recently released RESCUEicp trial, decompressive craniectomy was performed in patients with refractory elevated intracranial pressure and compared with ongoing medical care [39]. After 6 months the effects of craniotomy were lower mortality and higher rates of vegetative state, lower severe disability, and upper severe disability than medical care. The rates of moderate disability and good recovery were similar in the two groups. A recent retrospective study showed that early decompressive craniectomy for CT evidence of intracranial hypertension decreased abnormal ICP and CPP time and improved ICP and CPP thresholds but had no obvious effect on the outcome [40]. Focusing on ICP only may not be sufficient to improve patient outcome. Recent phase II RCT data indicate that a combined strategy to simultaneously measure and reduce ICP and improve brain tissue oxygen levels could reduce mortality and show better outcome compared to ICP control only [9].

The $PaCO_2$ is a powerful vasoconstrictor of cerebral arteries, and ICP can therefore be reduced by controlled hyperventilation by the prize of reduction CBF. The influence of cerebral perfusion was shown in several studies demonstrating, e.g., substantial increase in amount of critically low perfusion brain tissue when switching from normoventilation to hyperventilation [41]. The current 4th BTF guideline gives a level 2B recommendation that prophylactic hyperventilation with $PaCO_2$ of 25 mmHg or less is not recommended. However, hyperventilation may be considered as a temporizing measure for reduction of elevated ICP although it should be avoided in the first 24 h after injury when CBF is often critically reduced. Again, monitoring of brain tissue oxygenation is recommended for detection of local malperfusion induced by the hypocapnia [42]. Only one relatively old study evaluated the effects of hyperventilation in a prospective randomized controlled trial, which demonstrated worse clinical outcome when hyperventilation ($PaCO_2$ 25 ± 2 mmHg) was used compared with normoventilation ($PaCO_2$ 35 ± 2 mmHg) [43]. To the prompt lowering effect on cerebral perfusion, hyperventilation should be avoided and used as ultima ratio only.

## 11.5 Conclusion

In addition to modern concept of intensive care treatment, TBI patients require special attention to limit secondary brain injury. The basic concept is to maintain the individual normal physiology ("5 normos": normotension, normoxia, normocapnia, normothermia, and normoglycemia), to promptly treat elevated intracranial pressure, and to improve drop in cerebral oxygenation.

**Key Points**

- The basic concept is to maintain the individual normal physiology.
- Treatment of elevated intracranial pressure may have side effects that lower cerebral oxygenation level.
- Measurement of intracranial pressure and tissue oxygenation could allow treatment of both high ICP and tissue hypoxia.

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# 12 Intensive Care Management of Traumatic Spine Injury

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## 12.1 Introduction

The management of traumatic spinal cord injury (SCI) has advanced greatly over recent years because of more detailed understanding of SCI pathophysiology related to ischemia, hypoperfusion, hypoxia, and neuroinflammation. Improvements in technology and monitoring methods have facilitated better management and outcomes. Neurocritical care management of traumatic SCI initially addresses hemodynamic instability and respiratory perturbations resulting from the neurological dysfunction. The primary aims of critical care management should focus on improving survival, optimizing functional recovery, and decreasing secondary injuries. This chapter discusses critical care management of traumatic SCI, including airway and respiratory management, acute hemodynamic challenges from spinal shock, associated injuries, autonomic dysreflexia, and nutrition challenges. With research on traumatic SCI and acute management ongoing, we discuss potential emerging treatment options and how efforts to improve SCI outcomes are making headway.

## 12.2 Airway Management

The primary factor in deciding airway management in critical care conditions after traumatic spinal cord injury (SCI) is the spinal cord level

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affected. Special attention is paid to injuries involving the cervical spine. Cervical trauma leads to different levels of respiratory muscle paralysis and potential impairment of airway secretion clearance. The level of injury determines the degree of diaphragmatic and truncal respiratory muscle innervation deficit. Respiratory rate, increases in arterial $CO_2$ content, decline in vital capacity, and progressive hypoxemia determine whether invasive or noninvasive mechanical ventilation is needed for critical care following initial assessment of the injured patient [1]. Airway management in acute SCI is challenging because the patient's neck should be immobilized using either manual in-line stabilization or cervical collars. Awake fiberoptic or video-guided laryngoscopic orotracheal intubation is generally the first choice for initiating invasive mechanical ventilation. Laryngeal mask airway insertion might be required if intubation cannot be achieved [2]. Tracheostomy is an alternative for oral/nasal intubation, but there is no direct clinical evidence encouraging early tracheostomy instead of initial intubation in prevention of respiratory complications. However, tracheostomy should be considered in patients who are expected to require prolonged mechanical ventilation [2].

## 12.3 Hemodynamic Challenges

### 12.3.1 Acute Phase: Spinal Shock and Associated Injuries

To maintain proper autonomic control and autoregulation, the spinal cord requires intact sympathetic and parasympathetic pathways. This includes the sympathetic nervous system (SNS) preganglionic neurons that exit the spinal cord from T1 to T6 and synapse with cardiac postganglionic neurons in the middle cervical and stellate ganglion [2]. Parasympathetic innervation arises from the brain stem and synapses in cardiac tissue adjacent to the sinoatrial and atrioventricular nodes [3] and is left unopposed after SCI via an intact vagus nerve [4] (Fig. 12.1).

Sudden disruption between autonomic control centers and sympathetic neurons in the intermediolateral thoracic and lumbar spinal cord causes spinal shock, with loss of reflexes and functions below the level of injury [5]. The lesion level greatly influences how much cardiovascular regulation remains after injury. Sympathetic postganglionic fibers innervating the cardiovascular system originate from above T6. Acute neurogenic shock occurs after severe cervical or high-thoracic SCI that severs sympathetic descending communication to the cardiovascular system. Reflex bradycardia from unopposed vagus nerve input or cardiac arrhythmias ensue, and impaired autoregulation of vascular tone and blood pressure leads to low resting blood pressure (BP), orthostatic hypotension, and hypothermia [3] (Fig. 12.1). Blood pressure regulation and variability are also affected by impairment of descending splanchnic nerve innervation from below T6 and proper baroreflex functioning [6, 7]. Adequate cerebral perfusion relies on appropriate blood pressure maintenance [8], making timely detection of hemodynamic changes and spinal shock following acute SCI imperative for improving outcomes and minimizing secondary complications [8].

A study investigated the incidence of organ dysfunction and failure following cervical SCI. The cardiovascular system was the most frequent organ system to fail assessed using Multiple Organ Dysfunction Score (MODS), and the respiratory system was the most frequent when using the Sequential Organ Failure Assessment (SOFA). In addition, the American Spinal Injury Association (ASIA) impairment scores (AIS) were inversely correlated with the development of organ failure [9].

### 12.3.2 Subacute Phase: Venous Thromboembolism and Autonomic Dysreflexia

The incidence of venous thromboembolism (VTE) has decreased dramatically from the late 1970s to the early 1990s thanks to increased use of low-molecular-weight heparin prophylaxis and pneumatic compression [10, 11] devices. As with many

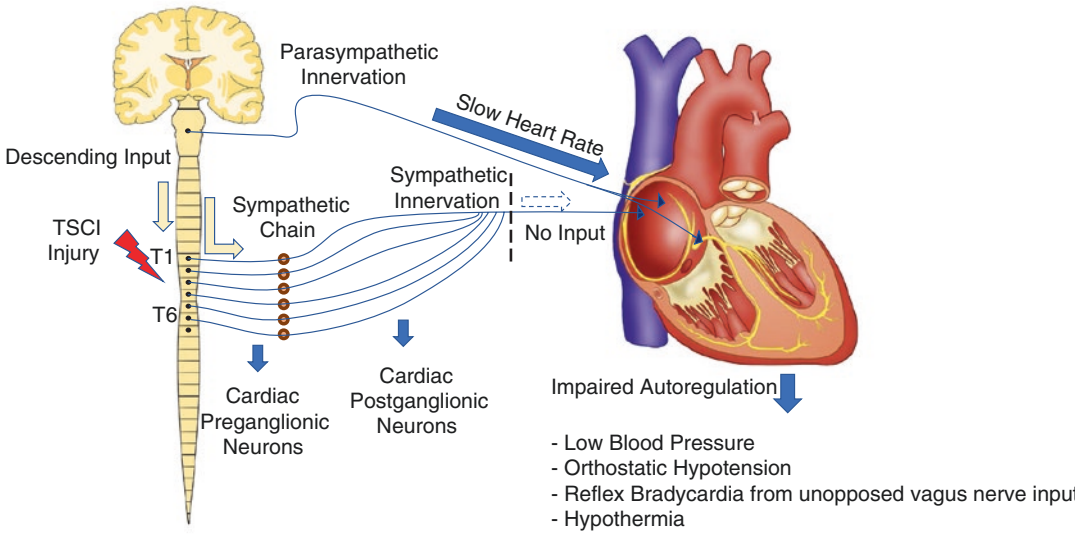


**Fig. 12.1** This figure demonstrates the sympathetic postganglionic fibers originating above T6 and innervating the cardiovascular system. Autoregulation requires sympathetic and parasympathetic pathways to be intact. Severe cervical or high-thoracic spinal cord injury disrupts sympathetic communication to the cardiovascular system leading to unopposed parasympathetic innervation. Acute neurogenic shock ensues

complications following SCI, the risk for VTE differs depending on the level of the lesion. A study using trauma registry data found that patients with SCI between T1 and T6 were at the highest risk for VTE. Though this group may have more secondary sequelae including long bone and pelvic fractures compared to those with lesions between C1 and C4, further analysis did not show these fractures to be an independent risk factor [12]. A large SCI cohort study found male sex, African-American race, multiple comorbid conditions, tracheostomy placement, and paraplegia to be independent risk factors for VTE. Those less than 30 years old were at decreased risk for developing VTE. Additionally, in line with previous studies, they found a higher incidence in the weeks immediately following SCI. They also found no change in risk-adjusted incidence between 1991 and 2001. Future investigation of these additional risk factors could help improve early detection of high-risk individuals and prevention of VTE [13].

When SCI disrupts the communication between sympathetic preganglionic neurons and supraspinal modulation, particularly the splanchnic nerves from T5 to T12 that regulate vasomotor tone of the splanchnic vascular bed [7], autonomic dysreflexia (AD) can occur. The splanchnic vascular bed receives 25% of cardiac output and has a large influence on total peripheral resistance [14] and blood pressure. AD is a potentially life-threatening situation that includes episodic hypertension and baroreflex-mediated bradycardia often stimulated by unperceived visceral or somatic noxious stimuli [15], including overdistension of bowel and bladder, urodynamic studies [16], pressure ulcers, and tight clothing [17]. While challenges after SCI are mostly attributed to the level and severity of the injury in the acute setting, awareness and proper management of the potential risks in the subacute phase and following hospital discharge are necessary to improve outcomes after SCI.

## 12.4 Respiratory Support

Respiratory issues after traumatic SCI are associated with high mortality risks during critical care management. Respiratory complications depend on the injury severity score, necessity of surgery, and level of spinal cord injury (above C5). High cervical lesions contribute to inadequate ventilation and hemodynamic instability. Weakening of

the respiratory muscles due to damaged neural pathways leads to decline in lung vital capacity, lower peak expiratory flow, and inadequate clearance of respiratory secretions. Inadequate expiratory effort, cough, and secretion clearance boost tracheobronchial resistance, increasing the tendency for atelectasis and infections [18]. Appropriate application of positive end-expiratory pressure during the acute and chronic injury periods can aid in lessening pathophysiological challenges. Respiratory complications including pneumonia, atelectasis, hemo/pneumothorax, and prolonged respiratory support are the main factors influencing critical care duration. However no established mechanical ventilation strategy is described regarding specific ventilatory modes following SCI. Several well-identified factors can prevent respiratory compromise under mechanical ventilation, including protective ventilation with low tidal volume and appropriate positive end-expiratory pressure, tracheostomy, monitoring of Clinical Pulmonary Infection Scores (CIPS), non-invasive ventilation attempts, adequate physical therapy with timely mobilization, and respiratory muscle training [19, 20]. Moreover, trauma-induced coagulopathy in the first 24 h of hospitalization is a recently designated risk factor for the development of ventilator-associated pneumonia [21]. Roquilly et al. conducted a retrospective cohort study of 164 traumatic tetraplegia patients followed over 9 years and reported that long-term neurologic status is negatively associated with the length of mechanical ventilation. Pneumonia, atelectasis, and high tidal volume respiratory support directly correlate with the length of mechanical ventilation [22]. Although tracheostomy enhances the weaning process by decreasing airway resistance and eliminating respiratory secretions, debate remains regarding its timing in critical care.

## 12.5 Traumatic Spinal Cord Injury and Nutrition

Although a frequently overlooked factor with little information in the literature, nutrition is nonetheless an important component in the treatment of patients suffering from traumatic SCI. Metabolic rate must be taken into consideration when caring for patients with SCI, as it has been noted that resting metabolic rates are 14–27% lower in this patient population. Obesity is another important consideration that is mainly attributed to lack of physical activity with chronic SCI [23]. Although early nutritional support (less than 72 h after injury) is thought to be beneficial in critically ill patients, a pilot study conducted by Dvorak et al. was unable to reproduce similar benefits in acute cervical SCI patients [24]. However, more data must be collected to make a definitive recommendation regarding early nutritional support in SCI, as this study used only 17 patients in their analysis. Nitrogen balance is another important variable that has been studied as part of nutritional support for patients with SCI, as positive nitrogen balance is of utmost importance for tissue repair. It has been widely established that paralysis, which is associated with muscle denervation and atrophy, prevents positive nitrogen balance in SCI patients. In fact, the negative nitrogen balance is so severe that Rodriguez et al. were not able to establish a positive nitrogen balance in SCI patients despite an average delivery of 2.4 g of protein/kg during a period of 7 weeks following injury [25].

While it is important to make sure that the SCI patient is not nitrogen depleted during the acute injury phase, hyperglycemia is now considered a major exacerbating factor that impairs functional improvement after SCI in humans and animal studies alike. Kobayakawa et al. analyzed data from 528 SCI patients and found that hyperglycemia (blood glucose concentration $\geq$126 mg/dl) on admission was an independent risk factor for poor motor outcomes even after excluding patients with chronic hyperglycemia due to diabetes mellitus. In an animal study, they were able to manipulate and normalize blood glucose during induction of SCI in hyperglycemic mice and reverse the negative impact on motor function [26]. Controlling blood glucose levels is an important component in early management of SCI that can improve long-term outcomes.

Due to the multifaceted pathophysiology underlying SCI, various supplements thought to induce anti-inflammatory and neuroprotective effects are being explored as potential treatments for this debilitating condition. Polyunsaturated fatty acids (PUFAs) are well-known components

of phospholipids, constituting the cell membrane. Consumption of PUFAs for neuroprotective effects has been previously studied in animal models. Omega-3 fatty acids were associated with improved locomotor performance after induction of SCI in adult rats [27]. An animal study investigating consumption of PUFAs and the influence on neurorehabilitation in patients suffering from chronic inflammatory states after SCI did not yield significant results [28]. A recent study by Galán-Arriero et al. revealed that intrathecal administration of oleic acid plays an important role in reduction of microglial cell reactivity, which is thought to exacerbate SCI-associated sensorimotor dysfunction and neuropathic pain [29]. Studies investigating the use of fatty acids to improve SCI outcomes are discovering benefits, and ongoing development of this treatment option may yield a future opportunity for improving SCI management.

## 12.6 Drug Therapy

Despite advances in SCI management and outcomes, treatment options remain limited. Methylprednisolone sodium succinate (MPSS) is the most widely recognized yet highly controversial treatment option for SCI. It is thought to be neuroprotective through inhibition of lipid peroxidation, ischemia, and other inflammatory processes involved in the pathophysiology of SCI [30]. The recommended high-dose steroid treatment, which includes administration of MPSS within 8 h of injury as a bolus of 30 mg/kg over 15 min followed by a maintenance infusion of 5.4 mg/kg per hour for 23 h, has not shown significant impact on indices of long-term recovery of neurological function and only confers a small positive benefit for patients suffering from SCI [31]. In addition, there are side effects associated with high-dose MPSS use in SCI, including hyperglycemia and increased risk for developing severe sepsis, pneumonia, or acute corticosteroid myopathy [32].

Considering the concerns regarding high-dose steroid use in treatment of SCI, physicians are desperately seeking novel treatments for this incurable condition. Numerous trials involving SCI in animal models are underway. A study conducted by Liu et al. combined MPSS and methotrexate, the latter of which is thought to possess anti-inflammatory and immunosuppressive qualities. When combined with MPSS, there was enhanced recovery of motor function in adult rats with SCI [32].

Another novel therapeutic agent being studied mimics the neuroprotective and spinal cord-blood-barrier maintaining abilities of apolipoprotein E (apoE), a plasma protein implicated in multiple neurological conditions. To test apoE as a potential therapeutic target for treatment of SCI, Cheng et al. developed an apoE-deficient mutant mouse that, along with wild-type mice, received a T9 moderate contusion SCI. When exogenous apoE particles were administered to apoE-deficient mice, there was significant improvement in recovery associated with partially reversing the severely increased permeability of spinal cord-blood-barrier, inflammation, apoptosis of neurons, and depressed locomotor ability found in apoE-deficient mice compared to wild-type mice [33].

Tamoxifen is a prodrug whose metabolites compete with estrogen receptors that is currently approved for treatment of breast cancer but may be a potential treatment option in SCI. Colón et al. discovered that continuous tamoxifen delivery started 6 h after SCI in adult male rats resulted in improved locomotor recovery and neuronal survival using [34]. Of note, there is a strong interest in utilizing nanotechnology and targeted delivery of therapeutic agents in the treatment of SCI. A recent study by Bin et al. utilized albumin-coupled nanoparticle carriers to deliver methylprednisolone and minocycline, drugs thought to be neuroprotective and anti-apoptotic agents, to SCI-associated inflammatory sites. Targeted administration resulted in reductions in lesional volume and improved behavioral outcomes in rats with SCI [34].

## 12.7 Conclusion

Management and treatment of SCI are multifaceted and challenging. From overcoming the difficulties associated with intubation and airway

management of cervical SCI to maintaining hemodynamic stability in spinal shock, proper care and monitoring in the acute setting are unequivocally pivotal in an individual's recovery from SCI. Complications during the acute SCI setting are vast and are not limited to multiple organ failure, infection, and hemodynamic instability. An astute critical care team recognizes the importance of airway management and hemodynamic stability to improve survival rates following SCI, but recent advances in additional treatment options are making headway, offering further support to the acute management and long-term outcomes of SCI.

**Key Points**

- A higher cervical spinal cord injury worsens ventilation and hemodynamic parameters, increasing the risk for secondary complications.
- Awake fiber-optic or video-guided laryngoscopic orotracheal intubation is generally the first choice for initiating invasive mechanical ventilation after cervical traumatic spinal cord injury.
- Tracheostomy should be considered in patients who are expected to require prolonged mechanical ventilation. The literature shows no clinical evidence that early tracheostomy instead of orotracheal intubation decreases respiratory complications while in the ICU.
- Vasopressor and inotropic agents should be considered in acute spinal shock due to the sudden disruption between autonomic control centers and sympathetic neurons in the spinal cord.
- Proper mechanical ventilation support, low-molecular-weight heparin prophylaxis with pneumatic compression, positive nitrogen balance, and avoiding hyperglycemia are the additional factors that affect the neurologic outcomes of spinal cord injury patients in the ICU.

**Declaration of Interest** Authors declare no conflict of interest.

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# Part III

# Neuromonitoring

# 13 Multimodal Monitoring in the Neurocritical Care Unit

Farhana Akter, Chiarra Robba, and Arun Gupta

## 13.1 Introduction

Multimodal monitoring (MMM) in the neurocritical care unit (NCCU) has become an important component of care of the severely brain-injured patient. It allows intensivists to acquire detailed information in patients with life-threatening brain injuries. MMM includes traditional tools for monitoring intracranial pressure (ICP) and cerebral perfusion pressure (CPP) as well as more recent developments to monitor complex parameters such as brain tissue oxygenation to facilitate early interventions and improve the outcome following secondary brain injury [1]. Clinical examination remains a core component of MMM and assessment of neurological function, including the Glasgow Coma Scale (GCS) and pupillary reactivity, which has been shown to be a highly predictive outcome in patients with traumatic brain injury (TBI) [2]. However, clinical examination can only provide information on gross neurological function. To evaluate whether the complex parameters of normal brain physiology are in range, a series of invasive and noninvasive measures of cerebral oxygenation, metabolism, hemodynamics, and function are commonly used. These allow the integration and summation of data to tailor therapy in the comatose patient following brain injury.

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## 13.2 Cerebral Hemodynamics

Intracranial pressure (ICP) is a function of the volume and compliance of the different components of the intracranial compartment. Eighty percent of the intracranial compartment is composed of the brain parenchyma, with cerebrospinal fluid and blood that represent 10% each. The cranial compartment is surrounded by a fixed rigid skull and is incompressible. Therefore, an increase in volume of any one of the components of the cranium must be compensated by a decrease in the other. This theory is known as the Monro-Kellie hypothesis, and it dictates the pressure-volume relationship of the brain and the need to keep the sum of the volumes of the brain, CSF, and blood constant (Fig. 13.1) [3]. As the volume of the cranial vault is fixed, any pathological conditions present in the intracranial compartment, such as hematomas and abscesses, can lead to displacement of other components of the brain or an increase in ICP. The brain parenchyma volume remains largely constant in adults; however, the CSF fluid and blood components of the intracranial space usually vary and can lead to an increase in ICP.

In normal adults, the CSF volume is 125–150 mL; approximately 20% of the CSF is contained in the ventricles; the rest is contained in the subarachnoid space in the cranium and spinal cord. It is produced in the choroid plexuses of the lateral, third and fourth ventricles at a rate of 20 mL per h [4]. The cranio-caudal pulsatile wave induced by



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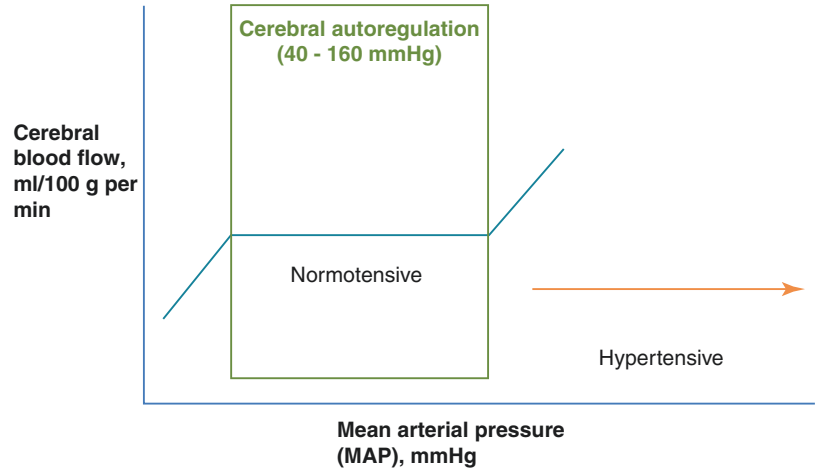


**Fig. 13.1** Pressure autoregulation of CBF

flow in the cerebral arteries propels the CSF along. CSF resorption occurs via the arachnoid villi, which are small protrusions of the arachnoid matter, located along the superior sagittal and intracranial venous sinuses and around the spinal nerve roots [5]. Any obstruction of this outflow, such as a venous sinus thrombosis, can lead to problems with CSF regulation. Other processes such as infection, bleeding, or tumor can also alter the regulation and cause intracranial hypertension [4].

### 13.2.1 Techniques for Monitoring ICP

The first technique for monitoring ICP was developed in the 1950s [6]. It involved the use of a catheter inserted into the CSF of the lateral ventricle through a burr hole. The catheter is connected to a recorder to display the ICP. This technique is still used today, and the gold standard for measuring the ICP is through an external ventricular drain (EVD). This technique has many advantages including relative ease of insertion in patients with normal-size ventricles with accurate readings and the ability to also drain CSF to reduce ICP. However, the main limitations are infection and hemorrhage [7].

### 13.2.2 Cerebral Perfusion Pressure

Cerebral perfusion pressure (CPP) is the net pressure gradient driving cerebral blood flow (CBF). It is the difference between mean arterial pressure (MAP) and intracranial pressure plus cerebral venous bed pressure. One of the major determinants of maintaining CBF is cerebral autoregulation which refers to the ability of the brain to maintain constant blood flow despite changes in CPP [8].

A MAP of between 60 and 160 mmHg allows sufficient blood flow to be maintained with autoregulation. Outside these limits, autoregulation is lost, and CBF becomes dependent on mean arterial pressure (MAP) [9]. If CPP is reduced beyond the limits of autoregulation, the resultant reduction in CBF may cause cerebral ischemia (Fig. 13.2). Large acute increases in CPP can also be detrimental, leading to cerebral edema. Patients with chronic hypertension often have elevated CPP levels, which are tolerated as the autoregulatory curve shifts to the right [10, 11].

### 13.2.3 ICP-/CPP-Directed Therapy

Increased ICP is associated with increased mortality [12], and thus, ICP monitoring is a key component in managing patients with TBI and regarded as standard of care. However, there has been no prospective trial that has demonstrated that measurement of ICP improves outcome. Indeed, a recent randomized controlled trial involving 324 patients in 6 intensive care units in Bolivia and Ecuador concluded that ICP-guided therapy was not found to be superior to traditional image-based treatment in reducing mortality [13]. However, this study has several

**CPP= MAP- ICP**

**Aetiology of raised ICP**

1. Decreased CSF absorption
2. Cerebral oedema
3. Increased cerebrospinal fluid (CSF) production
4. Idiopathic intracranial hypertension
5. Obstruction of venous outflow
6. Obstructive hydrocephalus

**CBF= CPP / CVR**

**Aetiology of reduced CBF**

1. Increased ICP beyond limits of autoregulation
2. Hypocapnia
3. Increased cerebral vascular resistance
4. Increased haematocrit

**Fig. 13.2** Etiology of increased intracranial pressures and reduced cerebral blood flow

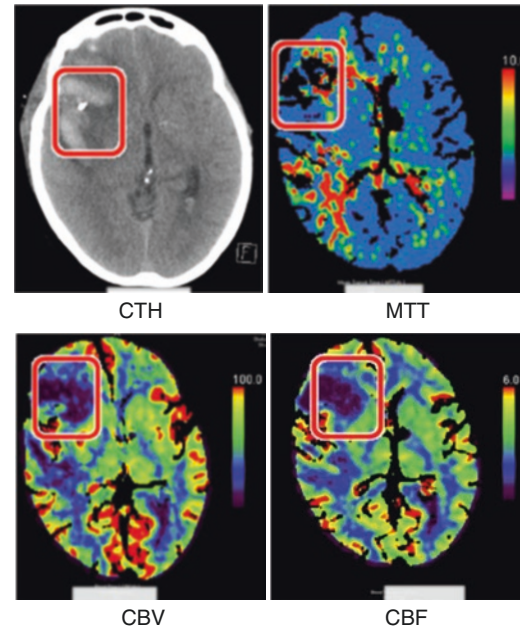


**Fig. 13.3** CT head and CT perfusion parametric maps, demonstrating an area of reduction of both CBV and CBF compatible with cerebral infarction

methodological limitations, and many other studies have shown that patients who received ICP monitoring and ICP-directed therapy had better outcomes than those without ICP-directed therapy [14–16].

It is generally accepted that an ICP greater than 20 mmHg should be treated [17], but most management protocols incorporate ICP and CPP targets to optimize brain physiology. Following trauma, as autoregulation is shifted to the right, a higher CPP of >70 mmHg was initially recommended to maintain an adequate CBF [18]. However, more recent studies have not shown an improvement in outcome with very high CPP [19, 20], although high CPP levels are associated with a significant risk of acute respiratory distress syndrome (ARDS) [21]. Optimal CPP targets are currently 60–70 mmHg if ICP is normal and 50 mmHg if the ICP is elevated [22, 23].

### 13.2.4 Techniques for Monitoring CBF

CBF measurement enables us to better understand the perfusion status of the brain. Techniques for quantitative measurements of CBF were developed in the 1960s and involved administration of a radioactive tracer to the brain followed by measurement of its clearance [24]. More recent developments to measure CBF include CT, CT perfusion, and magnetic resonance imaging (MRI). These allow the measurement of regional CBF; however, they only represent the time at which the scan was performed. Xenon-enhanced CT scanning and positron emission tomography (PET) allow quantitative measurements to be made; however, they again do not allow continuous measurements to be performed in the NCCU [25]. CT perfusion is a relatively new technique that allows rapid qualitative and quantitative evaluation of cerebral perfusion by generating maps of CBF, CBV, and mean transit time (MTT). The technique is based on the central volume principle (CBF = CBV/MTT), and it is commonly used for diagnosis of cerebral ischemia and for the assessment of vasospasm after subarachnoid hemorrhage (Fig. 13.3) [26].

Other techniques include Bowman perfusion monitoring and transcranial Doppler ultrasound imaging.

#### 13.2.4.1 Bowman Perfusion Monitor

The Bowman perfusion monitor (Hemedex®, Hemedex Inc., Cambridge, MA, USA) is a new device measuring focal CBF by a thermodilution technique. The thermal diffusion probe is a small catheter, which contains two thermistors. It is inserted 20–25 mm below the cortical surface to measure white matter perfusion. The distal (active) thermistor is heated 2° above the tissue temperature to create a constant spherical temperature field, and the distal (passive) thermistor is located outside this field, to compensate for any baseline fluctuations in tissue temperature. The power required to maintain the higher temperature is directly proportional to CBF; the greater the power required, the greater the flow. This technique allows direct bedside monitoring of CBF. However, it is an invasive technique and only provides very focal information and requires frequent recalibration; thus, for meaningful data to be obtained, the probe must be inserted into the exact region of interest [27].

#### 13.2.4.2 Transcranial Doppler (TCD) Ultrasonography

Transcranial Doppler (TCD) ultrasonography is a technique used to measure cerebral blood flow velocity (CBFV), an indirect estimation of CBF, and helps to assess cerebral autoregulation. It can also be used to visualize the intracranial arterial vessels (Singh et al. 2001) [28, 29].

The technique involves the use of a low-frequency (≤2 MHz) transducer fixed to the scalp for continuous CBFV recordings [30]. The Doppler shift principle is used to calculate the CBFV. The Doppler effect is the principle that a sound wave with a known frequency (f0) (from the probe) striking a moving object (red blood cells) leads to the reflected wave undergoing a change in frequency (fe) that is directly proportional to the velocity of the reflector (red blood cells). The difference between the f0 and fe is the Doppler shift, fd. The reflected wave can be a higher or lower frequency, which is termed positive or negative shift (Fig. 13.4) [30].

TCD can be conducted using two acquisition modalities. The first is transcranial color-coded duplex sonography (TCCS). Here, a two-dimensional color-coded image of the desired blood vessel is displayed, and, subsequently, blood flow velocities may be measured using a Doppler effect probe. The second method is conventional TCD, using only the Doppler effect probe function. This requires the experience of the clinician to identify the vessels. The TCCS is thought to be superior to TCD; however, there are no major differences in their accuracy to detect vasospasm in the setting of acute subarachnoid hemorrhage (SAH) [31].

TCD is a safe, noninvasive, and easy-to-perform technique; however, it is highly operator dependent. The probe is usually placed over the temporal acoustic window (TAW) or occipital

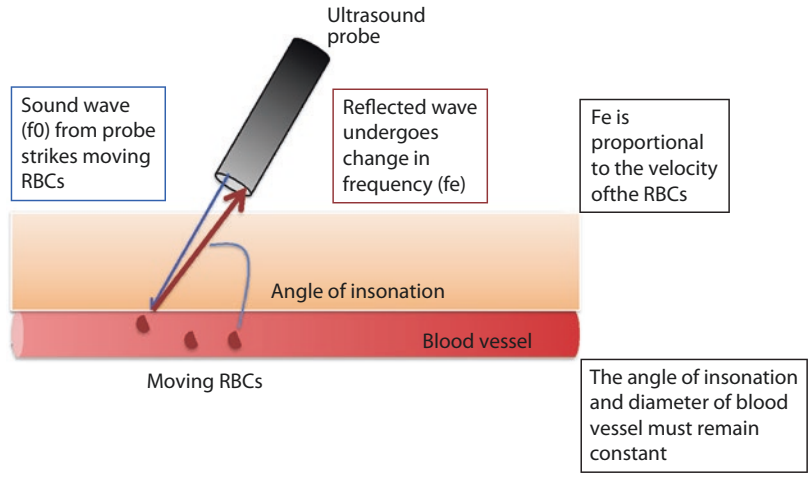


**Fig. 13.4** The Doppler effect

acoustic windows (OAW). The TAW is the thinnest area of the lateral skull, and OAW is an anatomical foramen; thus, both are used since ultrasound beams can be more easily transmitted and reflected. However, many patients, particularly elderly and female patients, have inadequate acoustic windows limiting its use [32, 33].

## 13.3 Cerebral Oxygen Metabolism

Techniques to allow monitoring of cerebral oxygenation include brain tissue oxygen tension (PbtO2) using focal tissue oxygen monitors and jugular venous oxygen saturation (SjvO2) to determine global oxygenation and near-infrared spectroscopy (NIRS).

### 13.3.1 Brain Tissue Oxygen Tension ($P_{bt}O_2$)

The benefits of monitoring of brain tissue oxygen partial pressure have been established since 1993 by Meixensberger et al. [34]. $P_{bt}O_2$ is defined as the partial pressure of oxygen in the interstitial space of the brain and is a product of CBF and cerebral arteriovenous oxygen tension difference [35]. $P_{bt}O_2$ represents CBF in metabolically stable conditions when the oxygen extraction fraction is stable rather than a direct measurement of total oxygen delivery or cerebral oxygen metabolism [36].

Several studies have demonstrated that a $P_{bt}O_2$ measurement of less than 10 mmHg is associated with a decrease in oxygen extraction, suggestive of a poor functional status [37]. Several guidelines therefore recommend PbtO2 be maintained at more than 15 mmHg. Techniques to improve $P_{bt}O_2$ levels include increasing CPP using vasopressors or decreasing ICP [38]. The impact of CPP-targeted therapy on $P_{bt}O_2$ has been investigated by several groups. Studies have shown that CPP levels that are less than 60 mmHg lead to reduction in $P_{bt}O_2$ [39, 40].

Other factors affecting $P_{bt}O_2$ include hyperventilation, hypothermia, and arterial oxygenation. Hyperventilation is widely used for the treatment of intracranial hypertension to reduce ICP and increase CPP. However, hyperventilation reduces $PaCO_2$ causing cerebral vasoconstriction and reduces oxygen supply to as low as 10 mmHg [41]; thus, hyperventilation should be used judiciously and avoided for prolonged periods of time. $P_{bt}O_2$ is influenced by changes in temperature. Inducing hypothermia can reduce oxygen utilization in the brain and impair brain tissue oxygenation [42, 43]. One technique for improving $P_{bt}O_2$ is thought to be increasing the fraction of inspired oxygen ($FiO_2$). Increasing $FiO_2$ is thought to increase $PaO_2$ in the blood and increase brain oxygenation. However, this technique is seldom used due to the perceived effects of free radical damage and the possibility of masking the underlying cause of the low $P_{bt}O_2$ [44]. Other techniques to increase $P_{bt}O_2$ include the use of inotropes such as dopamine or norepinephrine used to augment CBF in low cardiac output states. Decompressive hemicraniectomy often results in improved $P_{bt}O_2$ in large infarctions, most likely by decreasing ICP and increasing CPP [44].

There have been two commercially available systems for $P_{bt}O_2$ monitoring (the Licox® system from Integra and the Neurotrend® system from Codman). The latter is no longer being manufactured, although it has been previously used for both clinical and research measurements. The principle of the Licox® system employs the polarographic Clark-type cell for measuring tissue oxygenation. This is a semipermeable membrane that consists of silver electrodes in one end and gold electrodes in the other end. Dissolved oxygen diffuses from the brain tissue to penetrate the semipermeable membrane; it is then reduced by the gold polarographic cathode to produce a flow of electrical current directly proportional to the oxygen concentration. This information is delivered to the monitor to display the status of the brain tissue's oxygenation [45, 46]. The technique involves the insertion of a fine catheter through a burr hole or tunneling into the brain parenchyma. Probes are usually placed in the subcortical white matter adjacent to an ICP catheter and measure $P_{bt}O_2$ locally, in an area of about 15–20 $mm^2$ around the probe. The probe position

is confirmed with a post-insertion CT scan. An oxygen challenge whereby the $FiO_2$ is increased is usually performed post-insertion to evaluate the function and the responsiveness of the PbtO2 probe. $P_{bt}O_2$ sensors are extremely localized, which has an advantage of being able to better detect focal ischemic events with a higher sensitivity [47].

### 13.3.2 Jugular Venous Bulb Oximetry (SjvO2)

Jugular venous bulb oximetry (SjvO2) is considered as an indirect marker of CBF and cerebral metabolism. It gives an estimate of the global oxygen demand and supply of the brain (SjvO2) [48]. Oxygen saturation in the cerebral venous outflow may inversely correlate with global brain oxygen consumption. Therefore, oxygen saturation in the jugular bulb may be used to indirectly estimate cerebral oxygen consumption [44].

SjvO2 relies on the Fick equation, which determines the rate at which a person uses oxygen in the body. Oxygen that has not been used by the brain is carried to the systemic circulation via the internal jugular vein. The amount of oxygen taken up from the blood by the brain is reflected by the arteriovenous oxygen difference (AVDO2). AVDO2 is determined by the balance between cerebral metabolic requirement of oxygen (CMRO2) and CBF (AVDO2 = CMRO2/CBF). AVDO2 values are normally in the range of 4 mL/dL and 8 mL/dL. A reduction in AVDO2 is usually due to oxygen supply in excess of demand, e.g., hyperemia. Rising AVDO2 values are due to situations of increased demand such as ischemia [44, 48] or increased metabolism. Any increase in CMRO2 with concomitant increase in CBF leads to increased extraction of oxygen from the blood. This is associated with a decrease in oxygen content and saturation of the venous blood leaving the brain; and thus, it increases the AVDO2. In the normal brain, the SjvO2 ranges between 65 and 75%. Values less than 55% could represent a reduction in oxygen supply to meet the metabolic demand in situations of ischemia (Table 13.1). Values greater than 75% could represent cerebral hyperemia or decreased oxygen extraction, such as in cerebral infarction or shunting of arterial blood. In these situations, the coupling between CMRO2 and CBF is lost (Table 13.1) [49].

**Table 13.1** Causes of changes in jugular venous oxygen saturation

| Decreased jugular venous oxygen saturation (<50%) | Increased jugular venous oxygen saturation (>75%) |
|---|---|
| Reduced supply of oxygen, e.g., cerebral vasoconstriction, vasospasm | Increased supply of oxygen: cerebral vasodilation, hypercapnia |
| Due to increased oxygen requirement, e.g., fever, seizures | Due to reduced oxygen requirement: deep sedation, hypothermia, brain death |

Monitoring of SjvO2 has been used in various clinical conditions such as TBI and SAH in the NCCU. Placement of the SjvO2 catheter is a relatively simple clinical procedure, which involves retrograde insertion of a jugular venous catheter. The technique, however, is not without its limitations. It is an invasive procedure, which requires insertion of the catheter into the jugular vein and is associated with risks of inadvertent puncture of the carotid, pneumothorax, vein thrombosis, elevated ICP, infection, and hematoma formation. There may also be malpositioning or kinking of the catheter. Furthermore, as it reflects global cerebral oxygenation, small areas of regional ischemia may not produce any change in SjvO2 [48].

### 13.3.3 Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) is a noninvasive optical spectroscopy method that employs infrared light to characterize fluctuations in cerebral oxygenation.

NIRS is based on the differential absorption of near-infrared and infrared light by oxygenated and deoxygenated hemoglobin. The mathematical basis of *NIRS* is a *modified Beer-Lambert law*, which states that "a portion of the light transmitted through a solution containing a colored compound (chromophore) is absorbed by

$$A = \log_{10} I_0/I = \varepsilon lc$$

*A: Absorption of light expressed as optical density (log of the ratio of the intensities of incident and transmitted light),*
*C: The chromophore concentration (mol dm$^{-3}$)*
*ε: Molar absorptivity (known constant for a given compound)*
*I: Length of solution the light passes through (cm)*

**Fig. 13.5** The relationship between the absorption and concentration of a chromophore is provided by the Beer-Lambert law

the compound". As a result, there is attenuation of the intensity of the emerging light between the light source and receiver (Fig. 13.5) [50]. The enzymes in the mitochondrial respiration chain have differential light absorption characteristics depending on their redox state; thus, NIRS is also considered to provide information on cellular metabolism [51]. NIRS is an important tool in multimodal neuromonitoring for several conditions including TBI and SAH. NIRS can also be used post neurosurgery to detect brain hypoxia [52]. It is relatively inexpensive and has both good space and time resolution (about 1 s and 1 cm$^2$) [53] and can be used repeatedly or constantly with no adverse effects [54, 55].

A study on 94 randomly selected healthy adults reported mean cerebral oxygen saturation of 67.14 ± 8.84% using NIRS [56]. However, individual baseline variation has been reported to be as high as 10% [57]. Furthermore, no studies have been conducted to determine the mean cerebral oxygen saturation thresholds in TBI. Another limitation of NIRS is the contamination of signal by scalp blood flow particularly with swelling and epidural/subdural hematomas, which can lead to unreliable results [46].

## 13.4 Cerebral Metabolism: Microdialysis

Brain microdialysis (MD) is a technique that enables the chemistry of the extracellular space to be measured directly in the brain. The use of this technique has increased our understanding of the pathophysiology of traumatic brain injury, subarachnoid hemorrhage, and intracerebral hemorrhage.

The microdialysis catheter is inserted into subcortical white matter and perfused with a dialysate solution, at slow rates with a pump system. Molecules diffuse down their concentration gradient and equilibrate with the perfusion fluid, which is subsequently collected and analyzed hourly by enzyme spectrophotometry or high-performance liquid chromatography [58].

While any molecule that is small enough to diffuse through the microdialysis catheter can be measured, the most common molecules identified clinically are the concentration of glucose, lactate, pyruvate, glutamate, and glycerol.

Glucose, lactate, and pyruvate are three key molecules in the glycolysis pathway. In normal, aerobic conditions, glucose is metabolized to pyruvate and adenosine triphosphate. In anaerobic conditions such as ischemic injury, glucose is instead metabolized to lactate. Measurement of glucose, lactate, and pyruvate and the lactate-pyruvate ratio thus enable to measure anaerobic metabolism. Ischemia leads to a loss of energy and influx of calcium and disintegration of the cell membrane, liberating an important structural component—glycerol—into the interstitial fluid. Other important biomarkers, which are increased in ischemia, inflammation, and cell damage, include glutamate, an excitatory neurotransmitter.

The average concentration of glucose, lactate, and pyruvate in normal adults is 1.7 ± 0.9 mmol/L, 2.9 ± 0.9 mmol/L, and 166 ± 47 μmol/L. A brain glucose level below 0.7 mM is regarded as a sign of brain tissue energy depletion. Measurements of glucose levels itself are also important as a reduction in glucose levels could be due to hypoperfusion [58]. Under aerobic conditions, the average LPR value is around 15. Under anaerobic conditions, more lactate is produced, so the lactate/pyruvate ratio (LPR) surges. Thresholds of LPR considered significant for ischemia still remain uncertain with some investigators suggesting LPR of 25 [59] and others suggesting >40 [60, 61].

## 13.5 Cerebral Functional State

### 13.5.1 Electroencephalogram (EEG)

Prognostication of comatose patients in the NCCU can be difficult with clinical examination only; in these situations, neurophysiological assessment using electroencephalogram (EEG) and evoked potentials (EP) may be useful. Also, EEG is commonly used for monitoring of interventions and physiology assessment.

Conventional EEG refers to standard recording of electrical activity generated by the brain, presented as tracings of electrical waveforms and inspected visually by a qualified electroencephalographer. The most common indication for performing EEG in the NCCU is to detect seizure activity. The prevalence of nonconvulsive seizures in patients with brain injury ranges from 4 to 30% [62]. When nonconvulsive seizures are present, there is increased rate of mortality [63]. EEG is thought to be more sensitive than clinical neurological examination and is particularly useful in the sedated patient and those with neuromuscular blocking agents. After mild TBI, 86% patients with an abnormal neurological examination had an abnormal EEG, whereas 23% of abnormal EEGs were also accompanied by an abnormal neurological examination [64].

Conventional scalp EEG has its limitations, such as poor signal-to-noise ratio, poor spatial resolution, suboptimal electrode-to-scalp contact, and interference from electrical devices; all these are factors that hamper the interpretation of scalp EEG [65].

#### 13.5.1.1 Quantitative EEG (qEEG)

Digital recording combined with software-assisted data analysis allows quantitative EEG (qEEG) interpretation and identification of subtle shifts in the types and patterns of EEG activity. The EEG pattern can give valuable clues to the underlying diagnosis, e.g., broad repetitive slow waves are known to highly correlate with occurrence of vasospasm in SAH [66, 67]. The most widely used qEEG measures are "spectral analysis" to demonstrate the frequency composition of EEG over a given period; "coherence measurements" that correlate the EEG frequency between two channels to assess how "coherent" the underlying brain activity and "phase" refers to the temporal lead or lag of waveforms between two brain regions [68, 69].

### 13.5.2 Evoked Potentials

Evoked potentials are neurophysiology tools used in the NCCU to assist in the prognosis of patients who have sustained traumatic brain injuries. The somatosensory evoked potential (SSEP) is a small (<10–50 μV) electrical signal that can be recorded noninvasively from the skull after delivering electrical stimuli to one of the peripheral nerves. SSEPs are inexpensive and noninvasive methods to evaluate functional damage to the complete sensory pathway from the peripheral nervous system, dorsal column of the spinal cord, and lemniscal pathways in the brainstem, with eventual arrival at the somatosensory cortex [70].

SSEP measurements can be used to detect patients with brainstem herniation as a result of interruption of these functional connections [71] and cerebral ischemia [72] and can be used to predict rises in intracranial pressure [73].

SSEPs are graded between I and VI (Fig. 13.6). Normal SSEPs (grade I) after TBI are associated with a 57% chance of good recovery, whereas bilaterally absent SSEPs (grade VI) are associated with only a 1% chance of functional recovery [75]. However, using SSEP to predict mortality has yielded mixed results. Studies have shown SSEPs to have a 43% sensitivity with no false positives as a predictor for poor neurological outcome [76]. However, in other studies, TBI patients with bilaterally absent SSEPs only had very minor disabilities [77].

SSEPs are also limited by the need for specialist interpretation with intermediate results, which can be difficult to interpret. Furthermore, there may be moderate interobserver agreement even between experienced neurophysiologists, thus limiting its usefulness. The main source of disagreement is related to the noise levels [78]. In the polytrauma patient with coexisting spinal damage, results may not be accurate as spinal lesions can affect cortical responses [79, 80].

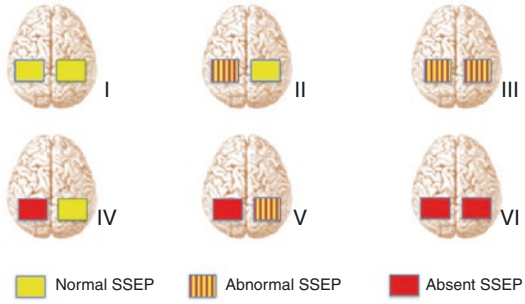


**Fig. 13.6** SSEP grades. Modified from Houlden et al. (2010) [74]

## 13.6 Neuroimaging

Neuroimaging is a one of the most important resources available for patients in the NCCU. The most common neuroimaging techniques used are (1) computed tomography (CT) scans such as plain CT, angiography (CTA), CT perfusion (CTP), and xenon CT scans; (2) magnetic resonance imaging (MRI) including MR angiography (MRA), MR perfusion, MR spectroscopy, and functional MRI; and (3) positron emission tomography (PET) and single photon emission CT (SPECT).

### 13.6.1 Computed Tomography (CT)

Neuroimaging with CT scans remains one of the most common and first-line investigations in patients with brain injuries. In the NCCU, CT scans are an extremely useful technique to detect intracerebral hemorrhage (ICH), cerebral edema, and signs of elevated intracranial pressure. Patients who require prompt surgical intervention can then be expedited to the neurosurgical unit or NCCU for further management. CT imaging is usually in the form of whole-body imaging to allow a full assessment of the polytrauma patient where clinical assessment is often difficult. Contrast-enhanced CT imaging has advanced the ability to identify abnormal regions in the brain because of blood-brain barrier disruption, leading to increased uptake of contrast. Contrast enhancement also forms the basis of CT perfusion scans. This involves sequential acquisition of axial data during the intravenous administration of iodinated contrast material. The change in CT enhancement (Hounsfield units) is proportional to the concentration of contrast. CT perfusion can provide parametric images of cerebral blood volume (CBV), mean transit time (MTT), CBF, and CTA alongside structural data. This technique is widely available, relatively quick, and cost-effective. It allows intensivist to direct therapy and assess cerebral vasospasm following SAH. CT perfusion can be performed with CTA in patients who may require thrombolysis. CT imaging has a number of limitations including the inability to accurately define the volume of the brain at risk of ischemic injury. Furthermore, serial CTP scans increase radiation risk and risk associated with contrast injection [25, 65].

### 13.6.2 Magnetic Resonance Imaging

MRI is increasingly being used for the acute head trauma patient. It has higher sensitivity in detecting white matter abnormalities following head injury compared to CT. Furthermore, fluid attenuation inversion recovery (FLAIR) MRI sequences possess a higher sensitivity for traumatic axonal injury and can help in prognostication [25, 65].

## 13.7 The Importance of Multimodal Monitoring and Application in the Clinical Practice

MMM encompasses various tools (Fig. 13.7) to provide continuous, real-time assessment of brain physiology to detect and treat abnormalities before irreversible brain injury occurs. Patients with brain injury have complex physiological abnormalities such as raised ICP, hypoxia, and excitotoxicity, which need to be carefully monitored. This can be difficult in the comatose patient; thus, MMM allows the intensivist to create an optimized and patient-targeted care plan with the goal to prevent secondary brain injury. MMM can be categorized into invasive and noninvasive techniques. Invasive

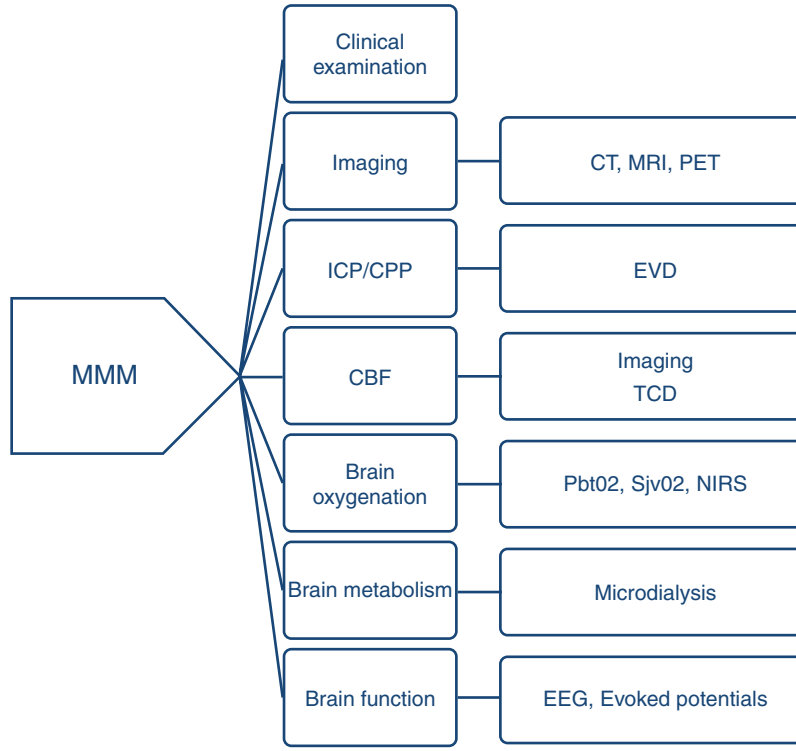


**Fig. 13.7** Schematic overview of multimodal monitoring in the neurocritical care unit

techniques include tissue monitoring using probes that are inserted directly into the brain parenchymal tissue via burr holes or after craniotomy. The exact location of the probe is crucial when interpreting data obtained from such monitoring. The ideal locations for probes for large cerebral infarctions are the perilesional frontal white matter. For diffuse TBI or SAH, non-dominant frontal matter is thought to be ideal [44].

MMM is a continuous process, allowing data to be collected simultaneously and displayed in an integrated fashion. MMM allows us to understand abnormalities in brain physiology in each patient and thus helps deliver patient-specific goal-directed therapy. A recent randomized prospective clinical trial of 119 patients with TBI in 10 ICUs in the United States showed that management of severe TBI informed by MMM reduced brain tissue hypoxia with a lower mortality at 6 months and better neurological outcome than ICP-only treatment [81]. MMM is, however, limited by the need for multiple measures and tools, which requires highly specialized personnel, is associated with high costs, and is time-consuming. Furthermore, since each parameter may reflect only one aspect of brain physiology, without thorough system integration of information obtained, meaningful data that can translate into better outcomes cannot be achieved. Moreover, MMM does not mean effective therapy; thus, studies need to focus on improving outcomes. Currently there is no single monitor that allows us to understand the complex brain physiology and target therapy; thus, MMM helps to individualize and better target management of patients with neurological injury.

## 13.8 Conclusion

The NCCU is a specialized unit designed to treat patients with severe brain injuries from trauma, stroke, or status epilepticus. Most patients present with a primary injury and some form of neurological damage. Many patients do go on to develop secondary brain injury, which can be irreversible; however, with optimal treatment, it can be preventable and reversible. The NCCU,

therefore, plays a significant role in improving morbidity and mortality in these patients. MMM refers to the digital simultaneous recording of multiple parameters of brain function, providing overall basic physiological information. MMM enables a thorough analysis of the brain hemodynamics, oxygenation, and function to provide individualized therapy to improve outcomes. However, limitations of each individual tool must be recognized to aid interpretation of data and improve the currently available techniques.

**Key Points**

- Multimodal monitoring (MMM) in the neurocritical care unit (NCCU) has become an important component of care of the severely brain-injured patient.
- MMM includes traditional tools for monitoring intracranial pressure (ICP) and cerebral perfusion pressure (CPP) as well as more recent developments to monitor complex parameters such as brain tissue oxygenation to facilitate early interventions and improve the outcome following secondary brain injury.
- To evaluate whether the complex parameters of normal brain physiology are in range, a series of invasive and noninvasive measures of cerebral oxygenation, metabolism, hemodynamics, and function are commonly used.
- Limitations of each individual tool must be recognized to aid interpretation of data and improve the currently available techniques.

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# Part IV

# Systemic Care

# Respiratory Care of Neurologic Patient

14

Lorenzo Ball, Denise Battaglini, and Paolo Pelosi

## 14.1 Introduction

Patients with neurological dysfunction typically present with inadequate protection of airway, and therefore endotracheal intubation is a first-line measure of respiratory assistance to overcome inadequate oxygenation, ventilation, and airway protection. Appropriate ventilator settings are fundamental to maintain an adequate cerebral oxygenation, blood flow, perfusion pressure, and normal vascular reactivity. Respiratory care of neurologic patients poses specific challenges for the clinician, both in the operating room and in the critical care settings: this chapter aims to provide an overview of their respiratory management.

## 14.2 Central Nervous System Anatomy and Pathophysiology Relevant to Ventilation

Physiologic breathing requires a complex interaction between brain, spinal cord, and respiratory muscles and chemo-sensors in the aortic arch and carotid bodies. Respiratory centers are localized in the medulla and connect with pontine nuclei and cortical and subcortical connections. Brain injury can change respiratory patterns and respiratory automaticity with various patterns under different conditions. Lesions causing unstable respiratory patterns are typically bilateral, with common causes including infarction, hemorrhage, tumor, vascular malformations, infection, encephalitis, and others. Another factor potentially affecting the respiratory pattern is respiratory alkalosis itself, secondary to patient or ventilator hyperventilation. Central hyperventilation usually is caused by loss of inhibitory input that can worsen brain injury because of development of alkalosis or cerebral vasoconstriction, as opposite to physiologic central hyperventilation potentially due to an increase of intracranial pressure or reduction of blood pH. Moreover, lesions of the parabrachial nucleus in the upper pons result in impaired airway protective reflexes that can lead to aspiration of gastric contents with possible colonization of upper and lower airways. Cough reflex is important to prevent the downward passage of secretions through the glottis and the subsequent formation of atelectasis. In summary, neurologic critically ill patients can fail to maintain a patent upper airway and/or have a pathologic respiratory pattern, resulting in increased risk of aspiration hypoxia, hypercarbia, and acidosis [1].

The cranium is a rigid container, enclosing the cerebral parenchyma (around 1500 mL), blood (150 mL), and cerebrospinal fluid

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(150 mL). Cerebral blood flow (CBF) represents 15% of the cardiac output (CO) and it is constantly 45–65 mL/min per 100 g of cerebral tissue. Basal cerebral metabolic rate of oxygen ($CMRO_2$) is about 3.5 mL/100 g/min, corresponding to around 20% of the oxygen total body consumption. An increase in neuronal activity is associated with an increase of local $CMRO_2$ consumption, with local alterations of CBF. Homeostatic mechanisms underlying brain self-regulation, with regard to the relations between volume of CSF, blood, brain tissue, and intracranial pressure and cerebral perfusion, are expressed in Monro–Kellie's hypothesis. Under physiologic conditions, the three cranial contents are in equilibrium, each volume increase in one of the compartments causes a compensatory volume reduction in the other two. Alterations in this mechanism are the basis for the development of brain homeostasis disorders including intracranial hypertension. Imbalances between the volume of parenchyma, CSF, and vascular volume can result in increased intracranial pressure (ICP). However, the physiologic range of ICP to be considered normal is still a matter of debate.

In head trauma, an alteration of this balance can be caused by hemorrhage, cerebral edema, post-traumatic hydrocephalus, pneumocephalus, hyperemia, thrombosis of venous sinuses, fractures, increased muscle tone, and Valsalva maneuver as a result of agitation or posture, hypoventilation with hypercapnia and cerebral vasodilation, cerebral vasospasm, and systemic hypertension. In response to these changes, brain self-regulation acts to maintain adequate intracranial pressure. Initially, there is a shift of the CSF into the subarachnoid space through the foramen magnum, followed by increased venous drainage. When the compensation mechanisms fail, an increase in intracranial pressure is observed.

Brain damage does not conclude at the time of physical trauma but continues to evolve over the course of days. Indeed, two types of brain damage can be observed: primary damage, due to the external forces acting on the cranial structures, and secondary damage due to alterations of the cerebral perfusion with subsequent ischemic damage. This type of damage may be due to extracranial causes (hemodynamic, metabolic, or thermal impairment) and intracranial causes (increased intracranial pressure and reduced cerebral perfusion pressure). Therefore, the critical parameter for cerebral survival is not intracranial pressure itself but the maintenance of an adequate CBF. CBF strictly depends on the cerebral perfusion pressure (CPP), defined as the difference between mean arterial pressure and ICP. Cerebral blood flow is also altered by the byproducts of cerebral metabolism, such as $PaCO_2$, $H^+$ concentration, and $PaO_2$. The increase in $PaCO_2$ causes cerebral vasodilatation and an increase in the cerebral blood flow because of $H^+$ concentration. As the $PaCO_2$ diffuses very easily through the blood–brain barrier, its action on CBF takes place very quickly. CBF varies around 1–2 mL/100 g/min for each increment in $PaCO_2$ of 1 mmHg. Brain is allegedly able to tolerate CBF reductions of 50% prior to developing ischemia, but in some pathologic conditions ischemia can develop with less relevant alterations in CBF. Increase of brain acidity determines an increase of cerebral blood flow, and $PaCO_2$ increases $H^+$ concentration because $CO_2$ within the blood combines with water to form carbonic acid which frees $H^+$ ions. Oxygen shortage can also lead to cerebral vasodilatation. The cerebral oxygen consumption remains constant at 3.5 mL/100 g/min, and regulation mechanisms are triggered by $PaO_2$ below 20 mmHg. Cerebral autoregulation is another important maintenance mechanism of the CBF, which attempts to maintain mean arterial pressure to ensure adequate CPP. The autoregulation mechanism protects the brain from sudden changes in blood pressure by modifying the vascular cerebral resistance.

Therefore, the crucial role of blood gases in brain hemostasis explains why ventilation is so important in the neurological patient. Through the modification of ventilatory parameters, the clinician can modify cerebral blood flow and prevent the development of secondary damage [2, 3].

## 14.3 Airway Management in Neurologic Patients

The aforementioned mechanisms clarify the crucial relevance of airway management of the neurologic patient, which has indications and management not necessarily equal to those of non-brain-injured patients.

### 14.3.1 Endotracheal Intubation in Neurologic Patients

In addition to the maintenance of airway patency per se, intubation in neurologic patients is important to maintain oxygenation and pH stability to prevent secondary cerebral damage. Before sedation and intubation, the patient should be neurologically assessed for the ability to maintain a patent airway in order to reduce the probability of secondary damage. The worst scenario is difficult bag and mask ventilation combined with a difficult intubation, and even if uncommon each intubation attempt should be performed with this potential risk in mind, being prepared for escalation of care [1]. Criteria for intubation include failure of protective airway reflexes, failure of oxygenation or ventilation (e.g., acute respiratory distress syndrome [ARDS], septic shock, neuromuscular disease, and cardiopulmonary arrest), and anticipation of a deteriorating clinical course.

Presence of gag reflex is not a specific indicator of the patient's ability to protect an airway. Also, arterial blood gases cannot be solely relied upon as an indicator for when to intubate. Although Glasgow Coma Scale (GCS) <8/15 requires intubation in severe brain injury because protective reflexes are lost, GCS alone is not sufficient for all situations in the neurocritical setting. For the same reasons, rapid sequence intubation is often preferred. This technique also allows to minimize the intracranial pressure increase associated with prolonged intubation attempt. First, cervical spine injury should be evaluated before performing laryngoscopy and hypotension, hypoxia and hypertension should be avoided. Recently, devices allowing intubation without neck hyperextension are being developed and might be useful in selected cases [4].

### 14.3.2 Alternatives to Endotracheal Intubation

While there are no absolute contraindications to tracheal intubation, several relative contraindications exist, e.g., the presence of critical brain ischemia, cervical spine injury, the need to perform neurological examination, or expected difficult airway in a patient in which intubation can be delayed. Intubation activates the sympathetic nervous system causing secondary tachycardia, hypertension, bronchospasm, and increased ICP. When avoidance of intubation is warranted, non-invasive support techniques could be considered. The use of continuous positive airway pressure (CPAP) or bilevel non-invasive ventilation (NIV) has been used, keeping an eye on airway pressure to avoid increase in ICP. However, there are contraindications to non-invasive ventilation, such as hemodynamic instability, GCS < 10/15, upper gastrointestinal bleeding, facial trauma or surgery, upper airway obstruction, inability to protect airway or to clear respiratory secretions, and risk of aspiration. Complications associated with this technique are especially prevalent in neuro patients able to properly ventilate and oxygenate, but unable to maintain a patent airway. More recently, humidified high flow nasal cannula have been introduced in adults. These devices are typically well tolerated and can be an alternative to NIV, but their efficacy seems to be lower due to the lack of a true positive-pressure effect [1].

## 14.4 Brain–Lung Crosstalk

In brain damaged patients, respiratory dysfunctions are a common medical complication associated with a poor outcome. Lung injury occurs shortly after brain damage because of pulmonary edema, effect of neurotransmitters, and activation of inflammatory response as well as dysfunction of the autonomic system. Determinants of pulmonary dysfunction after brain injury include an increase of the sympathetic activity with the release of catecholamine that can lead to pulmonary edema. The "blast injury" theory

hypothesizes that sympathetic activity can increase intracranial pressure and intravascular pressure, with alteration of the alveolo-capillary membrane [22]. Moreover, systemic inflammatory response causes release of cytokines into the systemic circulation potentially contributing to lung injury [23].

Several lung pathophysiologic alterations are observed in brain damage [7], including changes of the structure of type II pneumocytes [24], alveolar damage with neutrophilic infiltration [25], and increased susceptibility to VILI [26]. This might explain the recent findings suggesting that protective ventilation is an independent predictor of favorable outcome in brain-injured patients [27]. Moreover, many neurologic patients require prolonged ventilation, and this might increase the risk for VILI.

A specific entity is neurogenic pulmonary edema (NPE), of which the actual incidence among brain-injured patients is debated. In patients with subarachnoid hemorrhage, it is reported between 2% and 42.9% [28, 29], while above 20% in traumatic brain injury [30]. NPE results in increased extravascular lung water, which has been reported to be correlated with ICP. Several mechanisms could occur, including changes in the cardio-vagal reflex [31] and sympathetic activation with cardiac output and blood pressure increase [32]. The most common form of NPE is the early variant that develops within minutes to hours after the neurologic insult, while the delayed form develops in 12–24 h. Usually, NPE is described as a non-cardiogenic form of pulmonary edema. However, this mechanism and cardiac impairment can partly overlap, with further worsening of damage. The clinical management of NPE is not different from other forms of lung injury in brain-injured patients and comprises the reduction of ICP while maintaining normocapnia (35–40 mmHg) and avoiding hypoxia, thus a target of $PaO_2 > 60$ mmHg or $SaO_2 > 90\%$.

The severity of lung injury can vary from mild oxygenation impairment to ARDS. It has been proposed that the neurogenic form of ARDS could have a distinct inflammatory pathway. A study in mice showed that activation of adenosine-2A receptors contributes to lung damage because of a pro-inflammatory effect [33], while ARDS can be caused by activation of the sympathetic nervous system in the acute brain injury [34].

For all these reasons, any non-lung-injured neurologic patient should be considered at high risk of developing secondary lung injury.

## 14.5 Mechanical Ventilation in Neurologic Patients

Ventilatory strategies should aim to preserve oxygenation, while maintaining carbon dioxide levels within acceptable ranges avoiding hypercapnia and that could result in secondary brain damage. Like in any other mechanically ventilated patient, the risk of ventilator-induced lung injury (VILI) must always be weighted when setting the ventilator, especially in patients with an expected prolonged ventilation. Surfactant production is often abnormal in brain-injured patients due to injury of type II pneumocytes, and the formation of atelectasis is more prevalent than in other non-lung-injured patients. In this context, positive end-expiratory pressure (PEEP) could improve oxygenation, but higher levels impair cerebral venous drainage [5]. Moreover, when PEEP causes hyperinflation $PaCO_2$ increases, generating a consequent increase of ICP [6, 7]. Despite numerous clinical studies, the best safety ventilatory strategy for neurocritical patients has yet to be established. Moreover, several authors have reported high incidence secondary lung injury in neurocritical patients, such as ARDS or neurogenic pulmonary edema [8].

Ventilation can also be considered a therapeutic measure to prevent and even partly treat intracranial hypertension, exploiting the effects on cerebral blood flow of mild hypocapnia ($PaCO_2$ 30–35 mmHg). However, this requires an increase in minute ventilation, that should be achieved through increases in the respiratory rate rather than tidal volume (TV), as the latter is more injurious for the lung [6]. Table 14.1 resumes proposed intervention bundles in neurologic patients.

**Table 14.1** Ventilator management of the neurologic patient

| *Ventilator settings* |
|---|
| Target $PaO_2$ 100–120 mmHg and $PaCO_2$ 35–40 mmHg [9] |
| Consider non-invasive respiratory support (bilevel non-invasive ventilation—NIV, continuous positive airway pressure—CPAP, or high flow nasal canulae—HFNC) in the *absence* of [1]:<br>• Hemodynamic instability<br>• Glasgow coma scale <10/15<br>• Upper gastrointestinal bleeding<br>• Facial trauma or surgery<br>• Upper airway obstruction<br>• Inability to protect airway or to clear respiratory secretions<br>• High risk of aspiration |
| Always consider tracheal intubation and mechanical ventilation if Glasgow coma scale <8/15<br>• Set tidal volume to 6–8 mL/kg of predicted body weight<br>• Limit plateau pressure <30 $cmH_2O$<br>• Aim to maintain driving pressure <15 $cmH_2O$ [10]<br>• Low-moderate level of PEEP and avoid recruitment maneuvers [11] |
| *Weaning* |
| Consider start of weaning from mechanical ventilation when [12, 13]:<br>• Glasgow coma scale >8<br>• Orolingual control is achieved<br>• Cough with/without gag reflex<br>• $PaO_2$ >60 mmHg with $FIO_2$ <50%<br>• Positive end-expiratory pressure <8 $cmH_2O$<br>• Hemodynamic stability<br>• Airways suction not more frequent than 2 h |

### 14.5.1 Effects of Positive-Pressure Ventilation on Cerebral Hemodynamic

Increased intrathoracic pressure can reduce venous drainage and, through a reduction of preload and arterial pressure, the cerebral blood flow [7]. Respiratory elastance contributes to ICP elevation, as airway pressure increases pleural pressure: the detrimental effects of high pressures on cerebral hemodynamic are more relevant in patients with elevated respiratory system elastance [8]. Moreover, higher pressures might either recruit or hyperinflate lung tissue, modifying $PaO_2$ and $PCO_2$ that can indirectly influence ICP. Level of PEEP is one of the major determinants of intrathoracic pressure and must be often increased in case of oxygenation impairment. Absolute safe thresholds of PEEP are difficult to be determined in patients with elevated ICP; however, most physiologic studies suggest that a PEEP lower than the mean ICP is safe in terms of cerebral perfusion impairment [14]. The effects of higher PEEP levels are more debated. In a study, Boone et al. prospectively assessed the effects of PEEP on ICP and CPP, observing an average increase of 0.3 mmHg in ICP for every $cmH_2O$ increase in PEEP, while CPP decreased linearly [15]. However, other studies did not find an association between PEEP and the worst observed ICP value: Frost et al. found that PEEP between 5 and 12 $cmH_2O$ can improve arterial oxygenation without rising ICP [15], while Shapiro et al. observed an increase of ICP > 10 mmHg in more than 50% of patients with PEEP level between 4 and 8 $cmH_2O$ [16].

While there is wide consensus on the need to keep the tidal volume at 6 mL/kg of predicted body weight in lung-injured patients [17], the use of higher PEEP levels is debated [18]. Undoubtedly, PEEP can increase oxygenation, but might worsen ventilator-induced lung injury and, in neurologic patients, cerebral perfusion [19]. Therefore, in particular in these patients, PEEP should be kept at the minimum level ensuring adequate oxygenation, targeting $SpO_2$ to at least 90–92%. Another debated aspect of protective ventilation is the use of recruitment maneuvers (RMs), namely procedures aimed at increasing lung aeration through a transient increase in transpulmonary pressure. Few studies investigated the effects of RMs on cerebral perfusion, reporting an increase of intracranial pressure and an impairment of hemodynamic, resulting in reduced CPP [20, 21].

In conclusion, the clinician must balance between benefits and harms of positive-pressure ventilation in the neurologic patient.

### 14.5.2 Ventilation in Neurologic Patients with Injured Lungs

Management of patient with ARDS concomitant with acute brain injury is complex. The concept of "doubly protective ventilation" has been

proposed, as ventilation must be protective for both the brain and the lungs. Then, the aim of ventilation is also to maintain normal $PaCO_2$, and thus brain homeostasis, with low tidal volumes to protect the lungs [35]. High PEEP worsens cerebral circulation and can cause an ICP increase. It is often suggested that an increase in PEEP up to 15 $cmH_2O$ does not influence ICP, and a strategy protective for both the lungs and the brain must comprise low tidal volumes and moderate PEEP levels [36]. As in any ARDS patient, it is recommended to maintain low tidal volume (6–8 mL/kg of predicted body weight), limited plateau pressure (<30 $cmH_2O$), and low driving pressure (<15 $cmH_2O$) [10]. When these strategies fail to maintain oxygenation or unacceptably high pressures are required, rescue therapies must be considered. The use of prone positioning, now recommended in early severe ARDS [37], should be considered with extreme caution in neurologic patients, as it might impair cerebral spinal fluid circulation and induce ICP increase. The use of extracorporeal respiratory support is reserved for patients with refractory hypoxia [38], but the use of this technique in neurocritical care patients is poorly reported. Both extracorporeal membrane oxygenation (ECMO) and carbon dioxide removal ($ECCO_2R$) could be used, as they can allow a more lung-protective ventilation and a strict control on the $PaCO_2$, improving also the cerebral blood flow [39].

### 14.5.3 Ventilation in Patients with Acute Mechanical Respiratory Failure

Acute respiratory failure may also occur due to mechanical reasons, and three mechanisms are typically involved: weakness of the respiratory pump for muscular or neurological impairment, inability to keep the airways open, and poor cough reflexes. These mechanisms result in changes in drive, rhythm, mechanics, and dynamics potentially leading to a critical condition [40]. Acute traumatic spinal cord injury is a common cause of mechanic respiratory failure. Lesions at the C3–C5 levels result in damage above the level of phrenic motor neurons, resulting in the worst cause of loss of airway control with complete paralysis of the muscles and total dependence on mechanical ventilation; lesions below C5 reduce expiratory effort [41]. Other major causes of mechanical respiratory failure include myasthenia gravis, phrenic nerve lesion, Guillain–Barré syndrome, acute cervical myelitis, cervical cord infarction, chronic myopathies, tetanus, and botulism [42].

Patients with mechanic respiratory failure develop tachycardia (>100 bpm), tachypnoea (>20 breaths per minute), use of accessory muscles such as sternocleidomastoid or scalene, and asynchronous and paradoxical breathing. Chemoreceptors are overstimulated when $PaO_2$ decreases and $PaCO_2$ increases, increasing the respiratory drive. Dysphonia and dysphagia can develop due to weakness of the oropharyngeal muscles. Usually, abdominal paradox breath can be detected when the movements are not coordinated, and the breathing is asynchronous. Instead, the breathing pattern in patient with acute spinal cord injury with tetraplegia consists in small tidal volumes, rise of respiratory rate without change in minute ventilation [40].

Assisting the respiratory activity is a challenge. If the underlying condition is reversible, non-invasive ventilation can be considered in patients able to maintain airway patency, with low PEEP and low-pressure support. If the condition is more severe, involves airway control, or it is non-reversible, invasive ventilation and tracheostomy are often required. Ventilation can be assisted in patients with some degree of respiratory drive, while totally controlled modes must be used in patients with completely abolished muscular activity.

### 14.5.4 Mechanical Ventilation in the Neurosurgical Operating Room

Recent studies suggested that intraoperative lung-protective mechanical ventilation using low tidal volumes (6–8 mL/kg of predicted body weight) prevents postoperative pulmonary

complications (PPCs) that have an important impact on mortality and morbidity [43, 44]. The role of PEEP and recruitment maneuvers (RMs) is more debated, with several authors recommending a low-moderate level of PEEP and no recruitment maneuvers [11]. Neurocritical care patients often require prolonged mechanical ventilation also after surgery, and this increases the risk of developing respiratory complications. Furthermore, brain injury increases the risk of developing pulmonary complications due to alterations of consciousness and inability to protect the airways [7]. Induction of anesthesia causes atelectasis and a consequent increase in ventilation–perfusion mismatch, but the application of PEEP could maintain the alveoli open during mechanical ventilation [45]. However, in the intraoperative setting, the best level of PEEP remains uncertain [46, 47]. In the neurologic patient, ventilation techniques should be adequate to the cerebral hemodynamic. The maintenance of oxygenation of 100–120 mmHg $PaO_2$ and $PCO_2$ of 35–40 mmHg is mandatory to maintain cerebral autoregulation, while ensuring low driving pressure and low tidal volume to protect the lungs [9].

### 14.5.5 Ventilation During Prone and Sitting Positioning

Prone position is necessarily used during spinal surgery, and this influences lung volumes, ventilation, and perfusion [48]. Among the physiologic effects of prone positioning, oxygenation improves in obese and ARDS patients, mainly due to a redistribution of ventilation and aeration. In healthy subjects, the increase in oxygenation is associated with an increase in FRC [49], more homogeneous lung perfusion reduction of mismatching of ventilation/perfusion [48]. However, it has been reported that in healthy patients $PaCO_2$ increases in prone position, due to an increase in physiological dead space [49]. However, during general anesthesia for spine surgery, prone positioning reduces respiratory dynamic compliance and requires higher airway pressure to maintain TV [50].

The sitting position provides several advantages during neurosurgery, because it offers a direct view of the operating field [51], and improvement in venous return reducing brain swelling and intracranial pressure [52]. However, its use is debated as it is associated with specific complications including venous air embolism, pneumocephalus, and subdural hematoma [53]. In a recent retrospective study, Himes et al. describe an overall incidence of complications of 1.45% [54]. In 2008, the German Society of Anaesthesiology and Intensive Care (DGAI) published guidelines for the management of patient in sitting position undergoing neurosurgery, recommending the exclusion of patent oval foramen patients to reduce the risk of paradox air embolism and suggest the intraoperative use of transesophageal echocardiography [55].

## 14.6 Tracheostomy and Weaning from Mechanical Ventilation in the Neurologic Patient

The liberation from mechanical ventilation involves two separate processes: discontinuation from the ventilator and removal of the artificial airway. According to the American College of Chest Physicians, the Society of Critical Care Medicine, and the American Association of Respiratory Care, the principles of liberation from mechanical ventilation are: (1) frequent assessment of necessity of ventilatory support and artificial airway, (2) evaluation of factors determining ventilatory dependence, and (3) application of weaning protocols.

Weaning should be initiated as soon as possible because of the complications associated with prolonged intubation and tracheostomy. The weaning protocols can start when the lung injury is resolved and the patient is stable and requires low peep and low $FIO_2$, when has adequate gas exchange, when is hemodynamically stable, and when has the ability to start spontaneous breaths [12]. Scores and protocols used in general critically ill patients might not be directly applicable to neurocritical patients. Mullaguri et al. developed an algorithmic approach to evaluate spontaneous breathing trials

in these patients [13]. Patients selected for weaning and extubation had Glasgow coma scale >8, orolingual control, cough with/without gag reflex, $PaO_2 > 60$ mmHg ($FIO_2 < 50\%$), PEEP <8 $cmH_2O$, hemodynamic stability, and airways suction not more frequent than 2 h. The spontaneous breathing trial comprised zero PEEP and no pressure support for 30 min, or 5 $cmH_2O$ PEEP + 5 $cmH_2O$ pressure support. Patients were extubated if they maintained hemodynamic stability, saturation, and respiratory rate. The algorithm had high sensitivity but low specificity to identify patients ready for extubation.

Tracheostomy is performed in patients affected by dysphagia, prolonged mechanical ventilation, and reduced level of consciousness. However, the better timing to tracheostomy in neurological ICU patients is still unknown, but a cutoff of 2 weeks of mechanical ventilation is typically advocated in critically ill patients to prevent tracheomalacia and post-intubation tracheal stenosis. Studies suggest that, in neurocritical patients, tracheostomy could promote earlier weaning because the predominant cause of respiratory dysfunction is not ventilation itself but rather the inability to maintain upper airways patency [56]. Percutaneous tracheostomy is a safe procedure at the bedside, but it is associated with specific ethical and management aspects that need team discussion and possibly sharing with relatives, and when feasible with patients [57, 58]. Patients with high cervical traumatic injury and Guillain–Barré patients require early tracheostomy; while in myasthenia gravis weaning and extubation are performed after immunotherapy and tracheostomy can be performed later. A meta-analysis of studies conducted in 503 patients with acute brain injury found that early versus late (>10 days) tracheostomy reduced long-term mortality at 6–12 months, duration of mechanical ventilation, and length of stay in ICU but does not reduce short-term mortality. They conclude that the limited numbers of randomized patients are a limitation and suggest the need of future randomized trials focusing on patient-centered outcomes including quality of life [12]. Trials are ongoing in specific subpopulations such as in severe stroke [59].

## 14.7 Conclusions

Respiratory care of the neurologic patient is complex and requires a multidisciplinary approach. Brain and lungs have a complex interaction that makes difficult to translate directly to neurologic patients the findings concerning mechanical ventilation in non-brain-injured patients, and further studies are necessary to identify the best strategies in this specific population of patients.

**Key Points**

- Ventilatory strategy of neurologic patients requires a multidisciplinary approach, including lung-protective ventilation along with an adequate care of the injured brain in order to prevent the secondary brain damage.
- Prolonged mechanical ventilation is often required in neurologic patients due to the inability of airway protection. Non-invasive support techniques could be considered in selected cases.
- Prolonged intubation and tracheostomy are associated with severe complications, therefore weaning should be initiated as soon as possible.
- The correct timing for tracheostomy and weaning is still debated. Further studies are necessary to clarify this point.

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# 15 Endocrine Management in the Neurosurgical Patient

Shaun E. Gruenbaum, Christian S. Guay, Saul S. Siller, and Federico Bilotta

## 15.1 Introduction

The endocrine system is made up of a complex network of glands and their respective hormones (Fig. 15.1), which are secreted into the circulation and delivered to target organs where they elicit a specific response. The endocrine system regulates numerous biological processes throughout the body including growth and metabolism, reproduction, and mood, and is normally under tight homeostatic control. Endocrine dysfunction is common and can include disorders of endocrine gland hyposecretion (i.e., hormone deficiency), hypersecretion (i.e., hormone excess), and tumors of the endocrine glands. The perioperative management of patients with coexisting endocrine dysfunction requires an in-depth understanding of how hormone imbalances can impact the major organ systems. Because the endocrine and nervous systems closely interact to maintain hormonal homeostasis, there are several unique considerations in neurosurgical patients that must be appreciated by neuroanesthesiologists and neurointensivists. In this chapter, we will review the perioperative considerations in neurosurgical patients with coexisting endocrine dysfunction.

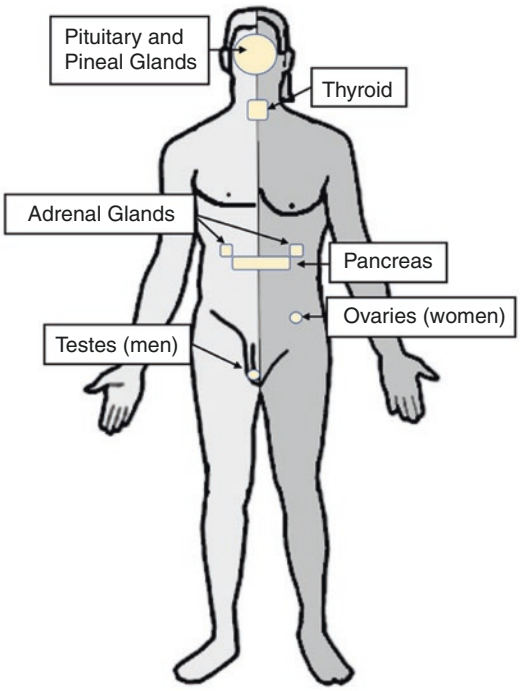


**Fig. 15.1** Anatomy of the endocrine system

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## 15.2 Basic Anatomy and Physiology

The anatomy and physiology of the endocrine system is generally classified according to the principal location of the endocrine organ: intracranial and extracranial. The hypothalamus, pituitary, and pineal glands make up the intracranial endocrine organs, whereas the extracranial endocrine glands include the parathyroid, thyroid, thymus, and adrenal glands. Extracranial endocrine glands are present in many organs throughout the human body, including the pancreas, kidneys, testes in men, and ovaries in women.

The primary intracranial endocrine organs, the hypothalamus and pituitary, form the hypothalamic–pituitary axis. The hypothalamic–pituitary axis governs the endocrine output from a wide range of extracranial glands. The hypothalamus, which is situated superiorly to the pituitary gland in the sella turcica, is composed of neuronal cell bodies and connects to both the anterior and posterior pituitary to transmit regulatory signals. The axonal projections of hypothalamic cell bodies compose the posterior pituitary. Antidiuretic hormone (ADH) and oxytocin are secreted via exocytosis from the axonal terminals in the posterior pituitary to regulate water reabsorption by the kidney and total peripheral resistance, as well as milk ejection from the female milk ducts in response to infant suckling and uterine contraction during labor, respectively. The hypothalamus secretes hormones into the hypophysical portal vessel network, which links the hypothalamus and anterior pituitary and ensures delivery of high concentrations of hypothalamic hormones to the anterior pituitary. The hormonal control by the hypothalamus regulates the secretion of multiple distinct anterior pituitary hormones: thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), prolactin, and growth hormone (GH). This collection of anterior pituitary hormones governs many disparate functions. For example, FSH and LH contribute to gonadal development and function in males and females, whereas prolactin contributes to breast development and lactation in females, GH in linear as well as organ growth, TSH in thyroid gland output, and ACTH in adrenal gland output. Consequently, the hypothalamic–pituitary axis has numerous and significant effects on human physiology.

The extracranial endocrine organs are the principle effectors of endocrine physiology. The parathyroid glands secrete parathyroid hormone (PTH), which is essential for calcium homeostasis. Enveloping the four parathyroid glands in the anterior neck, the thyroid gland secretes the thyroid hormones triiodothyronine ($T_3$) and thyroxine ($T_4$). Decreased or increased levels of $T_3$ and/or $T_4$ may lead to hypo- or hyperthyroidism, respectively. Hypothyroidism typically results in fatigue, weight gain, cold intolerance, constipation, hair loss, and dry skin, while hyperthyroidism frequently demonstrates as anxiety, hyperactivity, weight loss, heat intolerance, diarrhea, weakness, and polydipsia as well as polyuria. Subclinical, or asymptomatic, hyperthyroidism is also common. The systemic nature of both hypo- and hyperthyroidism symptoms reflects the broad functions of $T_3$ and $T_4$. The adrenal glands, otherwise known as the suprarenal glands due to their anatomical location, also secrete several hormones with systemic effects, including the corticosteroids such as aldosterone and cortisol, epinephrine, and the sex hormones testosterone and estrogen.

The pancreas has both exocrine and endocrine functions. The endocrine pancreas secretes insulin and glucagon, which are made by the β- and α-cells, respectively, which function to regulate blood glucose concentrations. To achieve this homeostatic balance, insulin and glucagon act antagonistically by driving glucose either into or out of cells, respectively. Diabetes mellitus (DM) results when either insulin is not secreted by β-cells (i.e., type 1 DM) or insulin does not elicit its desired effect on the target cell (i.e., type 2 DM) [1, 2].

## 15.3 Considerations in Pituitary Adenoma Resection

Perturbations of the hypothalamic–pituitary axis often result in symptoms for which neurosurgical intervention is warranted [3]. Clinically, nonfunctioning pituitary adenomas can often grow to

large sizes before the onset of symptoms, and the presenting symptoms typically reflect mechanical compression of surrounding structures. For example, patients with nonfunctioning pituitary adenomas can present with headache and bitemporal hemianopsia due to optic chiasm compression, cranial nerve palsies (e.g., III, IV, and VI), or symptoms related to increased intracranial pressure (ICP) from mass effect or compression of the third ventricle, including nausea, vomiting, and papilledema.

By contrast, patients with functional pituitary adenomas typically present with associated endocrinopathies and are often diagnosed before the tumor has grown to a size that is large enough to increase the ICP. The associated endocrinopathies can include acromegaly or growth failure, hypo- or hyperthyroidism, sexual dysfunction, inappropriate lactation, and/or irregular menstruation in females. Surgical resection is the gold standard in the treatment of most pituitary adenomas. A notable exception is for prolactinomas, a type of pituitary tumor that results in inappropriate lactation due to excess prolactin secretion, in which surgical resection is typically considered second-line after conservative (i.e., medical) management has failed [4].

### 15.3.1 Preoperative Evaluation

The preoperative assessment of a patient presenting for pituitary adenoma resection should include a thorough history, physical examination, and workup as indicated by their physiological reserve and comorbid conditions [5]. In addition to the syndromes associated with functional pituitary adenomas, hypopituitarism is an important consideration for all patients presenting for resection of a pituitary tumor. Mass effect exerted on the anterior pituitary most commonly causes secondary hypothyroidism and adrenal insufficiency, whereas compression of the posterior pituitary can cause diabetes insipidus. Mass effect can also cause prolactinemia by disrupting the tonic inhibition of pituitary lactotrophs.

Standard workup that should be considered in this patient population includes a complete blood count, a basic metabolic panel, and an endocrine panel. Hyperglycemia is a common finding, which may be due to comorbid DM (which might or might not have been previously recognized), or excessive secretion of gluconeogenic–glycolytic hormones such as cortisol and growth hormone. Hyponatremia suggests preoperative diabetes insipidus, whereas hypercalcemia is associated with multiple endocrine neoplasia type 1. A comprehensive endocrine panel should include TSH, free T3 and T4, cortisol, ACTH, IGF-1, testosterone, LH, FSH, and prolactin. Lastly, women presenting with secondary amenorrhea must be tested for pregnancy.

Hormone replacement therapy with corticosteroids forms the cornerstone of preoperative optimization for patients with hypopituitarism [5]. Hydrocortisone is often administered in the days leading to surgery, followed by perioperative "stress-dose" steroids to account for the physiological challenge of surgery. Because oral bioavailability may be reduced in hypopituitarism, parenteral routes are preferred in these patients. Importantly, it should be noted that dexamethasone is the agent of choice for patients with Cushing's disease because it does not interfere with postoperative cortisol assays. Thyroxine should also be replaced in patients with hypothyroidism.

### 15.3.2 Acromegaly

In addition to the standard perioperative considerations for an intracranial mass, acromegalic patients present unique cardiovascular and respiratory challenges for the perioperative physician. All acromegalic patients should have high suspicion for having a difficult airway, and induction of general anesthesia and endotracheal intubation should proceed with great caution. Studies have shown that in nearly two-thirds of acromegalic patients, endotracheal intubation proves difficult even in the setting of a normal preoperative airway examination [6]. Interestingly, IGF-1 levels were found to be an independent risk factor for difficult intubation in this cohort. Hypertrophy of upper airway structures such as the mandible, nose, lips, and tongue is often, but not always, apparent on clinical exam. A hoarse voice suggests laryngeal

stenosis, which may be due to soft tissue thickening, laryngeal calcinosis, or injury of the recurrent laryngeal nerve. Cervical spine abnormalities are also common. Importantly, because the preoperative airway assessment poorly predicts the difficult airway in these patients, advanced airway management techniques should always be immediately available [7]. Obstructive sleep apnea (OSA) affects up to 70% of acromegalic patients [8]. Therefore, benzodiazepines and narcotics in the perioperative period should be used sparingly and cautiously.

Acromegalic cardiomyopathy is the most common cause of death in untreated acromegaly and should be considered in all patients [9, 10]. Elevated plasma levels of GH cause concentric ventricular hypertrophy, which ultimately leads to diastolic dysfunction, most commonly affecting the left ventricle. Hypertension is also a common finding, and electrocardiogram changes such as bundle branch blocks, ST segment depression, and T wave abnormalities are present in more than 50% of patients [11]. These patients are also at increased risk of developing supraventricular and ventricular ectopy in the face of physiological stress. We recommend the use of invasive arterial blood pressure monitoring during pituitary adenoma resections due to the risk of sudden hypertensive episodes. Patients with acromegalic cardiomyopathy are particularly vulnerable to these episodes. However, impaired blood flow in the ulnar artery is common in these patients, especially in the presence of carpel tunnel syndrome [12]. Therefore, ulnar blood flow should always be assessed prior to radial artery catheterization, and other sites should be considered (e.g., femoral artery).

### 15.3.3 Cushing's Disease

Glucocorticoid receptors are expressed by almost every human cell. As a result, patients with Cushing's disease present with diverse perioperative challenges. One of the most vital functions of cortisol is to increase vascular smooth muscle sensitivity to endogenous vasoconstrictors such as catecholamines and angiotensin [5, 13]. These and other mechanisms contribute to the observation that most patients with Cushing's disease will present with systemic hypertension and left ventricular hypertrophy. Up to 40% of patients will also have evidence of diastolic dysfunction. The increased vascular sensitivity to catecholamines should also be considered whenever administering vasoactive drugs.

Common comorbid conditions that should be considered include OSA, DM, and osteoporosis [5, 14]. Due to thinning of the skin, difficult intravenous access and easy bruising should be anticipated [15]. Appropriate eye protection should be used to mitigate the increased risk of corneal abrasions in patients with exophthalmos. Although myopathies of the shoulder girdle and proximal lower limbs are often presented, there is no data to indicate that these patients have increased sensitivity to neuromuscular blockade. Therefore, normal weight-based dosing is recommended.

### 15.3.4 Perioperative Course

Transsphenoidal pituitary surgery has traditionally been guided by fluoroscopy, with the patient in the semi-seated position [5]. However, the endoscopic endonasal approach has recently become more widespread. Nasal intubations are contraindicated in either approach, and neuromuscular blockade is important to mitigate the risks of cerebrospinal fluid (CSF) leak, visual tract injury, and vascular damage secondary to patient movement during surgery. Visual-evoked potentials have been described to monitor for injury to visual pathways in proximity to the pituitary gland, but these evoked potentials are very sensitive to anesthetics and are not routinely recommended [16].

As discussed above, invasive arterial blood pressure monitoring should be considered in patients undergoing pituitary adenoma resection due to the high risk of sudden hypertensive episodes. Local infiltration of the nasal mucosa with epinephrine and lidocaine may also induce dysrhythmias and myocardial ischemia. The ability to quickly diagnose and treat sudden hypertensive

episodes is especially important for patients with known cardiomyopathy, congestive heart failure, poor exercise tolerance, and poorly controlled systemic hypertension. Patients under perioperative beta-blockade are particularly susceptible to unopposed alpha adrenergic stimulation by epinephrine. The resulting hypertension should be treated immediately by administering phentolamine, direct vasodilators, or by increasing the concentration of volatile anesthetic.

Lumbar intrathecal drains are commonly used to improve tumor visualization by injecting saline or draining cerebrospinal fluid. The surgeon may also inject air into the lumbar drain to outline the tumor on fluoroscopy, in which case nitrous oxide should be avoided. The presence of intracranial hypertension and risk of herniation should always be considered before placing a lumbar drain. A Valsalva maneuver can be used to detect CSF leaks once the resection is complete. If positive, the surgeon will typically pack the sella turcica with autologous fat before reconstruction.

Once the surgical field is closed, meticulous suctioning of the oropharynx is essential. Unless a nasopharyngeal airway was placed by the surgeon before nasal packing, nose breathing will not be possible in the early postoperative period. Therefore, placement of an oral airway should be considered in patients with confirmed or suspected OSA. A rapid emergence from general anesthesia is highly desirable, which will facilitate an optimal early postoperative neurological assessment. To achieve a fast emergence, we recommend the use of rapidly cleared analgesic agents such as remifentanil combined with a low-dose intravenous or volatile anesthetic agent.

## 15.4 Management of Chronic Extracranial Endocrinopathies in the Neurosurgical Patient

### 15.4.1 Hyperthyroidism

Thyroid hormones have important cardiovascular effects that should be considered in the perioperative period [17, 18]. The underlying principle is that T3 promotes beta adrenergic tone. This causes a decrease in systemic vascular resistance (SVR) via beta-2 receptors, which subsequently activates the renin–angiotensin–aldosterone system (RAAS), increasing circulating blood volume and cardiac output to maintain perfusion pressures. Inotropic and chronotropic effects of beta-1 receptors on cardiac myocytes also contribute to an increase in cardiac output by 50–300%. Through these mechanisms, chronic hyperthyroidism recruits much of a patient's physiological reserve, rendering them vulnerable to cardiovascular collapse in the perioperative period.

**Table 15.1** Pharmacological agents and their desired effects in the patient with uncontrolled hyperthyroidism undergoing emergency surgery

| Desired effect | Pharmacological agents |
|---|---|
| Inhibit sympathetic effects of T3/T4 | Beta blockers |
| Inhibit peripheral conversion of T4 to T3 | Beta blockers, and propylthiouracil (PTU) |
| Inhibit production of T3/T4 in the thyroid gland | PTU, methimazole, and inorganic iodide |

For elective procedures, hyperthyroidism should always be pharmacologically optimized prior to surgery to reduce the risk of thyroid storm [19], and patients should continue to take their medication on the morning of surgery [20]. For emergent procedures, perioperative management should focus on decreasing the secretion of T3 and T4 as well as blocking the systemic effects of these hormones (Table 15.1). Sympathomimetic and vagolytic drugs such as pancuronium, ephedrine, epinephrine, norepinephrine, and atropine should also be avoided in these patients.

### 15.4.2 Hypothyroidism

In contrast to the hyperthyroid state, hypothyroid patients suffer from a low beta adrenergic tone on their cardiac myocytes and unopposed alpha adrenergic tone in their vasculature. The resulting increase in SVR and decrease in cardiac inotropy and chronotropy leads to inhibition of RAAS and intravascular volume depletion.

Of note, hypothyroid patients also tend to have depressed respiratory responses to hypoxemia and hypercapnia [21]. Severe cases may also present with decreased lung diffusion capacity.

Like hyperthyroidism, hypothyroidism should be pharmacologically optimized prior to elective procedures, typically with levothyroxine (T4). Because the half-life of T4 is approximately 1 week, a missed dose on the morning of surgery should not have significant physiological effects [20]. However, we still recommend patients continue taking their usual dose of thyroxine throughout the perioperative period. Preoperative sedation with benzodiazepines or narcotics is best avoided in this patient population due to increased sensitivity to their effects. Signs of hypothyroidism that may be observed postoperatively include delirium, prolonged ileus, infection without fever, and myxedema coma.

If a patient with uncontrolled or newly diagnosed hypothyroidism presents for urgent or emergent surgery, perioperative management should focus on avoiding cardiovascular collapse. Severe hypothyroidism can be managed with a 200–500 μg infusion of levothyroxine over 30 min, followed by 50–100 μg IV daily [22]. These patients often have concomitant adrenal insufficiency, and 50 mg of hydrocortisone administered four times daily mitigates the risk of adrenal crisis following thyroid replacement. Intravascular volume should also be maintained with normal saline and dextrose.

### 15.4.3 Adrenal Insufficiency

The hypothalamic–pituitary–adrenal (HPA) axis plays an essential role in generating the surgical stress response, primarily due to the central role of glucocorticoids in modulating the sensitivity of vascular smooth muscle. Therefore, the timely diagnosis and management of adrenal insufficiency (AI) are essential skills for the perioperative physician.

The classic signs of adrenal insufficiency are hypotension, hyponatremia, and hyperkalemia. However, these signs may only become apparent intraoperatively when AI is unmasked by surgical stress. Therefore, preoperative risk assessment is important. Causes of primary AI include autoimmune adrenalitis, adrenalectomy, sepsis, and tuberculosis. Secondary AI, caused by suppression of the HPA axis by exogenous glucocorticoids, is much more common [23]. In general, any patient who has received at least 20 mg of prednisone (or its dose equivalent) daily for more than 5 days should be considered at risk of developing AI [24]. Furthermore, the HPA axis can remain suppressed for 6–12 months after discontinuing chronic (>1 month) corticosteroid therapy. Conversely, a maximum daily dose of 5 mg of prednisone (or equivalent) for any length of time is very unlikely to cause secondary AI [23].

Patients with suspected AI, or at risk of developing perioperative AI, should undergo the short ACTH stimulation test. Inappropriate adrenal response to ACTH stimulation is an indication for perioperative stress-dose steroids (Table 15.2). Other indications for stress-dose steroids in patients at risk of AI include emergent surgery, and unexplained hypotension despite adequate volume resuscitation [25]. Another management strategy is to titrate perioperative steroids to serum cortisol levels every 6 h, with a treatment threshold of 2 μg/dL [19]. Quick laboratory turnaround, usually <1 h, is essential for this management strategy. Etomidate should be avoided in all patients at risk of perioperative AI due to its inhibitory effects on steroid synthesis in the adrenal glands [26].

**Table 15.2** Approach to intraoperative steroid use in the patient with adrenal insufficiency

| | |
|---|---|
| *Stress-dose steroids: drug of choice* | Intravenous hydrocortisone. Adjust doses accordingly if using another steroid |
| *Frequency and duration of treatment* | Every 8 h, for 48 h |
| *Individual dose—minor procedure* | 25 mg |
| *Individual dose—moderate procedure* | 50 mg |
| *Individual dose—major procedure* | 100 mg |

In the postoperative period, the perioperative physician should consider measuring a random plasma cortisol, TSH, and T4 in patients exhibiting signs of AI, such as hypotension, orthostasis, altered mental status, nausea, vomiting, hyponatremia, and hyperkalemia. Empiric stress-dose steroids can also be considered.

### 15.4.4 Diabetes Mellitus

DM is associated with numerous comorbid conditions that impact a wide range of organ systems. For example, DM is associated with an increased incidence of obesity, hyperlipidemia, hypertension, atherosclerosis, coronary artery disease, cerebrovascular disease, depression, an increased risk of cancer, and chronic kidney disease and retinopathy secondary to vasculitis [27]. As many of these comorbidities also connote increased perioperative risk, the presence of DM and its associated comorbidities should be considered in all neurosurgical patients. An understanding of the effects of DM on endocrine regulation of human physiology and organ system dysfunction is essential in optimizing surgical outcomes in these patients.

Patients with insulin resistance or insufficiency are more susceptible to the gluconeogenic and glycolytic hormones released in response to surgical stress (e.g., cortisol, epinephrine, glucagon, and growth hormone), which are usually countered by a parallel increase in insulin. Perioperative hyperglycemia is therefore common in these patients, which increases the risk of infection, diabetic ketoacidosis, and hyperglycemic hyperosmolar coma. Diabetic patients are also at risk of developing perioperative hypoglycemia due to prolonged fasting.

The preoperative evaluation of the diabetic patient should thoroughly assess the severity of disease, including end-organ complications (Table 15.3), as well as current pharmacological management. Preoperative hemoglobin A1C is helpful in determining whether the glycemic management is optimal. Because diabetic nephropathy is common in diabetic patients, a preoperative assessment of renal function should be considered in diabetic patients scheduled for neurosurgery.

Effective glucose control is a major perioperative goal for diabetic patients. However, the optimal target glucose concentration that confers the best clinical outcomes in neurosurgical patients is currently unknown. Moreover, there is little evidence to support that any one approach to glycemic management is advantageous over another in improving perioperative outcomes. We recommend that, when possible, diabetic patients are best scheduled for surgery early in the day to minimize fasting time. Because diabetic patients undergoing intracranial neurosurgery are especially prone to hyperglycemia, we recommend frequent monitoring of blood glucose concentration and maintaining a target plasma glucose concentration of 140–180 mg/dL. Maintaining tight blood glucose concentrations between 80 and 120 mg/dL management is not recommended in these patients because of the potential risk of hypoglycemia.

Short-acting oral hypoglycemic agents, such as sulfonylureas, thiazolidinediones, and DPP-4 inhibitors, should be held on the morning of surgery and restarted postoperatively once the patient

**Table 15.3** Perioperative considerations and complications in the diabetic patient

| Diabetic complication | Perioperative consideration |
|---|---|
| Nephropathy | Adjust dosage of drugs cleared by kidneys and suspect hyporenin–hypoaldosterone state |
| Autonomic neuropathy | Rapid identification and treatment of hypotension |
| Gastroparesis | Avoid medications that prolong gastric-emptying time and consider a rapid sequence intubation |
| Cystopathy | Consider straight or Foley catheterization |
| Peripheral neuropathy | Carefully document preoperative somatosensory and motor function |
| Retinopathy | Carefully document preoperative visual function, especially for procedures with a risk of ischemic retinopathy |
| Peripheral vascular insufficiency | Monitor closely for signs of infection and poor wound healing |

is tolerating an oral diet [28]. Due to the risk of lactic acidosis, metformin should be held 24 h before surgery and restarted 24–48 h postoperatively, once baseline renal function is documented. Incretins can be continued perioperatively.

Insulin-dependent diabetics should continue their usual regiment up until the eve of surgery and be instructed to not skip dinner the night before their scheduled surgery [29]. Basal insulin is essential to decrease the risk of perioperative diabetic ketoacidosis and hyperglycemic hyperosmolar coma. Therefore, full-dose long-acting basal insulin analogues should be continued the morning of surgery. For patients who use an insulin pump, we recommend maintaining their basal rate perioperatively and titrating a dextrose infusion to stay in the target glucose concentration range. For patients on NPH or other mixtures, we recommend administering half the dose of intermediate-acting insulin on the morning of surgery. Short-acting insulins should be avoided preoperatively.

Patients with DM or glucose intolerance spend on average 50% more time in the hospital postoperatively and have worse outcomes than patients with normal insulin function. These patients are particularly at increased risk of hypoglycemia, dehydration, acute kidney injury, electrolyte imbalances, cerebrovascular accidents, myocardial infarction, and postoperative wound complications. Special attention should be paid in decreasing the risk of these complications in the postoperative period.

## 15.5 Acute Complications of Endocrine Dysfunction in the Neurosurgical Patient

### 15.5.1 Pituitary Adenoma Resection

The most common postoperative complaint after transsphenoidal surgery is headache [5]. Nonsteroidal anti-inflammatory drugs (e.g., ketorolac) or acetaminophen are usually effective at controlling the pain. Opioids may be also used but should be cautioned in the elderly and in patients with diagnosed or suspected OSA due to their sedative effects. Routine pharmacological prophylaxis for nausea and vomiting is recommended due to their high incidence in this patient population. There are many classes of antiemetic agents that have been successfully used, with no one agent conferring the highest efficacy in all patients [30].

Due to their proximity to the transsphenoidal surgical approach, cranial nerves II-VI should be systematically assessed after pituitary adenoma resection. A new cranial nerve deficit should be further investigated with imaging (i.e., CT or MRI). Depending on the nature of the deficit, an unexpected focal change in neurological status might warrant emergent surgical intervention. Another potential postoperative complication is CSF leak. Minor nasal drainage is expected postoperatively, but continuous fluid leakage that is exacerbated by leaning forward or associated with headache should be further investigated. Beta2-transferrin is a specific marker for CSF; if the draining fluid tests positively for this marker, autologous fat packing of the defect is indicated [5].

Up to one-third of patients will develop diabetes insipidus (DI) after pituitary adenoma resection, with most cases resolving spontaneously within the first postoperative week [31]. Polyuria and polydipsia are the hallmarks of DI and may appear abruptly in the postoperative period. Because most patients' thirst mechanisms are intact and they have access to water, intravascular volume contraction with hypernatremia and hyperosmolarity are rare. Postoperative DI can be distinguished from other causes of polyuria by measuring the urine specific gravity (SG). In DI, the urine SG is usually <1.005, in contrast to acromegalic diuresis and iatrogenic perioperative fluid administration, which usually cause a diuresis with urine SG >1.005. Glycosuria can be distinguished from these other causes of postoperative diuresis by measuring urine glucose concentration. Indications to treat postoperative DI are volume depletion (i.e., the patient cannot increase their fluid intake to compensate their diuresis) and sleep disruption secondary to polyuria [5]. Treatment typically consists of 0.1 mg of oral desmopressin (DDAVP), which is

usually sufficient to control this mostly self-limited postoperative complication. If the patient cannot tolerate oral medications, 1 μg DDAVP can be administered subcutaneously. Once treatment is initiated, monitoring the patient's oral hydration, urine output, and electrolytes is important to avoid inducing hyponatremia.

Patients may also develop a transient syndrome of inappropriate antidiuretic hormone (SIADH) after resection of a pituitary adenoma [32]. SIADH is characterized by low serum osmolarity and sodium, in association with high urine osmolarity and sodium. These patients are usually asymptomatic and euvolemic, distinguishing them from hypovolemic hyponatremic patients suffering from cerebral salt wasting [33]. In severe (sodium <120 mEq/L) or rapidly developing hyponatremia, patients can present with nausea, vomiting, altered mental status, and seizures. The first line of treatment for patients with SIADH is fluid restriction. For symptomatic or severe cases, a slow infusion of hypertonic saline or intravenous urea should be considered [5, 34]. The goal for hyponatremia correction should be about 1–2 mEq/L/h for the first 3–4 h until the symptoms have resolved or the serum sodium is above 120 mEq/L. To avoid the rare but serious complication of osmotic demyelination syndrome, the rate of sodium correction should not exceed 6–12 mEq/L over the first 24 h or 18 mEq/L over 48 h.

All patients should be screened for hypopituitarism after pituitary adenoma resection. The most common manifestations of hypopituitarism are adrenal insufficiency and hypothyroidism [35]. Therefore, as discussed above, the cornerstone of treatment includes corticosteroids and thyroxine, respectively, as indicated. Patients who received perioperative stress-dose steroids due to hypopituitarism may be discharged on low-dose steroids, with subsequent evaluation of their hypothalamic–pituitary–adrenal axis on an outpatient basis. Alternatively, exogenous steroids can be held 24 h postoperatively to measure morning cortisol levels and be titrated accordingly. This strategy is only effective in institutions with clinical laboratories capable of reporting cortisol assays in a timely fashion.

### 15.5.2 Pituitary Apoplexy

Pituitary apoplexy, i.e., hemorrhage of the pituitary gland, often results from an underlying pituitary tumor that has hemorrhaged after exposure to an external stressor, such as traumatic brain injury, pregnancy, or surgical stress [36]. Pituitary apoplexy will usually lead to pituitary failure with subsequent endocrine dysfunction due to the central role of the pituitary hormones on orchestrating endocrine output. If pituitary apoplexy results in impaired vision, transsphenoidal surgery is recommended in an attempt to preserve vision [37]. As previously discussed, surgical intervention for pituitary apoplexy carries similar inherent risk to the pituitary gland as surgery for pituitary adenoma or craniopharyngioma, and postoperative endocrine dysfunction must therefore be considered in the postoperative period.

### 15.5.3 Perioperative Hyperglycemia

Perioperative hyperglycemia is common in neurosurgical patients and might result from perioperative stress or administration of exogenous corticosteroids. Blood glucose monitoring and management is essential because chronic hyperglycemia is an independent marker of poorer clinical outcomes in neurosurgical patients [38]. Perioperative hyperglycemia is associated with poor wound healing, which is particularly concerning after craniotomy. Moreover, severe intraoperative hyperglycemia (blood glucose concentration > 180 mg/dL) was recently shown to be an independent risk factor for postoperative infection within the first 7 days after craniotomy [39]. Importantly, the association between severe intraoperative hyperglycemia and postoperative infection includes both intracranial and extracranial (e.g., lung and blood) infections. Diabetic patients with hyperglycemia may be at particularly high perioperative risk because of the presence of comorbid atherosclerotic disease of the coronary arteries, cerebrovascular network, and renal arteries and arterioles. This results in increased risk of cerebral ischemia,

cardiac ischemic events, hypertensive crises, and electrolyte abnormalities during the perioperative period.

Although the optimal blood glucose concentration that confers the least risk of perioperative complications is unknown, we recommend that the blood glucose concentration be maintained between 140 and 180 mg/dL. Importantly, it should be noted that perioperative hypoglycemia can also occur in the neurosurgical patient, most often due to aggressive insulin therapy [40]. The risk of insulin-induced hypoglycemia is thought to be higher in insulin-naïve patients, although evidence-based data on this is lacking. The optimal timing, dose, and method of insulin delivery in neurosurgical patients are unknown and are largely institution-dependent or at the discretion of the treating clinician. Moreover, it is currently unknown whether any one insulin regimen increases the risk of hypoglycemia more than another regimen.

### 15.5.4 Endocrine Stress Response

Contrary to the generalized endocrine dysfunction that can occur with surgical intervention on the pituitary, increases in endocrine output may also arise in the perioperative period resulting from surgical stress or underlying pathology. As detailed above, hyperglycemia may result due to excesses of glucagon, cortisol, and catecholamines in the setting of surgical stress. In addition to hyperglycemia, cortisol and catecholamine excess as part of the stress response can cause perioperative hypertension, which carries risks for hypertensive hemorrhage, coronary artery ischemia, aortic dissection, and subsequent cardiovascular collapse [41]. In contrast to endocrine dysfunction, hormonal excess also results in a unique set of perioperative complications and considerations for the neurosurgical patient.

### 15.5.5 Electrolyte Imbalance

Electrolyte imbalances are associated with several endocrinopathies and should be considered in the differential diagnosis in any neurosurgical procedure that is complicated by a perioperative seizure. The fact that seizure is a significant and relatively frequent complication of neurosurgical procedures [42], and the recognition of the associated risk in these patients have led to the development of effective guidelines for seizure prophylaxis [43]. However, electrolyte imbalances should be considered in the underlying etiology because they are often easily preventable and treatable. Perturbations in serum calcium concentrations might reflect changes in PTH levels or underlying parathyroid pathology, whereas sodium disturbances might be due to changes in either cortisol or aldosterone levels or by renal vascular changes as seen in the setting of DM.

### 15.5.6 Thyroid Storm

Hyperthyroid patients are most likely to develop thyroid storm intraoperatively or within 48 h postoperatively [19]. The cardinal signs of this rare complication include hyperpyrexia (up to 41 °C), tachycardia, and delirium. The differential diagnoses included malignant hyperthermia, neuroleptic malignant syndrome, and pheochromocytoma. Due to the high associated mortality (10–75%), it is often necessary to initiate empiric treatment before confirming the diagnosis with thyroid hormone assays [44].

Managing thyroid storm requires critical care resources. Intravenous beta blockade should be titrated for a heart rate goal of <90 beats per minute, and volume resuscitation should be supplemented with dextrose to replete glycogen reserves [19]. As in thyrotoxicosis, the thionamides methimazole and PTU are used to inhibit the peripheral conversion of T4 to T3 and decrease secretion from the thyroid gland. Acetaminophen is the antipyretic of choice because salicylates decrease thyroid protein binding, therefore increasing free T3 and T4 [28]. Although infection and sepsis are the most common underlying cause of thyroid storm, empiric antibiotics are not recommended unless there is evidence of infection. Blood, urine, and sputum cultures however should be ordered as soon as possible.

### 15.5.7 Myxedema Coma

Patients with poorly controlled hypothyroidism can rarely develop myxedema coma, a state of decompensated hypothyroidism. With a reported mortality reaching as high as 80% [45], timely diagnosis and treatment of myxedema coma are paramount. The most common perioperative precipitants are infection, cold exposure, sedatives, analgesics, and other medications. Signs and symptoms include a severely depressed mental status which can progress to coma and seizures, hypothermia, hypopnea, bradycardia, and heart failure. Management of myxedema is similar to the management of hypothyroid patients presenting for emergency surgery, and includes aggressive volume resuscitation with normal saline and dextrose, as well as intravenous administration of steroids and levothyroxine or liothyronine [22]. Rapid rewarming may result in widespread vasodilation and cardiovascular collapse for patients with heart failure and volume depletion. Therefore, correction of hypothermia should be gradual and in parallel with volume resuscitation [46].

## 15.6 Conclusions

Endocrine disorders are common and can affect numerous physiological processes throughout the body. Neurosurgical patients can present with intracranial or extracranial endocrinopathies that result in hormone hypo- or hypersecretion, each with unique clinical implications. Providing perioperative care for the patient with endocrine dysfunction can often be challenging, and successful management is dependent on an in-depth understanding of how endocrine dysfunction affects neurophysiology and postoperative outcomes. In this chapter, we reviewed the relevant principles in endocrine anatomy and physiology as well as a practical and evidence-based approach to the neurosurgical patient with endocrine dysfunction. We also highlighted some areas in which studies on optimal management strategies are lacking, and in which management is currently guided by expert consensus and applied theory.

**Key Points**

- Endocrine disorders are common in neurosurgical patients, and can include disorders of endocrine gland hyposecretion, hypersecretion, and tumors of the endocrine glands.
- The perioperative care of the neurosurgical patient with comorbid endocrine dysfunction can be challenging, and requires an in-depth understanding of how the endocrine dysfunction affects neurophysiology and postoperative outcomes.
- A thorough preoperative workup and optimization of all comorbid conditions is essential to minimize the risk of perioperative complications.
- Perioperative complications in the patient with endocrine dysfunction (e.g., electrolyte imbalances, thyroid storm or myxedema coma, and blood glucose derangements) can be severe and even life threatening, and must be promptly diagnosed and treated.

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# Hematological Management of Neurocritical Care Patients

16

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## 16.1 Introduction

Hemostatic derangements are common in neurocritically ill patients and may precipitate or exacerbate conditions of bleeding and thrombosis. The increased utilization of antithrombotic medications warrants a thorough understanding of these treatments as well as their reversal agents. Intracranial bleeding is the most feared complication of these derangements and results in significant morbidity and mortality. The main subtypes of intracranial hemorrhage include intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), and epidural hemorrhage (EDH). Similarly, thrombotic events, such as venous thromboembolism, myocardial infarction, and acute ischemic stroke, often complicate an ICU stay. This chapter will focus on acquired coagulopathies, from anticoagulant medications to systemic illnesses, that increase the risk of intracranial hemorrhage, primarily ICH, SAH and traumatic brain injury (TBI), with special attention paid to the resumption of anticoagulation.

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## 16.2 Primary Intracranial Hemorrhage

### 16.2.1 Intracerebral Hemorrhage

Primary intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes in the United States, causing severe disability among survivors [1]. The case fatality of ICH is extremely high, with rates of 40% at 1 month and 54% at 1 year. Of survivors, less than 40% regain functional independence at 1 year [2]. Notably, the incidence of ICH appears to be stabilizing in high-income countries; however, it is not decreasing. This is likely due to the fact that although hypertension, the most significant risk factor for development of ICH, is better controlled than in the past, the benefit is offset by an aging population that is more susceptible to both cerebral amyloid angiopathy and antithrombotic-related ICH.

The strongest predictor of 30-day mortality and functional outcome is the initial hematoma volume. For every 10% increase in hematoma volume, mortality increases by 5% [1]. Larger hematomas are more likely to expand, and approximately 30% of patients demonstrate hematoma



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expansion, which is defined as either an increase in volume by 33% or an absolute increase of 12.5 mL [3]. Pre-ictal antithrombotic medication use increases the likelihood of hematoma expansion, death, and poor functional outcome [1, 4, 5].

Antithrombotic-associated ICH portends a worse functional outcome and an increased risk of morbidity and mortality compared to ICH not associated with antithrombotic use [5]. It comprises nearly 20% of patients with ICH [5, 6]. The increased morbidity and mortality are due to larger hemorrhage volumes, increased hematoma expansion, and additional comorbidities among anticoagulated patients [4]. The case fatality rate of ICH ranges nearly doubles for patients with coagulopathic ICH [1]. Although antithrombotic-associated intracerebral hemorrhage (AA-ICH) carries a devastating prognosis, rapid reversal of coagulopathy may limit hematoma expansion and improve outcomes. Please see Fig. 16.1 for a review of antithrombotic mechanisms and Fig. 16.2 for the coagulation cascade.

#### 16.2.1.1 Antiplatelet Agent - Associated ICH

Antiplatelet medications are commonly used in clinical practice for prevention of heart disease and ischemic stroke. Evidence from coronary artery disease treatment trials have determined that the absolute risk of ICH associated with antiplatelet agents is very low, at approximately 0.12% [7]. Evidence from acute ischemic stroke trials also inform about the risk of ICH with antiplatelet medications. In the CAPRIE (clopidogrel versus aspirin in patients at risk of ischemic events) trial, clopidogrel did not increase the risk of intracranial hemorrhage compared to aspirin (0.33% vs. 0.47%) [8]. However, pre-ictal antiplatelet use results in a 27% (95% CI, 10–47) increased odds of death compared with those not taking antiplatelet medication [9]. Over 25% of ICH patients may be associated with antiplatelet use [10].

Regarding the newer antiplatelet agents, the thienopyridine antiplatelet agent, prasugrel, carries an increased bleeding risk compared to clopidogrel,

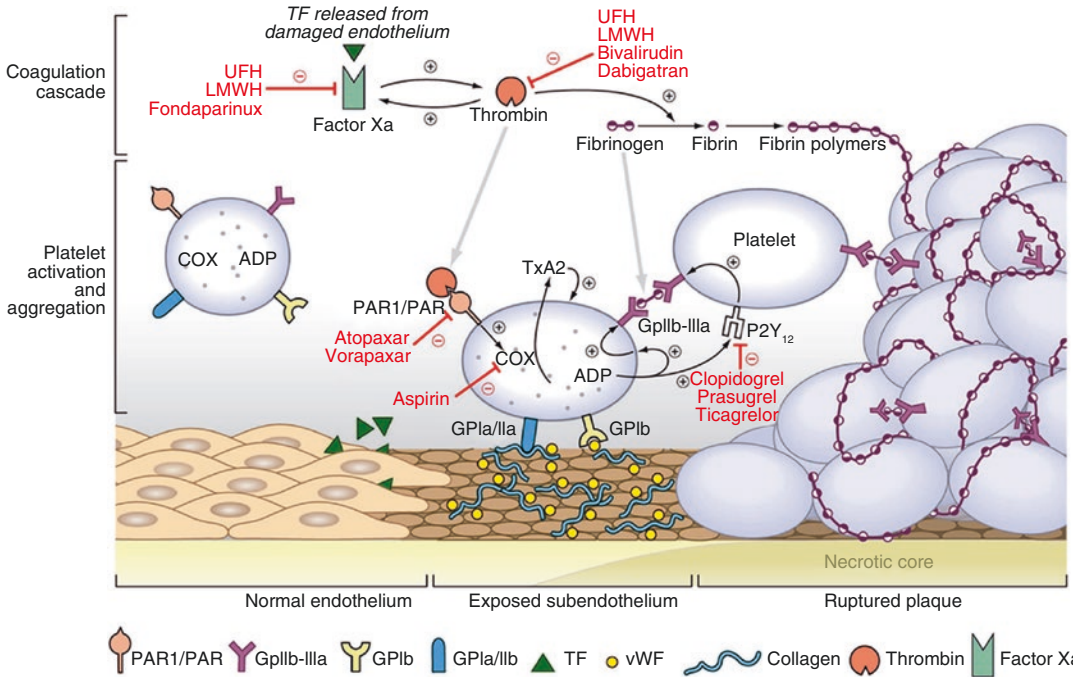


**Fig. 16.1** The role of platelets in the formation of a fibrin plug. Highlighted in red are common antiplatelet and anticoagulant drugs and their sites of action. Detailed mechanisms of action are provided in the accompanying text. Reproduced with permission from Lilly SM, Wilensky RL. Emerging therapies for acute coronary syndromes. Front Pharmacol. 2011;2:61. doi:10.3389/fphar.2011.00061

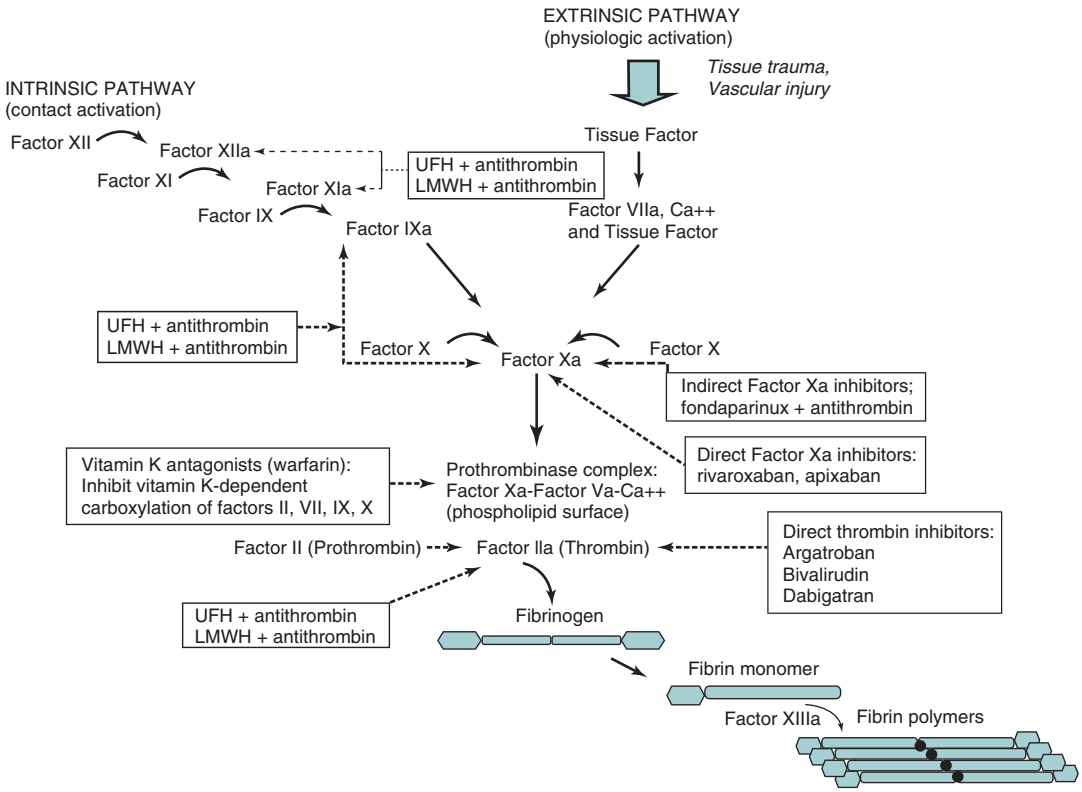


**Fig. 16.2** The coagulation cascade. Major classes of anticoagulants are shown in the black boxes flanking the cascade, and their sites of action are shown by the dotted black arrows. Reproduced with permission from Alquwaizani M, Buckley L, Adams C, Fanikos J. Anticoagulants: a review of the pharmacology, dosing, and complications. Curr Emerg Hosp Med Rep. 2013;1(2):83–97. doi:10.1007/s40138-013-0014-6

but not an increased risk of ICH [11]. Similarly, the non-thienopyridine agents, ticagrelor and cangrelor, do not carry a higher ICH risk than clopidogrel [12, 13]. While nonsteroidal anti-inflammatory drugs may cause a transient minor reversible antiplatelet effect, there are no data to suggest that it worsens ICH or that it should be reversed [14]. Many agents, including HMG-CoA reductase inhibitors, dietary supplements, and selective serotonin reuptake inhibitors, have antiplatelet properties. However, for these agents, it does not appear that reversal is warranted. Dual antiplatelet therapy, however, may cause a significant increase in the relative risk of ICH, early hematoma growth, and increased risk of death following ICH [15, 16]. Some studies have found that the risk of hemorrhage is similar to the risks of systemic anticoagulation [17, 18].

Regarding irreversible platelet agents (Table 16.1), platelet function is only restored with the generation of new platelets, which requires an average of 10 days to reconstitute a full blood volume [19]. For reversible platelet inhibition, normal platelet activity levels will resume after 3–5 drug half-lives.

Clinical testing for antiplatelet function is limited. The gold standard laboratory assessment is light transmission aggregation (LTA) assays, which are not routinely available. Second, more convenient platelet function assays, including the VerifyNow and PFA-100 assays, correlate poorly with LTA assays, having sensitivities of 62.1% and 39.3% and specificities of 80.2% and 96.4%, respectively [20].

### Platelet Transfusion

Platelet transfusion has long been employed to reverse the antithrombotic effect of patients with intracranial hemorrhage. The most compelling

**Table 16.1** Classes and reversibility of antiplatelet agents

| Class | Name | Reversibility |
|---|---|---|
| Cyclooxygenase 1 and 2 inhibitor | Aspirin | Irreversible |
| | Ibuprofen | Reversible |
| | Naproxen | Reversible |
| Adenosine reuptake inhibitor and phosphodiesterase inhibitor | Dipyridamole | Reversible |
| Phosphodiesterase-3 inhibitor | Cilostazol | Reversible |
| Glycoprotein IIb/IIIa inhibitors | Abciximab | Irreversible |
| | Eptifibatide | Reversible |
| | Tirofiban | Reversible |
| P2Y12 inhibitors | Clopidogrel | Irreversible |
| | Prasugrel | Irreversible |
| | Ticlopidine | Irreversible |
| | Ticagrelor | Reversible |
| | Cangrelor | Reversible |
| Protease activated receptor-1 inhibitor | Vorapaxar | Reversible |

data for platelet transfusions comes from a prospective double-blind trial conducted in China which randomized 780 aspirin-sensitive patients with deep ICH undergoing craniotomy to one of the three groups: (a) no platelet transfusion, (b) one preoperative transfusion, or (c) one preoperative and postoperative transfusion [21]. They found a striking reduction in mortality and improved functional outcome. However, despite the putative treatment effects, the study had notable limitations. Importantly, it was a single-center, Chinese-only cohort of ICH patients treated surgically, which is rarely performed in North American or European centers. Furthermore, there was no mention of transfusion-related complications, and patient selection was guided by LTA, which is not routinely available in most centers.

The PATCH trial provides the best evidence against the use of platelet transfusion in ICH [22]. This multicenter European study randomized 190 ICH patients taking any antiplatelet regimen for >7 days prior to symptom onset, to 1 single-donor apheresis unit for aspirin, 2 single-donor units for P2Y12 inhibitors, or no platelet transfusion within 6 h of symptom onset. No antiplatelet sensitivity testing was performed. There was no clinical or statistical difference in hematoma size between the groups. Importantly, platelet transfusion was associated with increased risk of death or dependency at 3 months. Additionally, 13% more patients in the platelet transfusion group had major side effects, including brain edema, herniation, intraventricular extension, and thromboembolic events.

In summary, platelet transfusion is not recommended in ICH unless a neurosurgical intervention is planned, in which case a single apheresis unit of platelets should be provided pre-procedurally [14]. It bears mention that providing platelet transfusions while an antiplatelet drug is still present in meaningful concentrations in plasma will only serve to inhibit the transfused platelets and providing platelet transfusions to antiplatelet agent nonresponders carries all the risks of platelet transfusions with presumably no benefit.

### Desmopressin

Desmopressin is a V2-receptor-specific vasopressin analogue that retains ADH activity without the vasoconstrictor or uterotonic abilities. Both desmopressin and vasopressin can trigger the release of von Willebrand factor (vWF) from the Weibel-Palade bodies within endothelial cells. It has been used to mitigate bleeding in hemophilia A and in uremic patients undergoing surgical procedures, but there is no prospective randomized data examining desmopressin in intracerebral hemorrhage. The best available data shows improvement in platelet function (using the PFA-100 epinephrine assay) upon receiving a single dose of 0.4 mcg/kg IV desmopressin with no meaningful adverse effects, but its single-arm, single-center design limits generalizability and

understanding of its impact on outcomes [23]. Given that hematoma expansion occurs within the first few hours after ictus, a single dose of 0.4 mcg/kg IV desmopressin may be considered for antiplatelet-associated ICH [14].

#### 16.2.1.2 Vitamin K Antagonist - Associated ICH

Vitamin K antagonists (VKA) inhibit the production of vitamin K-dependent factors II, VII, IX, and X at the γ-carboxylation stage, as well as proteins C and S. VKAs inhibit the enzyme vitamin K epoxide reductase, which results in vitamin K remaining in its oxidized form, unavailable for use. Thereafter, clotting factors and proteins are removed from plasma according to their half-lives.

##### Vitamin K

Vitamin K provides a safe, durable, and effective reversal to VKAs by providing the missing reduced substrate and enabling the synthesis of clotting factors and proteins again without requiring any vitamin K epoxide reductase activity. However, time to reversal is prolonged with vitamin K therapy monotherapy. Intravenous (IV) administration of vitamin K results in more rapid normalization of the INR than oral administration [24]; efficacy of subcutaneous administration is hindered by poor bioavailability. Treatment with a single 10 mg IV dose of vitamin K is recommended in patients with life-threatening bleeding, with consideration of a repeat dose in 24–48 h if INR remains >1.4 [14].

##### Fresh Frozen Plasma

Fresh frozen plasma (FFP) is a cell-free human blood product containing all coagulation factors. The data regarding efficacy are mixed, and doses range widely from 5 to 30 mL/kg [25, 26]. The Neurocritical Care Society guidelines suggest a dose of 10–15 mL/kg IV if alternate treatments are contraindicated [14]. The two major drawbacks of FFP are volume of administration and time to treatment. The delays in FFP administration are related to type matching, laboratory approval, thawing process, and product delivery.

##### Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCC) are derived from human plasma and contain factors II, IX, and X, at a minimum. The presence of factor VII differentiates between 3-factor PCCs and 4-factor PCCs. The factor VII can be supplied pre-activated; this is activated 4-factor PCC (aPCC; FEIBA, factor eight inhibitor bypassing agent). These agents provide the necessary clotting factors in a smaller volume (about 25 times less for Kcentra) than FFP. PCCs are stored at room temperature and require simple reconstitution prior to administration, allowing for a rapid administration.

There is high-quality data supporting the use of 3- and 4-factor PCC in VKA-associated ICH. The data for FEIBA is scant [27]. In a prospective trial comparing 3-factor PCC and FFP for VKA-related ICH reversal, successful INR correction and time to INR correction were equivalent between groups. However, treatment with 3-factor PCC was associated with a lower risk of major hemorrhage and a lower risk of death or severe disability at 3 months [28]. Two multicenter randomized clinical trials tested 4-factor PCC (Kcentra) against FFP for reversal of VKA-related coagulopathy. In the first, which tested patients with any VKA-related bleeding, treatment with 4-factor PCC resulted in hemostasis more often than in the FFP group [29]. Similarly, rapid INR reduction occurred more commonly in the PCC group. Side effects were comparable between groups. The second study, in which all patients had VKA-related ICH, was terminated early for safety concerns after demonstrating that 67% of patients receiving 4-factor PCC achieved INR <1.2 within 3 h of treatment initiation, compared to 9% of those receiving FFP [30]. Furthermore, there was a statistically significant reduction in hematoma expansion but no difference in clinical outcomes. There was no increased thrombosis in the PCC arm.

In summary, all ICH patients with VKA-related ICH should receive a single 10 mg dose of intravenous vitamin K. Additionally, 4-factor PCC, dosed by initial INR and patient weight, is recommended. If 4-factor PCC is unavailable, 3-factor PCC is a reasonable alternative. Only if PCC is unavailable or contraindicated should FFP (10–15 mL/kg) be considered [14].

#### 16.2.1.3 Direct Oral Anticoagulant - Associated ICH

**Factor Xa Inhibitors**

Rivaroxaban, apixaban, and edoxaban are clinically available factor Xa inhibitors which appear to be associated with a lower incidence of ICH and smaller hematoma volumes when compared to VKAs. A specific antidote for these agents, andexanet alfa, is a recombinant factor Xa derivative and acts as a decoy receptor with a stronger affinity for factor Xa inhibitors than native factor Xa. The ANNEXA 4 study sought to determine whether treatment with andexanet alfa resulted in effective hemostasis in patients treated with apixaban, riveroxaban or enoxaparin. Nearly 80% of treated ICH patients had effective hemostasis, defined as <35% hematoma expansion at 12 hours post infusion. The reported 30-day incidence of thrombosis was 18% and the 3-day incidence was 6.0%. Subsequent safety data reported a lower incidence of thrombosis, 11% at 30-days and 2.6% at 3-days. Andexanet alfa is the only FDA approved medication for reversal of oral Factor Xa inhibitors [31].

**Direct Thrombin Inhibitors**

Dabigatran, bivalirudin, and argatroban are some of the clinically available direct thrombin inhibitors (DTIs) and work by directly binding factor IIa (thrombin), preventing fibrinogen from becoming fibrin. An FDA-approved antidote, a monoclonal antibody called idarucizumab (Praxbind) specific to dabigatran, exists and has been shown in the RE-VERSE AD trial to safely, rapidly, durably, and effectively restore clinical hemostasis as well as correct laboratory coagulation parameters in those suffering from serious bleeding or requiring an urgent procedure [32]. As with the factor Xa inhibitors, the time of last dose should be determined, and activated charcoal is used to prevent oral absorption if a dose was taken within 2 h of presentation. Additionally, dialysis is effective at removing nearly 66% of the drug concentration and may be considered for life-threatening bleeding if idarucizumab is not available [28]. For patients with ICH due to parenteral DTIs, such as argatroban or bivalrudin, infusion of the medication should be discontinued immediately. The half life of these medications is quite short (<30min); however, should reversal agents be required, either PCC or activated PCC may be considered [14].

#### 16.2.1.4 Thrombolytic-Associated ICH

Plasminogen activators (such as the recombinant tissue plasminogen activator (rtPA) alteplase, reteplase, and tenecteplase) convert plasminogen into plasmin, which in turn degrades fibrinogen and fibrin, leading to thrombolysis. These newer plasminogen activators target fibrin preferentially as the plasminogen-to-plasmin conversion is catalyzed by the presence of fibrin; the older thrombolytic agents urokinase and streptokinase do not have this property, leading to a greater risk of hemorrhage in addition to thrombolysis. Symptomatic ICH, defined as ICH that results in an NIHSS increase of >4 points, occurs in 3–6% of patients following rtPA administration for acute ischemic strokes and 0.4–0.9% after coronary thrombolysis [33].

Recommended treatment for tPA-related intracranial hemorrhage is 10 units of cryoprecipitate [14]. A dose of cryoprecipitate is expected to raise fibrinogen levels by 70 mg/dL in a 70 kg patient. Cryoprecipitate consists of fibrinogen in addition to factors VIII, XIII, and vWF and is a concentrated derivative of FFP. The data demonstrating efficacy of cryoprecipitate is retrospective and limited; however, it remains the current standard of care. Antifibrinolytics (such as Ɛ-aminocaproic acid or tranexamic acid) may have a role in thrombolytic-associated ICH as they block the conversion of plasminogen into plasmin in direct opposition to plasminogen activators. Data on these agents is limited; however, renewed interest in these agents may result in data to support their use. Antifibrinolytic agents are suggested for reversal of tPA-related intracranial hemorrhage by both the NCS and AHA/ASA [14, 34].

#### 16.2.1.5 Heparin- and Heparinoid-Associated ICH

Unfractionated heparin (UFH) is a naturally occurring glycosaminoglycan polymer of variable size. UFH binds to antithrombin, and the

resulting conformational change causes factor Xa and IIa to be inhibited in a 1:1 ratio. While the anti-Xa activity of heparin is size-independent and only relies on the pentasaccharide binding site, heparin's anti-IIa activity is directly proportional to the length of the polymer and relies on heparin's high negative charge density for its effect. This property is exploited by the growing variety of low-molecular-weight heparins which contain the pentasaccharide binding site with fewer negatively charged sulfate groups and synthetic pentasaccharides (such as fondaparinux) which lack the negatively charged sulfate groups altogether.

Protamine is a naturally occurring, strongly cationic, basic protein involved in spermatogenesis that bonds with heparin to form a salt devoid of anti-Xa activity. A dose of 1 mg protamine for every 100 U UFH given over the preceding 2–3 h is recommended. No more than 50 mg in a single dose should be administered and at a rate of no faster than 20 mg/min. The dose accounts for the preceding 2–3 h of heparin as the half-life of unfractionated heparin is 60–90 min. Repeated administration of protamine may be considered if the aPTT remains prolonged, as the half-life of protamine is only 7 minutes. Notably, prophylactic doses of UFH, LMWH, or pentasaccharides do not meaningfully alter systemic anticoagulation; therefore current guidelines recommend against reversal of these compounds when administered in prophylactic doses unless aPTT elevation is present.

Protamine may be less effective for the LMWHs, as its ability to reverse the effects of LMWH varies based on the molecular weight and the sulfate charge density of the specific compound. For example, protamine is more effective at reversing the highly sulfated tinzaparin as compared to dalteparin or enoxaparin. A dose of 1 mg protamine per 1 mg enoxaparin is recommended for reversal of enoxaparin administered within 8 h of last dose; if the last dose was given within 8–12 h, the dose of protamine is 0.5 mg per 1 mg enoxaparin. Beyond 12 h (>3 half-lives of enoxaparin), reversal is felt to be unnecessary, unless there is significant renal impairment. For dalteparin or tinzaparin, 1 mg protamine should be provided for every 100 anti-Xa units given in the past 3–5 half-lives of the drug (dalteparin $t_{1/2} = 2.5$ h; tinzaparin $t_{1/2} = 3.4$ h), up to a maximum 50 mg dose. For evidence of continued bleeding, a repeat half-strength dose of protamine can be considered. For bleeding refractory to protamine, or should protamine be contraindicated, recombinant factor VIIa (rfVIIa) may be considered at a dose 90 mcg/kg IV. There is no data suggesting FFP, PCC, or aPCC can correct anti-Xa or anti-IIa activity in these settings, and their use is not recommended here. Andexanet alfa is not yet approved by the FDA for reversal of LMWH.

Protamine is ineffective for the uncharged pentasaccharides. There is data from in vitro, retrospective, animal, and healthy volunteer studies suggesting aPCCs at a 20 IU/kg dose can reduce bleeding times and hematoma volume in addition to normalizing laboratory coagulation studies; rFVIIa was also studied in many of these papers, and although it corrected the laboratory coagulation studies, it did not appear to affect the bleeding time or hematoma volume. Based on this evidence, aPCC (20 IU/kg) is currently recommended over rFVIIa (90 mcg/kg) for fondaparinux-related ICH reversal [14].

### 16.2.2 Subarachnoid Hemorrhage

Aneurysmal subarachnoid hemorrhage (SAH) represents a significant cause of morbidity and mortality and accounts for approximately 5% of all intracranial bleeds with an incidence that ranges from 2 to 16 per 100,000 [35]. Those who survive aneurysmal subarachnoid hemorrhage are at high risk of developing secondary neurologic insults, such as vasospasm, seizures, delayed cerebral ischemia, hydrocephalus, rebleeding, etc. [36]. It is well known that rebleeding represents a major cause of the early morbidity and mortality associated with SAH [37]. The risk of rebleeding is maximal within the first 24 h, with rates reported ranging from 4 to 13.6% [38]. Early surgery or endovascular therapy to secure the ruptured aneurysm (within 24 h) is now recommended, as it has been

**Table 16.2** Factors associated with increased rebleeding risk [41–45]

| |
|---|
| Delay in securing aneurysm |
| High Hunt and Hess grade on admission |
| Initial loss of consciousness |
| Prior sentinel headaches (severe headaches that do not lead to the diagnosis of aSAH) |
| Large aneurysm size |
| Intracerebral or intraventricular hemorrhage |
| Infratentorial hemorrhage location |
| Presence of multiple aneurysms |
| SBP >160 mmHg |

reported that up to 50% of rebleeding occurs within the first 6 h of symptom onset [39] and early rebleeding is associated with worse functional recovery in survivors [38, 40]. Risk factors associated with increased risk of rebleeding are listed in Table 16.2.

#### 16.2.2.1 Prevention of Rebleeding

Aneurysmal rebleeding is the most treatable cause of poor outcome after SAH, and the best measure to reduce the risk of rebleeding is the early treatment with coiling or clipping of the unsecured aneurysm. However, in cases where early aneurysm obliteration is not possible, a short-term (e.g., less than 72 h) treatment with antifibrinolytic therapy (aminocaproic or tranexamic acid) has been used to reduce aneurysmal rebleeding until definitive intervention can be performed [38]. The use of antifibrinolytics is based on the premise that early rebleeding is due to an activated fibrinolysis and reduced clot stability. Prolonged administration of antifibrinolytic has been associated with increased risk of cerebral infarction and thrombotic events [46, 47]. Recent studies suggest that a short course of aminocaproic acid may reduce the rate of aneurysmal rebleeding without an attendant increase in risk of delayed cerebral ischemia [47–49]. Delayed or prolonged therapy or the use of antifibrinolytics in patients with risk factors for thromboembolism is likely associated with an unacceptable risk of stroke and is not recommended.

Desmopressin has been studied on a limited basis in SAH. A retrospective study assessed the efficacy of a single dose of DDAVP (0.3 mcg/kg) on aneurysmal rebleeding in SAH patients [50]. Patients treated with DDAVP were identified from a registry of SAH patients spanning 20 years. Patients treated with DDAVP had a higher injury severity by both Hunt and Hess classification and modified Fisher group, and were twice as likely to be on antiplatelet agents. The authors found that administration of DDAVP was associated with a 45% reduction in the adjusted odds of rebleeding. Interestingly, preictal antiplatelet use was not associated with increased odds of rebleeding. Forty-four percent of patients in the DDAVP group were also treated with platelet transfusion; however, there was neither an effect of platelet transfusion on rebleeding, nor was there evidence of interaction between DDAVP administration and platelet transfusion. Given the retrospective nature of this single-center registry-based study, these results should be considered preliminary.

#### 16.2.2.2 Prevention of Vasospasm After SAH

Development of severe vasospasm is a dreadful complication of SAH, and its onset has been directly associated with the amount of blood in the subarachnoid and intraventricular spaces, as well as the rate of clot clearance [51–53]. Several randomized controlled trials have suggested that intracisternal thrombolytic administration may prevent development of severe vasospasm and hydrocephalus, decrease delayed cerebral ischemia, and improve long-term neurologic outcome [54–57]. One study suggested that patients treated with intraventricular thrombolysis had better outcomes, shorter hospital length of stay, decreased mortality, and less disability [58].

Ramakrishna et al. retrospectively assessed 41 high-grade aneurysmal SAH patients [59]. They observed that intraventricular injection of tPA with or without concurrent lumbar drainage appears to significantly reduce the number of days the patient has severe vasospasm by transcranial Doppler ultrasound (TCD), the need for angioplasty for vasospasm, the number of vessels treated by angioplasty, and the need for a CSF shunt during hospitalization or within 3 months after hemorrhage. Two other small open-label (unblinded) randomized trials reported that intraventricular tissue plasminogen activator (tPA)

enhanced intracranial blood clearance, but no definite effect on clinical outcomes was observed [60, 61]. A recent pilot study assessed the use of tPA in patients with SAH managed with endovascular coiling and EVD. They concluded that tPA administration accelerates the clearance of both intraventricular and subarachnoid blood, and the efficacy of tPA may be reduced by delays in administration. However, no evidence of improvement in vasospasm, DCI, and long-term neurologic recovery was observed [62].

In summary, evidence may favor the use of intraventricular tPA to accelerate the rate of clot clearance; however, evidence supporting the use of IV tPA to improve vasospasm or delayed cerebral ischemia remains controversial. Moreover, no long-term neurologic outcome improvement has been consistently observed after intraventricular tPA use. Similarly, the CLEAR III trial concluded that the use of intraventricular alteplase does not improve outcome in patients with intraventricular hemorrhage secondary to ICH [63].

### 16.2.3 Traumatic Brain Injury

Traumatic brain injury (TBI) is a devastating disease that affects 5.3 million people in the United States [64]. Hemostatic derangements occur commonly after severe TBI and may occur in as many as 90% of patients, depending on the definition of coagulopathy employed [65, 66]. The coagulopathy of TBI is associated with increased rates of disability and mortality [66–68] and may be implicated in hematoma expansion, also known as progression of hemorrhagic injury (PHI) [69, 70].

The complex pathophysiological mechanisms underlying the coagulopathy of TBI are multifactorial and remain poorly defined. TBI has long been attributed to disseminated intravascular coagulation (DIC) [71], although the lack of a standardized definition hampered determination of the true incidence until recently [72]. A study suggests that over one third of moderate-severely injured TBI patients meet the clinical criteria for overt DIC and that these patients are at higher risk for PHI, longer ICU length of stay, and higher mortality [72]. Alternate theories suggest that the coagulopathy of TBI may be mediated in part by (1) increased release of tissue factor (TF) [73, 74], (2) activation of protein C secondary to tissue hypoperfusion, (3) dysfunction of platelets [75–77], (4) release of inflammatory mediators [78], and/or (5) widespread fibrinolysis [79].

The temporal expression of coagulation biomarkers after TBI has been elucidated [80]. D-dimer and fibrin degradation products are abnormal within minutes of injury [80]. PT and PTT are normal immediately after injury, peak at 6 h postictus, and normalize by 24 h. PT prolongation is the most common abnormality of the routine coagulation tests [77]. Fibrinogen falls precipitously over the first 12 h and then rebounds to normal levels by 24–36 h, indicating transient DIC. Coagulation tests are rarely abnormal after 36 h, which is distinct from the coagulopathy of trauma or sepsis, which may persist for days [81]. Per the International Mission on Prognosis and Analysis of Clinical Trials in TBI (IMPACT) database, prolongation of the prothrombin time (PT) is linearly associated with poor outcome [82].

Platelet dysfunction and thrombocytopenia are also common after moderate–severe TBI and are associated with increased mortality [75, 76], although the underlying mechanisms remain unclear. Among moderate-severely injured TBI patients, thrombocytopenia was present in 14% of patients on admission but rose to 46% by day 3 [77]. A retrospective study of 310 patients with isolated severe TBI demonstrated that a platelet count below 100,000/mm$^3$ was associated with a ninefold increased risk of death [76]. Additionally, patients with platelet counts below 175,000/mm$^3$ were at higher risk for hematoma expansion, surgical intervention, and in-hospital death.

Routine tests of coagulation (PT, PTT) reflect the time to initial thrombin burst but fail to reflect the subsequent maximal thrombin generation [83] and are often normal despite significant changes in coagulation function [84]. Therefore, it is recommended that whenever possible, viscoelastic hemostatic assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) should be used to guide management [85]. These assays provide a real-time analysis of hemostasis based on the physical and kinetic properties of clot formation [86],

allowing to identify states of hypo- and hypercoagulability [87]. Windelov and colleagues demonstrated that a *hypo*-coagulable TEG phenotype on admission, defined by reaction time >8 min, angle <55°, and/or MA <51 mm, correlated with poor prognosis and higher 30-day mortality in patients with isolated TBI [88]. However, another VHA study demonstrated a progressive *hyper*-coagulable state as evidenced by significantly higher MA, thrombus generation, and *G* values over the subsequent 5 days following initial TBI [89].

Cerebral infarction may be another serious manifestation of TBI-related coagulopathy. Pathological studies have shown evidence of cerebral infarction in 80–90% of patients with fatal head trauma [90, 91]. The incidence of infarction has not declined despite improved surgical and medical management of TBI. In one study using advanced neuroimaging, post-traumatic cerebral infarction (PTCI) was demonstrated in 31/384 (8%) patients following TBI and was associated with increased mortality (45% vs. 19%, $p < 0.002$) [92]. Established causes of ischemia in TBI include brain edema, arterial vasospasm, intracranial hypertension, and arterial dissection; however, intravascular microthrombosis, occurring as part of a DIC-like phenomenon, might also play a role [93].

#### 16.2.3.1 Treatment Options

The management of disorders of coagulation and hemorrhage is a common and critically important challenge in severe TBI. Although there are no clear guidelines for the treatment of coagulopathy after TBI, therapeutic strategies should focus on the primary cause and adequate resuscitation and control of hemorrhage.

The best evidence for treatment of TBI-related coagulopathy is with antifibrinolytic therapy. Studies show that derangements of the fibrinolytic system, with either suppressed fibrinolysis or hyperfibrinolysis, increase mortality after severe TBI. As many as 60% of patients, when assessed with TEG, demonstrate abnormal fibrinolysis [79, 94]. Thus, early assessment with viscoelastic hemostatic assays may aid to guide treatment. The CRASH-2 trial (Clinical Randomization of Antifibrinolytic in Significant Hemorrhage-2) randomized over 20,000 patients with acute traumatic injury, associated with or at risk for significant bleeding, to treatment with tranexamic acid compared to placebo [95]. Treatment with tranexemic acid was associated with reductions in all cause mortality and bleeding-related mortality. However, a nested substudy of patients with TBI did not definitively demonstrate efficacy of tranexemic acid on ICH volume or hemorrhage expansion.

Among patients with TBI and hemorrhagic shock, resuscitation is guided by the results of the Pragmatic Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial, which demonstrated that early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio resulted in improved hemostasis when compared to a ratio of 1:1:2 without significant difference in either mortality. Despite a higher dose of plasma and platelets, there were no significant differences in the 23 pre-specified safety outcomes [96].

Transfusion thresholds for anemia remain somewhat controversial area in TBI, despite the fact that randomized controlled trial data demonstrate that targeting a hemoglobin concentration of greater than 10 g/dL with packed red cell transfusion does not result in improved neurologic outcomes at 6 months after injury [97]. Moreover, transfusion of blood products exposes patients to a number of systemic risks and may even lead to PHI after TBI [98]. However, cerebral oxygenation may be improved with higher hemoglobin concentrations [99, 100], whereas restrictive transfusion thresholds may predispose to brain tissue hypoxia and may increase the risk of early mortality [101].

Prophylactic administration of fresh frozen plasma (FFP) after TBI has been studied to bolster intravascular volume and treat coagulopathy; however it is associated with adverse events, such as PHI and in-hospital mortality [102]. Increased perioperative FFP infusion was also independently associated with mortality and poor functional outcome after TBI [103]. However, experimental evidence in TBI and hemorrhagic shock models suggest a benefit of early FFP administration via putative neuroprotective

effects [104, 105]. Generally, FFP should be administered based on the objective presence of coagulopathy and not a routine resuscitant.

It seems logical that patients with intracranial bleeding and thrombocytopenia or platelet dysfunction be treated with platelet transfusions. However, whether platelet transfusions truly stem intracranial bleeding after TBI remains unclear. As previously mentioned, a randomized controlled trial of platelet transfusion in patients on antiplatelet therapy with non-traumatic ICH resulted in increased mortality; however, whether these results may be generalized to those with traumatic ICH is not certain. Studies on the effects of pre-injury antiplatelet therapy and progression of hemorrhagic injury in patients with TBI have yielded conflicting results [106–110]. An observational study at six US trauma centers suggests that although platelet transfusion can improve the degree of platelet inhibition, radiological and clinical outcomes remain unchanged [111]. Similarly, the combination of desmopressin (DDAVP) and platelet transfusion did not decrease the incidence of PHI or death in a cohort of 408 blunt TBI patients [112]. Therefore the decision to transfuse platelets should be individualized, perhaps with laboratory guidance to assess platelet function.

Recombinant factor VIIa has also been studied for traumatic ICH. Similar to spontaneous ICH, treatment with rFVIIa trended toward a dose-dependent reduction of PHI without an increase in significant adverse events [113]. However, the sample size was small, and there was a nonsignificant but increased rate of symptomatic deep vein thrombosis, detected on surveillance ultrasound on post-TBI day 3. Given the marginal decrease in hematoma volume and the increased risk of arterial thromboembolism, systemic reviews suggest that rFVIIa not be used for off-label indications [114].

#### 16.2.3.2 Subdural Hematoma Risk with Antithrombotic Medications

The incidence of subdural hematomas (Fig. 16.3) has been on the rise since the 1980s, likely due to an aging population and the increased prevalence of patients receiving antithrombotic agents [115]. A Danish population-based study of over 10,000 patients found an incremental risk in the incidence of SDH with use of low-dose aspirin (adjusted OR, 1.24 [95% CI, 1.15–1.33]), clopidogrel (adjusted OR, 1.87 [95% CI, 1.57–2.24]), DOAC (adjusted OR, 1.73 [95% CI, 1.31– 2.28]), or VKA (adjusted OR, 3.69 [95% CI, 3.38–4.03]). The combination of a low-dose aspirin and a VKA (adjusted OR, 4.00 [95% CI, 3.40–4.70]) or clopidogrel and a VKA (adjusted OR, 7.93 [95% CI, 4.49–14.02]) resulted in the highest risk of SDH

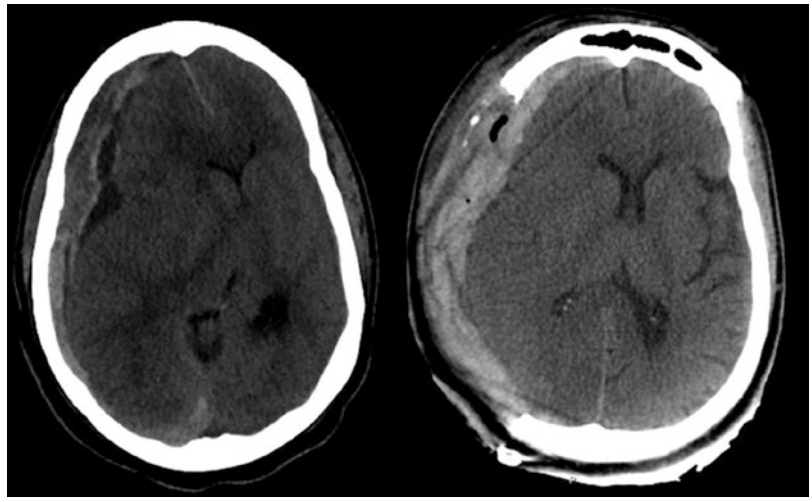

**Fig. 16.3** A 73-year-old patient who fell while on systemic anticoagulation. Left panel. Right-sided subdural hematoma with midline shift of >5 mm. Right panel. Head CT immediately after right decompressive hemicraniectomy. Note improvement in midline shift after decompression.

compared to no antithrombotic agent use [115]. The prevalence of antithrombotic drug use increased from 31.0 per 1000 individuals from the general population in 2000 to 76.9 per 1000 individuals in 2015 ($p < 0.001$ for trend). The overall incidence of SDH increased from 10.9 per 100,000 in 2000 to 19.0 per 100,000 in 2015. The largest increase was among older patients, with a near doubling over the same time period: from 55.1 to 99.7 per 100,000 person-years ($p < 0.001$ for trend).

In patients with acute SDH, surgical decompression may be required. It is rational to emergently reverse anticoagulant drugs in such patients. A study of 300 patients who suffered from acute SDH and were treated with medication reversal and craniotomy showed that pre-injury utilization of antithrombotic agents was not a significant risk factor for recurrence of SDH, radiologic outcome, or mortality [116]. Although a different patient population, the balance currently favors reversal of anticoagulation in a majority of patients with intracranial hemorrhage [14].

## 16.3 Systemic Diseases Associated with Intracranial Bleeding

### 16.3.1 Liver Disease

Patients with chronic liver disease are known to have aberrant coagulation profiles and thrombocytopenia with impaired platelet function. There is diminished and defective synthesis of coagulation factors resulting in prolonged bleeding times, which suggested an increased risk of bleeding. Lately, however, it has been questioned whether indices of coagulation used in a clinical setting truly reflect the risk of hemorrhage [117]. Emerging evidence suggests that patients with chronic liver disease may actually be prothrombotic, despite the results of routine coagulation tests, due to increased levels of von Willebrand factor and factor VIII, decreased levels of anticoagulants, and low plasminogen levels [118–121]. This fragile truce between depleted procoagulant and anticoagulant reserves creates a challenge when treating a patient who has acutely decompensated.

It is unclear whether there is an association between liver disease and intracranial hemorrhage. Some studies have shown that patients with cirrhosis are at higher risk of developing an ICH than the general population [122, 123]. Others have shown no association between the two, although the quality of the data is poor [124, 125]. A large Danish study of over 35,000 patients found that people with cirrhosis as well as non-cirrhotic alcoholic liver disease were at a fivefold increased risk of developing ICH, after adjusting for hypertension, and antithrombotic use. Similar results were reported in a Taiwanese study that demonstrated a trend towards an increased risk of ICH among cirrhotic patients over a 9-year period [126]. Finally, a retrospective US study followed over a million patients from 2005 to 2011 [127]. The disease was 1.7%, compared to 0.4% in patients without liver disease, a statistically significant difference. The difference remained statistically significant after adjusting for comorbidities and other possible confounders.

Intracerebral hemorrhage in the setting of liver disease has a very poor outcome with one large retrospective study reporting the incidence of mortality of 47.2% and another of 43.7% [128, 129]. Likewise, patients with TBI and concomitant cirrhosis have very high rates of in-hospital mortality [130]. Treatment of ICH in the general population includes the administration of platelets, fresh frozen plasma, cryoprecipitate, and reversal of anticoagulation if necessary. Patients with cirrhosis pose a unique challenge in that administration of blood products can lead to an increased risk of volume overload and variceal bleeding given the increase in portal pressure [131]. To date there are no clear guidelines in managing these complex patients, and co-management with a hepatologist is strongly encouraged for patients with decompensated cirrhosis admitted with intracerebral hemorrhage.

Recently there has been interest in using recombinant factor VIIa in the treatment of ICH. A randomized double-blinded placebo controlled trial was completed in patients admitted with

intracerebral hemorrhage receiving a single dose of 40 μg, 80 μg, or 160 μg/kg of rFVIIa within 4 h of onset of symptoms [132]. They concluded that administration of rFVIIa significantly reduced expansion of hemorrhage, improved clinical outcomes, and reduced 90-day mortality in comparison to a placebo group. They did however note increased risk of arterial thromboembolic events in the study groups in the first 3 days of hospitalization. Of note, patients with known coagulopathy were excluded from this trial. Although the last few years have seen a broader adoption of rFVIIa in patients with cirrhosis, caution is warranted [114, 133].

### 16.3.2 Kidney Disease

Kidney disease is one of the most common chronic conditions that intensivists face. Severity of disease is usually stratified using glomerular filtration rate (GFR) with patients >60 and <90 mL/min per 1.73 $m^2$ having mild chronic kidney disease (CKD, stage 2), 30–59 moderate CKD (stage 3), 15–29 severe CKD (stage 4), and <15 kidney failure/dialysis-dependent end-stage renal disease (ESRD, CKD stage 5) [134]. Diabetes and hypertension are the most common causes of chronic kidney disease in the United States where the incidence of ESRD reaches 400 cases per million [135, 136]. In fact, while GFR is inversely associated with increased risk of stroke, proteinuria is linearly associated with an increased risk of stroke [137–139]. Akin to patients with liver disease, patients with chronic kidney injury also have a known predisposition to both increased risk of uremic bleeding as well as thrombosis. The etiology of this is unclear but thought to be a combination of impaired platelet aggregation, endothelial dysfunction, aberrant coagulation factor milieu, chronic inflammation, and impaired toxin clearance [140–142].

Specifically, intracranial bleeding in patients with ESRD has become a major concern as the prevalence of patients with renal disease and need for anticoagulation has steadily increased over the last few decades. The most common reason for anticoagulation in patients with kidney disease is atrial fibrillation, which affects ~10 to 27% of patients on hemodialysis and 7% on patients on peritoneal dialysis [143–146]. In this patient population warfarin has been used for anticoagulation, but with the advent of new oral anticoagulants (NOAC), this may change. Interestingly, there is some compelling evidence that patients with ESRD and atrial fibrillation do not in fact have lower rates of ischemic stroke and improved mortality when on warfarin as previously thought and may have a significantly increased risk of intracranial hemorrhage, which questions the common practice of treating these patients with warfarin [147, 148]. However, the safety of NOACs is in this population less clear, and unfortunately there are no published evidence-based clinical trials targeted specifically for patients with impaired creatinine clearance except for subgroup analyses as below.

In the RE-LY clinical trial, dabigatran versus warfarin was studied in patients with atrial fibrillation. This was a prospective non-inferiority study completed in 951 clinical centers and 44 countries [149]. Patients were randomized into a warfarin arm with goal INR of 2–3 or dabigatran arm, where patients received 110 mg or 150 mg capsules twice daily. The primary study outcome was stroke or other systemic thromboembolism, and primary safety outcome was major hemorrhage. Both dabigatran doses were found to be non-inferior to warfarin in achieving the primary outcome. In this study the rate of hemorrhagic stroke was 0.38% per year in the warfarin group, 0.12% per year in the group receiving 110 mg dabigatran and 0.10% per year in the group receiving 150 mg dabigatran, with the difference between the warfarin group and the study groups being statistically significant. In a subgroup analysis, patients with moderate to severe kidney disease had a significantly better safety outcome in the 150 mg dabigatran arm compared to warfarin. In the EINSTEIN study rivaroxaban versus warfarin was studied in patients with deep-vein thromboembolism [150]. The study showed non-inferiority of rivaroxaban and trend toward superiority over warfarin in achieving primary

outcome of symptomatic recurrent venous thromboembolism. There was no statistically significant difference in rate of first major or clinically relevant non-major bleeding between the two groups, including in the subgroup analysis with impaired creatinine clearance (22.7% of patients had creatinine clearance of 50–79 mL/min, 6.6% clearance of 30–49 mL/min). In the ARISTOTLE study, patients receiving apixaban had a significantly lower rate of intracranial hemorrhage compared to the warfarin group [151]. This was statistically significant in patients with mild renal impairment and with a positive trend toward apixaban in patients with moderate and severe renal impairment. Similarly, in the AMPLIFY study comparing apixaban with warfarin in patients with acute venous thromboembolism patients, there was a nonsignificant trend toward improved efficacy of apixaban in patients with kidney disease [152]. Lastly edoxaban, has also been compared to warfarin in patients with atrial fibrillation and venous thromboembolism, again with a nonsignificant trend toward improved efficacy of edoxaban in patients with impaired creatinine clearance [153].

One of the major concerns with the NOAC studies as discussed above is that they largely excluded patients with GFR <30 mL/min (apixaban trials <25 mL/min) and to date there are no clinical trials examining outcome of patients with ESRD on hemodialysis while taking NOAC. In a small prospective study, a reduced 10-mg dose of rivaroxaban given to 18 HD patients without residual kidney function resulted in serum drug concentrations similar to the standard 20-mg dose administered to healthy volunteers. Additionally, elimination of Rivaroxaban was not affected by HD, and there was no drug accumulation after multiple daily dosing [154]. A small open-label study with administration of a single dose of apixaban in ESRD patients on HD concluded that apixaban can be used in this population without necessary dose adjustment [155].

Unfortunately, multiple medical societies have reached differing conclusions on utility of anticoagulation in stage 5 chronic kidney disease. Guidelines from the AHA/ACC provide B level recommendation on using warfarin for stroke prevention with atrial fibrillation for patients with ESRD [156]. The European Medical Agency does not recommend the use of NOACs in patients on HD [157]. In the United States, the FDA does support the use of lower-dose rivaroxaban and apixaban in patients with CKD-5 and atrial fibrillation [158]. There are currently three clinical trials that compare novel anticoagulants with warfarin in patients with end-stage renal disease: RENAL-AF (clinical trials identifier NCT02942407), AXADIA (NCT02933697) and AVKDIAL (NCT02886962). Until there is a clear consensus, choice of anticoagulation should be individualized, taking into account patient age, stroke risk, and other comorbidities.

### 16.3.3 Intracranial Monitoring and Coagulopathy

Patients admitted to the neurocritical care unit often require placement of external ventricular drains (EVDs) or other ICP monitors to appropriately guide therapy. Many patients admitted to the unit for management of intracranial hemorrhage often are anticoagulated with warfarin or NOACs, and attempts at reversal are made on admission. Despite reversal, patients undergoing EVD placement are still at risk of new intracranial hemorrhage during placement. Studies approximate the risk of intracranial bleeding or tract hemorrhage from EVD placement ranging from 25 to 35%; however most of these hemorrhages are small petechial hemorrhages, often not of clinical significance [159, 160]. Sussman et al. recently showed rate of ICH of 31.9% in their cohort after EVD placement; however only 1.4% was found to be of any clinical significance [161].

The vast majority of patients are started on VTE pharmaco-prophylaxis with either LMWH or unfractionated heparin. Timing of prophylaxis in the periprocedural period of EVD placement remains a concern. A recent retrospective review analyzed 99 patients with 111 EVD placed [162]. Reason for EVD placement included SAH (30.7%), hypertensive thalamic

and IVH (29.1%), TBI (13.7%), and others (26.5%). Low-dose unfractionated heparin (LDUH) was anticoagulation of choice and was administered within 24 h of placement ($n$ = 56, mean 8.74 h to EVD placement) and after 24 h of drain placement ($n$ = 55, mean 108 h to EVD placement). All patients underwent post-EVD placement head-CT, and there were no significant difference in the incidence of new hemorrhage between the two groups. Mechanical VTE prophylaxis is recommended in all patients with contraindications to pharmacological prophylaxis. In patients with additional risk factors for VTE, pharmacological prophylaxis is recommended by the Neurocritical Care Society after an intracranial hemorrhage has been ruled out or is stable [163].

### 16.3.4 Resumption of Anticoagulation

For those patients with chronic subdural hematomas, the decision to resume antithrombotics postoperatively is a complex one and should therefore be highly individualized. This decision should balance the risks of rebleeding versus the risks of thromboembolism. A study assessing 150 patients who underwent craniotomy for chronic SDH showed no significant difference in the development of postoperative hemorrhagic complications in the group taking antithrombotic agents. However, they found a significant difference in the incidence of postoperative thromboembolic complications between patients with and without antithrombotic therapy (9.1% vs. 0.9%, respectively) [164]. According to a recent meta-analysis, it is feasible to resume early antithrombotic treatment without additional hemorrhagic or thromboembolic risk [165]. In patients with mechanical valves, warfarin resumption at 3–5 days post-evacuation of chronic SDH did not increase the risk of subsequent recurrence [166, 167]. Based on current evidence, it seems reasonable to resume antithrombotic agents as soon as possible when no hemorrhagic complication is confirmed after neurosurgical intervention for CSDH.

Patients treated with OAC are at an increased risk of hemorrhagic complications with yearly incidence of 2–5% for major bleeding and 0.4% for intracranial bleeding [168]. Anticoagulation therapy may increase the risk of intracranial hemorrhage 10- to 15-fold compared to the general population [169]. Unfortunately, there are no clear guidelines to guide resumption of anticoagulation in patients admitted with intracranial hemorrhage and persistent need for anticoagulation. Phan et al. retrospectively reviewed records of 141 patients admitted with intracranial hemorrhage who were on oral anticoagulation for prosthetic mechanical valve, atrial fibrillation, and recurrent stroke of unknown etiology [170]. Median time off OAC was 10 days; three patients experienced an ischemic stroke. No recurrence of ICH was noted during hospitalization for patients who were started on anticoagulation. A larger retrospective review concluded that OAC (mostly warfarin) could be safely resumed in 10 weeks after an intracranial hemorrhage [171]. Hawryluk et al. published a systematic review of available literature on topic of ICH and anticoagulation and hypothesized that anticoagulation could be safely restarted 3 days after the sentinel event [172]. In contrast, a large observational cohort study from the Danish National Patient Register, a mandatory 10-week anticoagulation holiday for patients admitted for VKA-related ICH reduced all-cause mortality for patients in both non-traumatic ICH and traumatic ICH groups [173].

In a large international non-randomized prospective observational study of anticoagulation resumption after cardioembolic stroke, the risk of intracranial hemorrhage was 3.6%, and systemic hemorrhage was 1.4% [174]. This study reported that high CHA2DS2-VASc score, high National Institutes of Health Stroke Scale, large ischemic lesion, and anticoagulant class each independently led to a greater risk of recurrence and bleedings. They also found significantly better outcomes for all outcome events and also rate of ischemic stroke/TIA/systemic embolism for patients in whom anticoagulation was started between 4 and 14 days of admission, as compared with after 14 days or before 4 days. There was also a trend of improved outcomes of

symptomatic hemorrhage in the 4–14 days group, compared to the other groups, but this was not statistically significant. These findings persisted to 90 days post-event (mRS > 3 or deceased). These studies suggest a more aggressive approach in resuming anticoagulation after an intracranial hemorrhage or starting anew after an acute stroke.

## 16.4 Conclusion

Coagulopathy is common in the neuro-ICU and poses intricate challenges. Routine coagulation assays do not reliably reflect true in vivo clotting potential. New oral anticoagulants may result in a lower intracranial hemorrhage. There is a lack of data regarding the management of coagulopathy in the neurocritical care population; however, data derived from studies of general critical care populations, ICH, traumatic brain injury, hematology, and cardiology may guide treatment decisions. Emergently identifying and correcting coagulopathy in ICH and TBI are crucial to minimize hematoma expansion and to improve the chances for best functional outcome.

**Key Points**

- Hemostatic derangements are common in neurocritically ill patients and may precipitate or exacerbate conditions of bleeding and thrombosis.
- Intracranial bleeding is the most feared complication of these derangements and results in significant morbidity and mortality.
- Venous thromboembolism, myocardial infarction, and acute ischemic stroke often complicate an ICU stay.
- Routine coagulation assays do not reliably reflect true in vivo clotting potential, and some point-of-care tests or viscoelastic assays may be useful to identify or monitor progression of coagulopathy.

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# Part V

# Supportive Care

# Nutrition and the Neurologic Patient

17

Neeraj Badjatia, Nikhil Patel, and Tachira Tavarez

## 17.1 Introduction

The importance of nutrition in critical illness has been increasingly recognized, and this is no different with neurological critical illness. Critical illness is associated with a catabolic state which is frequently associated with secondary complications such as increased infection rates, multiple organ dysfunction, prolonged intubation, further morbidity, and worsened mortality. Moreover, patients with neurological injury often have an associated dysphagia, poor mental status, and prolonged immobilization, putting them at further risk of malnutrition.

Nutritional support in neurological patients is a complex issue, dependent on such factors as a patient's baseline metabolic status, severity and temporal progression of illness, use of mechanical ventilation, and use of sedatives. The appropriate dose of nutrition should be administered early in the hospital course once hemodynamic stability is established. Improper administration can lead to overfeeding, underfeeding, or poor glycemic control. However, traditional methods of assessing baseline energy expenditure may not apply to patients with neurological injury.

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## 17.2 Metabolic Response to Injury (Fig. 17.1)

### 17.2.1 Inflammatory Response

Brain injury triggers a robust cascade of neuroendocrine and inflammatory responses. Injury detected in the hypothalamus leads to activation of the neuroendocrine response, involving the sympathetic nervous system and hypothalamic-pituitary axis [1]. The adrenal medulla releases norepinephrine and epinephrine into the bloodstream. Stimulation of the hypothalamic-pituitary axis results in the release of counterregulatory hormones—adrenocorticotropic hormone, thyroid-stimulating hormone, growth hormone, follicle-stimulating hormone, and luteinizing hormone—causing increased substrate catabolism. This response ultimately leads to hyperglycemia and lipid and protein catabolism.

The inflammatory response implicated in the pathogenesis of cerebral ischemia and traumatic brain injury has been well studied [2, 3]. Cytokines and chemokines produced by immune cells from the periphery along with microglia, astrocytes, and neurons from the CNS mediate the inflammatory response. Interleukin-1β is a pro-inflammatory cytokine thought to be produced primarily in the brain within the first 24 h after injury. Studies have correlated increases in CSF IL-1β with increases in ICP and poorer outcome in TBI. In human studies, IL-6 has had


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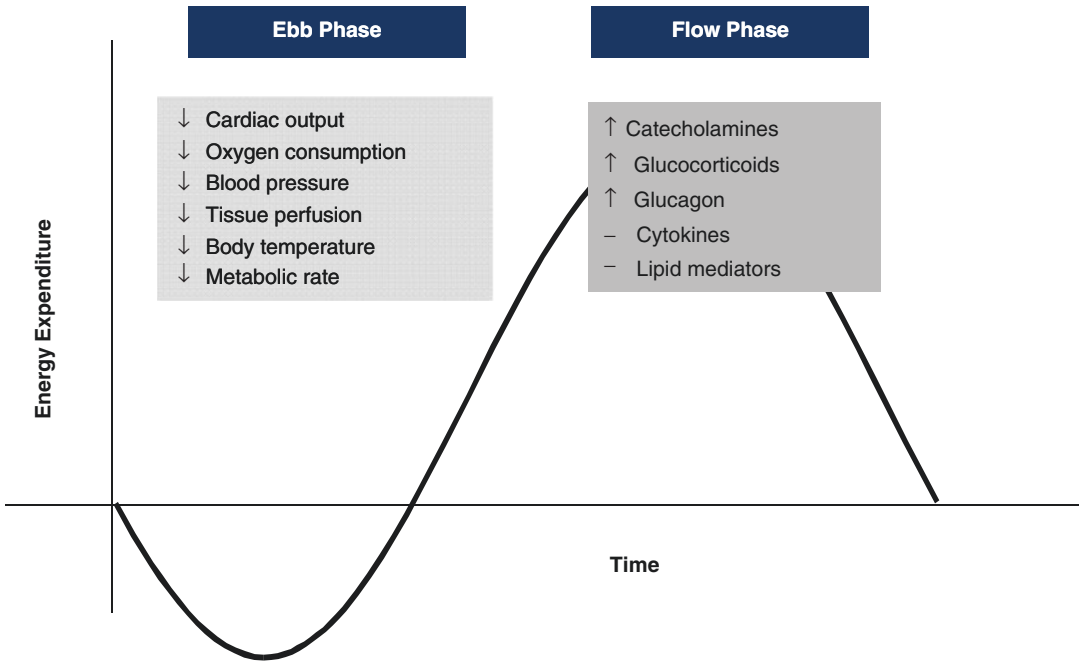


**Fig. 17.1** Metabolic response to injury. Characterization of the Ebb and Flow phases of metabolic response to injury. The primary response involves a decrease in metabolic rate, reflected by a decrease in cardiac output, oxygen consumption, and tissue perfusion. The next phase involves a ramp up in catecholamine activity and subsequent increase in metabolic rate. Adapted from: Cutherbertson DP, et al. *Adv Clin Chem* 1969;12:1-55

more of a neuroprotective role and peaks after IL-1β, Although systemically it is associated with hyperpyrexia and anorexia [1]. Elevations in complement have been associated with blood-brain barrier dysfunction. Together, tumor necrosis factor alpha and IL-1 stimulate the release of interleukin 8 (IL8) from astrocytes. IL8 is chemokine that promotes neutrophil infiltration and is associated with increase blood-brain barrier permeability.

### 17.2.2 Substrate Utilization (Fig. 17.2)

Glucose is the primary source of energy with uptake neuronal cells mediated primarily by glucose transporter 3 [4]. Metabolic changes in the setting of critical illness cause a utilization of glycogen with subsequent hyperglycemia due to hepatic gluconeogenesis and diminished peripheral uptake of glucose caused by increased insulin resistance [1]. Hyperglycemia has been associated with worsened outcomes in various subpopulations of neocritical care patients including the setting of traumatic brain injury, aneurysmal subarachnoid hemorrhage, and spontaneous intracerebral hemorrhage. A systemic review and meta-analysis of glycemic control in the neurocritical care population by Kramer et al. found that tight glycemic control had no impact on mortality; however, improved outcomes were seen in a subgroup of studies with looser targets, receiving therapy when glycemia was above 200 mg/dL [5].

During relative hypoglycemia, the brain utilizes other substrates for energy such as ketones, lactate glycerol, and amino acids [6]. Ketone synthesis occurs in the liver through ketogenesis and is regulated by insulin, glucagon, and catecholamines. Ketones are then transported by monocarboxylate transporters (MCTs) for utilization. In the setting of brain injury, studies have shown increases in both vessel and neuronal monocarboxylate transporters, favoring transport of ketones to the brain. As previously mentioned, glutamate toxicity leads to a sequence of events

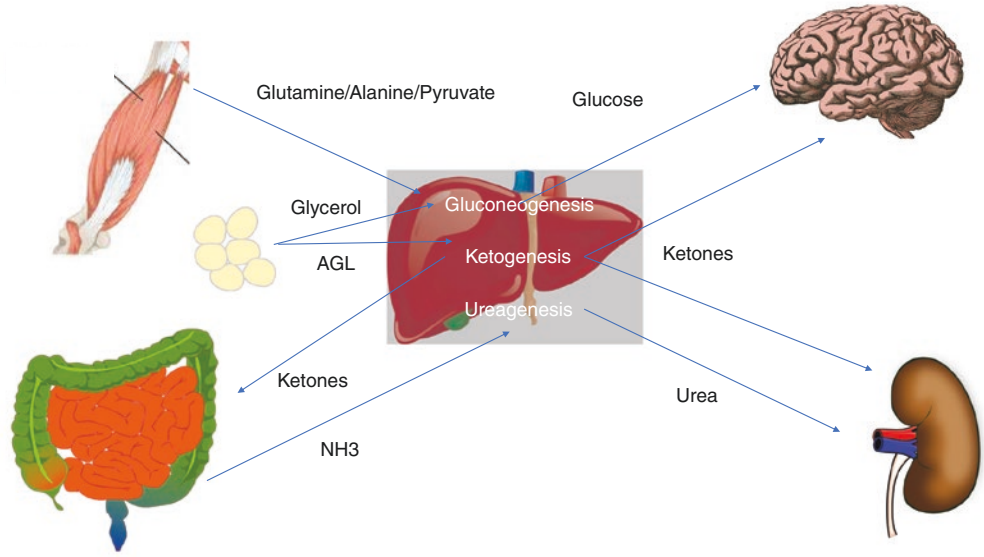


**Fig. 17.2** Substrate utilization in critical illness. Depiction of pathways and substrates involved in metabolism during injury

that ultimately lead to neuronal death, and experiments in animals have shown reduction in neuronal damage with the use of ketone supplementation in the setting of glutamate-induced excitotoxicity indicating a potential neuroprotective effect [4].

Protein catabolism exceeds protein synthesis during the inflammatory response as indicated by a negative nitrogen balance. Amino acids, primarily alanine and glutamine, are then utilized in gluconeogenesis or oxidized and excreted in the form of urea and ammonia. As a result, critically ill patient will experience skeletal muscle depletion and lean body mass [1]. Currently ASPEN guidelines do not recommend glutamine supplementation in the general ICU population, but it is recommended in patient with TBI based on a clinical trial where patient with brain injuries was provided supplementation with glutamine and probiotics. This control group in the study that did not receive supplementation had longer lengths of stay in the ICU, more days of mechanical ventilation, and greater infection rate [7].

The role of lipolysis during critical illness is to produce glycerol from free fatty acids. Glycerol is then for both glucose and ketone production. These free fatty acids are susceptible to peroxidation by reactive oxygen species produced in the setting of mitochondrial dysfunction. This oxidative stress, defined as a state of imbalance between reactive oxygen species and nitric oxide synthetase, results in consumption of antioxidants and their stores and is associated with increased morbidity and mortality in the critically ill [8]. Studies have demonstrated low serum levels of antioxidants and altered levels of zinc, copper, and iron in brain injury and ischemic stroke [8, 9]. Despite an abundance of clinical and preclinical data suggesting micronutrients as potential therapeutic targets, no studies have demonstrated a clear benefit in their use as supplementation.

### 17.2.3 Brain-Gut Microbiome

There has been increasing interest in the brain-gut axis, a bidirectional physiologic model, as both a mechanism of insult in the CNS and potential target for therapy. Neuronal components include the autonomic nervous system, and the gastrointestinal component consists of

the intestinal flora and wall [10]. Based on preclinical and clinical data, Sundman et al. hypothesized how disruption of the brain-gut axis created a positive feedback, causing secondary injury in traumatic brain injury. They propose that brain trauma creates a focal inflammatory response, producing microglial hypersensitivity. Additionally, dysautonomia from the head injury creates dysbiosis of the gut flora and compromise of the intestinal wall, allowing pathogens and harmful substance to enter the bloodstream; as a result, the hypersensitive microglial cells become neurotoxic, producing this state of perpetual neuroinflammation. Studies focusing on the influence of intestinal flora on ischemic stroke suggest that the intestinal flora may function as a modulator of the inflammatory response, like the hypothesis proposed in TBI. Additionally, the microbiota may contribute to the pathogenesis of ischemic stroke with the promotion as atherosclerotic plaque formation [11].

## 17.3 General Clinical Approach

### 17.3.1 Measurement of Caloric Requirements

Nutritional assessment begins with the evaluation of the resting energy expenditure (REE), which is the amount of energy (in kilocalories) expended by the body in resting conditions over a 24-h span (Table 17.1). The total amount of energy required in a normal, healthy adult includes not only the REE but also the amount of physical activity and the thermal effect of food intake. Since physical activity and food intake can be variable, the REE forms the basis of the 24-h energy expenditure [12]. Although there is limited data on the optimal methods to assess the energy requirements within the neurocritical care population, indirect calorimetry (IC) is the gold standard used in the general critical care setting.

When IC is not readily available, the REE can be estimated using various equations. The first calculations formulated are the Harris-Benedict equations. There have subsequently been numerous equations attempting to estimate the REE, with accuracies ranging from 40 to 75% when compared to the gold standard of indirect calorimetry [13]. The calculation of REE is more difficult in the ICU setting, as patients have wide fluctuations in temperature, use of sedatives, and varying levels of engagement with physical therapy. Even the use of the gold standard indirect calorimetry can be limited based on many ICU-specific patient factors, such as the use of chest tubes, supplemental oxygen sources, positive end-expiratory pressure, use of anesthesia, and continuous renal replacement therapy [14].

**Table 17.1** Resting energy expenditure equations

| Predictive equation | Population cohort |
|---|---|
| Harris and Benedict equation | Healthy volunteers (men) |
| Mifflin equation | Healthy volunteers (men and women) |
| Ireton-Jones equations | Burn patients |
| Owen equation | Hospitalized patients |
| Penn State equations (1998 and 2003) | Critically ill patients |
| Swinamer equation | Critically ill patients |

Equations that have been derived to estimate resting energy expenditure. The original equation was the Harris-Benedict equation, which has been followed by numerous estimations based on different patient populations

### 17.3.2 Assessment of Nutritional Risk (Fig. 17.3)

Since the majority of neurocritically ill patients have poor volitional intake due dysphagia and altered mental status, the use of a nutritional risk predictor can be used to identify patients who are most likely to benefit from early nutrition. The NUTRIC and NRS-2002 scoring systems are the most widely used scores. The NRS-2002 score considers both disease severity and malnutrition, with those scoring greater than three nutritionally at risk and those with scores above five at high risk. The NUTRIC score incorporates age, baseline APACHE II, SOFA, days from hospital admission to ICU admission, patient characteristics

such as number of comorbidities, body mass index (BMI) <20, estimated % oral intake in the week prior, weight loss in the last 3 months, and levels of inflammatory markers serum interleukin-6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP). A NUTRIC score of greater than or equal to five identifies patients at risk [15]. Both scoring systems are recommended by the 2016 ASPEN guidelines, and additional recommendations suggest that all hospitalized patients should be screened within 48 h of admission [13].

When IC is not readily available, there are recommendations for the use of published predicted equation, such as the Penn State or Harris-Benedict, or a weight-based equation of 25–30 kcal/kg/day can be used. However, these are inadequate given dynamic variables in critically ill patient like fevers and metabolic changes due to medication and have not been validated in the neurocritical care population [13, 16]. Other traditionally used methods such as serum biomarkers like albumin, prealbumin, transferrin, and retinol-binding protein are not adequately studied for monitoring of nutrition due to changes in acute-phase response [6].

### 17.3.3 Nitrogen Balance and Protein Provision

Aside from assessing general nutritional risk, measuring the adequacy of protein intake is important in the critically ill patient. This can be assessed by the nitrogen balance. Since critical illness is a catabolic process involving the breakdown of proteins into amino acids, this increases overall nitrogen expenditure and results in a negative nitrogen balance. Most of the nitrogen excreted by patients is in the form of urea nitrogen in the urine. Protein requirements in a critically ill patient range from 1 to 1.2 g/kg/day and may be higher in burn and multi-trauma patients.

Ultrasound presents an inexpensive and easily accessible modality to assess qualitative changes in skeletal muscle. Rapid skeletal muscle wasting is a common result from critical illness, which leads to poor functional outcome. Puthucheary et al. compared sequential histologic specimens and rectus femoris echogenicity and found that fasciitis and muscle necrosis can be readily detectable using ultrasound. These qualitative changes in critically ill patient may have implication in mobilization and rehabilitation [17]. A more widely accepted method to monitor protein energy metabolism is

**a**

| Variable | Range | Points |
|---|---|---|
| Age | <50 | 0 |
| | 50 -<75 | 1 |
| | ≥75 | 2 |
| APACHE II | <15 | 0 |
| | 15 -<20 | 1 |
| | 20-28 | 2 |
| | ≥28 | 3 |
| SOFA | <6 | 0 |
| | 6 -<10 | 1 |
| | ≥10 | 2 |
| Number of Co-morbidities | 0-1 | 0 |
| | ≥2 | 1 |
| Days from hospital to ICU admission | 0 -<1 | 0 |
| | ≥1 | 1 |
| IL-6 | 0 -<400 | 0 |
| | ≥400 | 1 |

**Fig. 17.3** Examples of nutrition risk scores. (**a**) NUTRIC score. (**b**) NRS-2002

**b**

*Nutritional Risk Screening (NRS 2002)*

**Table 1** Initial screening

| | | Yes | No |
|---|---|---|---|
| 1 | Is BMI <20.5? | | |
| 2 | Has the patient lost weight within the last 3 months? | | |
| 3 | Has the patient had a reduced dietary intake in the last week? | | |
| 4 | Is the patient severely ill ? (e.g. in intensive therapy) | | |

**Yes**: If the answer is 'Yes' to any question, the screening in Table 2 is performed.
**No**: If the answer is 'No' to all questions, the patients is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.

**Table 2** Final screening

| **Impaired nutritional status** | | **Severity of disease (≈ increase in requirements)** | |
|---|---|---|---|
| Absent **Score 0** | Normal nutritional status | Absent **Score 0** | Normal nutritional requirements |
| Mild **Score 1** | Wt loss >5% in 3 mths or Food intake below 50 75% of normal requirement in preceding week | Mild **Score 1** | Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*, *Chronic hemodialysis, diabetes, oncology* |
| Moderate **Score 2** | Wt loss >5% in 2 mths or BMI 18.5 20.5 + impaired general condition or Food intake 25 60% of normal requirement in preceding week | Moderate **Score 2** | Major abdominal surgery* Stroke* *Severe pneumonia, hematologic malignancy* |
| Severe **Score 3** | Wt loss >5% in 1 mth (> 15% in 3 mths) or BMI < 18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week in preceding week | Severe **Score 3** | Head injury* Bone marrow transplantation* *Intensive care patients (APACHE>10).* |
| **Score:** | + | **Score:** | **=Total score** |
| **Age** | if ≥ 70 years: add 1 to total score above **= age-adjusted total score** | | |
| **Score ≥3:** the patient is nutritionally at-risk and a nutritional care plan is initiated<br>**Score <3:** weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status. | | | |

**NRS-2002** is based on an interpre-tation of available randomized clinical trials.
*indicates that a trial directly supports the categorization of patients with that diagnosis. Diagnosis shown in *italics* are based on the prototypes given below.
**Nutritional risk** is defined by the present **nutritional status** and risk of impairement of present status, **due** to **increased requiremnts** caused by stress metabolism of the clinical condition.

**A nutritional care plan** is indicated in all patients who are

(1) severely undernourished (score 3), or (2) severely ill (score 3), or (3) moderately undernourished + mildly ill (score 2 + 1), or (4) mildly undernourished + moderately ill (score 1 + 2).
**Prototypes for severity of disease**
**Score = 1:** a patient with chronic disease, admitted to hospital due to complications. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.

**Score=2:** a patient confined to bed due to illness, e.g. following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.
**Score=3:** a patient in intensive care with assisted ventilation etc. Protein requirement is increased and cannot be covered even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.

**Fig. 17.3** (continued)

the measurement of nitrogen balance, and although not an optimal marker of total nutritional therapy, negative nitrogen balance has been associated with infectious complications and injury severity in several neurocritical care subgroups [16].

### 17.3.4 Enteral Nutrition

Starting enteral nutrition (EN) early during the neurocritically ill patient's admission is important for combating the hypermetabolic status and preventing secondary complications. The 2016 SCCM/ASPEN guidelines recommend initiating EN within 24–48 h in patients who cannot maintain a proper volitional intake. This recommendation is based on a meta-analysis of multiple randomized trials comparing early to delayed EN that found improvements in mortality and infectious morbidity in the early EN group [13]. This adds on data that indicate that early EN is associated with reduced mortality [18], length of stay, and hospital-acquired infections [19].

There remains concern in initiating early EN in patients who are being treated with high-dose vasopressors, as these medications increase splanchnic vasoconstriction and decrease gastric motility [20]. For these patients, careful attention should be paid for signs of mesenteric ischemia or rising gastric residual volumes as an indicator of intolerance.

### 17.3.5 Parenteral Nutrition

Enteral nutrition is preferred over parenteral nutrition (PN) whenever possible due to the beneficial effects on normal gut flora growth, bowel motility, and normal balance of nutrient uptake. PN is only indicated in patients who cannot receive at least 60% of their energy and protein requirements via EN [13]. Recommendations on timing of when to initiate PN depend on the patient's nutritional risk. In patients at low nutritional risk, PN should be withheld 7 days after admission and started only if EN remains unfeasible [13]. However, in patients with high nutritional risk as indicated by an NRS-2002 greater than five or NUTRIC greater than six, PN should be initiated as early as possible to reduce mortality and infection rates [21].

## 17.4 Nutrition for Specific Neurocritical Care Diagnoses

### 17.4.1 Traumatic Brain Injury

Traumatic brain injury (TBI) induces a significant hypermetabolic response that can last for up to 4 weeks after the initial injury [22]. The increase in metabolic rate is on par with that of burn patients with 20–40% of body surface area affected [23]. This response is likely due to the release of cytokines and counterregulatory hormones activated in the acute-phase response [24, 25]. An increased resting energy expenditure and protein catabolism make it difficult to maintain a positive nitrogen balance, which can last for up to 4 weeks after the initial injury [26].

Due to these physiological responses, the lack of appropriate feeding can lead to malnutrition and secondary complications. In addition, patients with sustained TBI commonly have feeding intolerance due to damage to neurologic pathways responsible for swallowing. Patients with moderate to severe TBI frequently require mechanical ventilation, necessitating enteral feeding. Early nutrition, once a patient is hemodynamically stable, is an important goal for these patients, with data showing that early nutrition within the first 5 days is associated with a lower rate of mortality, poor outcome, and infectious complications. There is inadequate data to support total parenteral nutrition versus enteral nutrition [27, 28].

Sparse data exists to recommend a specific formulation of nutrition support. Small studies have shown a potential benefit of a carbohydrate-free diet [29] as well as zinc supplementation, but there is a lack of confirmatory data, and larger trials are needed to determine the proper formulation and supplementation for patients with TBI. Currently, best practices are adopted from the general critical care literature.

### 17.4.2 Spinal Cord Injury

Unlike most neurological conditions, spinal cord injury (SCI) results in a decrease in resting energy expenditure [30]. The extent of this decrease is related to the level of the injury, with larger decreases observed in patients with upper spinal injuries. Failure to account for lower REE can lead to overfeeding and prolonged mechanical ventilation [31]. Other metabolic abnormalities include increased calcium excretion that peaks 3 weeks after injury resulting from immobilization and increased bone resorption. Oral intake can become a significant problem, with dysphagia being a common issue following SCI, particularly with cervical spine-injured patients. Percutaneous endoscopic gastrostomy (PEG) insertion may provide a safe alternative for these patients, although no data from controlled trials exists in this patient population to inform optimal timing for PEG insertion.

### 17.4.3 Acute Ischemic Stroke

Malnutrition is a common issue in the stroke population which associated with poor functional outcomes and increased length of stay in

the hospital and rehabilitation setting. A large percentage of stroke patients present with dysphagia, which is not only a risk factor for malnutrition but also increases risk of complications such as aspiration pneumonia [32].

Feed or Ordinary Diet (FOOD) trial collaboration consisted of three separate studies addressing factors implicated in undernutrition within the stroke population [33, 34]. Two of the three trials involved dysphagic patients. The first trial compared early enteral feeding versus delayed feeding for at least 7 days. Results from this trial suggested that earlier feeding was better. In the second trial, the use of tube feeding via nasogastric versus percutaneous endoscopic gastrostomy which demonstrated that PEG feeding to be associated with an increased risk of death or poor outcome. The third study compared standard nutrition with oral nutrition supplementation with protein. No significant difference was noted between the groups in terms of poor outcome or death. Also, increased development of pneumonia, infection, pressure sores, and gastrointestinal hemorrhage was noted within population that was classified as malnourished [35].

### 17.4.4 Intracerebral and Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) results in a hypermetabolic state, with an increase in REE comparable to that seen in TBI. This catabolic state results in a net negative nitrogen balance that is associated with worse neurological outcome and increased hospital-acquired infections [36]. The degree of hypermetabolism is proportional to the clinical severity of SAH [37]. Additionally, injury severity and hypermetabolism are associated with higher n-free fatty acid (FFA) levels and an increase in the n6:n-3 FFA ratio, providing a potential therapeutic target to mediate the inflammatory response in SAH [38]. Another factor exacerbating poor nutritional status in SAH patients is the use of nimodipine for prevention of delayed cerebral ischemia, as this medication commonly causes diarrhea. The use of banana flakes or loperamide can help prevent this issue.

Despite the known risks of malnutrition, there are sparse data to recommend specific interventions to improve the nutritional status in SAH. A small, prospective randomized trial demonstrated that supplementation with 2700 mg/day of eicosapentaenoic to SAH patients who underwent for up to 30 days post clipping was shown to decrease both symptomatic vasospasm and cerebral infarction caused by cerebral vasospasm [39]. More studies are needed for specific recommendations to optimize the nutritional status of these patients.

### 17.4.5 Fulminant Hepatic Failure

Fulminant hepatic failure results in the well-recognized metabolic abnormalities of hypoglycemia, due to impaired gluconeogenesis, and hyperammonemia, due to reduced hepatic synthesis of urea and glutamate. The degree of hyperammonemia is proportional to the severity of the condition as well as the risk of cerebral edema and herniation [40].

Despite substantial loss of functioning hepatic cells, studies have shown increase in energy expenditure in fulminant hepatic failure. One series demonstrated an increase in energy expenditure in patients with acetaminophen-induced fulminant hepatic failure as compared with both healthy controls and patients actively undergoing liver transplantation during the anhepatic phase [41]. Another series confirmed this finding in a cohort of patients with more heterogenous causes of fulminant hepatic failure [42]. Malnutrition can have an especially detrimental impact on the prognosis after liver transplantation, as hypermetabolism and inadequate nutrition can lead to an increased lactate: pyruvate ratio, inducing a pro-inflammatory cytokine response rendering the patient at increased risk of systemic inflammatory response syndrome and multiorgan failure [43].

Despite the known risks of malnutrition, there are insufficient data from clinical trials to guide nutritional therapy. Most suggestions are

extrapolated from animal and physiological data. ESPEN guidelines recommend the measuring energy expenditure for individual patients via indirect calorimetry [44]. Glucose provision is regarded as mandatory, with the administration of lipid preferred in the case of insulin resistance. Amino acid administration is not considered mandatory in the hyperacute phase but should be used in the acute and subacute phase.

### 17.4.6 Coma After Cardiac Arrest

While there is sparse data on the metabolic response to cardiac arrest, most studies have focused on the metabolic implications during therapeutic hypothermia. While active cooling reduces cerebral metabolic demand, a small series of patients receiving hypothermia demonstrated a higher than expected resting energy expenditure. This expenditure rose proportionally with body temperature during active rewarming. There was also a significant association between energy deficit and ICU length of stay in patients with a good neurological outcome, indicating that these patients may have been malnourished [45]. Despite concern for decreased gastric emptying and high gastric residuals, enteral feedings appear to be safe. A small observational study of patients undergoing therapeutic hypothermia for cardiac arrest showed that 72% of enteral feeds are tolerated during cooling [46]. Another small cohort of ICH patients undergoing active hypothermia showed no GI-related adverse effects to enteral feeds [47].

## 17.5 Conclusion

The nutritional considerations in the neurocritical care population are complex. Despite the various pathophysiological mechanisms of neurocritical care conditions, early and adequate nutrition remains an imperative component of care. Adequate nutrition appears to blunt the secondary complications that can occur with under- or overfeeding, and accurate measurement of patients' metabolic demands remains important. Overall, acute neurological injury creates a distinctive challenge for nutritional therapy and compels a careful assessment of the patient's underlying mechanism of injury and comorbidity.

**Key Points**

- Critical illness is associated with a catabolic state which is frequently associated with secondary complications such as increased infection rates, multiple organ dysfunction, prolonged intubation, further morbidity, and worsened mortality.
- The appropriate dose of nutrition should be administered early in the hospital course once hemodynamic stability is established.
- Improper administration can lead to overfeeding, underfeeding, or poor glycemic control.
- Adequate nutrition appears to blunt the secondary complications that can occur with under- or overfeeding, and accurate measurement of patients' metabolic demands remains important.

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# 18 Nursing Care in the Neurointensive Care Unit

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## 18.1 Introduction

Neurocritical care specialty units (neurointensive care units) have emerged as a distinct medical subspecialty and discipline, integrating complex critical care medicine, neurosurgical care, and neurological care with the goal of interdisciplinary and multidisciplinary care of complex life-threatening central and peripheral nervous system disorders. As the field continues to evolve, a multidisciplinary team approach and management is paramount for the key role patient care optimization. In turn, a well-run neurocritical care unit is ideally staffed by trained neurointensivist physicians, which may hail from different disciplines such as neurology, neurosurgery anesthesia, or critical care medicine. Tantamount to this, nurse staff trained in critical care with a major emphasis on neurological and neurosurgical patients care management is essential for a safe and optimal care of such patients [1–4].

## 18.2 Multidisciplinary Care

Neurointensivists can only function as a multidisciplinary care practice. The intensivist integrates contributions from respiratory therapists, pharmacists, nursing staff, physical and occupational therapist, and other allied team member. The end goal is delivery of quality- and evidence-based clinical care, in an integrated multidisciplinary and effective care setting [2–7]. The organizational structure of the nursing staff in a neurocritical care vision should be in alignment with the specific vision that drives the neurointensive care unit. A well-organized nursing staff in a neurocritical care ICU will drive the ICU to quality, cost-efficient, and competent patient care [1–4]. The ideal factors that should drive such force should include:

## 18.3 Clinical Standards

Providing and establishing set clinical standards is essential to the success of the neurointensive care unit. Such aspect should be the backbone standard that dictates nursing staffing of the ICU. The goal is to establish safe acceptable standards of patients' care, regardless of their acuity, and during specific nursing shift. In addition, nursing should be able to exert some degree of autonomy with the goal to act semi-independently to initiate appropriate treatment and interventions based on a dictated plan of care during earlier interdisciplinary and multidisciplinary rounds. These standards may be set around a specific disease process (i.e., guidelines to treat stroke, traumatic brain injury, intracerebral hemorrhage)

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which are then tailored according to the specific patient's clinical scenario. In addition such clinical standards must identify clearly what are the set expectation of the nurse in terms of assessment, intervention, documentation, and management. Examples include protocols, standardized plans of care, and orders. Nonetheless, in order to have team members communicate at the same level of "language," it is important to have clinical team leaders partake in the development of such standard and review/revise them at least annually with feedback incorporated from all team members such as physicians, mid-level providers, and nursing staff.

## 18.4 Operational Standard

In addition to clinical standard, it is important to establish operational standards in order to effectively address operational or administrative issues and establish a clear set of communication system. None withstanding, such operational standards must be in alignment to a productive task force in fostering adequate teamwork. Nurses need to clearly understand who to notify when, let's say a clinical scenario escalates or warrant additional resource or if a specific clinical issue arises. The ultimate focus is the provision of safe and effective patient care, while providing adequate nursing staff resource and ensuring "job satisfaction." Once an algorithm is set in place, nursing must be able to effectively determine how to escalate notification within the chain of command. Commonly used system includes nurse-manager and nursing staff communication at least twice daily (i.e., during morning handoffs and midafternoon or end of shift hands-off) [1–3].

## 18.5 Adequate Staffing

Within the neurological ICU, and the ever-evolving complexity of patient care, it is imperative that adequate staffing, particularly during periods of high-acuity scenarios, is set in motion. It is essential that hospital administrations strive to hire skilled neurocritical care nursing staff and ensure realistic retention strategies. One method is to set compensation standards among different intensive care units, with a comparable compensation plan commensurate to the intensity of patient's care or load. Additionally, an on-call system when nursing staff may be compensated by payback or back-roll strategy of additional overtime work (i.e., such as after-hours providing emotional support to family members, documentation, nurse to nurse support or backup, etc.) is a cost-effective way of assuring retention in the long run. In addition, identifying a pool of nursing staff that are available for backup when census or patients acuity is high, or mobilize additional nursing by calling them on a rotational basis, is another effective strategy employed by large neurointensive care unit [5–8].

## 18.6 Nursing Leadership

A well functional neurocritical care ICU should identify a nurse or nurses leader (or a team of "nursing leadership") that has the primary responsibility of ensuring the smooth operational standard of neurointensive care nurse staffing. Typically, a senior nursing staff with additional administrative duties is identified, but a rotational basis where a senior nursing staff rotate throughout the unit is another model that can be employed. The latter model ensures the diversity in the leadership skill set and open doors to improvement. The role of such nurse leader, in additional to their typical patients' care duty, should include monitoring the work environment, ensuring adequate teamwork relationship among the multidisciplinary care, addressing issues early on, and providing adequate effective support system [1–3, 6, 7, 9–12].

## 18.7 Nursing Qualification

Ideally, a neurocritical care ICU nurse should be qualified in the management of critically ill patients, with additional skills, exposure, and training in the management of those patients with

acute neurological or neurosurgical diseases. Nursing staff in the neurointensive care units should possess the clinical knowledge and skills for the initial and ongoing assessment, monitoring, management, and stabilization of such patients. While some key and standard critical care skill set may be universal among the different critical care subspecialties, there are nonetheless specific skill set that are unique to the neurointensive care unit that cannot be substituted. Provisions of neurological examination as well as recognition of abnormal neurological exam findings, interpretation of baseline intracranial pressure wave monitors, correct placement of intracranial drains and pressure bags/lines, basic understanding of ventilator principle, understanding of hemodynamic monitors and vasopressor therapy, and interpretation of vital signs and multimodal brain monitors are just some of the key skills for effective and safe patient care in the ICU [8–12]. However, there are no set standard guidelines that establish provisions of neurocritical care skills for nursing staffing neurointensive care units, and often, each neurointensive care unit develops its own set of protocol to safely and effectively address such shortcoming.

## 18.8 Decision-Making System

The likelihood of change or emergence of new neurological problems in patients admitted to neurointensive care unit is ever-present. In turn, it is imperative in order to determine the proportionality of care and minimizing secondary insults that set established decision-making systems are set in motion. The aim of this approach is inevitable, with the aim of minimizing secondary insults. Such approach requires tactful clinical judgment that take into account not only the primary neurological illness but the interplay of secondary systems, along pre-existing patient's wishes and disease-specific characteristics. In cases where unexpected or less than favorable outcomes occur, it is important to establish whether merely it was "a natural course of a disease" or opportunities for improvement could be identified. Retrospective multidisciplinary care review to establish what may have been done differently is therefore imperative. If a specific issue is identified, then a formal mechanism of follow-up must ensue. Nonetheless, a system of transparency where no fear of retaliation should be set in motion and should be the initial step in identifying areas of improvement.

## 18.9 Multidisciplinary Care Approach

The role of the neurocritical care ICU nurse in the multidisciplinary patients care approach in the neurointensive care unit is fundamental. Because the nurse in the neurointensive care unit spends most of their time directly at bedside with the patient compared to any other team members, his or her contribution during multidisciplinary care rounds is therefore essential for the safe and effective delivery of care. There is mutual synergistic benefit of nursing contribution during multidisciplinary rounds: The nurse benefits from participating in open dialogues, improves their knowledge skill base, and identifies core clinical issues that need to be monitored during a specific shift, while at the same time, the clinical team learn new issues that may have been missed or overlooked. In most academic centers in the United States of America, nursing staff participate daily during morning round whether formally or informally. This may include a brief overview of overnight or most recent clinical events, to direct contribution of organ-based or system-approach identification of patient's care issues [1–3, 5, 6, 10–12].

## 18.10 Delivery of Effective Care

There are several models of effective nursing-patient care delivery models in the neurointensive care units. However, whether any specific model is superior to another is a matter of open debate. In essence, effective patient's care delivery must be consistent, accountable, and effective. An effective method of establishing such system is though providing continued support to

the nursing staff, through both early identification of clinical and nonclinical issues, providing consistent continuity of care (i.e., a nurse may be reassigned to the same patient in subsequent shifts), and capitalizing on the nurse's individual talents. In addition, continued mentorship through the pairing of junior-senior nursing helps foster continued learning experience [1–3].

## 18.11 Professional Development

In a successful neurointensive care unit, it is important to emphasize and capitalize on individual nursing's talent as previously mentioned. This is shown to help improve retention, job satisfaction, and effective patient's care. Ongoing learning opportunities, participation in learning conference, national meetings, CME (continued medical education) lectures, and clinical workshop are just some of the potentially employed strategies. Leadership skills should be fostered, and involvement of select nurses with hospital administrative duties capitalizes the above point. Nursing talent must be nurtured to support individual ambitions, maximize interpersonal relationship, and support constructive environment in the neurointensive care unit. The end goal is a cohesive structure to the neurointensive care unit.

## 18.12 Interpersonal Relationship

Interpersonal relationship is a key element in fostering open and transparent professional relationship in the complex setting of neurointensive care units. Nurses should be educated on how to provide effective feedback among peers and how to communicate effectively and neutrally within the upper chain of commands. Conflict resolution workshops should be encouraged, as it is unrealistic to expect that no difference of opinions or no occasional tense moments will ever arise in such complex and intense care setting. Mechanisms of fostering positive interpersonal professional relationship may include periodically establishing workshops on conflict resolution, accepting feedback and delivering constructive criticism, and establishing peer-review committees. Essential to this is the role of nurse managers. Nurse managers should always be alert for opportunities for improvement, as well as educate and empower nursing staff.

## 18.13 Quality Improvement

A successful model approach of effective care delivery in the complex setting of a neuroICU care unit should identify benchmarks that set the bar of what constitute a successful neurointensive care. While subjective factors such as happiness at work, degree of job satisfaction, or even staff retention are all one positive aspect, perhaps the ultimatum of quality success of effective and successful nursing care is through the identification of quality assurance projects that reflect effective and safe care. For example, identification of fall rates, patient's satisfaction, effective communication with family, or catheter-related infection are some of the quality assurance aspects that may be benchmarked. Such a quality assurance or improvement projects ensure that nursing staff are an integral part of the larger complex healthcare system in which they are the key and critical care element. At the same time, this ensures their understanding of the process and improve practice parameters. It is to no surprise that certain large academic centers in the United States of America will require nursing staff in certain neurointensive care unit to at least partake in one quality improvement project per year [1–6, 9–12].

## 18.14 Summary

In essence, the most valuable commodity in a neurointensive care unit is in its nursing staff, each and every individual striving to the same shared mission which connects its different team members. Beyond merely the care of critically ill neurological and neurosurgical patients, we must aim at supporting each person's individuality as we are all driven by a common vision that sets the driving force behind the foundation of an effective neurocritical care intensive care model.

**Key Points**

- Become familiar with the systems of care in the neurointensive care unit
- Acknowledge the clinical standards and operational standards of the neurointensive care unit
- Recognize the different decision-making systems in the neurointensive care unit
- Acknowledge the shortcomings and potential issues as well as conflict resolution in the neurointensive care unit

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# 19 Physiotherapeutic Management of Critically Ill Neurological Patients

Rajeev Aggarwal and Vandana Dua

## 19.1 Introduction

Critically ill patients in an intensive care unit (ICU) are most vulnerable and challenging cases to be dealt with. The rate of mortality and morbidity is disproportionately high in these patients. The mainstay of management of critically ill patients is to treat the primary problem and prevent any secondary complication facilitating an early discharge from ICU. Prolonged stay in ICU is associated with neuromuscular weakness, anxiety, depression and deterioration in quality of life apart from sequel of primary illness responsible for ICU admission.

Immobility and associated disability in an acquired neurological injury present a significant health-care and social problem globally. This along with a decrease in mortality due to technological advancements in critical care medicine has led to an enormous increase in the scope of rehabilitative practices to promote functional recovery and societal participation of ICU survivors. For an effective rehabilitation, it is essential to customize the therapy to the individual needs of the patients and must be initiated as soon as possible after the initial injury. Physiotherapeutic management in ICUs vary significantly amongst units owing to factors such as the country in which the ICU is located, local clinical guidelines, availability of specialist physiotherapists and reimbursement policy [1]. The goals of physiotherapy in ICU are summarized in Table 19.1. The physiotherapy in neurological patients is focused on encashing the neuroplasticity of central nervous system before it leads to plastic changes in musculoskeletal system in terms of contractures or deformity. Available literature regarding evidence of physiotherapy in critically ill patients has demonstrated its safety and efficacy [2–4], but their

**Table 19.1** Goals of physiotherapy in a neurological ICU

| |
|---|
| Prevention and management of pooling of tracheobronchial secretions |
| Prevention and management of atelectasis |
| Optimization of global and regional ventilation |
| Optimization of ventilation perfusion matching |
| Optimization of work of breathing |
| Reduction of airway resistance |
| Prevention of postoperative respiratory complications |
| Prevention or postpone the need for tracheal intubation |
| Facilitation of weaning from mechanical ventilator |
| Early mobilization |
| Facilitating neural recovery |
| Prevention and management of abnormal muscle tone |
| Prevention and management of tightness, contractures and deformities |
| Promoting functional improvement |
| Improving sensorium and cognition |
| Management of musculoskeletal and neuropathic pain |
| Prophylaxis and management of decubitus ulcer |
| Prophylaxis of venous thromboembolism |

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referral for physiotherapy is frequently delayed. It may be attributed to lack of awareness about its efficacy among health professionals, lack of rigorously performed research in this area owing to non-standardized terminology and techniques, poorly designed studies, inadequate outcome measures and follow-up.

## 19.2 Respiratory Physiotherapy

The respiratory system poses a great challenge in management whenever it gets involved. The impact of neurological disorders on respiratory system depends upon location, extent, severity and progression of the disorder. Neurological disorders can affect the ventilation by altering the rate, depth and pattern of breathing. Aspiration pneumonitis, ventilator-acquired pneumonia, adult respiratory distress syndrome, sepsis and cardiac arrest are amongst the commonest secondary causes of death in patients with neurological disorders. Aspiration pneumonitis, ventilator-acquired pneumonia, adult respiratory distress syndrome, sepsis and cardiac arrest are amongst the commonest secondary causes of death in patients with neurological disorders. Intracranial disorders like brain trauma, infections and tumours may lead to altered sensorium, obtundation, delirium, seizures, raised intracranial pressure (ICP) and decreased cerebral perfusion pressure (CPP) which all may alter the respiratory drive. Hypoventilation due to anaesthesia and/or pathology, physical compression of the lung parenchyma by virtue of positioning, pain, splinting, external devices, obstruction of airways or respiratory muscle weakness may lead to atelectasis of varying severity [5]. Extent of atelectasis may be patchy, segmental, lobar or whole lung. Acute lobar atelectasis may develop due to clogging of lobar bronchus by mucus plug, endo-bronchial intubation or aspiration of any foreign body. Smaller atelectasis, also known as micro-atelectasis, may not be radiologically evident but may be associated with lower $PaO_2$ and laboured breathing. Involvement of lower cranial nerves can compromise maintenance of airways and gag reflex putting the patient at risk for aspiration. Extracranial disorders involving spinal cord or peripheral nerves innervating respiratory muscles may lead to ventilatory failure. Kyphoscoliosis as in certain neuromuscular disorders like Friedreich's ataxia, poliomyelitis, spina bifida and some muscular dystrophies can also compromise the respiratory functions. Patients in recumbent position have lower functional residual capacity (FRC) and higher closing volume putting the patient in mechanically disadvantageous position forcing them to breath at low lung volumes [6]. Breathing at low lung volume requires higher work of breathing predisposing them to rapid shallow breathing pattern. In addition, the presence of artificial airways, dehydration, impaired cough manoeuvre and weakness of respiratory muscles especially in neuromuscular disorders can compromise the mechanism of airway clearance. All these factors together may lead to atelectasis, retention of tracheobronchial secretions, increased work of breathing, pneumonitis or even pneumonia. Respiratory abnormalities may be quick to appear and demand an emergent management; therefore periodic assessment and monitoring of respiratory system are essential in a neuro-critical care setup.

### 19.2.1 Assessment

Physiotherapeutic assessment is based on review of file notes, vital parameters, level of consciousness, orientation and cognitive functions, general condition of the patient, interpretation of ongoing monitoring, renal and liver function, electrolyte level, haemoglobin level, blood cell counts, bleeding profile, microbiology reports, lung functions, mode of ventilation, ventilator settings, oxygen requirement, chest radiographs, arterial blood gas analysis, arterial oxygen saturation, respiratory reserve, mode and constituents of nutrition, range of motion and alignment of joints. Level of consciousness is usually assessed by Glasgow Coma Scale and Ranchos Los Amigos Scale. General condition of the patient includes body type, positioning in bed, drainage tubes (extraventricular drainage (EVD), pleural drainage and surgical drain), infusion lines, catheters, skull fixators or traction, cyanosis, pallor, icterus, oedema, clubbing, pressure ulcers and skin condition. Monitoring of ICP, mean arterial

pressure (MAP) and CPP deserves special attention in selected patients. Renal and liver function may affect respiratory functions by influencing proteins, fluid and electrolyte balance. Any prolonged exposure to steroids and immunosuppressants warrants very careful handling of patients. Respiratory function depends on patency of airways, efficacy of cough reflex, strength of respiratory muscles, pattern of ventilation, airway resistance and lung compliance. A thorough clinical examination of chest by auscultation helps in delineating atelectasis or accumulation of tracheobronchial secretions. Mechanically ventilated patients are often sedated and medically unstable and require extensive haemodynamic monitoring. Airway pressure, lung volumes and oxygenation status deserve attention in these patients. One of the early signs of respiratory muscle involvement in neuromuscular disorders is presented by nocturnal desaturation and hypercapnia that correlates with diaphragmatic weakness [7]. Respiratory reserve may be objectively assessed by ratio of partial pressure of oxygen in arterial blood ($PaO_2$) to fraction of oxygen in inspired air ($FiO_2$) [4].

Respiratory reserve ($PaO_2/FiO_2$)

- Normal value = 100 mmHg/0.21 = 475.
- >300 is indicative of sufficient respiratory reserve.
- 200–300 indicates marginal respiratory reserve.
- <200 indicates poor respiratory reserve for early mobilization [4].

### 19.2.2 Management

Preoperative physiotherapeutic assessment, education and management of elective surgery patients are beneficial in postoperative risk reduction. Six to eight weeks of smoking cessation in the preoperative period was associated with reduced wound-related complications (5% vs 31%), cardiovascular complications (0% vs 10%) and median length of stay (11 days vs 13 days) compared to control group [8]. Lung expansion exercises such as incentive spirometry, deep breathing exercises and forced expiratory techniques (FET) such as huffing and coughing are best taught in the preoperative period. It may be difficult to train these manoeuvres in a postoperative patient who might be sedated or in pain [9]. Inspiratory muscle training, aerobic training and breathing exercises in the preoperative period were found to be associated with lower incidence of postoperative atelectasis and pneumonia in various surgical patients [9]. Preoperatively patients should be educated about the role of postoperative postures in bed, artificial airways, mechanical ventilation, airway clearance techniques, tracheobronchial suctioning and early mobility to gain confidence and co-operation.

Postoperative pulmonary complications can be significantly reduced by employing a multidisciplinary team approach. *ICOUGH* program inclusive of *i*ncentive spirometry, *c*oughing and deep breathing exercises, *o*ral care (brushing teeth and using mouth wash twice daily), *u*nderstanding (patient and family education), *g*etting out of the bed frequently (at least 3 times daily) and *h*ead of bed elevation (more than 30°) was developed and implemented in the National Surgical Quality Improvement Program in the USA for all general and vascular surgical patients [10]. Implementation of ICOUGH program led to reduction of postoperative pneumonia from 2.6% to 1.6% and unplanned intubation from 2% to 1.2% [10]. Routine chest physiotherapy including breathing exercises, incentive spirometry and airway clearance techniques is not indicated in postoperative mechanically ventilated patients where bronchial hygiene is not compromised [11–13].

### 19.2.3 Lung Expansion Therapy

Therapeutic body positioning and mobilization recruit collapsed alveoli by adjusting ventilation, perfusion and ventilation-perfusion matching [3]. Therapeutic body positions are derived from West's lung zones model based on effect of gravity on ventilation and perfusion in lungs (Fig. 19.1). A lung here is compared with water-filled sponge where upper zone of the sponge will retain more air while lower zone will retain more water. In a similar fashion, the upper zone (zone 1) of the lungs has lower intra-pleural pressure and so will

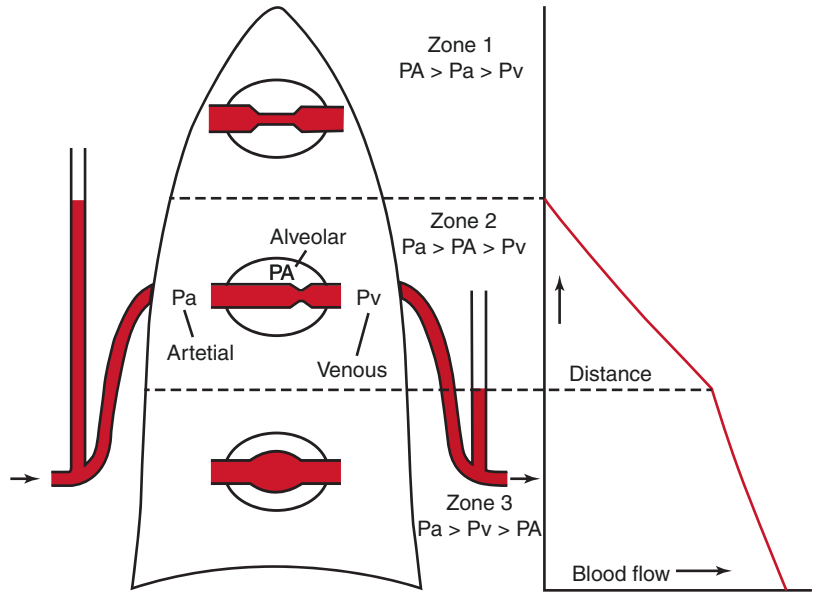


**Fig. 19.1** West lung model. *Pa* arterial pressure, *PA* alveolar pressure, *Pv* venous pressure. Used with permission from: Rozet I, Vavilala MS. Risks and benefits of patient positioning during neurosurgical care. Anesthesiol Clin. 2007 Sep;25(3):631–53

have more air at FRC level, while the lower zone (zone 3) has lesser air in the alveoli by virtue of gravity. In order to expand an atelectatic area, therapeutic positioning must aim to make it as zone 1. The position once adopted must be monitored for its effects on oxygenation and other relevant parameters like ICP, MAP and CPP [14]. Every beneficial position when assumed for a long period becomes detrimental due to hydrostatic, gravitational and compression forces acting on the lungs, heart, brain tissues, blood and other organ systems. Hence, the duration of any therapeutic position should be primarily response-dependent rather than time-dependent [6].

Incentive spirometry, manual or ventilator-assisted hyperinflation and non-invasive ventilation [3] also help in re-expansion of collapsed areas. Inspiratory pause or sustained inspiration at the end of inspiration helps in expansion of collapsed alveoli through collateral inter-alveolar, inter-bronchial and inter-segmental connections. Analgesics and transcutaneous electrical nerve stimulation in painful conditions, musculoskeletal interventions for chest wall abnormalities and clearing the airways for any mucus plug or foreign body help in re-expansion of atelectatic segments. In adult respiratory distress syndrome, invasive mechanical ventilation and prone position help in re-expansion and are likely to reduce mortality [15].

### 19.2.4 Bronchial Hygiene Therapy

Neurological patients have preponderance for retention of tracheobronchial secretions due to multiple reasons. The airway clearance depends on efficient mucociliary escalator, adequate inspiratory volume, expiratory volume and expiratory flow rate, optimal viscosity of secretions and synchronized mechanics of the lungs and chest wall [12, 13]. Normal mucociliary clearance should be facilitated by minimizing the sedation and paralytic agent, avoidance of artificial airways, heated humidification of inspired air (relative humidity of 100% at 34–36 °C) in patients on supplemental oxygen and frequent change of body positioning.

Inadequate inspiratory volume compromises the forced expiration, a prerequisite for clearing the secretions. Patients with inadequate inspiratory volume should be managed with lung expansion techniques [3] to facilitate forced expiration. Patients with inadequate expiratory flow should be managed with forward bend positioning, assisted coughing manoeuvres and forced expiration manually or mechanically by means of exsufflator [3]. Thick and sticky secretions need to be mobilized by using oscillatory techniques where mechanical energy is transferred to airways to increase kinetic energy

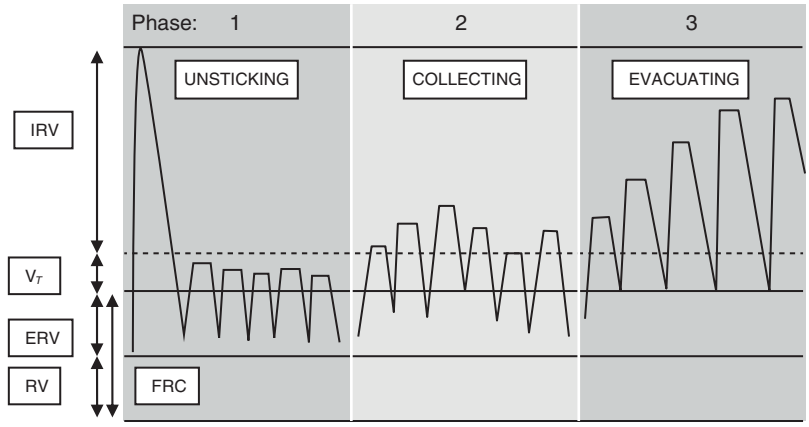


**Fig. 19.2** Autogenic drainage. Phase1, unsticking phase; phase 2, collecting phase; phase 3, evacuating phase. *IRV* inspiratory reserve volume, *ERV* expiratory reserve volume, *RV* residual volume, $V_T$ tidal volume, *FRC* functional residual capacity. Used with permission from: McIlwaine M. Chest physical therapy, breathing techniques and exercise in children with CF. Paediatr Respir Rev. 2007 Mar;8(1):8–16

of the secretions. Manual techniques (percussion, vibration, rib cage compression), mechanical vibrator, high-frequency chest wall oscillator and oscillatory positive expiratory pressure devices like Acapella® and Flutter® in postural drainage position may be employed to loosen the secretions [13]. Postural drainage positions are based on the concept of keeping the affected broncho-pulmonary segment uppermost. For instance, to drain basal broncho-pulmonary segments of lower lobes, trendelenburg position is used. Tipping the neurosurgical patient is often restricted due to various drains, lines, haemodynamic instability and monitoring so these patients are put in modified postural drainage position where patient's head end is not tilted downward. Manual chest physiotherapy techniques are found to be safe in neurological patients and do not increase ICP [16].

Selection of technique for individual patient is of paramount importance. Conscious patients with sufficient ventilatory force should be able to clear their secretions by using deep breathing and forced expiratory techniques like huffing and coughing. Huffing is differentiated from coughing by open glottis and generating lower peak expiratory pressure. Self-assisted forced expiratory techniques like active cycle of breathing technique (ACBT) and autogenic drainage (AD) should be employed whenever feasible to gain patient cooperation, acceptance and compliance which in turn magnify its effectiveness in the long term. ACBT consists of breathing control (relaxed diaphragmatic breathing), thoracic expansion exercises (deep breathing exercise) and forced expiratory techniques (huffing and coughing) in a cyclical manner. The number of cycles and duration of each phase may vary according to patient tolerance and requirement [6]. AD consists of three phases, viz., unsticking phase, collecting phase and evacuating phase (Fig. 19.2). In unsticking phase, patient breathes at low lung volume (at FRC). Collecting phase consists of breathing at mid lung volume (mainly in range of tidal volume and expiratory reserve volume), while evacuating phase comprises of breathing at high lung volume (approaching inspiratory reserve volume) [6]. AD requires good strength and control of expiratory muscles as it is mainly focused on producing high expiratory flow rate to mobilize the secretions.

Patients with poor ventilatory muscle function, e.g. in neuromuscular disorders and disoriented or unconscious patients, require manual techniques to mobilize the secretions. Tracheobronchial suctioning is required for intubated patients and in those who are unable to expectorate the secretions. Intubated patients

with inadequate ventilatory muscle function may require ventilator or manual hyperinflation (MHI) to expand atelectatic area and facilitate airway clearance [3]. MHI consists of slow deep inspiration (usually 1.5 times of normal tidal volume) with manual resuscitator bag, an inspiratory hold (of 1–2 s) and then a quick release of the bag to augment expiratory flow and mimic a forced expiration. A safety exit valve in resuscitator bag set at 35–40 mmHg pressure prevents accidental barotraumas [3]. MHI should be used with caution in neurosurgical patients as it may increase ICP by compromising venous return from cranial vessels. It also reduces venous return from peripheries affecting the cardiac output. Patients with compromised CPP or hypotension are not suitable candidates for MHI.

### 19.2.5 Optimization of Work of Breathing

Normal work of breathing constitutes about 5% of the total body oxygen consumption [6]. Decreased compliance of the lung and chest wall, increased airway resistance and increased respiratory drive or minute ventilation increase the mechanical work load on inspiratory muscles [17]. It is frequently an issue in patients with neuromuscular weakness as it reduces the work capacity of ventilatory muscles. An imbalance between workload and work capacity can eventually lead to respiratory failure. Lung compliance can be improved by re-expansion of atelectatic area and resolution of consolidation of lung tissues. The reduction in airway resistance can also be achieved by clearance of tracheobronchial secretions, increasing the diameter of airways, i.e. bronchodilation and/or reducing the length of endotracheal tube and ventilator tubing. Patient education and psychological and emotional support are instrumental in reducing the ventilatory muscle load in conscious patients. The work capacity of inspiratory muscles may be increased by inspiratory muscle training (IMT). Inspiratory muscles can be trained as skeletal muscles for strength and endurance with similar principles of overload and specificity. The training-related improvements in inspiratory muscle are more pronounced in less severely affected patients by their disease. In hypercapnic patients there is little change in muscle performance with training as probably they are already breathing at their peak capacity [18]. IMT can be provided by inspiratory threshold resistors or isocapnic hyperpnea. Threshold resistor provides a preset inspiratory load to the patient for breathing. In isocapnic hyperpnea, patient breathes at higher rate and volume using rebreathing bag to maintain isocapnic state. The signs of fatigue should be carefully assessed while prescribing or implementing IMT.

### 19.2.6 Facilitation of Weaning

An early discharge from mechanical ventilator remains at highest priority in any critical care unit as weaning failure and re-intubation are associated with prolonged ICU length of stay and poor functional outcomes [19, 20]. Impaired protective airway reflexes, absence of spontaneous cough, presence of copious secretions, colonization with multidrug-resistant bacteria, neuromuscular weakness, deteriorating consciousness, deranged respiratory mechanics and psychological and emotional aspects are amongst common causes for extubation failure [20]. The extubation in these patients should be initiated only after initial cause for mechanical ventilation is resolved and risk and benefit have been carefully assessed for continuing the ventilatory support [21].

Therapeutic body positioning, airway clearance techniques, strategies to reduce ventilatory load, strengthening of ventilatory and peripheral muscles, and pain management are the mainstay of physiotherapy in facilitating the weaning process. Patients breathing at inspiratory effort level similar to healthy subjects at rest might accelerate liberation from ventilation [22]. Inspiratory muscle training improves strength and endurance of inspiratory muscles in mechanically ventilated patients, but currently there is not enough literature to support weaning success with inspiratory muscle training [23].

## 19.3 Early Mobility

Generalized muscle weakness due to critical illness that can't be explained due to any cause prior to ICU admission is termed as ICU-acquired weakness. According to a systematic review, it is reported to occur in 40% of ICU patients requiring more than a week of mechanical ventilation [24]. The ICU-acquired weakness is commonly associated with multiple organ failure, sepsis, prolonged mechanical ventilation, hyperglycaemia, and use of various pharmacological agents like neuromuscular blocking agents and glucocorticoids [25].

The nomenclature and classification of ICU-acquired weakness lack consensus. Steven et al. have classified the ICU-acquired weakness using the electrophysiological, histological and clinical evidence [26]. The evidence of an axonal polyneuropathy is termed as critical illness polyneuropathy (CIP) while that of myopathy as critical illness myopathy (CIM). Patients who have coexisting findings of both are classified as critical illness neuromyopathy (CINM).

Mobilization of critically ill patients is frequently delayed [3]. Removing gravitational stress from the body as in recumbent position shifts the intravascular fluid to thoracic cavity from extremities which cannot be combated by any bed exercise unless an upright position is assumed. The deleterious effects of immobility on multiple organ systems are summarized in Table 19.2.

**Table 19.2** Adverse effects of immobility on various organ systems in critically ill patients

| | |
|---|---|
| Respiratory | Ventilation-perfusion mismatch, atelectasis, ↓maximal inspiratory pressure and forced vital capacity, pneumonia, pulmonary embolism |
| Cardio vascular | ↓Left ventricular stroke volume and cardiac output, orthostatic intolerance, ↓venous compliance, ↓diastolic blood pressure, systolic dysfunction, ↓exercise capacity |
| Haematologic | ↓Blood and interstitial volume, ↓red blood corpuscles, ↑risk of venous thromboembolism |
| Musculoskeletal | Muscle atrophy, ↓strength, endurance and flexibility, tightness, contracture and deformities, change in muscle fibres from type I to II, ↓bone density, pressure ulcers, critical illness myopathy |
| Peripheral nerves | Compression neuropathy, critical illness polyneuropathy |
| Endocrine | ↓Insulin sensitivity, ↓aldosterone and plasma renin activity, ↑atrial natriuretic peptide, ↓endorphin production |
| Metabolic | ↓Protein synthesis, ↑muscle catabolism, ↑urinary excretion of $Na^+$, $K^+$, $Ca^{2+}$, $PO_4^{3-}$ |
| Urinary tract | Urolithiasis, urinary tract infection |
| Skin | Pressure ulcers |
| Gastrointestinal tract | ↓Appetite, constipation |
| Nutritional | Hypermetabolic or hypercatabolic state, malnutrition, cachexia |
| Psychological | Anxiety, agitation, delirium and depression, ↓self-image and ↓stress tolerance |

↓ Decreased; ↑ increased
Compiled from Truong et al [25], Malone et al [27]

Early mobility in critically ill neurological patients is safe, feasible and cost effective [28, 29]. Early mobility is an intervention progressing from head-end elevation, bed mobility, transfer training, out-of-bed activities to ambulation. Passive and active range of motion exercises, strength and endurance training, electrical stimulation, tilt tables, motor imagery, continuous kinetic bed, robotics (Lokomat®) and wheel chair and other mobility aids like walker and quad cane can be used to administer early mobility in ICUs. Type, intensity, frequency and duration of intervention should be gauged as per patients' haemodynamic status and other co-morbid conditions. It has shown to improve muscle strength and physical function and reduce the incidence of pressure ulcers, infections, anxiety and duration of mechanical ventilation [28, 29]. In a recent study on 637 neurological mechanically ventilated patients, early mobilization was found to be associated with reduced ICU length of stay (LOS), hospital LOS, days on ventilator and overall cost of stay by 36%, 33%, 70% and 30%, respectively [28].

The readiness for early mobility in terms of pathology, pain, mode of ventilation, drains and monitoring devices, comprehension, etc. should be assessed objectively before implementing a

structured mobility protocol. Surgical ICU Optimal Mobility Score [30], Perme ICU Mobility Score [31], etc. are validated tools to assess readiness for early mobilization. Adverse events, red flag signs and contraindications of early mobilization reported in trials on non-neurological critical care patients seem relevant in a neurological ICU (NICU) setup as well. The contraindications and termination criteria of early mobility in ICU are compiled in Table 19.3. Safety issues like accidental dislodgement of endotracheal tube, vascular lines, disturbances in monitoring, skin grafts, flaps, raised ICP, caregivers' and/or patients' apprehension, physical constraints, staffing and time constraints and cost factors are common hurdles to delivery of early mobility in ICU [32]. A 4-week prospective audit of 106 ICU patients to explore the barriers to early mobility reported only 1.1% adverse events during mobilization. Potential avoidable factors identified were femoral line, timings, agitation and reduced level of consciousness [33]. Later a trial reported no femoral catheter-related mechanical or thrombotic complications with mobilization [34].

An evidence-based strategy for putting early mobility into practice is referred to as the *ABCDE* bundle: *a*wakening and *b*reathing *c*oordination, *d*elirium monitoring/management and *e*arly exercise/mobility. The ABCDE bundle is a multidisciplinary coordinated effort aimed at reducing sedation, immobility and the management of delirium facilitating the participation of patients in early mobilization [35]. However, sedation in the NICU may be required to reduce cerebral metabolic demand, improve brain tolerance to ischemia and control seizures, temperature and ICP [36]. Also, interrupting sedation in such patients may not ensure cooperation and participation of patient.

### 19.3.1 Stroke

The Australian Stroke Guidelines 2017 recommend that all patients should begin out of bed activities by 24–48 h post-stroke [37, 38]. Baseline stroke severity and type of stroke are to be considered when deciding the duration and frequency of mobilization post-stroke [38]. A unique indication

**Table 19.3** Contraindications and termination criteria for early mobility in ICU

| |
|---|
| Contraindications |
| • Level of consciousness of patient |
| – Richmond agitation sedation scale score: −4, −5, 3, 4 |
| • Recent myocardial ischemia and/or ventricular arrythmias |
| • Heart rate <40 and >130 beats/min |
| • Mean arterial pressure <60 mmHg and >110 mmHg |
| • Intracranial pressure >20 mmHg |
| • Oxygen saturation <90% |
| • Respiratory reserve <200 |
| • Parameters of ventilation |
| – Fractional concentration of inspired oxygen >0.6 |
| – Positive end expiratory pressure > 10 cm $H_2O$ |
| – Partial pressure of arterial carbon dioxide >50 mmHg |
| • Respiratory frequency >40 breath/min |
| • Respiratory distress |
| • Haemoglobin <7 gm/dl |
| • Platelet count <20,000 |
| • High inotrope doses |
| – Dopamine ≥10 mcg/kg/min |
| – Noradrenaline/adrenaline ≥0.1 mcg/kg/min |
| • Temperature > 38.5 °C or < 36 °C |
| • Spinal instability |
| • Active bleeding |
| • Untreated deep venous thrombosis |
| • Medically uncontrolled seizures |
| • Ongoing renal replacement therapy |
| • Ongoing intravenous sedation |
| Relative contraindications: |
| • Patient's unwillingness |
| • Emotional instability |
| • Inadequate safety measures |
| • Fatigue |
| • Disturbance in monitoring |
| • Untractable pain |
| • Orthostatic hypotension |
| • ICP monitoring |
| Termination criteria: |
| • Oxygen desaturation <88% with supplemental oxygen during activity, unless otherwise specified by physician |
| • Hypotension associated with dizziness, fainting and/or diaphoresis |
| • Tachycardia>130 bpm |
| • Change in heart rhythm |
| • Worsening of breathing pattern with an increase in accessory muscle use, paradoxical pattern, nasal flaring or an appearance of facial distress |
| • Extreme fatigue |
| • Severe intolerable dyspnoea with respiratory rate greater than baseline by >20/min |
| • Significant chest pain |
| • Excessive pallor or flushing of skin |
| • Request of patient to stop |

Compiled from Sommers et al. [52], Perme et al. [53] and Hodgeson et al. [44]

of early rehabilitation in stroke is to prevent the learned non-use of the affected side; therefore it is important to mobilize the paralysed side in every possible way.

A randomized controlled trial (AVERT trial) was conducted on 2104 patients with acute stroke over five countries. They reported that the odds of a favourable outcome (modified Rankin Scale score of 0–2) were decreased when mobilization was commenced less than 24 h post-stroke. At the same time, they showed that mobilizing patients within 48 h of stroke is associated with a low risk of death and adverse events. Also, the odds of the favourable outcome were increased when the mobilization sessions were shorter and more frequent [37]. Therefore, it is suggested that early mobilization of stroke patients within 24 h of onset should be approached on individual basis with careful monitoring of haemodynamic and physiologic responses.

An elevated head position, which usually is the first step to early mobility, within the 24 h of onset of an ischemic stroke may reduce cerebral blood flow and hence may reduce cerebral perfusion on the affected hemisphere [39]. The potential long-term effects and clinical significance of improved blood flow reported with flat positioning compared to head-end elevation within the first 24 h post-stroke onset are under investigation in 'the head position in stroke trial' (HeadPoST) [40].

Maintenance of arterial hypertension in acute ischemic stroke is desirable due to its reported potential of improving perfusion to the penumbra. This can be particularly challenging while bringing the patients to upright position. Orthostatic hypotension associated with upright positioning can be combated with the use of low-dose vasopressors in conjunction with serial monitoring of blood pressure (BP) to allow more patients to remain within an appropriate blood pressure range during early mobilization [41]. On the other hand, in case of haemorrhagic stroke, the early management focuses on maintaining systolic blood pressure (SBP) below 140 mmHg [42] so early mobilization should not be initiated until the volume of haemorrhage has stabilized for at least 24 h [36].

Early mobilization is considered safe and feasible in patients who have received recombinant tissue plasminogen activator (rTPA) with close monitoring [37, 43]. The improved perfusion or recanalization after the use of rTPA or mechanical thrombectomy makes the patients as better candidates to participate in early mobilization [36].

### 19.3.2 Subarachnoid Haemorrhage (SAH)

The mobilization in patients with SAH is frequently delayed, but recent recommendations suggest that early mobility is safe for patients even with unclipped aneurysmal haemorrhage [44]. Early mobilization is considered safe for patients with EVD provided it is secured and ICP is below 20 mmHg [45]. The catheter must be clamped before raising the head end to avoid catheter dislodgement and excess drainage of cerebrospinal fluid [45]. Head-end elevation and in-bed activities can begin the first day after aneurysm treatment, and activities out of bed can begin the next day except in poor-grade SAH, i.e. World Federation of Neurological Surgeons (WFNS) scale grade 3, 4 and 5 [46]. Early exercise reduces cerebral vasospasm after aneurysmal subarachnoid haemorrhage [46]. It may be due to aggressive cerebrospinal fluid (CSF) drainage with mobilization leading to less sedimentation of blood products allowing less clot burden and thus less vasospasm [46].

### 19.3.3 Spinal Cord Injury

Early mobility should be initiated as soon as the spine is stabilized in spinal cord injury (SCI) patients [47]. In patients who are unable to do so, techniques like use of mental imagery are utilized to promote motor recovery wherein a patient is made to cognitively rehearse a motor event without any actual movement [48]. A spinal cord-injured patient especially quadriplegic often experiences orthostatic intolerance. In acute SCI, MAP is shown to be positively correlated with neurologic recovery, and hence it is recommended to maintain it more than 85–90 mmHg for the first few days. Pharmacological, i.e. use of vasopressors and restricted use of diuretics, as well as non-pharmacological interventions like use of functional electrical stimulation in lower

limb muscles, abdominal binders and graduated elastic stockings may be utilized to encash the benefits of early rehabilitation in SCI.

### 19.3.4 Traumatic Brain Injury (TBI)

Mobilization in patients with TBI is usually delayed by approximately 1 week compared to other neurological patients [49]. Mobilization is initiated with passive mobility exercise, followed by gradual upright position with tilt table as tolerated by the patients. The altered consciousness, alertness, impaired cognition, associated musculoskeletal and other injuries make it difficult to mobilize such patients. A multicentric observational study to evaluate the effect of early mobility in TBI patients reported improved consciousness and reduced disability [49]. A close monitoring of BP, ICP and neurological presentation is a mandate while attempting early mobilization in patients with TBI due to altered auto regulation of cerebral perfusion.

### 19.3.5 Spinal Surgery

Early mobilization is relatively safe in spinal surgery patients. Out-of-bed activities and ambulation can be safely initiated on the day following discectomy or laminectomy. An early ambulation after spinal surgery reduces postoperative complications and shortens ICU and hospital LOS [50]. A trial on early mobilization after spinal fusion showed that 70% of patients (320/457) successfully ambulated at least 30 feet on the day of surgery which eventually led to their shorter hospital LOS (1.85 days versus 2.79 days) compared to those ambulating less [51].

## 19.4 Management of Muscle Tone and Prevention of Contractures

Tone disturbance in neurological patient results in abnormal posture, joint malalignment, tightness, contracture and deformities that lead to functional impairment. Hypotonicity can be managed by passive range of motion exercises, facilitating muscles by quick stretches, tapping, electrical stimulation, neurodevelopmental facilitatory techniques and promoting weight bearing on affected limb. Therapeutic positioning with pillows, splints, bolsters and shoulder sling are recommended to maintain joint alignment and prevention of development of abnormal tone and deformities [54]. Hypotonic patients with concomitant sensory impairment are at high risk for developing decubitus ulcers. These patients should be frequently assessed for pressure areas. Pneumatic beds, frequent change in body position, maintaining skin hygiene and adequate hydration are key elements for their prevention.

The increased stiffness of a muscle is a combined result of nonneural mechanisms like changes in connective tissue, reduced contractility of muscle fibres and neural mechanism like exaggerated reflexes. The clinical pattern of motor dysfunction, voluntary muscle control and extent of reversible component of muscle stiffness should be assessed in hypertonic patients. Modified Ashworth Scale (MAS) and Modified Tardieu Scale (MTS) are the most commonly used tools to assess muscle tone [55]. MAS measures the level of resistance to passive movement but does not evaluate the effect of its velocity on muscle tone, while MTS takes into account the passive movement at three velocities (low, normal and fast). Antispastic medications given around half an hour before the physiotherapy session appears to be beneficial practically.

The aim of physiotherapy in hypertonicity is to preserve the viscoelasticity of connective tissue to maintain the range of motion and prevent contractures. Management of hypertonicity is done by optimal positioning in antispastic pattern, active and passive range of motion exercises, stretching, neurodevelopmental inhibitory techniques, strengthening of antagonists, functional electrical stimulation and splints [56].

Hypertonic muscle should be kept in a lengthened position to gain range [57]. Prone position puts hip flexors into stretched position and decreases the flexor synergy in upper limbs. Passive movements preceding positioning may

help in gaining mobility and maintaining a better length of muscle. Upright positioning activates antigravity muscles, optimizes musculoskeletal flexibility and reduces the risk of contractures [58]. Tilt table, robotic frame or hydraulic units are utilized in difficult to attain situations. Ankle splints, knee gaiters, knee ankle foot orthosis, etc. are useful adjuncts to modulate hypertonicity by providing prolonged stretch and altered sensory inputs. Prefabricated ankle splints are associated with more skin complications as compared to customized ones [59]. The routine use of resting hand splints is not recommended for hypertonicity [56, 59]. Splints should be prescribed with great caution in patients with lower arousal levels, sensory impairment, concomitant fracture, poor skin integrity, oedema, deep vein thrombosis, acute inflammation, dystonia, hypersensitivity, vascular disorder, incontinence and haemodynamic instability [59].

## 19.5 Coma Arousal Techniques

The altered sensorium of patients in neuro-ICU widely varies ranging from coma and delirium to cognitive impairment. Coma is characterized by severe disruption in arousal and awareness with limited or no response to sensory stimuli. Coma and delirium are independently associated with increased short-term mortality, while cognitive impairment is associated with poor functional outcome and decreased quality of life in critical care survivors [60].

Multisensory modality stimulation, use of assistive technology and augmented communication are used for coma arousal [61, 62]. Multisensory modality stimulation deploys vestibular, proprioceptive and kinaesthetic, auditory, visual, olfactory, gustatory and tactile stimuli to elicit purposeful response in minimally responsive patients. Sensory stimulation is believed to stimulate reticular activating system to increase arousal and attention level that in turn may improve the quantity and quality of motor response towards purposeful activity. It may facilitate the patient to interact with the environment and regain confidence. For coma arousal in patients with traumatic brain injury, right median nerve stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, hyperbaric oxygen therapy and cell transplantation have been used [63]. The role of family members and other caregivers is crucial in coma arousal and cognitive training. Familiarity with likes and dislikes of the patient, emotional attachment and continuous observation of the patients' response facilitate the caregivers to get an early response. Often caregivers are first to notice new response. But one should keep in mind the exceptionally high expectations of the caregivers about the patient's recovery. It is imperative for physiotherapists to liaison between medical practitioners and caregivers by explaining the aims of therapy, potential outcomes and patients' best interests [64].

## 19.6 Prevention of Venous Thromboembolism (VTE)

Venous thromboembolism (VTE) comprised of deep vein thrombosis (DVT) and pulmonary embolism is a common yet preventable cause of morbidity and mortality in an immobile patient. Risk factors for VTE in neurocritical patients are widely reported in literature [65]. Only 30–40% of DVT shows clinical signs and symptoms including warm, tender, swollen calf or positive Homan's sign [65]. Doppler ultrasonography, venogram, D-dimer assay test and impedance plethysmography are warranted in high-risk patients. All high-risk patients should be considered for prophylactic anticoagulants, intermittent pneumatic compression, graduated compression stockings and mobilization of limbs.

Intermittent pneumatic compression (IPC) is designed to improve blood flow by intermittently applying pressure on calf muscles and peripheral veins creating a pumping action by inflating and deflating at regular intervals and creates a pressure gradient of about 15 mmHg. When inflated, it creates 35 mmHg compression at the ankle and 20 mm Hg at the thigh creating a pressure gradient for proximal flow. Graduated compression stockings promote venous blood

flow by applying a distal to proximal pressure gradient of around 10 mmHg (18 mmHg external pressure at ankles and 8 mmHg at thigh [66]). However, CLOTS1 (The Clots in Legs Or sTockings after Stroke) trial found prefabricated compression stockings ineffective in preventing VTE and also lead to skin complications in stroke patients [67]. The success of compression stocking depends on maintaining pressure gradient across the leg so pressure-monitored stockings may be tested in future trials. CLOTS3 trial showed that IPC significantly reduces the risk of DVT. There was an absolute risk reduction of VTE of 3.6% (95% CI 1.4–5.8%) with the utilization of IPC beginning 0–3 days post-stroke [68]. In clinical scenarios wherein anticoagulation cannot be initiated within 24 h like in TBI, post-craniotomy, post-rTPA administration or before securing the ruptured aneurysm, the use of IPC remains the mainstay of DVT prophylaxis. However, it is important to objectively screen the bedridden patients prior to application of IPC to avoid any dislodgement of existing thrombus. Early mobility is the safest prevention yet not achievable at many clinical instances and, hence, wherever possible must be attempted.

Mobilization is safe in patients with acute DVT on anticoagulant therapy provided their therapeutic levels are achieved, i.e. in 24–48 h with the use of unfractionated heparin and 3–5 h in case of low molecular weight heparin [69]. Early weight-bearing exercise is also helpful to prevent or improve the post-thrombotic syndrome which is characterized by leg pain, swelling, rubor and ulcers [70].

**Key Points**

- Routine tracheobronchial suctioning should be avoided.
- ICP <10 mmHg, MAP >80–90 mmHg and CPP >70 mmHg should be maintained. During intervention, ICP should not exceed 20–25 mmHg.
- Neck of the patient should be kept neutral to promote venous return.
- Elevation of the head to 30° promotes venous return from the head and reduces the ICP. It is preferred position in post-operative intracranial surgery patients.
- Upright position is best for cognitive arousal.
- Prone position improves oxygenation in adult respiratory distress syndrome.
- Instruct the patient to avoid any activity that may entail the Valsalva manoeuvre as it may raise the ICP.
- Early mobility in critically ill patients is feasible and safe.
- In craniectomy patients where bone flap has been removed, direct pressure over the brain tissue should be avoided. Protective measures like helmets are advisable in these cases.
- Any CSF leakage from nose, ear or any incision site must be observed carefully and notified to the appropriate authority.
- No movement is advisable in a limb with acute DVT without anticoagulant cover.

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# Palliative Care in Neurological Diseases

20

Shoba Nair

## 20.1 Introduction

Chronic neurological diseases are debilitating and difficult to manage and cause considerable burden to both patients and carers. A spectrum of neurological diseases can be classified as chronic, including diseases such as amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND), Huntington's disease, Parkinson's disease (PD), the associated progressive supranuclear palsy and multiple systems atrophy, and multiple sclerosis (MS). Other common conditions like stroke and epilepsy can also be considered under chronic neurological diseases. Brain injury, brain tumor or metastasis, or progressive multifocal leukoencephalopathy (PML) in people living with HIV or other immunosuppressed conditions can also be brought under this category [1]. Dementia needs special mention here as it is a manifestation of multiple neuropathologic processes, including neurodegenerative diseases and vascular disease. In the pediatric population, this condition can vary from epilepsy to congenital disorders [2].

The Lancet Neurology published recently on global, regional, and national burden of diseases stating that DALYs from all neurological diseases combined was higher than other injuries, cardiovascular diseases, cancer, mental disorders and substance use disorders. Increase in life expectancy and growing population was found to be the reason for this [3, 4].

## 20.2 Is Palliative Care Relevant in Neurology?

There are many challenges that patients with neurological disease face. Long duration of the disease, fluctuating disease course, complex treatments, and neuropsychiatric problems like behavioral and cognitive changes are some of them. The challenges become more toward end of life.

The Center to Advance Palliative Care defines palliative care as "specialized medical care for people with serious illnesses. This type of care is focused on providing patients with relief from the symptoms, pain and stress of a serious illness—whatever the diagnosis. The goal is to improve quality of life for both the patient and the family. Palliative care is provided by a team of doctors, nurses, and other specialists who work with a patient's other doctors to provide optimum care" [5].

Palliative care is not end-of-life care or terminal care. End-of-life care forms a major part of palliative care. Palliative care is often mistaken for terminal or end-of-life care. Palliative care focuses on symptom relief and can be given alongside curative care. Hospice care is for terminal disease and focuses on symptom relief alone [6].

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Symptom management would be beneficial for patients who suffer from distressing symptoms in neurological disease. Palliative care has a major role in this aspect of care [7].

## 20.3 Symptom Burden in Progressive Neurological Diseases

The care of people with long-term neurological conditions is often complex and varied due to the symptoms they face and the rate of progression of the disease.

Studies that looked at symptom burden in neurological diseases like Parkinson's and motor neuron disease have stated that patients suffer from symptoms that range from loss of mobility to anxiety and depression. Every system is affected, and patients can have breathlessness to swallowing problems, diarrhea, and constipation [8–10]. Fatigue is another major symptom that most of these patients exhibit and express [11].

In multiple sclerosis (MS) patients, a 10-year follow-up that looked at pain measures (chronic pain grade or CPG) and quality of life (QoL) found that pain scores had progressed to CPG III or CPG IV and QoL of participants had deteriorated significantly [12]. Even in patients with normal examination findings, nonspecific symptoms such as fatigue and dizziness are common in MS [13]. They often have at least one persistent gastrointestinal symptom like constipation, dysphagia, fecal incontinence, or dyspeptic symptoms [14]. Comorbidity may influence disability outcomes in MS. Presence of psychiatric comorbidities like anxiety and depression may increase the severity of subsequent neurologic disability [15].

Patients with advanced dementia suffer a range of symptoms similar to those with advanced cancer. These symptoms can range from pain and dyspnea to pressure sores, eating problems, and agitation [16]. In a study that looked at symptom burden in a population that met palliative care criteria, tiredness (34.6%), pain (31.1%), weakness (28.8%), and psychological discomfort (low mood 19.9%; anxiety 16.1%) were noted as being prevalent. The study identified that those with non-malignant illnesses, especially dementia, may experience high levels of physical and psychological burden [17].

Given the fact that deaths are increasing from neurological conditions [3], end-of-life care is very much needed for these patients to ensure symptom control and dignity in death. The WHO resolution in 2014 reflects the fact that everyone should have the right to spend their final days, weeks, or years without unnecessary suffering, including people who have severe acute and chronic neurological disorders [18].

## 20.4 Symptom Management in Neurological Diseases

National guidance for long-term neurological conditions in the UK describes about the interface between neurological diagnosis, rehabilitation, and palliative care (Fig. 20.1). Symptom control and rehabilitation form the most important aspect of management in neurological diseases [19]. Cochrane and other systematic reviews have given strong evidence that multidisciplinary rehabilitation can improve the experience of living with long-term neurological conditions [20–22]. These patients have a myriad of symptoms from pain, nausea and vomiting, constipation, breathlessness, anxiety/depression, insomnia, confusion, agitation to fatigue, spasticity, weakness, visual loss, sexual dysfunction, swallowing and speech problems, epileptic seizures, and myoclonus [23, 24].

## 20.5 Symptom Assessment

A thorough symptom assessment is required for managing symptoms ranging from pain to swallowing and speech problems. Each symptom can be assessed with a complete history and examination. Apart from this, there are tools available for comprehensive symptom assessment like

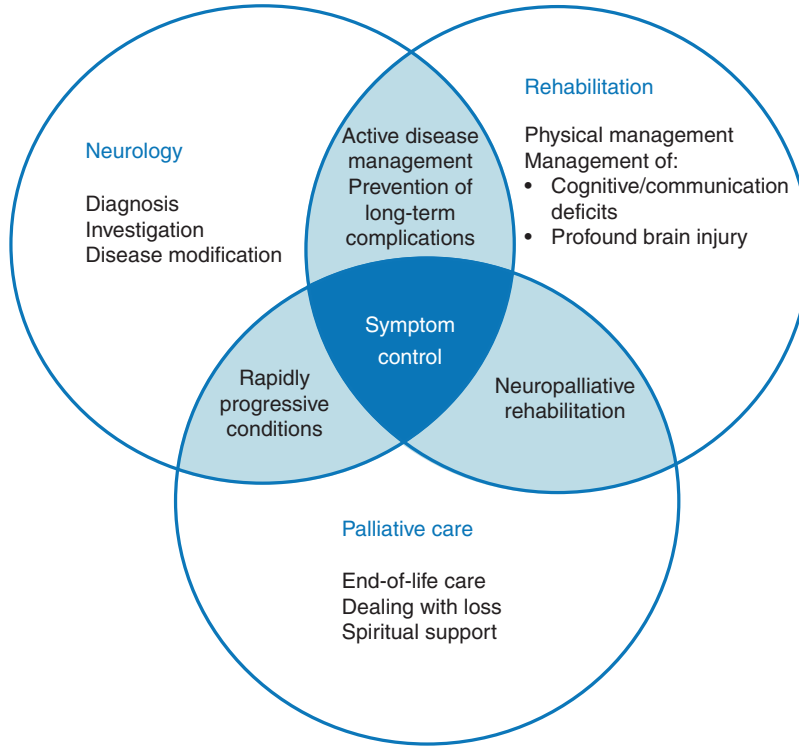


**Fig. 20.1** Palliative care in neurology. Reproduced from Royal College of Physicians, National Council for Palliative Care, British Society of Rehabilitation Medicine. Long-term neurological conditions: management at the interface between neurology, rehabilitation, and palliative care. Concise Guidance to Good Practice series, No 10. London: RCP, 2008. Copyright © 2008 Royal College of Physicians. Reproduced with permission

Edmonton Symptom Assessment Scale (ESAS) or Palliative Care Outcome Scale (POS), which can be used to assess all domains of assessment including physical, psychological, social, and spiritual symptoms. There are many tools that can be used to assess individual symptoms like pain, breathlessness, depression, fatigue, etc.

## 20.5.1 Pain

About 20–40% of patients with neurological diseases have pain [25]. Pain can originate from the central or peripheral nervous system and later becomes centralized through responses of the central nervous system.

### 20.5.1.1 Parkinson's Disease

In Parkinson's disease (PD) alone, 40–60% of patients report pain, and it includes more than one type of pain [26]. Musculoskeletal pain followed by dystonic pain, radicular-neuropathic pain, and central neuropathic pain is commonly found in PD [27]. Patients report decreases in pain level with dopaminergic therapy in this group of patients [28].

### 20.5.1.2 Neuromuscular Diseases

Amyotrophic lateral sclerosis (ALS) has a pain prevalence of 15–20% [29]. Cases of chronic central pain [30] and muscle neuropathic like pain syndrome exist in ALS [31].

### 20.5.1.3 Multiple Sclerosis

Chronic pain is experienced in 40–75% of patients with multiple sclerosis [32]. It has been associated with multiple pain syndromes including extremity pain, trigeminal neuralgia, Lhermitte's sign, painful tonic spasms, back pain, and headache [33].

### 20.5.1.4 Stroke

Stroke produces central pain syndromes which is caused by damage to classical pain sensory system like the spinothalamic tract [34]. Stroke can also produce musculoskeletal pain like

hemiplegic shoulder pain [35]. It begins as early as 2 weeks post-stroke but typically occurs within 2–3 months post-stroke [36].

### 20.5.2 Assessment of Pain

Pain can be classified as adaptive (protecting the body from injury or injury progression) or maladaptive (pain as disease).

Adaptive pain includes nociceptive pain and inflammatory pain. Nociceptive pain involves the normal neural processing of pain that occurs when free nerve endings are activated by tissue damage or inflammation. Neuropathic pain is a prime example of maladaptive pain. The International Association for the Study of Pain (IASP) has defined neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction of the nervous system. These lesions may be in the peripheral or central nervous system, and frequently both systems are involved with chronic neuropathic pain states" [37].

Pain assessment can be challenging because of the subjectivity and multidimensionality of the pain experience. The patient's self-report of pain includes the sensory, emotional, psychological, and cultural components of the pain experience, which cannot be captured on the unidimensional tools. A comprehensive pain assessment includes

1. Pain location and quality
2. Aggravating and alleviating factors
3. Timing and duration
4. Pain relief and functional goals
5. Intensity
6. Effectiveness of any pain treatment
7. Effect of pain on quality of life (QOL) [37]

Assess for the presence of neuropathic pain where pain or discomfort resulting from injury to the peripheral or central nervous system is often described as "burning, stabbing, or shooting." Allodynia or hyperalgesia may be found on examination and suggests the presence of neuropathic pain. Allodynia which is something that is usually not painful is now experienced as painful, and hyperalgesia which is something that is usually a little painful is now experienced as more painful [38].

### 20.5.3 Pain Assessment Tools

Common unidimensional pain intensity tools are Visual Analogue Scale (VAS) where there is a 10 cm line on which patients can mark according to his or her pain intensity and numerical rating scale (NRS) with numbers 0 to 10 on them, where 0 is no pain and 10 is worst possible pain. Multidimensional tools can achieve comprehensive pain assessment, and tools like Brief Pain Inventory and McGill Pain Questionnaire are used mostly for research.

In patients with neurological diseases, assessments can become difficult as they might not be able to communicate appropriately. Behavioral indicators in this group of patients can be grimacing or other indicative facial expressions, bracing, rocking, or changes in activity [39]. Different tools that can be included under this are:

1. The Critical Care Pain Observation Tool (CPOT) that assess pain in critically ill adults. It uses facial expression, body movement, muscle tension, and ventilator compliance or vocalization as pain indicators.
2. The Payen Behavioral Pain Scale, which uses facial expression, upper extremity movement, and ventilator compliance as pain indicators, may also be used for critically ill adults who are intubated.
3. The Pain Assessment in Advanced Dementia (PAINAD) is used to assess pain in patients who have dementia or Alzheimer's disease and are nonverbal. It uses breathing, negative vocalization, facial expression, body language, and consolability as pain measures [40–42].

### 20.5.4 Pain Management

#### 20.5.4.1 Non-pharmacological Measures

Physical therapy (PT) has been known to improve functional ability and reduce pain in patients [43, 44]. Psychophysiological therapy consists of

reassurance, counseling, relaxation therapy, stress management programs, and biofeedback techniques. With these treatment modalities, the frequency and severity of chronic pain may be reduced [45].

#### 20.5.4.2 Pharmacological Measures

**Neuropathic Pain**

- Patients with neuropathic pain should have a trial of a tricyclic antidepressant and/or an anticonvulsant.
  - Amitriptyline 500 mg/kg once at night.
  - Gabapentin starting at 10–15 mg/kg/24 h in divided doses twice (bid) or thrice (tid) a day (max of 60 mg/kg/24 h).
  - Pregabalin starting from 75 mg HS gradually increased to 150 mg or 300 mg or 600 mg in 2–3 divided doses.
- The effectiveness of opioids, especially methadone and to a certain extent tramadol, must not be forgotten when treating neuropathic pain.
- Combination therapy with two or more drugs should be considered in the event of partial response to a single medication.
- Other options such as NMDA receptor antagonists (e.g., ketamine) and antiarrhythmic agents (e.g., lidocaine) are not routinely used as first-line but are tried by specialists [38].

**Nociceptive Pain**

Opioids are recommended by the World Health Organization as part of the analgesic ladder for nociceptive pain in cancer [46]. Opioids also have a place in the management of chronic non-cancer pain in carefully selected patients with regular monitoring and as part of the multimodal therapy [47].

**For Mild Pain**

- Acetaminophen/paracetamol 650 mg–1 G every 4 h or 1 G every 6 h (qid) (daily maximum 4 g/d)
  - Hepatotoxicity can occur at doses higher than this.
  - Acetaminophen/paracetamol can also be combined with NSAIDs.
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Produce an analgesic effect within 1–2 h.
  - Serious side effects can occur with NSAIDS including:
    Gastrointestinal (GI bleed)
    Renal toxicity
    Congestive heart failure
- If GI symptoms occur, the NSAID can be discontinued or the risk of GI toxicity can be reduced by the addition of a protective agent such as an H2 receptor antagonist (e.g., ranitidine, misoprostol, or omeprazole)
- Examples of NSAIDs include:
  - Ibuprofen 200–400 mg tid PO
  - Diclofenac 50 mg tid PO/SC
  - Naproxen 250–500 mg bid PO/PR
  - Ketorolac 10 mg qid PO or 10–30 mg tid SC

**For Moderate Pain**

- A "weak" opioid such as codeine 30–60 mg q4h PO or tramadol 50 mg qid PO can be tried.
- Morphine can also be used at this point and should definitely be used if the pain is not controlled by codeine or other means.
- Can consider adjuvants (see below) along with the opioid.

**For Severe Pain**

- Morphine or another opioid should be started.
- The initial starting dose will depend on the patient's previous exposure to opioids:
  - A dose of morphine 2.5 mg regularly q4h PO (or 1–2 mg SC/IV) and a breakthrough or rescue dose every hour, as required, are suitable for an opioid-naive patient.
  - A dose of morphine 5–10 mg regularly q4h PO (or 2.5–5 mg q4h SC/IV) and a breakthrough or rescue dose every hour, as required, should be used for patients who have already been on codeine/tramadol.
  - It is necessary over the next days to titrate the regular dose to achieve good control.
  - To determine the new dose, add the number of breakthroughs being used in a 24 h period to the regular total daily dose. Then divide by 6 to determine the new q4h dose.

Alternatively, increase the total daily opioid dose by 25–50% depending on the severity of the patient's pain.
  - There is no "upper ceiling" dose to the amount of morphine that can be used. The right dose is the dose that works.
- Alternative routes for morphine include rectal, subcutaneous, buccal, intravenous, and via a gastrostomy tube. The oral route for morphine should be the route of choice in most cases:
  - The PO: SC morphine ratio is 2:1.
  - The PO: IV morphine ratio is 2–3:1.
  - For example, 10 mg oral morphine = 5 mg SC morphine.
- Prevent and treat the common side effects of morphine:
  - Constipation (prescribe laxatives/stool softeners when starting someone on morphine)
  - Nausea (usually only temporary—ensure an antiemetic is available especially if just starting someone on morphine)
  - Excessive sedation or drowsiness (usually only temporary)

#### Adjuvants

- Adjuvants in the context of analgesia are medications or measures that provide relief to the patient in addition to the analgesic medications themselves.
- They are often used in neuropathic pain (e.g., anticonvulsants) or infection (e.g., antibiotics) [38].

### 20.5.5 Dyspnea

Dyspnea in neurological diseases is primarily due to muscle weakness, dystrophy, or deconditioning [48]. These patients experience significant respiratory muscle weakness, which is a common cause of death from respiratory failure, often associated with aspiration and pneumonia [49].

#### 20.5.5.1 Assessment of Dyspnea

Acute respiratory distress can be picked up easily by observing the patient and assessing oxygen saturation. Dyspnea in patients with chronic neurological diseases can be assessed by asking them to lie down flat. If they become dyspneic, it is an important symptom and indicates that diaphragm, which is the main muscle of respiration, is affected [50]. Checking for nocturnal hypoventilation by assessing whether their sleep is disturbed, whether they wake up choking in the night, or whether they feel tired during the day helps in identifying respiratory muscle weakness, early [51]. Dysphagia, dysphonia, drooling, cough after swallowing indicating aspiration, or a weak cough can indicate bulbar palsy or respiratory muscle weakness [49].

Multidimensional tools like chronic respiratory disease questionnaire (CRQ) that assess functionality also or unidimensional tools like the numerical rating scale (NRS) that assess severity can be used in patients with chronic progressive dyspnea.

Investigations like chest radiograph can diagnose a pneumonia, pleural effusion, or pulmonary edema. Arterial blood gas can help to differentiate between Type 1 respiratory failure ($PaO_2 < 11$ kPa, Pa $CO_2$—normal) and Type 2 respiratory failure ($PaO_2 < 11$ kPa, Pa $CO_2 > 6$ kPa). A full blood count can rule out anemia [52, 53].

#### 20.5.5.2 Management of Dyspnea

#### Non-pharmacological Measures

- Breathing training, activity pacing, and energy conservation techniques can be useful. Physiotherapist or an occupational therapist can help patients with these techniques.
- Simple measures such as repositioning, opening a window, or providing a fan and relaxation techniques can be very helpful.
- Ensure patients do not "feel trapped" by being crowded by people and equipment.
- Oxygen may or may not be helpful for dyspnea and is not necessary for all patients. For some patients it may make their feeling of dyspnea worse to have their face covered by an oxygen mask or nasal prongs.
- Fresh air may be as helpful as oxygen for many patients.

#### Pharmacological Measures

- Morphine and other opioids are an effective treatment for dyspnea. The initial starting dose will depend on the patient's previous exposure to opioids:

  - A dose of morphine 2.5 mg regularly q4h PO (or 1–2 mg SC/IV) and a breakthrough or rescue dose as required are suitable for an opioid-naive patient.
  - A dose of morphine 5–10 mg regularly q4h PO (or 2.5–5 mg q4h SC/IV) and a breakthrough or rescue dose as required should be used for patients who have already been on codeine.
  - Patients who are already on strong opioids for pain will usually benefit from an increase in their regular dose.
  - Titrate morphine in the same way as for pain management. Some patients may require high doses for dyspnea.
- Benzodiazepines, corticosteroids and bronchodilators, and anti-secretory agents like hyoscine butyl bromide may also be helpful. Benzodiazepines like lorazepam which is intermediate acting given in doses of 250–1000 micrograms or midazolam which is short acting given in doses of 1–2 mg to begin with and titrated according to symptom can relieve anxiety that can be contributory to dyspnea in these groups of patients. Short-term corticosteroids can reduce inflammation and help the patients especially when other comorbidities like asthma or COPD are present [48].
- Respiratory insufficiency in neuromuscular disease is commonly treated with noninvasive positive pressure ventilation (NIPPV), which has been shown to prolong survival and improve quality of life [54, 55].
- Mucous congestion of airways is difficult to manage. Treatment with mucolytics such as ambroxol or N-acetylcysteine is of limited evidence. A combination of beta-receptor agonists, nebulized saline, and furosemide can be helpful [55].

#### 20.5.5.3 Gastrointestinal Symptoms

##### Sialorrhea

Sialorrhea and drooling are commonly associated with swallowing deficits.

##### Non-pharmacological Measures

Consultation with a speech and language therapist to improve swallowing can be helpful. Chewing gum or sucking on a hard candy can help. Having something in the mouth gives an unconscious reminder to swallow (in patients who still can swallow), and so drooling lessens.

##### Pharmacological Measures

There is some evidence that at least three anticholinergic drugs (benzatropine, glycopyrronium, and trihexyphenidyl hydrochloride) are effective in the treatment of drooling [56]. In the NICE full clinical guideline on the management of Parkinson's disease, sublingual 1% atropine ophthalmic solution twice daily is one option suggested for the treatment of hypersalivation [57]. There is some evidence for the use of amitriptyline, hyoscine hydrobromide, and trihexyphenidyl hydrochloride in sialorrhea [58–60]. The NICE full clinical guideline on the management of Parkinson's disease also suggests (off license) injection of salivary glands with botulinum toxin A as one option for the treatment of hypersalivation [56].

#### 20.5.5.4 Nausea and Vomiting

##### Assessment

Identification of the cause of nausea and vomiting is extremely important in its management. There are multiple receptors in the central nervous system, which are involved in the development of nausea. Blocking of these receptors forms the basis of antiemetic medications. These receptors are dopaminergic, muscarinic, cholinergic, histaminic, and serotonergic [38]. Drug-induced causes can be a major contributing factor especially in patients with Parkinson's disease. But patients develop tolerance to nausea and vomiting, and antiparkinsonian treatment can be continued [61]. Nausea is likely to occur in untreated parkinsonian patients as well, and such cases might be explained by underlying gastroparesis [62]. Exclude raised intracranial pressure and CT head and constipation (erect abdominal X-ray), if necessary.

##### Non-pharmacological Measures

- Make sure that meals are small and palatable—snacks consisting of a few mouthfuls are less challenging than big meals.
- Carbohydrate meals are often better tolerated.

- Offer cool, fizzy drinks (citrus flavors are often preferred)—these are more palatable than still or hot drinks.
- Consider the use of complementary therapies; relaxation and acupressure bands may be useful to relieve symptoms.
- Consider cognitive behavioral therapy for anticipatory nausea or vomiting [63].

**Pharmacological Measures**

Central Causes

1. Drugs, biochemical, or toxic causes
   a. Haloperidol—1.5 mg nocte—increase to bid: Maximum of 5 mg bid if nausea persists (avoid in Parkinson's due to dopaminergic effect)
   b. Levomepromazine 6–25 mg daily
   c. Ondansetron (short term)—orally 8 mg bid or tid
2. Parkinson's disease
   a. Domperidone 10–20 mg 3–4 times daily (generally less effective, but less dopaminergic effect)
3. Delayed gastric emptying: Large volume vomiting with undigested food
   a. Adjust meal pattern.
   b. Eat little and often.
   c. Start metoclopramide10 mg tid, and titrate up to 80 mg per day.
   d. If PEG-fed, give slow feeds with nighttime continuous feeding. If vomiting persists, consider endoscopy to exclude pyloric obstruction by balloon. Can also consider per jejunostomy feeding tube [64].

### 20.5.5.5 Constipation

Several factors can be contributory to constipation in neurological patients. Medications, reduced mobility and physical activity, and less oral intake apart from the disease process itself cause constipation. Constipation is mainly considered as a delay of the GI transit; some evidence suggests that it can also be ascribed to a paradoxical contraction of voluntary sphincters during defecation, resulting in difficulties with rectal expulsion [65, 66].

**Non-pharmacological Measures**

- Drink adequate amounts of fluids—at least 48 ounces (6–8 glasses) of fluids daily.
- Include sufficient fiber in the diet. Fiber can be obtained from fresh fruits and vegetables, whole grain breads, and cereals.
- Physical activity can help with bowel movement.
- Establishing a regular time and schedule for emptying the bowels (bowel training/retraining) can be helpful.

**Pharmacological Measures**

- Stimulant laxatives: Bisacodyl 10–20 mg bid
  - Senna 15–30 mg bid
  - Sodium picosulphate (different strengths from 10 mg to 16.1 g are available)
- Stool softeners: Docusate 100–200 mg bid (can go up to 500 mg/day)
- Osmotic laxatives: Glycerin, lactulose, polyethylene glycol [64]

### 20.5.5.6 Anxiety and Depression

Anxiety and depression are present in various stages of different neurological diseases, and this can affect the outcome of the disease as well as overall quality of life [67–69]. It is important to screen for anxiety and depression in this group of patients with a view to intervene.

### 20.5.5.7 Assessment

Screening tools like Hamilton anxiety and depression scale (HADS) or Patient Health Questionnaire (PHQ) anxiety and depression scale can be used. If screening is positive, a diagnostic tool like DSM IV criteria can be utilized to manage or refer to a psychiatrist if required.

### 20.5.5.8 DSM-IV Criteria for Major Depressive Disorder (MDD)

- Depressed mood or a loss of interest or pleasure in daily activities for more than 2 weeks.
- Mood represents a change from the person's baseline.
- Impaired function: social, occupational, educational.
- Specific symptoms, at least five of these nine, present nearly every day:

1. Depressed mood or irritable most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. Decreased interest or pleasure in most activities, most of each day
3. Significant weight change (5%) or change in appetite
4. Change in sleep: insomnia or hypersomnia
5. Change in activity: psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Guilt/worthlessness: feelings of worthlessness or excessive or inappropriate guilt
8. Concentration: diminished ability to think or concentrate or more indecisiveness
9. Suicidality: thoughts of death or suicide or has suicide plan

#### 20.5.5.9 DSM-V Proposed (Not Yet Adopted) Anxiety Symptoms that May Indicate Depression

1. Irrational worry
2. Preoccupation with unpleasant worries
3. Trouble relaxing
4. Feeling tense
5. Fear that something awful might happen [70]

#### 20.5.5.10 Management

**Non-pharmacological Measures**

- Dedicate time for discussion to clarify areas of concern and allow expression of patient's feelings.
- Explore support mechanisms.
- Explore the patient's preferred method of treatment, and involve them in decisions and plans.
- Explain their disorder in terms of reaction to their illness and situation.
- Offer information to the patient, e.g., information about prescription.
- Explain potential role for a variety of therapies, e.g., relaxation therapies, creative therapies, etc.
- Consider discussion with palliative care specialist.
- Consider referral to psychiatrist if patient expresses suicidal thoughts and plans and has previous psychiatric history or if condition resistant to treatment.
- Consider referral for psychological therapies, e.g., cognitive behavioral therapy (CBT) via Improving Access to Psychological Therapies (IAPT) service [71]

**Pharmacological Measures**

- Anxiety.
  - Acute/long-standing anxiety can be managed by benzodiazepines:
    - Short acting—midazolam—1–2.5 mg every 1–2 h (subcutaneous).
    - Intermediate acting—lorazepam—1–4 mg daily (sublingual/oral).
    - Clonazepam for anxiety without depression if an SSRI (serotonin reuptake inhibitors) is insufficient or if REM sleep behavior disorder is a problem. Can be given as a night dose (500 micrograms to 2 mg subcutaneously or orally). Dose can be slowly titrated up to 2 mg.
- All benzodiazepines should be used with caution in marked neuromuscular respiratory weakness, sleep apnea syndrome, and unstable myasthenia gravis.
- Depression
  - SSRI are preferred if patients have anxiety and depression (sertraline, citalopram).
  - Mirtazapine is chosen if insomnia or weight loss is a problem.
  - Tricyclic antidepressant is chosen if drooling is a problem and patient is not demented.
  - Serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine or duloxetine can be used in those who do not tolerate an SSRI [69].

### 20.5.6 Caregiver Issues

A caregiver is an individual who helps with physical and psychological care for a person in need, and very often this is a family member, and they are usually unpaid [72]. Neurological diseases

leave its patients with varying degrees of disability. The caregivers assume multiple responsibilities, and very often their own needs get neglected. They have been found to have worse emotional well-being, more difficulty with caregiving tasks, and more distress in general [73, 74].

### 20.5.7 Assessment

One of the most widely used assessment tools for caregiver burden is that of the Zarit Burden Interview (ZBI). Primarily, the scale measures the caregiver's subjective understanding of his or her burden and distress within the context of physical and emotional health as well as social and financial hardships related to caregiving [75]. Another tool called caregiver self-assessment questionnaire is an 18-item questionnaire developed by the American Medical Association to help physicians [76].

### 20.5.8 Management of Caregiver Issues

High-quality comprehensive care from skilled personnel is required for both the recipient of care and the caregiver, and this includes attention to symptom management and quality of life (QOL).

- Emotional support: Referring to a mental health practitioner for specific interventions can be helpful. Sharing emotions with others relieve stress and can offer a different perspective on problems.
- Caregiving essentials: Most of the caregivers have no prior knowledge or skills of how to look after a patient. Relaying of information and referral to services such as the national societies. Support groups or associations can be helpful in providing caregivers with useful skills.
- Wellness activities: Many caregivers neglect their own emotional, physical, and spiritual needs. Wellness encompasses healthy all-around living. Eating a balanced diet, getting at least 7 h of restorative sleep and regular exercise (i.e., 30 minutes of aerobic exercise 4 or more days a week), maintaining friendships and hobbies, and, for those with a spiritual alignment, spending time on that can all be helpful [77].

### 20.5.9 Legal and Ethical Issues

When a patient is suffering from an incurable disease, the standards for making ethical decisions should be no different than what they would be when caring for all patients such as appropriate medical interventions, carefully weighing their benefits and burdens, and trying to honor the wishes of the patient [78]. In their book Principles of Biomedical Ethics, Beauchamp and Childress chose the principles which can be called the primary ethical concerns of medicine: beneficence, nonmaleficence, autonomy, and justice [79]. The principle of autonomy overrides other principles of ethics. Patients with neurological diseases might lack the capacity to make an informed decision about their treatment.

In palliative care, interdisciplinary approach is the standard of care. The ethics of palliative medicine emphasizes on scientific accuracy and best traditions of medicine: kindness, respect of person, setting goals, compassion, empathy, and non-abandonment. These are principles of excellent medical care [78]. When cure of the disease is not possible, the balance between benefits and burdens of therapy should shift to a greater consideration of reducing the burden. At the very least, any interventions should not add to the patient's suffering [80].

### 20.5.10 Informed Consent

The principle of autonomy encompasses the right to informed consent and truth disclosure. Any intervention or care plan that is undertaken should be with the consent of the patient. Patients should be able to assimilate the pros and cons of undertaking a procedure or going through a particular care pathway and should be able to convey

their decisions to the treating team. Even when patients require help for managing their lives, they might still retain capacity for managing decisions about their future care.

In India, collusion is a common phenomenon as the relatives feel that by not disclosing the diagnosis, they are protecting their ill family member emotionally [81]. Informed consent becomes impossible in this context. One can ask the patient whether they would like to be informed about everything or would they like their family members to assume that responsibility. If the patient is asking direct questions, then it should be answered honestly and as gently as possible.

### 20.5.11 Advance Directives

An advance directive (AD) or living will (LW) is a document prepared by a person to instruct doctors and caregivers on what must be done and not done if and when that person is no longer able to take decisions on their own health on account of illness or incapacity [82]. Advance directives or living will have been recently declared as legally valid by the supreme court of India. It is important for individuals to appoint healthcare proxy agents or surrogates to speak for them when as patients they may not be able to speak for themselves. Advance care planning (ACP) is very important for people with neurological disease, who may face later cognitive change.

### 20.5.12 Futility, Withholding and Withdrawing Treatment, and Do Not Resuscitate Orders

The American Medical Association in its Code of Medical Ethics discusses futility as follows: "Physicians are not ethically obligated to deliver care that, in their best professional judgment, will not have a reasonable chance of benefiting their patients. Patients should not be given treatments simply because they demand them. Denial of treatment should be justified by reliance on openly stated ethical principles and acceptable standards of care, not on the concept of 'futility,' which cannot be meaningfully defined." [83]

When treatment is inappropriate, there should be no ethical difference between withholding it and withdrawing it. It is important that the caregivers clearly understand the reason for withholding or withdrawing treatment. When controversy occurs, it may be wise to negotiate a limited trial of the questionable therapy. Goals and end points must be agreed upon beforehand, and it should be understood that the intervention would be discontinued if they are not met.

Do not resuscitate (DNR) can fall under the category of withholding treatment. Patient with capacity may give consent for DNR at any time. For a patient who lacks capacity, the patient's surrogate may consent to a DNR only if one of the following conditions exists: (1) the patient is permanently unconscious; (2) the patient is terminally ill; (3) burdens would outweigh benefits; or (4) CPR would be medically futile [84]. Obtaining consent for DNR should be done with care and sensitivity. When advising a DNR order, it is not recommended to use a futility argument. Rather, the patient must be made to understand the consequences and adverse effects in the event that CPR is temporarily successful. The patients and their relatives should be reassured that a DNR status will not interfere with any other treatment that would be symptomatically beneficial for the patient. Although DNR can be written against the patient's wishes, this is rarely done in practice. In India the Supreme Court has upheld its own observation that withdrawing and withholding therapy are legal in a recent verdict. But this is yet to be passed as a bill by the two houses of parliament.

### 20.5.13 Palliative Sedation and the Doctrine of Double Effect

Palliative sedation sometimes referred to as terminal sedation is very rarely needed for a patient with intractable distress. The intention

is to relieve symptoms and not to cause or hasten death. The level of sedation should be compatible with control of symptoms. If possible, it should be discussed with patients and under all circumstances with the patient's family/caregivers. There is adequate justification in using sedation if the benefit far outweighs the adverse effect of sedation. But as the adverse effect of sedation is hastening death, the discussion and initiation of sedation for intractable symptoms become complicated. Therefore, palliative sedation is always accompanied by the discussion on doctrine of double effect. This is invoked when there are two effects—one intended good effect, which is relief of suffering, and the other unintended bad effect which is unconsciousness or death. In palliative sedation unconsciousness is the unintended bad effect and not death. The dosage of medications for symptom control can be titrated and fine-tuned. The so-called unintended bad effect of unconsciousness is the effect that we actually need and can be considered as good effect as this provides relief from intractable suffering [78, 85].

### 20.5.14 End-of-Life Care

End-of-life care (EOLC) is defined as care of people whose death is imminent (expected within a few hours or days) and those with (a) advanced, progressive, incurable conditions, (b) general frailty and coexisting conditions that mean they are expected to die within 12 months, (c) existing conditions if they are at risk of dying from a sudden acute crisis in their condition, and (d) life-threatening acute conditions caused by sudden catastrophic events [86].

Good death is achieved when it is free from pain and is supported by family and friends and is in the place of our own choice [87].

Ten key elements of care for the dying patient includes:

1. Recognition that the patient is dying.
2. Communication with the patient (where possible) and always with family and loved ones
3. Spiritual care.
4. Anticipatory prescribing for symptoms of pain, respiratory tract secretions, agitation, nausea and vomiting, dyspnea.
5. Review of clinical interventions should be in the patient's best interests.
6. Hydration review, including the need for commencement or cessation.
7. Nutritional review, including commencement or cessation.
8. Full discussion of the care plan with the patient and relative or carer.
9. Regular reassessment of the patient.
10. Dignified and respectful care after death.

### 20.5.15 Challenges in End-of-Life Care for People with Neurological Conditions

- The long duration of disease.
- Potential for sudden death (e.g., motor neuron disease, multiple system atrophy, epilepsy).
- Lack of predictable course (e.g., Parkinson's disease).
- Complex multidisciplinary care (e.g., multiple sclerosis).
- Specialist treatments (e.g., deep brain stimulation in Parkinson's disease/disease-modifying therapies in multiple sclerosis).
- Neuropsychiatric problems (e.g., behavioral and cognitive changes).
- Rapidly advancing diseases may need palliative care early in the progression.
- Many people die with but not from their neurological condition [88].

### 20.5.16 Recognizing Dying

Accurate prognostication is difficult in EOLC. This poses as a challenge when the family members or patients themselves want to know about how much time they have remaining. It is therefore advisable to give arrange of time rather than a specific time and talk in terms of "days," "weeks," or "months."

Signs and symptoms of imminent death are:

1. The face may be gaunt; patient is often cachectic.
2. There is profound weakness/patient is bed bound/needs help for all activities.
3. Decreased intake of food and fluids.
4. Decreasing urine output.
5. The peripheries get cool and clammy and may get mottled and gray; the mouth and conjunctiva get dry.
6. The pulse gets weaker; blood pressure gradually falls.
7. Respiration becomes shallow, slow, and gradually irregular, may vary in depth, and has a Cheyne-Stokes pattern.
8. Patient may be disorientated in time, place, and person.
9. The patient becomes gradually more and more dull and cannot concentrate.
10. Decreased spontaneous verbalization, interacts less with people, and usually loses consciousness.

If impending death is diagnosed, the following can be prevented from happening:

1. Further invasive and inappropriate interventions and investigations.
2. Unrealistic expectations of the patient and the family.
3. Emergency hospital or even intensive care unit admissions. Patients may have specific wishes on where they would like to die. Patients often want to spend last hours at home.
4. Failure to address symptoms leading to continual distress.
5. Loss of trust in the doctor.
6. Dissatisfactions about the care received, e.g., nutrition and hydration. Explain to the family that the patient does not need much food as he or she is bedridden and nearing end of life. Explain about parenteral hydration that it might cause more harm like pulmonary edema and breathlessness than any benefit.
7. Difficult bereavement. Bereavement support should begin with identifying high-risk individuals before the death of the patient [89].

### 20.5.17 Symptoms in EOLC, Assessment, and Management

The five commonest distressing symptoms are pain, breathlessness, death rattle, agitation, and nausea and vomiting. Other problems include constipation, oral problems, sleep disturbances, and development of pressure sores. Physical assessment would include examination of:

1. Site(s) of pain
2. Eyes/oral cavity
3. Evidence of pressure sore
4. Bowel and bladder disturbances
5. Other symptoms suggested either by verbal or nonverbal means

Psychological assessment of their beliefs, their fears, and their anxieties bring succor to patients and their families. Exploring spiritual distress is not easy at all and is characterized by overwhelming distress often related to unresolved conflict, guilt, fears, and/or feeling of loss of control. Spiritual distress may be relieved by talking with a person with whom the patient feels comfortable.

Management of distressing symptoms includes pharmacological measures, and administration of medications in EOLC is often troublesome as these patients have no intravenous access and have difficulty in swallowing. Alternate routes like subcutaneous and rectal routes work well in EOLC. If patients are with NG feeds, this route can also be used [89].

### 20.5.18 Management of Common Symptoms

1. Pain and breathlessness: Morphine or opioid equivalent can be used subcutaneously, IV injections, or as a patch. For opioid naïve patients, small doses like 2.5 mg can be started as required or can be made regular medications 3–4 times a day. For patients who are already receiving opioids, the dose can be increased by 25 percent to begin with and can be titrated up.

A syringe driver (SD) that will give continuous medications can also be started.
2. Breathlessness with anxiety can be treated with added lorazepam that can be given as sublingual liquid or tablet in a dose range of 0.25 mg to 1 mg three times a day. Morphine should not be stopped.
3. Refractory breathlessness can be treated with short-acting benzodiazepines like midazolam in the dose range of 1–5 mg every 4 h. Morphine should be continued.
4. Respiratory secretions that can cause "death rattle" can be controlled with suctions and hyoscine butyl bromide 20 mg every 4–6 h subcutaneously or via SD and glycopyrrolate 0.2–0.4 mg 2–4 hours.
5. Nausea and vomiting can be addressed with metoclopramide 10–20 mg every three or four times a day subcutaneously or via a syringe driver if a prokinetic action is needed or with haloperidol 0.5 to 1.5 mg twice or thrice a day or via syringe driver, when a centrally acting agent is required.
6. Terminal restlessness/agitation/refractory hyperactive delirium can be controlled with haloperidol 1.5 to 5 mg three times a day subcutaneously. Midazolam can also be added to this in a dose of 2.5 to 5 mg every 4 h. Both medications can be put together in a syringe driver as well [90].
7. Communication at each stage is important and cannot be ignored. Patient's and family's needs should be taken into consideration, and communication should be open and at the same time gentle and compassionate.

### 20.5.19 Palliative Sedation

Palliative sedation and the doctrine of double effect has been discussed earlier. It should be considered only under the following circumstances:

1. The patient must have a severe, chronic, life-threatening illness such as, but not limited to:
   a. Advanced incurable cancer.
   b. End-stage major organ failure and organ transplantation and organ replacement therapy either are not feasible or have been declined by the patient.
   c. Advanced AIDS and antiretroviral therapy either is no longer effective, causes intolerable side effects, or has been declined by the patient.
   d. Advanced neuromuscular disease
   e. Advanced dementia, unable to take adequate oral nutrition.
2. The patient must be suffering from one or more severe physical or neuropsychiatric symptoms such as, but not limited to, pain, dyspnea, vomiting, seizures, agitated delirium, anxiety, or depression.
3. The distressing symptom or symptoms must be refractory to standard palliative interventions such as, but not limited to:
   a. Medications such as opioids, neuroleptics, anticonvulsants, anxiolytics, and antidepressants
   b. Neuromodulatory procedures for pain such as nerve block and intrathecal analgesia
   c. Palliative radiation therapy
   d. Palliative endoscopic or surgical procedures
   e. Consultation by the best available medical specialists from disciplines relevant to the patient's disease or symptoms such as palliative care, pain medicine, or psychiatry and by those who can provide psychosocial support such as social workers and chaplains
4. Comfort must be the overriding goal of the patient's care as determined by the responsible physician in dialogue with the patient or, if the patient does not have capacity to make medical decisions, with the legal surrogate decision-maker.
5. Where possible, an active order must exist to withhold life-sustaining treatments.
6. Informed consent for palliative sedation that may unintentionally hasten death must be obtained in advance from the patient or from an appropriate surrogate decision-maker. The informed consent or decision-making process must be documented in the medical record.
7. If possible, all staff members involved in caring for the patient should be informed in advance of the plan to initiate palliative sedation.

### 20.5.20 Special Circumstances

1. Severe, refractory social, or "existential" suffering

Very rarely, a patient's severe social or "existential" problems such as social isolation, loss of dignity, or loss of a sense of meaning in life may cause severe suffering that is refractory to intensive and sustained intervention by the best available clinicians and supporters. In these very rare cases, respite sedation to unconsciousness may be considered. Only after respite sedation has been tried at least once in addition to all other intensive palliative interventions without an acceptable reduction in the patient's suffering should permanent palliative sedation be considered.

2. Respite sedation

Time-limited sedation to unconsciousness or respite sedation may be used for terminally ill patients with severe refractory suffering in a variety of situations:

- Incident pain: some patients may experience particularly severe pain or other symptoms due to therapeutic or diagnostic procedures or to necessary movement for other clinical care.
- Severe refractory social or "existential" suffering: one or more trials of respite sedation may "break a cycle of anxiety and distress" that has evoked a request for palliative sedation.
- Patient requests trial of temporary sedation to unconsciousness: some patients with severe refractory physical or neuropsychiatric symptoms who are not imminently dying may benefit from a temporary respite from their discomfort.
- Terminal discontinuation of mechanical ventilation [91].

### 20.5.21 Medications for Sedations

Ideal medications for palliative sedation have a rapid onset of action and a short duration of action that facilitate titration to the desired effect. Opioids, benzodiazapines, neuroleptics, barbiturates, or anesthetic induction agents are mentioned in literature for use for sedation. Opioids might not be that effective in producing continued sedation for patients. Benzodiazepines and phenobarbital have better evidence in the use of sedation.

1. Midazolam—Loading dose: 0.03–0.05 mg/kg slow intravenous (IV) push and an infusion at 0.02–0.1 mg/kg/h. Titrate to desired level of sedation.
2. Phenobarbital—Loading dose: 2–3 mg/kg slow IV push and an infusion at 1–2 mg/kg. Titrate to the desired level.
3. Propofol—Start infusion via a central venous catheter at 2.5–5 micrograms/kg/min (for adults approximately 10–20 mg/h) and titrate to desired level of sedation every 10 min by increments of 10–20 mg/h.

Palliative sedation is well accepted and should be resorted to only when patients suffer with intractable symptoms [92].

### 20.5.22 Bereavement Support

End-of-life care is not complete without excellent bereavement support. This can be started even before the actual event of death. Talking about what is going to happen and explaining how support can be given will be a stress reliever for the caregiver. Family members should be supported after the death of the patient. It may involve information, practical support, social support and, for some, counseling and psychological support. Interventions can include individual, family and group interventions, and volunteer supports [93].

## 20.6 Conclusion

Patients with chronic neurological disease have distressing symptoms throughout the course of their illness. Palliative care is a right for these patients and families, as it provides holistic care and helps maintain the quality of their life and also the end of their life.

**Key Points**

- Palliative care provides holistic support to patients and their carers who suffer from chronic and incurable disease and adds quality to their lives.
- Symptom control is key for effective palliative care.
- Goals of care can be discussed at an appropriate time with patients or their carers so that unnecessary distress and suffering are prevented.
- Legal and ethical issues need to be considered when taking decisions about treatment and care.
- End-of-life care is an important aspect of holistic care.

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# Part VI

# Pain Management

# Sedation in the Critical Care Unit

# 21

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## 21.1 Introduction

As a fundamental goal in intensive care units (ICUs), sedation aims to provide relief from uncomfortable medical therapies such as mechanical ventilation or invasive procedures. Sedation is routinely used in combination with analgesia to relieve pain and anxiety, which if left untreated can lead to serious long- and short-term consequences [1]. Balancing patient comfort with patient safety requires frequent, often hourly, consideration of variables, such as alterations in organ function or hemodynamic status. These variables could contribute to states of over- or undersedation that negatively impact patient outcomes. Negative sequelae from states of over- or undersedation may be avoided with careful selection, titration, and discontinuation of sedatives. An emphasis on close patient monitoring aids with determining when changes to the sedative regimen are warranted. Sedative practices should be dynamic in nature and personalized to each patient's condition and status. A working knowledge of available sedatives, including their pharmacokinetic, pharmacodynamic, and adverse effect profiles, is essential for optimizing patient care in ICUs.

## 21.2 Indications and Importance of Sedation in Neurocritically Ill Patients

While sedatives have many indications in neurocritically ill patients, this chapter focuses on routine ICU sedation defined as sedatives used to minimize patient discomfort, anxiety, or agitation as a result of general ICU care, such as mechanical ventilation or procedures. Pertinent concepts to consider when sedating this patient population include indication, allergies, drug pharmacokinetics, patient-specific characteristics, potential adverse effects, drug interactions, and presence of organ dysfunction. Special attention should also be directed to a sedative agent's potential to impact cerebral physiology. As with other organs, the brain is highly dependent on oxygen, demanding ~3–3.5 mL $O_2$/100 g/min (cerebral metabolic demand of $O_2$ [$CMRO_2$]), and is ultimately responsible for the maintenance of many body functions. Sedatives play a pivotal role in reducing cerebral blood flow (CBF) and $CMRO_2$, as both parameters are dependent on cerebral perfusion pressures (CPP) [2]. In turn, these effects improve cerebral tolerance while

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protecting the brain against insult and secondary cerebral ischemia (Fig. 21.1). Maximal suppression of $CMRO_2$ is achieved with sedation when burst suppression occurs [3].

Sedation impacts mean arterial pressures (MAP) and intracranial pressure (ICP). The relationship between these parameters is listed in Table 21.1. CPP normally ranges from 50 to 150 mmHg and can be reduced with increases in ICP, decreases in blood pressure, or a combination of both factors. In a normal, intact brain, physiologic processes are maintained by a check-and-balance system that involves regulation of cardiac output, electrical activity, and cellular homeostasis. Both CBF and CPP are maintained through a process known as pressure autoregulation. Thus, when there is neurologic injury, CPP is compromised along with a decline in CBF. During this time and even in the setting of a normal CPP, CBF can be compromised [4]. Ironically, MAP reductions with the use of sedation can decrease CPP which results in vasodilation of the cerebral vessels. This response is known as the compensatory vasodilatory cascade and essentially allows CBF to remain unaffected when autoregulation is intact. Consequently, this results in an increase in ICP. Necessary sedation can still be employed in these instances; however, close attention should be given to ensure that MAP is maintained [5]. Preventing hypotension and maintaining euvolemia are imperative in this setting along with careful consideration in those with heart diseases. In these situations, assessing patient's preload should occur prior to implementing sedatives [2]. Ultimately, patients may require additional therapies (e.g., volume repletion), modifications to the sedation regimen, vasopressors, or a combination of modalities to balance the intricate cerebral and hemodynamic parameters in the setting of an underlying brain disorder.

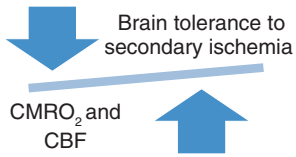


**Fig. 21.1** Sedative effects on cerebral physiology. *CBF* cerebral blood flow, *CMRO*$^2$ cerebral metabolic rate of oxygen

**Table 21.1** Cerebral dynamic equation

| |
|---|
| CPP = MAP-ICP |
| *CPP* = cerebral perfusion pressure |
| *MAP* = mean arterial pressure [MAP = (1/3 SBP) + (2/3 DBP)] |
| *ICP* = intracranial pressure |
| *SBP* = systolic blood pressure |
| *DBP* = diastolic blood pressure |

For neurologically injured patients requiring routine ICU sedation, there is increasing focus on achieving a comfortable yet arousable patient under the least amount of sedation. One notable exception is when intracranial hypertension is present. Under these circumstances, sedation priorities are often targeted at maintaining adequate cerebral perfusion pressures (CPP) while avoiding elevations in ICP and using the amount of sedation appropriate to achieve this effect [6]. There are numerous indications for sedation of neurologically injured patients, some requiring higher doses than others to achieve a desired endpoint (Table 21.2). The use of high-dose sedation with the intent of managing alcohol withdrawal, seizure cessation, or burst suppression is beyond the scope of this chapter.

Patients with neurologic injuries pose unique sedative challenges, even in the setting of routine

**Table 21.2** Common indications for sedation [7, 8]

| General intensive care indications | Neurocritical care indications |
|---|---|
| • Patient discomfort<br>• Anxiety and agitation<br>• Facilitation of procedures<br>• Prevent ventilator dyssynchrony<br>• Blunt central hyperventilation<br>• Shivering secondary to therapeutic hypothermia<br>• Withdrawal from alcohol and other agents[a] | • Reduction of cerebral metabolic demand<br>• Improved brain tolerance to ischemia<br>• Reduction of intracranial pressure[a]<br>• Status epilepticus and refractory status epilepticus[a]<br>• Metabolic encephalopathies<br>• Neurodegenerative disorders<br>• Central nervous system infections<br>• Neoplastic pathologies |

[a]Indication is more likely to require high-dose sedatives versus lower/routine dosing

ICU sedation. First, these patients require frequent neurologic examinations that for accuracy should be performed off sedation. However, sedation may be essential for endotracheal tube tolerance, ventilator compliance, prevention of inadvertent removal of life-saving devices, and prevention of self-inflicted harm or harm to healthcare providers [9–11]. In addition, undersedation can compound a patient's already amplified physiologic stress response resulting in myocardial or cerebral ischemia, predisposition to arrhythmias, elevated ICPs, and hypertension [1].

Undersedation can result from sedation holidays, inadequate sedative dosing, or inappropriate sedative selection. Undersedating a patient may result in unwanted or exaggerated patient movement that may lead to short-term consequences such as device removal and direct harm to the patient or staff. Indirect consequences may also occur, such as increased infection risk as a result of inadvertently disconnecting the external ventricular drain sterile system or tract hemorrhage from improper device removal [7]. Many other indirect consequences from premature device removal exist (Table 21.3). Overall, these scenarios increase hospital costs, specifically staff time and resource utilization.

**Table 21.3** Potential indirect consequences of patient-initiated device removal related to undersedation

| Consequence of undersedation | Potential risks |
|---|---|
| EVD removal | Infection; EVD tract hemorrhage |
| Vascular catheter | Infection; hemorrhage; medication extravasation |
| Endotracheal tube removal | Airway/laryngeal injury, respiratory compromise, aspiration, need for reintubation, and increased risk of medication adverse effects from exposure to drugs for rapid sequence intubation |
| Foley removal | Urethral injury; hemorrhage; increased risk of adverse effects from prophylactic antibiotics after urethral trauma |
| Enteral tube removal | Trauma from reinsertion (PEG); reduced nutrition intake until reinserted; potential for missed medication doses of oral medications |

*EVD* external ventricular drain, *PEG* percutaneous endoscopic gastrostomy

The merits of performing sedation holidays or neurological wake-up test should be patient-specific and weighed against potential adverse effects. For example, if the patient is experiencing malignant ICPs, the benefit versus risk of daily awakenings from sedation for a "neuro-check" should be considered. Contrary to popular belief, wake-up tests have not shown to have detrimental effects on cerebral energy metabolism or oxygenation in traumatic brain-injured patients although there may be transient alterations in ICP or CPP [12].

Exceptions to performing wake-up test in the neuro-specific population include patients with arteriovenous malformations (AVMs) and those receiving barbiturates secondary to significant intracranial hypertension elevations. Patients with AVMs may require immediate sedation in the setting of recent embolization. Barbiturates have the tendency to confound accurate neurological assessments due to prolonged sedative effects secondary to their long half-lives (53–118 h) [6]. In both instances, awakening trials should be reconsidered when appropriate.

An emerging area of research is the long-term consequences associated with undersedation, including post intensive care syndrome (PICS) defined as new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization [13]. Up to 30% of ICU survivors will develop mental health conditions such as post-traumatic stress disorder, anxiety, or depression (included under the definition of PICS) within 1 year after leaving the ICU [7, 14].

Like undersedation, over-sedation imparts harmful consequences. Over-sedation of neurocritically ill patients may happen more easily compared to patients without neurologic injury. After brain injury, gamma-aminobutyric acid (GABA) neurotransmitter concentrations can range from normal to deficient in different parts of the brain. In areas deficient of GABA, GABA receptors become over-sensitized [15]. As such, GABAergic medications like benzodiazepines or propofol work unpredictably on these sensitized GABA receptors which may explain why brain-injured patients can respond more profoundly to sedation than non-brain-injured patients.

Sedatives have central nervous system depressing mechanisms, which uniquely impair cognitive function leading to difficulty obtaining accurate neurologic exams that are vital in guiding the next critical steps in the care of the patient. These assessments become difficult or impossible in patients with intracranial pathologies [8]. Over-sedation hampers patient mobility, contributes to venous stasis and venous thromboembolism risk, and often causes hypotension [6]. Over-sedation has historically been responsible for increasing ventilator days, hospital length of stay, incidence of delirium and complications such as venous thromboembolism and ventilator-associated pneumonia, and increased utilization of diagnostic testing [1, 10]. When a change in neurologic status is noted in a patient receiving sedation, over-sedation must be considered a possible etiology among others such as seizures, cerebral edema, hypoactive delirium, or new ischemia or hemorrhage. Ruling out these other etiologies when sedation is the cause results in unnecessary utilization of healthcare resources such as imaging and electroencephalograms [10]. These diagnostic tests are costly and expose patients to increased risk of harm from radiation, contrast administration, and possibly medications such as anticonvulsive agents if administered preemptively [2].

## 21.3 Sedative Monitoring

Numerous rating scales have been developed for quantifying depths of sedation in the ICU. Of these, the Riker Sedation-Agitation Scale (SAS) and the Richmond Agitation-Sedation Scale (RASS) have been validated in critically ill patients, and both are supported by current guideline recommendations to appropriately measure the depth of sedation in general intensive care patients [1]. Monitoring the level of consciousness of a neurologically injured patient receiving sedative medication proves challenging due to the complex interactions of sedatives with a damaged brain [16]. These complexities necessitate careful sedative titrations with frequent assessment of the patient's degree of sedation.

A study of RASS in neurocritical care patients demonstrated that RASS performed by nurses and physicians had high inter-rater reliability [17]. In addition, a recent article reviewing standardized sedative assessment scales concluded that the RASS and SAS are valid and useful clinical tools for neurocritical care patients [7]. Validation of these scales was based on the ability to differentiate various levels of sedation in correlation with electroencephalogram (EEG) and bispectral index values (BIS). Importantly, validation studies for the RASS included neurologically ill patients in the validity and reliability analyses [18, 19]. Despite the importance of standardized assessment tools for titrating sedation, the utility of these clinical scoring tools diminishes when the goal of sedative therapy is to elicit a therapeutic response such as burst suppress or seizure termination rather than achieving a particular depth of sedation. In other words, it is appropriate to allow a RASS of −5 (unarousable) if a patient requires this depth of sedation to terminate seizure activity. Furthermore, sedation holidays may lead to deleterious consequences in certain subsets of neurologically ill patients, such as those requiring sedation for burst suppression or shivering cessation; thus, sedation holidays in these types of patients should be avoided.

In contrast to clinically subjective measures of sedation using bedside rating scales, EEG and BIS monitoring may provide additional information about a patient's depth of sedation. For example, EEG monitoring detects nonconvulsive seizures that could influence a patient's score when assessed by the RASS. Continuous EEG monitoring allows for real-time monitoring during sedative titration to burst suppression for termination of refractory status epilepticus or intracranial hypertension [20]. Unfortunately, EEG monitoring can be cost-prohibitive and requires highly trained providers to interpret the electrographic readings. The amount of time it takes to interpret EEG readings can also be prohibitive [16].

The BIS is a statistically derived variable of the EEG that measures depth of sedation via four leads placed on the patient's forehead. BIS is more commonly used perioperatively but is gaining popularity outside of the operating suite. The limitations of BIS monitoring preclude its widespread use in neurointensive care units. While BIS proves useful for measuring brain activity on a spectrum of deep sedation to complete wakefulness during general

anesthesia, its use has not been well-studied in brain-injured patients in the ICU. A statistical correlation was demonstrated between BIS, SAS, RASS, and GCS for depths of sedation in a small subset of neurocritical care patients that did not include severe traumatic brain injury [16]. In addition, BIS readings can be influenced by targeted temperature management, shock states, and metabolic disturbances—therapies and conditions routinely seen in neurocritically ill patients. Under these conditions, BIS monitoring lacks reliability as an objective scoring system. The BIS monitor may produce artifacts, rendering it an unacceptable mode of sedation monitoring in noncomatose, nonparalyzed patients since these artifacts could further complicate interpretation of the results [21–23]. In a study of 45 neurocritical care patients who received BIS monitoring adjunctively to standard clinical assessment scales, sedation requirements with propofol decreased. It was emphasized that BIS monitoring in this trial was not a replacement for the bedside clinical sedation assessment, but rather it was used as an add-on for the nurse to have more information about the real-time, clinical picture of the neurologically ill patient [24]. Anecdotally, BIS monitoring may be considered as part of a paralytic protocol to monitor and titrate sedatives during neuromuscular blockade for indications such as elevated ICP or shivering when EEG monitoring is not available or feasible and when standardized clinical rating scales such as RASS are indeterminate. The limitations of BIS monitoring should be considered when using the results for clinical decision-making.

## 21.4 The Ideal Sedative in Neurocritical Care

Although there is no single sedative that would be ideal for each unique patient, identification of the characteristics of an ideal sedative is important for comparing and contrasting individual agents. The ideal sedative should have a rapid onset and short duration of action when used for procedural sedation. When used as a continuous infusion, the duration of effects should be short-lived when the infusion is discontinued; the ideal agent should be free of any adverse effects and drug interactions. In addition, it should be easily titratable to the desired level of sedation, and no dose adjustments should be necessary in the setting of organ dysfunction or in special populations such as hypermetabolic patients or the elderly. Finally, the ideal agent should be cost-effective with no ceiling dose and no tachyphylaxis. Although there are no sedatives boasting each of these advantages, the characteristics of the ideal sedative are those that are considered in the selection of an optimal sedative agent for a specific patient. The benefits of a sedative for a particular patient should always outweigh any potential harm.

## 21.5 Analgosedation in Neurocritical Care

According to the Society of Critical Care Medicine guidelines published in 2013 [1] and 2018 [25], there was overwhelming evidence to employ analgesics as first-line therapy prior to starting a traditional sedative (analgosedation). The rationale for this practice was secondary to the evidence that all critically ill patients experience some degree of pain when undergoing standard procedures [26] commonly employed within the ICU but also at rest [27]. The administration of a bolus analgesic, such as fentanyl or perhaps a continuous analgesic infusion if multiple bolus doses are required, allows for the following: pain control, possible omission of traditional sedative therapy, and reductions in the amount of sedation required. This ultimately minimizes the adverse effects and potentially allows for accurate patient neurological assessments [28]. Special considerations should be given prior to initiation of sedation therapy (Table 21.4). Contrary to supporting data and practices favoring analgesia first-based sedation in the general ICU population, total reliance on analgesics for initial management of various neurocritical care patients is often essentially impossible depending on the acuity of the intracranial pathology. For example, a patient experiencing increased ICP after severe head trauma would likely benefit from hypnotic-like, sedative therapy with an agent such as propofol in addition to fentanyl due to the lack of profound ICP-reducing properties associated with analgesic therapy alone.

**Table 21.4** Factors that influence the initiation of sedative [1, 29]

| Factor | Suggested intervention |
|---|---|
| Agitation and anxiety | Non-pharmacologic—noise reduction, normal sleep-wake cycles, etc.<br>Pharmacologic—assess for pain first and use analgesia when appropriate; consider light sedation; use a PRN sedative regimen if possible |
| Baseline neurological function | Consider omission of sedation unless patient has other indications [e.g., comfort (pain medication first), paralytic usage, status epilepticus, ICP management, etc.] |
| Concomitant administration of psychoactive therapies (e.g., corticosteroids, anticonvulsants, antimicrobials, gastric motility increasing agents) | Consider removing agent, lowering dose when appropriate, or transitioning to an alternative agent without psychoactive effects |
| Hemodynamic variables | Fentanyl, remifentanil—can be used in hemodynamically unstable patients<br>Ketamine may be considered in hypotensive patients without a significant cardiac history<br>Avoid or use lower doses of propofol or dexmedetomidine, both which can lower blood pressure and heart rate more than a benzodiazepine infusion |
| Pain | Analgosedation; if hypotensive—nonhistamine-releasing opioid of short duration (fentanyl)<br>Consider neuropathic pain medications (e.g. gabapentin, carbamazepine, and pregabalin) as adjunctive therapy to opioid when appropriate |
| Level of sedation required: deep versus light | Light—use analgosedation<br>Deep—use pain medication ±-traditional sedative preferred |
| Organ function | Fentanyl can be used in patients with both hepatic and renal insufficiencies<br>If continuous infusion is not required, consider PRN morphine in patients without renal failure and hydromorphone in renal insufficiency |
| Alcohol withdrawal syndrome | Sedation—benzodiazepines titrated based on symptoms as needed benzodiazepines (PRN) are preferred over continuous infusions. |
| Paralysis | Deep sedation—fentanyl ± benzodiazepine, or propofol titrated to RASS of −5; continuous infusions are required |
| Refractory ICP | Propofol or midazolam infusions in addition to an analgesic infusion titrated to control of intracranial pressures or burst suppression, whichever comes first |
| Shivering during therapeutic temperature modulation | Fentanyl—reduced metabolism during cooling; midazolam and propofol can also result in decreased clearance during cooling |
| Delirium | Non-pharmacologic strategies favored |

Analgosedation strategies for pain management should always be considered in the critically ill patient. Agents such as opioids can be initiated first-line for non-neuropathic pain with the addition of non-opioid therapies such as acetaminophen administered by various routes or ketamine when deemed appropriate. Analgosedation may involve increasing titrations of continuous opioid infusions, with fentanyl appearing to be most common based on its favorable pharmacokinetic profile. With up-titration of analgesics such as opioids, patient comfort may be enhanced not only by pain relief but also by offering light sedation to relieve patient discomfort. Employing analgosedation is beneficial for multiple reasons. The patient's opioid requirement can be drastically reduced or possibly eliminated. Additionally, minimizing the number of therapies introduced also reduces adverse event exposure [1]. For example, analgosedation has been found to reduce midazolam utilization and the incidence of delirium [30]. Other non-opioid pharmacological therapies that may alleviate pain include acetaminophen, nonsteroidal anti-inflammatory medications (NSAIDs), nefopam, ketamine, topical lidocaine, neuropathic agents, and glucocorticosteroids in the presence of an inflammatory component. Regardless of the selection, patient-specific characteristics and neurologic therapeutic goals should be considered prior to initiation. If sedative therapy becomes necessary, careful consideration should be given to each medication's pharmacokinetic and pharmacodynamic properties to appropriately customize a safe and effective analgosedative regimen (Tables 21.5 and 21.6).

**Table 21.5** Common sedatives and analgesics in the neurocritically ill population [1, 29, 31]

| Class/drug | Sedation/ analgesia | MOA | CNS effects | Adverse drug reactions | Clinical pearls | Place in therapy |
|---|---|---|---|---|---|---|
| *Opioid* | | | | | | |
| Morphine<br>Bolus: 1–4 mg<br>IV × 1<br>CI: 1–10 mg/h titrated to desired response. | +/+++ | Mu receptor agonist | Indirect elevation of ICP (hypercarbia); may lower MAP/CPP | Respiratory depression, gastric dysmotility, hypotension, hallucinations | Avoid in renal failure (morphine-3 and 6-glucoronide<br>Accumulation and prolonged sedation in obese and elderly<br>Histamine release associated with itching and hypotension | Continuous infusion is not routinely used except in end of life issues.<br>Boluses are ideal for pain reduction in patients without renal insufficiency |
| Hydromorphone<br>Bolus: 1–2 mg<br>IV × 1 | +/+++ | Mu receptor agonist | Indirect elevation of ICP (hypercarbia); may lower MAP/CPP | Respiratory depression, gastric dysmotility, nausea, hypotension | | Ideal for intermittent boluses in patients that are intolerant or morphine allergic<br>non-histamine releasing so not anticipated to lower blood pressure; not renally cleared so good for patients with renal insufficiency |
| Fentanyl<br>Bolus: 50–100 mcg<br>IV × 1<br>CI: 0.5–1 mcg/kg/h titrated to desired response. | +/+++ | Mu receptor agonist | Indirect elevation of ICP (hypercarbia); may lower MAP/CPP | Respiratory depression, chest wall rigidity, gastric dysmotility, hypotension | Rapid onset<br>Preferred for hemodynamically unstable<br>Hepatically metabolized by CYP3A4 | Ideal when both pain and sedative properties are desired<br>Advantageous for hemodynamically unstable patients. Can be used in renal impairment but may have prolonged effects in patients with hepatic impairment |
| Remifentanil<br>Bolus: 0.4–0.8 mcg/kg<br>IV × 1<br>CI: 0.5–2 mcg/kg/min titrated to desired response | +/+++ | Mu receptor agonist | Indirect elevation of ICP (hypercarbia) during endotracheal suctioning<br>No effects on ICP or CBF related to infusions | Respiratory depression, chest wall rigidity, gastric dysmotility, hypotension; nausea, bradycardia | Ultrashort acting; mostly reserved for perioperative use by anesthesiology<br>Does not accumulate with prolonged infusion<br>Metabolized by plasma esterases | Ideal for quick onset with short duration of action. Can be used safely in both hepatic and renal insufficiencies due to plasma esterase metabolism |

(continued)

**Table 21.5** (continued)

| Class/drug | Sedation/ analgesia | MOA | CNS effects | Adverse drug reactions | Clinical pearls | Place in therapy |
|---|---|---|---|---|---|---|
| *Benzodiazepine* | | | | | | |
| Lorazepam<br>Bolus: 1–4 mg<br>IV × 1<br>CI: 1–10 mg/h | +++/+ | $GABA_A$ receptor agonist | Indirect elevations in ICP (hypercarbia)<br>Decrease in CBF and $CMRO_2$ | Respiratory depression, hypotension, confusion | Contains propylene glycol; osmolar gap of 10–12 may identify those at risk for propylene glycol toxicity<br>IV infusion not recommended for status epilepticus | Ideal for alcohol withdrawal syndromes and patients with renal insufficiency<br>Not primarily used in brain-injured patients due to concern for propylene glycol toxicity |
| Midazolam<br>Bolus: 1–5 mg<br>IV × 1<br>CI: 0.5–10 mg/h | +++/+ | $GABA_A$ receptor agonist | Indirect elevations in ICP (hypercarbia)<br>Decrease in CBF and $CMRO_2$ | Respiratory depression, hypotension, confusion | Active metabolite causing prolonged half-life in renal dysfunction | Ideal for patients requiring dual sedation and refractory status epilepticus therapy |
| *$Alpha_2$ agonist* | | | | | | |
| Dexmedetomidine<br>CI: 0.2–1.5 mcg/ kg/h | ++/+ | $Alpha_2$ receptor agonist (pre- and postsynaptic) | ICP unaffected or decreased | Dry mouth, bradycardia, hypotension, adrenal suppression, atrial fibrillation, rebound hypotension with prolonged administration | Greater specificity for $alpha_2$ receptor ($\alpha_2$:$\alpha_1$ activity 1620:1)<br>Reduce dose ~50% in hepatic insufficiency and elderly<br>Has sedative and mild analgesic properties but should not be used as a primary analgesic<br>Hypotension and bradycardia are common<br>Does not suppress respiratory drive<br>IV loading doses can cause hemodynamic instability | Common alternative to benzodiazepines in ventilated and nonventilated patients when a more interactive and communicative patient is desired |

| Class/drug | Sedation/ analgesia | MOA | CNS effects | Adverse drug reactions | Clinical pearls | Place in therapy |
|---|---|---|---|---|---|---|
| *Other* | | | | | | |
| Propofol<br>CI: 5–80 mcg/kg/min | +++/− | Possesses $GABA_A$ receptor agonist activity; sodium channel blocker | Decreases ICP, $CMRO_2$, CBF | Hypotension, respiratory depression, metabolic acidosis, rhabdomyolysis, anaphylaxis, pain on injection | Rapid onset and offset<br>Easily titrated; short duration of action<br>PRIS risk factors: doses >70 mcg/kg/min, >4 mg/kg/h for >48 h, catecholamine infusions, concomitant steroids, cerebral injury, and low glycogen stores<br>PK of drug not affected by metabolism but can accumulate in adipose tissue with prolonged use<br>Contains 1.1 kcal/mL of lipid content<br>Can cause green discoloration of urine but this is not harmful | Patients in which minimal depth and duration of sedation are desired<br>Patients in which short-term sedation is desirable for preservation of neurological exams<br>Ideal for ICP reduction |
| Ketamine<br>Bolus: 0.25–1 mg/kg IV × 1<br>CI: 0.1–0.5 mg/kg/h | +++/+++ | Dissociative agent; NMDA receptor antagonist; activity at opioid and GABA receptors | ICP unaffected or decreased; CPP may increase | Hypertension, emergence reactions, injection site pain; tachycardia, excessive salivation, hypertension, laryngospasm, nausea, and vomiting | Extensively hepatically metabolized consider dose reductions with liver dysfunction<br>No adjustments necessary with renal insufficiency<br>Highly lipophilic and may accumulate in obese patients<br>Psychotomimetic effects with sub-anesthetic doses (~0.3 mg/kg) to include emergence reactions (hallucinations and psychosis)<br>Avoid in patients with history of ischemic cardiac disease<br>High infusions rates associated with high infusing volume | Great short-term sedative for cardiac stability (lacks hypotensive effects) and/or maintenance of respiratory reflexes |

**Table 21.6** Commonly used sedatives, analgesics, and their respective metabolic pathways [32–35]

| Drug | Elimination half-life | Active metabolite/metabolic pathway | CYP enzyme interactions | Effects during hypothermia |
|---|---|---|---|---|
| Midazolam | 3–11 h | Yes/hepatic—active metabolite (1-hydroxymethylmidazolam) cleared renally | Yes<br>3A4 | Ranges from no effect to ~11% ↓ in clearance |
| Lorazepam | 8–15 h | No/hepatic conjugation and glucuronidation | No | No data |
| Fentanyl | 2–4 h (IV) | Yes/hepatic, primarily via CYP3A4 by N-dealkylation (to norfentanyl) and hydroxylation to other inactive metabolites | Yes<br>3A4<br>Extensive | Decreased clearance during cooling but minimal to no changes during the rewarming phase |
| Propofol | 4–7 h; may be up to 1–3 days with prolonged infusions (>10 days) | No/hepatic conjugation | Yes<br>2B6, 2C9, 2C19, 3A4 | ↓ clearance during cooling<br>↓serum concentration (~3% per °C increase) during rewarming |
| Remifentanil | 3–10 min | No/rapid metabolism via blood and tissue esterases to a minimally active metabolite; no liver metabolism | No | Cardiopulmonary bypass patients showed a decrease in clearance by 6.37% for each degree below 37 °C<br>Reductions in clearance may not be clinically relevant for short procedures due to short half-life |
| Dexmedetomidine | 1.8–3 h | No/hepatic—glucuronidation and oxidation | Yes<br>2A6 | No data |
| Ketamine | 30 min to 2.5 hours | Yes/norketamine with 1/3 potency of parent compound; Hepatic/hydroxylation and N-demethylation | Yes<br>2B6, 2C9, and 3A4 | No data |

## 21.6 Sedative Pharmacology

### 21.6.1 Benzodiazepines

Benzodiazepines cause sedation, anxiolysis, amnesia, and hypnosis through activation of the $GABA_A$ chloride channel in the central nervous system [1, 29]. Within this class of structurally related compounds, lorazepam and midazolam emerged as cornerstone therapies for the sedation of mechanically ventilated patients due to their favorable pharmacokinetic profiles when compared to other benzodiazepines. Unfortunately, neither of these agents represent the ideal agent for routine ICU sedation of the neurologically injured patient for several reasons. Although midazolam has a short onset of action, two mechanisms contribute to prolonging the clearance and half-life beyond just a few hours. After 48 h of continuous infusion, midazolam accumulates in fat tissue resulting in a prolonged duration of effects after infusion discontinuation. This phenomenon may be mitigated using daily sedation interruptions and timely weaning strategies [36]; however, midazolam and lorazepam have longer half-lives when compared to most non-benzodiazepine sedatives, necessitating longer awakening times prior to performing an accurate neurologic examination. In regard to metabolism, the liver metabolizes midazolam through Phase I oxidative metabolism to an active renally eliminated metabolite. In the setting of renal impairment, sedative effects may be prolonged relative to the amount of drug administered and the severity of renal dysfunction. The metabolism of midazolam to the active metabolite is mediated by CYP3A4 and CYP3A5. In the presence of CYP3A4 inhibitors, midazolam concentrations increase yielding the potential for undesirable degrees of central nervous system (CNS) depression. Unlike midazolam, lorazepam has no active metabolite. Lorazepam is metabolized by the liver to an inactive metabolite through conjugation and glucoronidation and is not affected by hepatic impairment. Administration of large doses of lorazepam over short periods of time may cause anion gap metabolic acidosis due to the propylene glycol vehicle within the lorazepam injectable formulation. The same is true for diazepam formulations which precludes the use of high doses of diazepam as well.

The use of benzodiazepines for routine ICU sedation has markedly decreased over the past decade in light of growing evidence supporting the association of benzodiazepines and the increased incidence of delirium in critically ill patients [1]. Another notable disadvantage of benzodiazepines is their ability to cause vasodilation leading to hypotension. Benzodiazepine-induced hypotension occurs more frequently with high rates of continuous infusions, but it can also present during procedural sedation where relatively large bolus doses are given over short periods of time. Ensuring adequate volume status is critical for preventing benzodiazepine-induced hypotension in many circumstances. There appear to be no differences in the incidence of hypotension when midazolam is compared to lorazepam [37] or when midazolam is compared to propofol at routine doses for ICU sedation [38]. Studies have demonstrated a lower incidence of hypotension with benzodiazepine administration compared to dexmedetomidine at routine sedative doses, and most studies comparing hemodynamic parameters between benzodiazepines and dexmedetomidine involved midazolam [38, 39].

Flumazenil, a selective GABA receptor antagonist, can be used to competitively reverse the effects benzodiazepines. Benzodiazepines are not routinely reversed in the neurocritical care setting since flumazenil can induce symptoms of benzodiazepine withdrawal, including anxiety, agitation, tremor, myoclonus, insomnia, and occasionally seizures. In the absence of flumazenil, these symptoms emerge after abrupt withdrawal of prolonged benzodiazepine use [1].

Benzodiazepines, including midazolam and lorazepam, have historically been used across all ICUs. They are specifically being used for either short- or long-term sedation in mechanically ventilated patients, respectively, owing to their drug-specific properties. Particularly, benzodiazepines have anterograde amnestic properties preventing recall of unpleasant events and information making them beneficial in the majority of mechanically ventilated patients. Beginning in

2007, their usage began to become controversial due to association with ICU delirium. The MENDS and SEDCOM trials compared dexmedetomidine to the most commonly used benzodiazepines, midazolam and lorazepam, and demonstrated less delirium and ventilator free days with dexmedetomidine [39, 40]. Contrary to these findings, midazolam and lorazepam are uniquely versatile, and their roles have not diminished in the setting of managing refractory intracranial hypertension, status epilepticus, and various withdrawal syndromes where they are still regarded as first- and second-line therapies.

Benzodiazepines have demonstrated permanent negative effects on cognitive recovery in animal models dating back to 1986 [41]. A meta-analysis found a dose correlation with non-resolving cognitive dysfunction in patients that received a minimum of 17 mg/day of diazepam [42]. Additional negative effects with benzodiazepine use greater than 30 days include long-term memory loss and decreases in visuospatial abilities, verbal learning, and speed of processing [43]. Aside from prolonged cognitive impairment, withdrawal side effects unrelated to anxiety, such as tinnitus, involuntary movements, and perceptual changes, have been noted to occur after long-term, therapeutic benzodiazepine administration [44].

### 21.6.2 Opioid Infusions

Although opioid agents interact with many receptors, analgesic effects of opioids are primarily mediated by their interactions with μ- and κ-receptors, the latter of which is responsible for the sedative properties of the medications. Fentanyl, hydromorphone, and morphine are the most commonly used agents within the ICU setting. Fentanyl, a highly lipid-soluble medication, is a popular opioid prescribed for neurocritically ill patients since it is available as an intravenous (IV) formulation, and unlike morphine, fentanyl lacks histaminergic effects making it a suitable consideration for hemodynamically unstable patients or patients at risk of hypotension [45]. Additionally, fentanyl is hepatically metabolized to norfentanyl, an inactive metabolite, and can be used at normal doses in the setting of renal insufficiency. The benefits of morphine in brain-injured patients must be carefully considered with the risks. Morphine is known to stimulate the release of histamine, yielding drops in blood pressure. Morphine undergoes glucuronidation to produce active metabolites (3- and 6-glucoronide morphine) which accumulate in patients with renal insufficiency. The later metabolite is thought to possess 2–8 times the potency than the parent compound and with accumulation can cause excess sedation and respiratory depression [1].

Lastly, a potentially favorable opioid option is remifentanil. Remifentanil is a selective μ-agonist primarily utilized for anesthesia induction and maintenance in the operative setting (vs. postoperative or long-term analgesia) owing to its ultrarapid onset and extremely short half-life that is independent on the duration of the infusion. Remifentanil also possesses unique blood and tissue metabolism by nonspecific plasma esterases, eliminating concern for use in patients with both renal and hepatic diseases [46]. In a small study of approximately 100 surgical ICU patients (primarily with abdominal surgeries), remifentanil decreased the rate of delirium compared to sedation with fentanyl or midazolam. Remifentanil and fentanyl both reduced benzodiazepine sedative requirements, but there were no differences in the duration of delirium, length of stay, ventilator days, or 28-day mortality [30]. Ultimately, the literature comparing remifentanil and fentanyl for general sedation of critically ill patients does not demonstrate superiority of remifentanil over fentanyl, but it could be considered as part of an opioid-based sedative regimen in mechanically ventilated medical and surgical patients [47]. The scarce literature evaluating remifentanil in neurologically ill populations is limited to the anesthetic setting, during awake craniotomies and endovascular procedures primarily [31].

Tolerance, intestinal dysmotility, CNS depression resulting in respiratory depression, and hypotension are characteristic adverse effects of opioids as a class. Tolerance can be described as receptor changes happening overtime that result in the need for higher doses of medication to achieve the same desired effects. Tolerance does not develop with gastrointestinal side effects;

therefore, all critically ill patients prescribed opioids should receive some form of routine stimulant laxatives to minimize or prevent constipation or gastric ileus.

Long-term opioid use, generally described as more than 7 days of scheduled opioid doses or an infusion, can lead to withdrawal if the opioid is discontinued abruptly. The constellation of opioid withdrawal symptoms includes nausea, vomiting, diarrhea, yawning, tachycardia, hypertension, fever, and tachypnea. Opioid withdrawal can be prevented by designing a careful down-titration schedule. When transitioning off an opioid infusion, oral opioid medications may be included in the opioid down-titration plan.

### 21.6.3 Propofol

Propofol, like benzodiazepines, activates the $GABA_A$ receptor but does so by binding to a different subunit of the channel. Propofol is structurally unrelated to benzodiazepines but is highly lipophilic, similar to lorazepam and diazepam, which allows the drug to readily cross the blood-brain barrier into the central nervous system where it exerts its effects. Due to its high lipophilicity, propofol is manufactured in a lipid formulation that at higher rates of infusion can provide relevant caloric intake (1.1 kcal/mL). Propofol's rapid onset and short duration of action is ideal for sedation of brain-injured patients and can be easily titrated. With prolonged infusions, propofol, like midazolam, can accumulate in adipose tissue yielding a longer than predicted duration of action and awakening time after the infusion has been discontinued.

Propofol-related infusion syndrome (PRIS) symptoms vary, but may be characterized by bradycardia, hypotension, hyperlipidemia, metabolic acidosis, rhabdomyolysis and renal failure. This condition is a rare adverse effect associated with high mortality rates. PRIS has been identified with high rates of propofol infusions and prolonged durations of infusions (Table 21.5). Risk factors for PRIS include younger age, administration of catecholamine vasopressors, and high cumulative dosages of propofol [48]. An infusion rate limit of 5 mg/kg/h with careful monitoring is recommended in the most recent guidelines for brain trauma [49]. Triglycerides should be monitored at least weekly with higher doses and prolonged infusions since triglyceridemia can result in acute pancreatitis. Green discoloration of urine has been noted, but this effect is the result of an unharmful by-product of propofol metabolism. Therapy should not be discontinued only for urine discoloration. Like most other sedatives, propofol is associated with bradycardia and hypotension and occurs in up to 30% of patients [36]. A retrospective study comparing propofol and dexmedetomidine demonstrated no difference in the incidence of hypotension (23 vs 26%, $p = 0.52$) or bradycardia (8.6 vs 5.5%, $p = 0.28$) between the agents [50]. The need for renal replacement therapy and a baseline MAP of 60–70 mmHg independently predicts propofol-induced severe hypotension in neurocritically ill patients [51]. In addition, high doses of propofol as boluses or high rates of infusion can cause profound hypotension. Interestingly, emerging preclinical data in animals has demonstrated conflicting evidence regarding the neuroprotective effects versus the neurotoxic effects of propofol [52, 53]. Additional data is needed to determine the impact of propofol on neurologic recovery in humans with different neurologic injuries.

### 21.6.4 Dexmedetomidine

Sedation with dexmedetomidine has grown in popularity for neurocritically ill patients, though high-quality evidence for its use in this cohort of patients is lacking. When dexmedetomidine selectively activates central alpha-2 receptors, the result is suppression of neuronal and central norepinephrine release without reducing cerebral metabolism [54, 55]. Since dexmedetomidine lacks agonist activity at GABA receptors, it is void of any antiseizure properties. Interestingly, dexmedetomidine has mild analgesic effects, though it is not recommended as monotherapy for analgesia. Dexmedetomidine is an appealing agent for neurocritical care patients in need of frequent neurologic assessments since, like propofol, its onset and duration of action are short. Another benefit of dexmedetomidine that is also similar to propofol is the reduction in the incidence of delirium and days of mechanical

ventilation compared to benzodiazepines [39]. Dexmedetomidine does not interfere with the respiratory drive which makes it a useful agent for patients that require mild sedation during weaning trials and extubation. Patients with delayed extubation post-craniotomy have benefited from dexmedetomidine compared to control patients, demonstrating lower pain scores and greater percent of time at optimal depths of sedation [56]. Dexmedetomidine may also be useful in sedating non-mechanically ventilated patients when other agents are ineffective or contraindicated. Additionally, therapeutic temperature modulation protocols often include dexmedetomidine as an anti-shivering agent for its ability to lower the shivering threshold [28].

The use of dexmedetomidine for routine sedation of neurocritical care patients is controversial. In healthy human subjects, dexmedetomidine was shown to reduce CBF and $CMRO_2$ in a dose-related manner; however Wang et al. demonstrated no reductions in CBF or $CMRO_2$ in patients with brain injury [57]. Dexmedetomidine has been studied clinically in small, uncontrolled trials in brain-injured patients. In a single-center study of 85 TBI patients, dexmedetomidine was found to reduce analgesic and sedative requirements while also significantly reducing hemodynamic parameters. RASS and GCS improved from baseline to post-infusion indicating that dexmedetomidine did not negatively impact cognitive function in these patients [55]. A retrospective study of dexmedetomidine in brain-injured patients demonstrated a need for high doses of dexmedetomidine to achieve the desired levels of sedation and to wean off adjunctive sedatives or analgesics. Starting doses in this study population were higher than FDA-approved and ranged from 0.4 to 1 mcg/kg/min to achieve the desired levels of sedation. These doses appeared to be safe [58]. In both trials, dexmedetomidine caused a statistical, but not a clinical, reduction in blood pressure and heart rate.

As described, dexmedetomidine is associated with a high incidence of hypotension and bradycardia that is more profound with bolus doses and in the setting of induced hypothermia [58]. Other adverse effects that patients may experience are dry mouth and atrial fibrillation.

Dexmedetomidine has many attributes that make it attractive for use in brain-injured patients; however, its use remains limited due to adverse effects, the potential for harmful effects in neurocritical care patients, and high cost.

### 21.6.5 Ketamine

Known as a dissociative agent, ketamine inhibits N-methyl-d-aspartate receptors with activity at opioid and GABA receptors, thereby yielding its analgesic and sedative properties [59]. Ketamine has a high volume of distribution and is highly lipophilic. The high lipophilicity of the drug can be of concern in obese patients since ketamine has the potential to accumulate in adipose tissue [59]. Ketamine causes psychomimetic effects with as many as 30% of patients experiencing psychosis and hallucinations. These adverse effects occur during recovery from ketamine and are known as emergence reactions [60]. In general it is recommended to avoid the use of ketamine in patients with a history of psychosis or drug withdrawal that could cause or precipitate psychotic reactions. While other sedatives such as benzodiazepines and propofol are associated with hypotension, ketamine can increase heart rate and blood pressure through its sympathomimetic effects. In some patients, these hemodynamic effects are of benefit, while other patients, such as those with a history of ischemic cardiac disease or cardiac conditions that could be aggravated by ischemia, should avoid ketamine. Paradoxically, ketamine can rarely cause hypotension when patients are catecholamine depleted [59, 61]. While there has been concern for increased ICPs with ketamine administration, more recent literature suggests no substantial adverse effects in brain-injured patients. Of note, ketamine can interfere with BIS monitor readings [62]. The use of ketamine as a general ICU sedative for neurocritically ill patients remains limited to refractory status epilepticus. Ketamine is not routinely used in acutely brain-injured patients due to limited evidence and the availability of alternative sedative agents that have been shown to be safe and effective for routine sedation in this unique critically ill population. However, this

agent's use may increase during sedative and analgesic drug shortages.

### 21.6.6 Butyrophenones

Butyrophenones, though not generally described as typical sedative agents, are also called neuroleptics, with the most common being haloperidol and droperidol. Through inhibition of particular dopamine receptors subtypes, the butyrophenones impart mild sedative, anxiolytic, and antipsychotic properties. These agents also have the propensity to antagonize other receptors such as adrenergic, serotonergic, acetylcholinergic, and histaminergic. The interactions with these other receptors contribute to the medication's side effect profile. Neuroleptics can be beneficial when seeking control of the combative, agitated, demented, or even delirious patient. Butyrophenones utilization in neurocritically ill patients is low owing to their adverse effect profile and the potential unfavorable implications on neurologic recovery, making them least attractive for general sedative use in the ICU. Of benefit, these agents begin working quickly and are devoid of respiratory depressant effects. The convenience of having multiple formulations for oral, IM, or IV routes of administration makes haloperidol the preferred butyrophenone under many circumstances. Unlike haloperidol, droperidol is only available in a parenteral formulation. Metabolism of both haloperidol and droperidol occurs hepatically and may be reduced in the elderly population, necessitating lower starting doses.

Additional concerns with neuroleptics are extrapyramidal side effects (Parkinsonism, acute and tardive dystonias, tardive dyskinesia, akathisia, and perioral tremor), systemic hypotension with IV dosing, neuroleptic malignant syndrome, and QT prolongation. The latter is more pronounced with droperidol, which has been assigned a black box warning for the adverse effect and is contraindicated for patients with a prolonged QT interval at baseline. QT interval thresholds for avoiding use are commonly physician dependent, and patients should have an initial 12-lead electrocardiogram (EKG) performed along with additional monitoring for the duration of use, especially in the setting of repeated cumulative dosing. Due to the heightened concern with droperidol, continuous serial EKG monitoring is warranted during the initial hours after administration with preparation of necessary medications to treat arrhythmias/dysrhythmias and hypotension should they occur. Maintaining electrolytes ($K^+$ and $Mg^{+2}$) within goal range prior to and during administration of the neuroleptic is recommended. It is also recommended to avoid the use of concomitant QT-prolonging medications if possible, and it is an absolute contraindication to administer droperidol when a patient is already receiving another QT-prolonging agent [63].

The effects of haloperidol on ICP have not been studied, although some data indicate a reduction in CBF secondary to hypotension in a limited clinical study with droperidol usage [64].

Butyrophenones, by mechanism of action, have the potential to negatively impact neurologic recovery after acute brain injury. Dopaminergic tone plays an essential role in mood, memory, reward, motivation, attention, learning, movement, and plasticity—all of which are necessary for optimal recovery after brain injury [65]. Dopamine has been shown in preclinical studies to be an integral neurotransmitter during the neuro-recovery period, and the presence of chronic dopamine antagonists after brain injury has the potential to impair cognitive and motor recovery [66]. A more recent animal study demonstrated that *intermittent* quetiapine and haloperidol did not worsen TBI-induced cognitive and motor deficits in rats. Moreover, cognitive deficits from chronic haloperidol administration can persist up to 3 months based on data from preclinical trials which also demonstrate that antipsychotic medications that dissociate more quickly from the D2 receptor may be associated with less potential for worsening or impairment of cognitive recovery [66].

## 21.7 Unique Pharmacokinetic/Pharmacodynamic Circumstances and Sedative Considerations

Several patient-specific variables have the potential to impact the pharmacokinetics and pharmacodynamics of sedatives in neurocritical care patients.

Some examples of subgroups of neurocritical care patients at risk of increased sedative concentrations or increased sedative effects include older adult patients, patients undergoing therapeutic temperature modulation [67], and patients with particular genetic polymorphisms [68]. In contrast, patients with histories of chronic opioid, benzodiazepine, or alcohol use disorders, patients with augmented renal clearance, or patients with hypermetabolic states may demonstrate relative inefficacy of usual sedative doses. The pathophysiology of these conditions drives the need for higher sedative doses to achieve the desired effects. Patients with chronic opioid use (defined by the FDA as >60 mg of morphine equivalents per day for 7 days) experience desensitization, internalization, and downregulation of opioid receptors that necessitate higher opioid doses to achieve analgosedative goals. Similarly, those with chronic benzodiazepine use or alcohol use disorder also demonstrate a reduction and desensitization of GABA receptors resulting in increasing benzodiazepine doses to achieve desired effects.

Data has shown that drug metabolism and clearance are increased in patients with acute brain injury. In particular, it is postulated that drugs undergoing renal clearance will require higher doses to achieve usual effective concentrations likely due to augmented renal clearance. Augmented renal clearance has been noted in traumatic brain injury and subarachnoid hemorrhage patients [67]. In addition to heightened renal clearance of renally eliminated medications, hypermetabolic states (often seen in neurocritically ill patients) increase drug metabolism through Phase I oxidative metabolism.

## 21.8 Pharmacogenomics and Sedative Considerations

Pharmacogenomics is an emerging area of interest and may have some future application in pharmacotherapeutic decision-making for sedation of neurocritically ill patients. Polymorphisms of the CYP3A4 enzyme have been shown to impair the metabolism of midazolam leading to increased concentrations and sedative effects; however, these clinical outcomes may only be relevant in combination with medications that have strong CYP3A4 inhibitor properties, such as some of the azole antifungal agents. Ketamine metabolism can also be influenced by genetic variants of CYP enzymes. In particular, at higher doses, ketamine metabolism by CYP2B6 is enhanced. Genetic polymorphisms of this enzyme can reduce ketamine metabolism and clearance by approximately 40–60%. Fentanyl and morphine serum concentrations may also be influenced by genetic variations of enzymes or target receptors [68].

## 21.9 Sedation Considerations During Therapeutic Temperature Modulation

The combination of sedation and analgesia is paramount in the pharmacological management of patients requiring therapeutic hypothermia. Therapeutic temperature modulation may be considered as part of the management of refractory ICP, neurological central fever, and those experiencing coma secondary to cardiac arrest. It allows for both rapid attainment of targeted temperatures and improved maintenance of target temperatures. The medication's clearance during the cooling and rewarming phase may be heavily dictated by its metabolism [32]. Anticipation of drug effects during hypothermia and relevant dose adjustments must be made to avoid concentration-dependent toxicities while achieving optimal therapeutic effects. The cytochrome P450 enzyme system plays an active role in activating prodrug medications, yet it is also responsible for deactivation. For medications reliant on CYP450 for metabolism, clearance diminishes by 7–22% in the setting of therapeutic hypothermia (Table 21.6) [33]. Reduced clearances are also coupled with impairments in hepatic blood flow which leads to even lower medication doses to attain the same therapeutic effect. During the rewarming phase, resumption of usual drug metabolism may occur resulting in normalization of drug clearance, or basal activity may be hampered prolonging decreased drug

metabolism [34]. Expectant drug effects during the cooling process are both complex and multifactorial depending on the extent of temperature reduction, metabolic pathway at stake, routes of elimination, and medication half-life. Ideal management of medications during temperature modulation centers around careful consideration of the medication's elimination pathway. Heightened sedative and analgesic monitoring coupled with appropriate dose adjustments will ensure patient comfort, desired therapeutic effects, and absence of adverse effects. For example, cardiopulmonary bypass patients showed a decrease in the clearance of remifentanil by 6.37% for each degree below 37 °C. One way to offset this decrease in clearance is to reduce the remifentanil infusion rate by 30% per 5 °C decrease in temperature which should achieve target concentrations [35].

Therapeutic temperature modulation with normothermia is a relatively common treatment modality initiated in neurocritical care units for fever management. Patients are cooled to goal normothermic temperatures of 36–37 °C. Unlike therapeutic hypothermia, patients undergoing cooling to normothermia may experience increased elimination of renally-cleared medications explained by the augmented renal clearance of brain-injured patients. The augmented renal clearance can offset increases in drug concentrations from reduced metabolism in the liver when medications are both renally and hepatically eliminated. The impact of these altered pharmacokinetic processes working in tandem is difficult to predict. Literature evaluating alterations in pharmacokinetics and pharmacodynamics of sedatives and analgesics in the setting of temperature modulation is scarce in brain injured patients. [67].

## 21.10 Conclusion

Providers encounter unique challenges in the sedation of neurocritically ill patients. Sedative selection requires thoughtful consideration of the risks and benefits of specific pharmacologic agents. Sedative agents should provide enough sedation to maintain patient comfort while allowing frequent and accurate neurologic examinations during sedation interruption. The ideal sedative agent is patient-specific, taking into account the pharmacokinetic and pharmacodynamic characteristics of the drug and patient, drug interactions, and comorbid conditions as examples. A working knowledge of available sedatives and neurocritical care sedative concepts is essential for ensuring patient safety while optimizing patient outcomes.

**Key Points**

- Sedatives impact cerebral physiology and dynamics and must be monitored closely.
- The Riker Sedation-Agitation Scale (SAS) and the Richmond Agitation-Sedation Scale (RASS) have been validated for assessing the depth of sedation in general critically ill patients, but providers must recognize the limitations of these scales for neurointensive care patients.
- For general neurointensive care sedation, analgosedation is preferred over traditional sedatives when the goal is to maintain patient comfort.
- Patient-specific characteristics carefully matched to the pharmacokinetic and pharmacodynamic profiles of sedatives will attenuate risk of adverse effects while maintaining patient comfort and allowing for frequent neurologic examinations.

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# Pain in the Neurocritical Care Unit

22

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## 22.1 Sources of Pain in the Critical Care Unit

Pain is commonplace for patients in the neurocritical care setting. This can include pain related to the patient's underlying disease process or as a result of surgical intervention. Pain is also commonly associated with invasive monitoring modalities, nursing cares, and invasive positive pressure ventilation.

## 22.2 Physiologic Consequences of Pain

Pain leads to increased catecholamine activity that can exert negative impact across a variety of organ systems [1–3]:

- Neurologic: sleep deprivation, anxiety, delirium, increased $CMRO_2$, post-traumatic stress disorder, and sensitization leading to chronic pain states.
- Cardiac: positive inotropy and chronotropy, and myocardial ischemia.
- Respiratory: splinting leading to atelectasis and pneumonia, and ventilator dyssynchrony.
- Hematologic: hypercoagulability.
- Endocrine: initial hypercortisolemia leading to hyperglycemia, impaired wound healing, and immunosuppression; hormone depletion if pain stimulus does not abate (e.g., severe weakness, and inability to wean from mechanical ventilation).

## 22.3 Monitoring Pain in the Critical Care Unit

Pain monitoring is a critical component of patient care in the ICU. In addition to ethical justification for appropriate analgesia [4], it has been linked with improved patient outcomes: routine assessment of pain allows for optimization of analgesic and sedative medications which has been associated with decreased ventilator days as well as decreased duration of ICU stay [5]. In order to effectively apply analgesic modalities, physicians must be able to reliably gauge a patient's existing level of pain. There are several validated methods for following pain scores; however, there is limited data to support a single method as superior to the rest. Moreover, there are very few studies that specifically validate tools in a neurocritical care population, so most clinical recommendations are derived from investigations of medical and surgical intensive care units [6].

In selecting an algorithm for pain monitoring, a physician must first determine the patient's ability to reliably and effectively communicate

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with healthcare providers. If the patient is awake and alert, patient self-report is considered the gold standard for pain monitoring; it is difficult for surrogates to accurately assess a patient's pain state and this often leads to underdiagnosis of pain by, for example, nursing staff [7]. Several quantitative scales are commonly employed for communicative patients:

- The Numeric Pain Scale (NPS) asks patients to verbalize a numeric rating from 0 (no pain) to 10 (worst pain ever experienced) and is broadly utilized due to its applicability across a variety of patient populations [8].
- The Visual Analog Scale (VAS) asks patients to rate their pain by marking a line ranging from no pain to severe pain. This provides a continuous scale rather than the range of integers that comprises the NPS.
- The Verbal Rating Scale (VRS) is an ordinal scale that asks patients to rate their pain as none, mild, moderate, or severe, and is useful for patients who find it difficult to assign a number to their pain state [9].

Many patients in the critical care unit, however, are noncommunicative due to various contributions from their underlying disease states, sedative medications, neuromuscular blockade, and/or intubation. In this circumstance, it becomes necessary to use both objective and subjective observations to guide assessments of a patient's pain (Table 22.1). Notably, although vital signs suggestive of agitation (e.g., tachycardia, and hypertension) can indicate increased pain, they lack utility as stand-alone markers; unless they are employed as part of a broader and validated tool, vital signs suggestive of adrenergic surge should not be interpreted as clear evidence of increased pain per se [10]. For noncommunicative adults, there are several validated scales in existence, including:

- Behavior Pain Scale (BPS), which includes assessment of facial expression, upper limb movement, and ventilator compliance for an overall score ranging from 3 (no pain) to 12 (highest pain). The BPS is commonly employed due to its validity in the critical care population as well as its high inter-rater reliability [11].
- Nonverbal Pain Scale (NVPS), which includes assessment of facial expression, body movement, guarding, vital signs, as well as skin and pupillary changes (e.g., pain manifesting as perspiration or mydriasis), for an overall score ranging from 0 (no pain) to 10 (highest pain) [12]. A modified NVPS has also been adapted based on Payen's work with the BPS to include assessment of ventilator compliance instead of skin and pupillary changes [13].
- Critical-care Pain Observation Tool (CPOT), which includes assessment of facial expression, body movement, ventilator compliance, and muscle tension for an overall score ranging from 0 (no pain) to 8 (highest pain) [14].

**Table 22.1** A comparison of selected pain scales for noncommunicative patients

| | Behavior Pain Scale (BPS) | Nonverbal Pain Scale (NVPS) | Critical-care Pain Observation Tool (CPOT) |
|---|---|---|---|
| Number of domains | 3 | 5 | 4 |
| Range of scores | 3 (no pain)<br>12 (highest pain) | 0 (no pain)<br>10 (highest pain) | 0 (no pain)<br>8 (highest pain) |
| Variables | Facial expression<br>Upper limb movements<br>Ventilator compliance | Facial expression<br>Body movement<br>Guarding<br>Skin/pupillary changes<br>Vital signs | Facial expression<br>Body movement<br>Ventilator compliance<br>Muscle tension |

Three commonly used pain scores for noncommunicative patients are compared. Despite the varying domains included in each scale, higher scores indicate increased pain by each system

## 22.4 Monitoring Sedation and Delirium in the Critical Care Unit

In addition to pain states, it is critical to monitor sedation levels and screen for delirium in critically ill patients. As discussed earlier, admission to the critical care unit can be a traumatic experience. Patients with inadequate sedation may exhibit agitation and risk unintentional harm via removal of monitoring and supportive devices, whereas deep sedation has been linked to delirium as well as increased number of ventilator days and days in the ICU; the Society of Critical Care Medicine recommends not only that sedation levels be iteratively monitored but that precise goals for sedation depth be established for each patient [15]. For example, deeper levels of sedation may be targeted for a patient with acute traumatic brain injury with a goal to manage intracranial hypertension, with specific pharmacologic selections based on goals of achieving frequent reliable exams of neurologic status [16].

Multiple scales are validated for monitoring sedation levels although, similarly to pain scales, there is little data to identify one as superior to the rest. Three of the most extensively studied and commonly employed scales are discussed here [8]. Of these three, the Richmond Agitation-Sedation Scale (RASS) and Riker Sedation-Agitation Scale (SAS) have been demonstrated to be effective in neurocritical care settings (Table 22.2) [6].

- Richmond Agitation-Sedation Scale (RASS). The RASS monitors patient response to verbal and physical stimuli, with scores ranging from "+4" (combative) to "−5" (unarousable) [17]. Positive scores correspond to agitation, and negative scores correspond to sedation with differentiation based on response to verbal and physical stimuli. Alert and calm patients score "0" in this scheme.
- Ramsay Sedation Scale (RS). The RS scores patients from 1 to 6, with lower scores representing restlessness (e.g., agitated patients score "1") and higher scores representing increased levels of sedation (e.g., nonresponsive patients score "6"). Alert and calm patients score "2" in this scheme.
- Riker Sedation-Agitation Scale (SAS). The SAS scores patients from 1 to 7, with lower scores representing sedation (e.g., nonresponsive patients score "1") and higher scores representing restlessness (e.g., combative patients score "7"). Alert and calm patients score "4" in this scheme.

**Table 22.2** A comparison of selected sedation scales

| | Richmond Agitation-Sedation Scale (RASS) | Ramsay Sedation Scale (RS) | Riker Sedation-Agitation Scale (SAS) |
|---|---|---|---|
| Range of scores | −5 to +4 | +1 to +6 | +1 to +7 |
| Unresponsive patient | −5 | +6 | +1 |
| Calm and cooperative | 0 | +2 | +4 |
| Combative patient | +4 | +1 | +7 |

Three commonly used sedation scales are compared. Greater scores correspond to increased agitation by RASS and SAS, whereas greater scores correspond to increased sedation by RS. Note the values allocated to calm and cooperative patients under each scheme

Delirium is commonly experienced among patients in the intensive care unit, occurring in nearly one-third of patients [18]. It is linked with prolonged duration of intubation, ICU stay, and increased mortality [19]. Despite the potential for confounding patient characteristics endemic to the neurocritical care setting, it is important to screen for delirium and take steps to prevent its incidence.

A detailed description of these methods is beyond the scope of this chapter, but one screening tool will be briefly reviewed here: the Confusion Assessment Method for Intensive Care Unit (CAM-ICU). In patients who are sufficiently alert to participate (e.g., RASS >−4), the CAM-ICU allows healthcare providers to screen for delirium by assessing for acute changes in mental status, inattention, altered consciousness, and/or disorganized thinking; it is broadly used due to its high sensitivity and specificity, speed of assessment, and high inter-rater reliability [20].

## 22.5 Pharmacologic Analgesia and Sedation

Analgesic and sedative medications are frequently used in the ICU to help facilitate routine cares, help patients better tolerate mechanical ventilation, and to address opioid tolerance [21]. In order to provide safe and effective sedation and analgesia, avoid oversedation, and minimize adverse effects ICU providers must be well-versed in the uses, pharmacodynamics, pharmacokinetics, and adverse effects of the medications commonly used in the ICU for analgesia and sedation. The discussion below explores these properties for commonly used medications including opioids, benzodiazepines, propofol, and dexmedetomidine.

## 22.6 Opioids

Opioid medications are the most widely used analgesic medications in many ICUs. Fentanyl, morphine, and hydromorphone are the most commonly used opioids in the ICU with remifentanil, methadone, and meperidine being used less frequently [22–24]. Intravenous administration is the preferred route of administration in critically ill patients as this route is easily titrated and results in the fastest onset and highest bioavailability [25]. Intermittent intravenous bolus dosing is the preferred initiation method for opioids, and continuous infusion should be reserved for those patients who cannot be appropriately managed with intermittent dosing. Table 22.3 provides some initial starting doses for commonly used opioid and sedative medications for adult patients but it must be stated that these are only recommendations and the appropriate dose will be patient specific. There is no maximum dose for most opioid medications, and instead maximum doses will be dictated by adverse effects such as sedation, confusion, and constipation. Regardless of the opioid medication, they should be titrated to the minimum necessary dose to provide adequate pain control while at the same time minimizing adverse effects. Titrating opioids and establishing the correct dose can be challenging in ICU patients as there are often barriers to effective doctor–patient communication such as sedation and mechanical ventilation. In order to effectively titrate opioids, ICU providers should use a combination of validated pain assessment tools and physiologic endpoints such as heart rate, blood pressure, and respiratory rate. Finally, daily awakenings and sedation holidays

**Table 22.3** Dosing of commonly used opioid and sedative medications

| Drug | Intermittent dose | Infusion dose |
|---|---|---|
| Fentanyl | 0.35–0.5 mcg/kg q 0.5–1 h | 0.7–10 mcg/kg/h |
| Hydromorphone | 10–30 mcg/kg q 1–2 h | 7–15 mcg/kg/h |
| Morphine | 0.01–0.15 mg/kg q 1–2 h | 0.07–0.05 mg/kg/h |
| Methadone | 10–40 mg po q6–12 h | Not recommended |
| Diazepam | 0.03–0.1 mg/kg q 0.5–6 h | – |
| Lorazepam | 0.02–0.06 mg/kg q2–6 h | 0.01–0.1 mg/kg/h |
| Midazolam | 0.02–0.08 mg/kg q 0.5–2 h | 0.04–0.2 mg/kg/h |
| Propofol | Induction dose: 1–2.5 mg/kg | 5–80 mcg/kg/min |
| Ketamine | *Induction dose*: 1–4.5 mg/kg IV<br>*Intramuscular dosing*: 6–13 mg/kg × 1<br>*Acute pain*: 0.5–1 mg/kg q 15 min<br>*Procedural sedation*: 1–2 mg/kg q 5–15 min | 0.12–0.4 mg/kg/h |
| Dexmedetomidine | – | Optional 0.5–1 mcg/kg loading dose given over 10 min can be given prior to infusions below<br>*ICU sedation:* 0.2–0.7 mcg/kg/h<br>*Intubation:* 0.6–0.7 mcg/kg/h |

Dosing of analgesic and sedative medications commonly used in the ICU. Doses are recommendations, and most effective doses for particular patients may be outside of the doses presented

are recommended as these have been shown to decrease the amount of opioids administered, decrease the duration of mechanical ventilation, and decrease the length of ICU stay [26].

### 22.6.1 Opioid Pharmacokinetics

With the exception of remifentanil, which is metabolized by plasma and tissue cholinesterases, opioids are metabolized by the liver and their metabolites are excreted by the kidneys. Within the liver, different metabolic pathways are used to break down opioids. Specifically, hydromorphone and morphine undergo glucuronidation, fentanyl undergoes *N*-dealkylation via CYP3A4/5, methadone undergoes *N*-demethylation via CYP3A4/5, 2D6, 2B6, and 1A2, and meperidine undergoes *N*-demethylation and hydroxylation via CYP3A4/2B6 [25]. There is significant genetic variability in the CYP450 system which can result in considerable differences in individual's ability to metabolize particular opioid medications [25]. One common example is the CYP2D6 gene which has been studied extensively and has been linked with differences in the metabolism of codeine and methadone [27–29]. In addition to genetic-mediated differences, the CYP450 enzyme system can be affected by a host of medications that can either induce the system resulting in more rapid drug metabolism (e.g., carbamazepine) or inhibit the system resulting in decreased drug metabolism (e.g., omeprazole).

Another important corollary of both the liver and kidneys being used for opioid metabolism is that this metabolism can be significantly impaired if either of these organs is dysfunctional. This is of particular importance when treating patients in the ICU as studies estimate that some degree of hepatic dysfunction is present in more than half of critically ill patients, and acute kidney injury is present in 20–50% of ICU patients [30–32]. Patients suffering from renal failure deserve special attention as they provide unique challenges when attempting to use opioid medications. Many opioids have metabolites that are not effectively cleared in patients with renal failure. As a result, these metabolites can accumulate and cause adverse effects. Morphine is metabolized to morphine-3-glucuronide (55%), morphine-6-glucuronide (10%), and normorphine (4%), and each of these metabolites is excreted by the kidney under normal physiologic conditions [33, 34]. Morphine-6-glucuronide is an active metabolite and its accumulation can lead to respiratory depression and sedation [22]. Because of the potential accumulation of morphine-6-glucuronide, morphine should be avoided in patients with renal failure. Hydromorphone is metabolized by the liver to hydromorphone-3-glucuronide (36.8%), dihydromorphine (0.1%), and dihydroisomorphine (1.0%), as well as small amounts of hydromorphone-3-sulfate, norhydromorphone, and nordihydroisomorphone [35]. Hydromorphone-3-glucuronide can accumulate in patients with renal dysfunction and while it has not analgesic properties it can cause neural excitation. As a result, hydromorphone should be used cautiously in patients with renal disease [35–38]. Fentanyl is metabolized by the liver predominately to norfentanyl (99%). There is no evidence that this metabolite is active however in patients with renal failure the parent compound can accumulate and cause adverse effects [39, 40]. As a result, fentanyl can be used in patients with renal failure; however, the patient should be closely monitored for signs of accumulation of the parent compound. Methadone is metabolized to pyrrolidine and then to pyrroline. Excretion of these metabolites is via the urine and the feces. These metabolites are inactive and in renal failure the metabolites are excreted into the gut [41, 42]. Consequently, methadone can be used safely in patients with renal dysfunction.

### 22.6.2 Opioid Pharmacodynamics

Opioid medications are agonists of common opioid receptors including mu, kappa, and delta receptors which are located in both the central nervous system and in peripheral tissues [22]. Individual opioid medications stimulate these receptors to varying degrees, and this variable stimulation is

partially responsible for each opioid's unique analgesic properties and side effect profile. Opioid receptors are located throughout the body and as a result opioid medications can have a plethora of effects in addition to their desired effects. Some established adverse effects of commonly used opioids include respiratory depression, nausea and vomiting, drowsiness, itching, constipation, and opioid-induced hyperalgesia [43]. In addition to these general adverse effects, certain opioids have unique side effects that may impact the decision to administer them to particular ICU patients. Some of these medications include morphine which can cause histamine release which ultimately leads to urticaria, hypotension, and bronchospasm and methadone which can cause QTC prolongation. Another important unfavorable effect of opioids is that they can cause hallucinations and have been associated with the development of delirium [44]. This association with delirium is of considerable importance when managing ICU patients as delirium has been shown to be an independent risk factor for higher 6-month mortality and longer hospital stays in patients receiving mechanical ventilation [19].

In addition to adverse systemic effects, patients can also develop a tolerance to opioid medication especially synthetic opioids such as fentanyl [45, 46]. This tolerance results in decreased drug effectiveness over time despite constant plasma concentrations and necessitates dose escalations. There are a variety of methods to deal with opioid tolerance; however, one common strategy employed is opioid cycling. In this method, when the provider feels that the opioid dose required has escalated too high, the opioid is switched to an equal analgesic dose of a different opioid being sure to account for cross tolerance. Closely linked with tolerance is physiologic dependence. Physiologic dependence refers to adaptation made in the body secondary to continuous exposure to a medication [47]. The predominant manifestation of physiological dependence is drug-specific withdrawal symptoms that occur when the medication is discontinued or the dose is decreased [47]. The time required to develop this dependence as well as the degree of dependence is patient specific; however, it has been estimated that ICU patients exposed to high-dose opioid therapy can develop physiological tolerance after 1 week of exposure [48]. Some opioid-specific withdrawal symptoms include hypertension, tachycardia, tachypnea, and agitation. These symptoms can easily contribute to alternative pathologies in the ICU patient which further complicates the diagnosis of opioid withdrawal. In order to avoid opioid withdrawal, opioid infusion and intermittent opioid regimens should be down-titrated slowly. No specific weaning strategy has been proven to be superior to others. A common opioid weaning strategy at our institution is to wean total opioid dose by 10–25% daily or every other day and monitor the patient for signs of withdrawal with assessment tools such as the *Withdrawal Assessment Tool (*WAT). In addition to slowly reducing opioid doses, methadone can also be used the help minimize withdrawal symptoms in ICU patients who have developed opioid dependence [48–50].

## 22.7 Benzodiazepines

Benzodiazepines are most commonly used in the ICU as sedatives but are also used to help manage specific conditions such as alcohol withdrawal and seizures. The most commonly used benzodiazepines in the ICU are midazolam, lorazepam, and diazepam. Benzodiazepines are often categorized based on their duration of action: short, intermediate, and long. Midazolam is the mostly widely used short-acting benzodiazepine in the ICU with a duration of action of approximately 2 h. Diazepam is the most common intermediate-acting benzodiazepine with a duration of action between 1 and 2 h. Finally, lorazepam is the mainstay long-acting benzodiazepine in the ICU with a duration of action between 6 and 8 h. Intravenous administration is the preferred route in ICU patients as it enables easier titration and provides the fastest onset and highest bioavailability. Intermittent bolus dosing

should be used if possible as continuous infusion of benzodiazepines in ICU patient has been associated with prolonged duration of mechanical ventilation [26]. As a result, benzodiazepine infusions should be reserved for those patients whose symptoms cannot be controlled with intermittent bolus dosing. ICU providers should titrate benzodiazepines using a combination of physiologic markers and validated sedation tools such as the Ramsay sedation score and the Richmond Agitation Sedation Scale (RASS). In general, the ICU patient should be comfortable but easily arousable.

### 22.7.1 Benzodiazepine Pharmacokinetics

Benzodiazepines derive their name from their structure which consists of benzene and a diazepine ring. Termination of the effects of benzodiazepines is due to the combination of redistribution and hepatic metabolism. Elimination of benzodiazepines is achieved by hepatic metabolism and renal excretion of the various metabolites. There are two primary mechanisms of hepatic metabolism for benzodiazepines, hydroxylation, and conjugation with glucuronide. Of the benzodiazepines commonly used in the ICU, midazolam undergoes hydroxylation, lorazepam undergoes glucuronidation, and diazepam undergoes *N*-demethylation and hydroxylation. This distinction is important because benzodiazepines that undergo oxidation are much more likely to have their metabolism affected by things such as increased age, hepatic dysfunction, drug interactions, and medications that alter the activity of the CYP450 enzyme system. One important example of this is the metabolism of midazolam. Midazolam metabolism results in 1-hydroxymidazolam glucuronide which has CNS depressant effects. In patients with renal failure of in those taking medications that decrease the function of CYP3A4 1-hydroxymidazolam glucuronide can accumulate and result in prolonged CNS depression.

### 22.7.2 Benzodiazepine Pharmacodynamics

Benzodiazepines bind GABA receptors which are one of the primary inhibitory neurotransmitters in the central nervous system [51]. Binding of the GABA receptor results in more frequent opening of chloride ion channels which subsequently leads to an increase in intracellular chloride [51]. This increased level of chloride in turn results in hyperpolarization and makes the neuron resistant to excitation [51]. Benzodiazepines cause anxiolysis, sedation, and anterograde amnesia, and have antiepileptic activity. GABA receptors are mostly confined to brain, spinal cord, cerebral cortex, cerebellum, and hippocampus. Benzodiazepines have limited hemodynamic effects; however, there are several important adverse effects of benzodiazepines that are important to understand when using them in patients with critical illness [51]. Benzodiazepines can cause a dose-related decrease in central ventilation which results in respiratory depression. This respiratory depression is enhanced by the coadministration of opioid medications. Consequently, care should be taken when administering opioids and benzos to ICU patients especially those not receiving mechanical ventilation. Benzodiazepines cause a mild reduction in muscle tone which may be advantageous for mechanical ventilation but could complicate weaning from mechanical ventilation. Propylene glycol toxicity is a rare but feared complication of continuous infusion of benzodiazepines such as lorazepam [52, 53]. Lorazepam can dissolve in either propylene glycol or a lipid emulsion in order to allow it to become a useful liquid injectable. If propylene glycol is used, it along with its metabolites can accumulate and cause several adverse effects including metabolic acidosis, acute tubular necrosis, and multi-organ failure. Propylene glycol is considered safe and while toxicity can occur with normal doses in patients with normal renal function, toxicity usually occurs in patients receiving doses of propylene glycol exceeding 0.1 mg/kg/h and/or those with renal impairment [52, 53]. In order to identify

propylene glycol accumulation, providers should monitor the osmol gap in patients receiving doses of lorazepam greater than 50 mg or 1 mg/kg with osmol gaps greater than 10–15 suggesting significant propylene glycol accumulation [54]. Midazolam is water soluble and thus the risk of propylene glycol toxicity is nonexistent.

In addition to the stated adverse effects, patients can develop tolerance to benzodiazepines after only a few hours of treatment [55]. Patients can also develop physiologic dependence on benzodiazepines, and these medications must be weaned with caution as withdrawal can occur. Enteral lorazepam or diazepam may help limit benzo withdrawal and facilitate safer and more effective benzodiazepine weaning. Finally, specific benzodiazepines such as lorazepam have been associated with delirium and all of the adverse consequences of delirium [56]. The precise mechanism underlying this association is not known. The combination of the adverse systemic effects and the association with delirium cause many ICU providers to limit the use of benzodiazepines in ICU patients. One important strategy to this end is daily sedation holidays from benzodiazepines which have been shown to decrease the duration of mechanical ventilation while at the same time maintaining patient safety [57].

## 22.8 Propofol

Propofol is widely used in intensive care units. Propofol is most commonly used as a sedative and as an induction agent when patients in the ICU require intubation. Propofol is only available in IV formulation. Bolus dosing of propofol is traditionally used in the ICU for induction prior to intubation, while continuous infusion is routinely used to provide sedation for patient requiring mechanical ventilation. Propofol is preferred over benzodiazepine as a sedative for mechanical ventilation as benzodiazepines have been shown to result in longer durations of mechanical ventilation compared to propofol even when intermittent doses of benzodiazepines are used in combination with sedation holidays [48, 58]. In addition to being an effective sedative for mechanical ventilation, propofol has several other favorable properties that have resulted in it being a mainstay in many ICUs.

### 22.8.1 Propofol Pharmacokinetics

Propofol is extremely lipid soluble but almost entirely insoluble in water. As a result, propofol has to be formulated in a white aqueous emulsion usually composed of soybean oil and purified egg phosphatide [51]. There are water-soluble formulations of propofol such as fospropofol; however, these are not as widely used as propofol especially in patients with critical illness. Propofol is metabolized via conjugation by the liver to propofol-glucuronide, 4-(2,6-diisopropyl-1,4 quinol)-sulfate, and 4-(2,6-diisopropyl-1,4-quinol)-glucuronide [59]. These metabolites are not active and are renally excreted. Clearance of propofol is not significantly affected by renal or hepatic dysfunction [59]. However, propofol clearance can be slower in patients with critical illness likely secondary to decreased hepatic blood flow [56]. Further, there is a slightly longer recovery time following prolonged infusions of propofol because it can accumulate in peripheral tissues [60].

### 22.8.2 Propofol Pharmacodynamics

Propofol is an agonist of $GABA_A$ receptors and may have some NMDA blockade resulting in decreased glutamatergic activity [51]. Propofol enhances the effects of glycine which is one of the chief CNS inhibitors and also inhibits sodium channels and 5HT3 receptors [51]. Propofol affects several systems; however, its most important effects are on the central nervous system, cardiovascular system, and respiratory system.

In the central nervous system, propofol causes unconsciousness, amnesia, decreased cerebral metabolic rate, decreased cerebral blood flow, decreased intracranial pressure, and decreased intraocular pressure [51]. Because of its high lipid solubility, propofol is able to cross the blood–brain barrier and has a rapid onset of

action (~30 s) following bolus dosing. Recovery of consciousness following propofol administration is rapid (~3 to 10 min) because the drug redistributes rapidly [51].

Propofol causes a significant decrease in arterial blood pressure when given as a bolus dose [51]. The primary mediator of this decrease in arterial blood pressure is a decrease in the systemic vascular resistance; however, propofol also causes decrease in preload and a decrease in contractility [51]. These effects combine to cause hypotension which is common after bolus dosing of propofol [51]. In addition to hypotension, propofol also impairs the normal baroreceptor-mediated responses to hypotension [51]. Propofol-induced hypotension can be reversed via the stimulation from intubation or via vasoactive medications. If bolus dosing of propofol is required, hypotension can be reduced by slow administration of the bolus. Hypotension with infusion of propofol is rare [51].

Bolus dosing of propofol results in apnea. The bolus dose resulting in apnea will be patient dependent. Infusions of propofol decrease respiratory rate and reduce patient's tidal volume. Propofol also inhibits the hypoxic ventilatory drive and decreases the ventilatory response to carbon dioxide. Propofol-induced ventilatory depression if enhanced by concomitant use of opioids. Finally, both infusions and bolus dosing of propofol cause airway obstruction thus professional trained in airway management should be available anytime propofol is to be used.

In addition to the adverse effects that have already been discussed, propofol has many other adverse effects that warrant further discussion. Propofol is notorious for causing pain on injection, and it is estimated that approximately 40% of patient experience pain on injection [51]. Propofol causes both immediate and delayed pain [61]. The immediate pain is thought to be secondary to irritation of the veins endothelium, and the delayed pain is thought to be secondary to propofol-induced release of mediators from the kinin cascade [61]. Some commonly used strategies to help reduce pain from propofol injection include injecting into larger veins, giving a small amount of lidocaine prior to propofol injection, and mixing a small amount of lidocaine with the propofol prior to injection [51]. Allergic reactions to propofol have been reported [51]. Propofol can cause hypertriglyceridemia especially in those patients receiving high infusion rates of propofol and concomitant administration of parenteral lipids. As a result, patients on prolonged infusion of propofol should have their lipids monitored routinely [51]. Finally, the most feared complication of propofol use is propofol-related infusion syndrome (PRIS). PRIS is a rare condition that has been reported in patients receiving high-dose propofol infusions, usually greater than 83 mcg/kg/min, for more than 48 h [62–64]. PRIS is thought to be caused by propofol-induced impairment of mitochondrial oxidative phosphorylation and free fatty acid utilization which results in lactic acidosis and myocyte necrosis [65]. The presentation of PRIS is variable but some commonly reported features include rhabdomyolysis, myocardial failure, acute renal failure, severe metabolic acidosis, cardiac arrest, dyslipidemias, and hypotension [25, 65]. If there is concern for PRIS, the propofol infusion should be stopped immediately and any metabolic derangements should be corrected promptly.

## 22.9 Dexmedetomidine

Dexmedetomidine is one of the newer medications being used in the ICU. Dexmedetomidine is predominately used for sedation; however, it can also be used to help facilitate awake intubations and as an adjuvant in neuraxial anesthesia. Dexmedetomidine is available in IV and intranasal formulation with the intravenous route being the most widely used. Dexmedetomidine is most commonly used as a continuous infusion, and boluses of dexmedetomidine are frequently given as loading doses prior to the start of continuous infusions. Dexmedetomidine is growing in popularity as a sedation drug in the ICU with some provider preferring it over both propofol and benzodiazepines. The cause of this increase in popularity is likely multifactorial; however, beneficial effects of dexmedetomidine such as its

ability to maintain spontaneous respiration, its ability to produce a level of sedation that more closely mimics sleep, and its ability to maintain arousability are likely important factors [66]. In addition to these effects, dexmedetomidine also has several other favorable pharmacodynamic and pharmacokinetic properties which make it a promising medication for patients with critical illness.

### 22.9.1 Dexmedetomidine Pharmacokinetics

Dexmedetomidine is metabolized in the liver via the combination of *n*-glucuronidation, *n*-methylation, and CYP2A6. To date, there are no active or toxic metabolites of dexmedetomidine. Dexmedetomidine is excreted predominantly by the urine (95%) with a small amount being excreted in the feces (5%) [67]. Dexmedetomidine clearance can be decreased in patients with decreased hepatic function thus the dose should be decreased in this population. The pharmacokinetics of dexmedetomidine are preserved in patients with severe renal disease; however, the increased volume of distribution can lead to prolonged sedation and thus dose decrease are also recommended in this patient population [66–69]. The onset of action following a loading dose of dexmedetomidine is 5–10 min, the time till peak effects is 15–30 min, and the duration of effect is 60–120 min [66–69].

### 22.9.2 Dexmedetomidine Pharmacodynamics

Dexmedetomidine is a selective alpha 2 adrenergic agonist. Dexmedetomidine causes sedation and analgesia, and opposes some of the downstream effects of the sympathetic nervous system. The body systems predominantly affected by dexmedetomidine are the central nervous system and the cardiovascular system.

Within the central nervous system, the primary area impacted by dexmedetomidine is the locus coeruleus. The locus coeruleus is important in the regulation of arousal and autonomic activity. Dexmedetomidine inhibits the release of norepinephrine in the locus coeruleus. This inhibition of norepinephrine results in sedation and decreased alertness. The sedation produced by dexmedetomidine is distinct from that produced by other commonly used sedatives and is often described as "cooperative sedation." Further, of all the medications used to induce sedation, dexmedetomidine most closely mimics sleep. This is an important feature of dexmedetomidine as sleep deprivation and disruptions in sleep cycle are common in many ICUs and have been associated with delirium [70, 71]. Dexmedetomidine has been shown to produce comparable sedation to propofol and midazolam for moderate to light sedation (RASS 0 to −3); however, dexmedetomidine results in unreliable sedation when RASS scores of −4 or less are desired. Dexmedetomidine does not reliably produce amnesia and thus dexmedetomidine should not be used as the sole agent if amnesia is the primary objective. Finally, in addition to its effects on the locus coeruleus, dexmedetomidine also affects the presynaptic C-fiber and postsynaptic spinal neurons of the dorsal horn [72, 73]. These properties make intrathecal dexmedetomidine a useful adjuvant for patients receiving intrathecal analgesia, and intrathecal dexmedetomidine has been shown to prolong the duration of motor and sensory blockade of local anesthetics and decrease visual analog pain scores [72, 73].

Dexmedetomidine's cardiovascular effects are dependent on the plasma concentration [74]. At low plasma concentrations (0.7–1.2 ng/ml), dexmedetomidine results in decreased heart rate and decreased blood pressure with no significant changes in systemic vascular resistance, central venous pressure, or pulmonary capillary wedge pressure [74]. It is important to mention that bolus doses of dexmedetomidine have been shown to cause transient hypertension with reflex bradycardia [74]. At higher plasma concentrations (1.9 ng/ml), dexmedetomidine causes further decreases in heart rate, cardiac output, and stroke volume [74]. Additionally, higher plasma concentrations result in increases in blood pressure, systemic vascular resistance, and peripheral

vascular resistance [74]. It is often not feasible to check plasma concentrations of dexmedetomidine for patient in the ICU and thus providers must be vigilant when using dexmedetomidine infusions at both high and low doses.

The most common adverse effects of dexmedetomidine are bradycardia and hypotension. Other rare but possible side effects include agitation, headaches, hyperhidrosis, tremor, nausea, and vomiting [75, 76]. Importantly, dexmedetomidine has not been shown to cause respiratory depression. Further, withdrawal symptoms following dexmedetomidine infusions are rare and the rebound hypertension and tachycardia associated with other alpha-2 agonist is not common with dexmedetomidine [75, 76].

**Key Points**

- Untreated pain begets problematic physiologic consequences across multiple organ systems.
- Effective multimodal analgesia commonly includes a combination of pharmacologic agents to achieve optimal pain control while minimizing untoward side effects.
- In order to provide safe and effective sedation and analgesia, avoid oversedation, and minimize adverse effects, ICU providers must be well-versed in the uses, pharmacodynamics, pharmacokinetics, and adverse effects of the medications commonly used in the ICU for analgesia and sedation.

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# Part VII

# Ethical Considerations

# Brain Stem Death

# 23

Argyro Zoumprouli and Konstantina Ilia Karydi

## 23.1 Historical Overview

Historically, death was believed to occur at the moment that all vital signs ceased permanently. For scientists, death in the past coincided with the permanent arrest of all bodily functions. Since the mind is the expression of brain functions, the cessation of its activity was assumed as part of the physical effects of death. For philosophers and religions, death signifies the departure of the soul and the mind alongside with the cessation of the bodily functions.

Death causes the irreversible loss of those essential characteristics which are necessary to the existence of a living human being. Thus, the definition of death should be considered as "the irreversible loss of the capacity of consciousness combined with the irreversible loss of the capacity to breathe".

Death took a different meaning after the invention of mechanical ventilation, and patients with catastrophic brain injury were supported in hospitals. This drastic intervention created a new state. In this comatose state, the brain function came to an end, but the rest of the bodily functions were supported by intensive care interventions.

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One of the earliest references (1902) of the concept of brain death was made by H. Cushing when he described a patient who was maintained alive by artificial ventilation for 23 h. The landmark article (1959) by Mollaret and Goulon (neurologists) was an extension of previous anecdotal cases. The authors presented a case series of 23 patients with a new type of coma: "coma dépassé". This neurological state was associated with complete absence of cognitive and vegetative functions, which went beyond the deepest comas so far described.

Despite the ethical dilemmas that this observation generated, the authors managed to give a precise description of what is nowadays called "brain death". This description included the neurological (clinical and electroencephalographical (EEG)) characteristics as well as observations of diabetes insipidus, cardiovascular instability, hormone derangement and neurogenic pulmonary oedema. Later reports of coma dépassé linked this neurological state with lack of cerebral blood flow.

In 1968, the report of the Ad Hoc Committee of the Harvard medical school followed, "defining irreversible coma as a new criterion for death". This state of coma had the characteristics of unreceptivity and unresponsiveness, the absence of breathing and the loss of brain stem reflexes.

Later, in 1971, Mohandas and Chou (neurosurgeons) published the Minnesota code of Brain Death Criteria. Their definition included specific



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time of apnea (4 min of disconnection), the need for exclusion of metabolic factors, longer observation time (12 h) and a known cause of irreparable intracranial damage. Most importantly, they introduced that the irreversible damage to the brain stem was a critical component.

In 1976, the conference of Royal colleges and faculties in the United Kingdom (UK) published the memorandum on brain death. This later (1995) changed to brain stem death, and the UK's position was: "if the brain stem is dead, the brain is dead, and if the brain is dead, the person is dead".

Since then, relevant professional bodies worldwide have published criteria for confirmation of death with neurological criteria, describing the conditions under which the diagnosis should be made.

The incentive of diagnosing death using neurological criteria was derived by the need for defining futility and finding a way to help physicians to withdraw support in cases that the damage of the brain is irreversible rather than the need to facilitate organ transplantation.

## 23.2 Brain Stem Death or Whole Brain Death?

There are differences of the definition of death in different countries even when we apply neurological criteria. In many countries, the neurological criteria include the irreversible cessation of the function of the whole brain, including the brain stem. Most of these countries require the use of confirmatory tests such as EEG or demonstration that the cerebral blood flow has ceased.

In contrast, there are also countries that align the concept of brain death with that of brainstem death. In the UK, this definition exists and is used since 1995. In these cases, confirmatory tests are not required.

## 23.3 Clinical Examination

Although the clinical examination, who is performing it, how and when are varying in each country, there are universal principles that should be followed to reach a safe and correct diagnosis. The clinicians involved should be senior and competent, and the tests should be repeated twice by two different clinicians. Although the specialty of the clinicians is not strictly specified, they should not be members of the organ procurement or transplant teams.

**Preconditions** The patient should be in deep coma, totally unresponsive and apneic (ventilator dependent). There should be no doubt that the coma is due to irreversible brain damage. The underlying cause of the coma should be known.

**Exclusions** Confounding conditions or reversible causes of the coma and the absence of brain stem activity/reflexes should be excluded.

*Temperature (Table 23.1)* Primary hypothermia as the cause of unconsciousness should be excluded. Although brain stem reflexes are abolished if the temperature falls below 28 °C, temperatures between 32 and 34 °C are occasionally associated with impaired levels of consciousness. In clinical practice, it is recommended the temperature to be above 34 °C at the time of the assessment. The effects of hypothermia on the central nervous system (CNS) are reversible when the temperature is corrected.

**Table 23.1** Effects of temperature on CNS and neuromuscular coupling

| Core temperature | CNS | Neuromuscular |
|---|---|---|
| 35–32 °C | Apathy, dysarthria and impaired consciousness | Increased muscle tone, shivering and ataxia |
| 32–28 °C | Hallucinations, reduced consciousness and pupillary dilatation | Hyporeflexia and rigidity |
| <28 °C | Coma, impairment of brainstem auditory evoked potentials, absent corneal reflex and absent bulbar reflex | Areflexia |

*Drugs* It is essential to review the history of drug administration or drug ingestion before brain stem testing. The presence of drugs and toxins that can either cause reversible coma or mimic brain stem death should be excluded (history, and toxicology screening).

Barbiturates and tricyclic antidepressants, in particular, can cause neurological states similar to brain stem death. The effects of sedative drugs on the CNS can be prolonged in the presence of hypothermia, renal or hepatic failure. Also, lipophilic drugs are cumulative when used as prolonged infusions.

The time between discontinuation of CNS depressant drugs and safe brain stem testing is difficult to be determined and depends on the pharmacokinetics of the drug, the length of infusion, the total dose, the renal and hepatic metabolic function, body temperature and prior use of therapeutic hypothermia. A safe calculation is by using five times the drug's half-life, but also taking into account the factors above.

When possible, plasma levels should be measured. It is not recommended to perform brain stem test if thiopentone plasma levels are >5 mg/L, or midazolam levels are >10 μg/L. Levels of alcohol below the legal driving limit are considered safe.

The presence of muscle relaxants should also be excluded by reviewing the drug administration and with a peripheral nerve stimulator.

*Metabolic* Severe endocrine, metabolic and electrolyte abnormalities may impair consciousness and CNS function or may indicate ingestion of substances that may have been missed on drug/toxic screen. Some electrolytes, although do not have an effect on CNS, may impair neuromuscular transmission and cause myopathy and even flaccid quadriplegia in extremely low levels. However, brain stem death is accompanied by metabolic and electrolyte imbalance, and aiming for normal range values may be unrealistic.

Throughout the clinical examination, mean arterial pressure should be maintained >60 mmHg (UK guidelines) or systolic blood pressure should be >100 mmHg (American guidelines). The UK code of practice has given the safe range of electrolytes for brain stem testing as guidance. (Table 23.2)

*Other Causes of Apnea (Table 23.3)* The ventilator settings should be carefully reviewed, and appropriate levels of ventilator sensitivity should be set. The presence of neuromuscular blocking agents should be excluded (use of peripheral nerve stimulator).

Severe neuromuscular disorders that can abolish brain stem reflexes should be excluded. Establishing a clear diagnosis of irreversible brain damage before brain stem testing is paramount.

Head injuries are commonly associated with cervical spinal injuries. High-level cervical spinal injuries can cause central apnea, and in these cases, ancillary testing should always be performed.

**Table 23.2** Safe electrolyte range for performing brain stem testing

| Electrolyte | Safe range for brain stem testing (mmol/L) |
|---|---|
| Sodium | 115–160 |
| Potassium | >2.0 |
| Glucose | 3.0–20 |
| Phosphate | 0.5–3.0 |
| Magnesium | 0.5–3.0 |

**Table 23.3** Levels of spinal cord injury and validity of apnea test

| Levels | Valid apnea test | Rational |
|---|---|---|
| $C_1$–$C_3$ | No<br>Ancillary tests are needed | Ascending oedema can reach the level of the medulla and cause central apnea |
| $C_4$–$C_6$ | CAUTION<br>Ancillary tests are highly recommended | Phrenic nerve originates from $C_4$<br>There are case reports of central apnea even with injuries at $C_5$ level |
| $C_6$–$T_1$ | Yes | Apnea test is not affected |

## 23.4 Brain Stem Clinical Examination

The absence of the following brain stem reflexes should be confirmed. Clinical examination should only proceed if the preconditions have been met and confounders have been carefully excluded.

- Pupillary response to light (sensory II, motor III):
  The direct and indirect response to bright light should be absent in both eyes.
- Corneal reflex (sensory V, motor VII):
  There is no corneal reflex when the cornea is touched with a cotton swab (inability to blink).
- Oculovestibular response (sensory VIII, motor III, VI):
  There are no eye movements during or after the injection of 50 ml of ice-cold water into the external auditory meatus. A direct inspection should first confirm the patency of the canal. The head should be elevated to 30°, and the injection of the water should be over 1 min. Observation should exclude delayed response (after the injection).
- Motor response to supraorbital pain (sensory V, motor VII):
  There should be no facial grimacing or limb movement in response to supraorbital pressure.
- Cough and gag reflex (sensory IX, motor X):
  There should be no cough reflex during bronchial suctioning or gag reflex during stimulation of the posterior larynx with a spatula or Yankauer suction tip.
- Apnea (Table 23.4):
  Performance of apnea testing should be reserved as the last test of brainstem function. There are variations of how to perform the apnea test internationally. The principles though are the same. The $CO_2$ should rise abruptly from a predetermined baseline to result in a decrease of the cerebrospinal fluid's pH which triggers the respiratory centres in the medulla oblongata. To achieve this, the patient is disconnected from the ventilator, and oxygenation is maintained via either an endotracheally placed catheter connected to an oxygen flow metre (flow 2 l/min) or application of continuous positive airway pressure (CPAP) via a T-piece with an adjustable pressure limiting valve. During the test, the patient is observed continuously for any respiratory effort.
  At the end of the test, the patient is reconnected to the ventilator and ventilated in order for the $CO_2$ to reach pretest values.

During apnea testing, any respiratory muscle activity (including accessory muscles) is considered as breathing effort, and the test should be stopped at that point. In this case, brain stem death is precluded. The apnea test should be aborted if oxygen saturation falls persistently <85%. In patients with chronic $CO_2$ retention, the apnea test should be commenced after the $CO_2$ is raised to a level that causes a mildly acidotic pH.

The legal time of death is the time of the conclusion of the first set of tests for determination of brain death. In countries where two tests are a requirement, there is no specific timeframe between the two sets of clinical examination. In the USA, it is recommended to wait for 6 h.

## 23.5 Ancillary Testing

Brain death is a clinical diagnosis. Confirmatory tests are not mandatory in all countries. In all cases, ancillary testing to determine the absence of intracranial flow or electrical brain function is indicated when comprehensive neurological examination cannot be reliably performed or evaluated (extensive maxillofacial injuries, high cervical spinal injuries, presence of pharmacological or metabolic cofounders). Ancillary testing does not eliminate the need for carrying out the clinical tests by two physicians to the extent possible. None of these ancillary tests can replace the clinical examination, and none can give conclusive answers.

*Cerebral Angiography* When the intracranial pressure exceeds arterial perfusion pressure, it causes cerebral-circulatory arrest. A selective

**Table 23.4** Variations of apnea test

| Country | Apnea test |
|---|---|
| UK | Pre-oxygenate the patient with 100% oxygen<br>Maintain $SpO_2 > 95\%$ and reduce minute ventilation to raise $CO_2$. Confirm that the $PaCO_2$ is at least 6.0 KPa and pH is less than 7.40<br>After disconnecting the patient from the ventilator, deliver oxygen via an endotracheal catheter with a flow of 5 L/min. Observe for 5 min. $PaCO_2$ should have an increase of more than 0.5 KPa from starting $PaCO_2$<br>*Aim: Starting $PaCO_2 \geq 6.0$ KPa and pH < 7.40*<br>*$PaCO_2$ should rise > 0.5 kPa*<br>*Time of observation: 5 min* |
| Australia | Pre-oxygenate the patient with 100% oxygen for at least 5 min. Mechanically ventilate to mild hypercarbia ($PaCO_2$ ~ 45 mmHg [6 KPa]) before disconnecting the patient from the ventilator. Disconnect the patient from the mechanical ventilator. At the end of the period without mechanical ventilation, apnea must persist in the presence of an adequate stimulus to spontaneous ventilation, i.e. an arterial $PaCO_2 > 60$ mmHg (8 kPa) and an arterial pH < 7.30. If starting from normocapnia, the $PaCO_2$ is likely to be >60 mmHg (8 KPa) after 10 min<br>*Aim: $PaCO_2 > 60$ mmHg (8 kPa)*<br>*Time of observation: Not clearly defined* |
| USA | Pre-oxygenate the patient with 100% oxygen for at least 100% oxygen to a $PaO_2 > 200$ mmHg. Reduce minute ventilation to normocapnia. Maintain $SpO_2 > 95\%$ and obtain baseline arterial blood gas. Disconnect the patient from the ventilator<br>Preserve oxygenation via insufflation catheter through the endotracheal tube and deliver 6 L/min oxygen. Look carefully for respiratory movements for 8–10 min. If no respiratory effort is observed, repeat arterial blood gas after 8 min. If the $PaCO_2 > 60$ mmHg, the test supports the clinical diagnosis of brain death<br>*Aim: $PaCO_2 > 60$ mmHg (8 kPa)*<br>*Time of observation: 8–10 min up to 15 min if needed* |
| Canada | It is recommended that a $PaCO_2 > 60$mmHg be achieved to ensure that an adequate stimulus is presented to the respiratory centre. The arterial or capillary blood pH should be <7.28 by the end of the apnea test. An initially normal $PaCO_2$ before apnea testing begins (40 ± 5 mmHg). Pre-oxygenation with 100% oxygen allowing a $PaO_2 > 200$ mmHg<br>During the apnea test, it is suggested that 100% oxygen is delivered via a cannula placed in the trachea. The arterial $PaO_2$, $PaCO_2$ and pH should be checked at 8–10 min. The apnea test is positive if no respirations are observed over the 8–10 min, provided that the $PaCO_2$ rises to greater than 60 mmHg<br>*Aim: $PaCO_2 > 60$ mmHg*<br>*$PaCO_2$ should rise > 20 mmHg*<br>*$pH \leq 7.28$*<br>*Time of observation: 10–15 min* |

four-vessel cerebral angiogram allowing to visualize both anterior and posterior circulation is considered the gold standard of the ancillary tests. External carotid circulation should be evident, and there should be no intracerebral filling at the level of the carotid bifurcation or circle of Willis. Filling of the superior sinus may be present. The reliability of cerebral angiography is very good, but it requires expertise that may be available only in neuroscience units, requires transporting a potentially unstable patient to the radiology department and is an invasive technique with potentially serious complications.

*Radionuclide Imaging Techniques* The most common tracer used is the Tc-99m hexamethyl propylene-amine oxime (Tc-99m HMPAO). It is lipid soluble and crosses the blood–brain barrier, providing information on arterial cerebral blood flow and uptake of tracer within perfused brain tissue. The absence of isotope uptake produces a characteristic "hollow skull" phenomenon, while increased extracranial flow may result in enhancement of the nose ("hot none sign"). This picture supports the diagnosis of brain death. The sensitivity of the technique improves with repetition of the test within 24–48 h.

*Transcranial Doppler Ultrasonography* This technique requires substantial clinical experience, but the advantages are its portability and noninvasiveness. It should be noted that the absence of Doppler signals does not necessarily mean lack of cerebral flow as 10–25% of patients do not have trans-temporal windows. In brain death, the typical picture is systolic spikes or oscillating flow in any cerebral artery. Posterior and anterior circulation should be examined.

*Electroencephalography* Electroencephalography (EEG) has long been used as a supplementary test for brain death. In some countries, it remains mandatory despite its lack of accuracy. The sensitivity and specificity of the technique are reported around 90% with up to 20% false-negative results. It should be noted that although EEG can detect cortical activity, it cannot exclude or confirm deeper cerebral or brainstem function. Hypothermia, metabolic abnormalities, drug presence and electrical interference are some of the limitations. In Canada, EEG is no longer recommended as an ancillary test.

*Somatosensory Evoked Potentials* Both brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SSEP) have been used as ancillary tests. While the early components of BAEPs and SSEPs are minimally affected by sedative drugs, hypothermia, drugs and metabolic disorders can affect middle and late somatosensory and auditory potentials.

False-positive (patient does not meet the clinical criteria for brain death) results have been recorded with transcranial Doppler, radionuclide imaging and CT angiogram. This emphasizes the importance of a robust clinical diagnosis.

## 23.6 Red Flags and Challenging Cases

### 23.6.1 Time of Testing

Not all the countries have a set timeframe between loss of brainstem reflexes and clinical testing. Most professional bodies recommend waiting between 4 and 6 h from the time of the loss of the last brain stem reflex.

When the cause of death is anoxia, it is recommended to wait for 24 h before testing.

In cases that therapeutic hypothermia was used (i.e. out of hospital cardiac arrest), it is advised that the tests to be performed 24 h after rewarming to normothermia.

### 23.6.2 Isolated Brainstem Pathology

An acute irreversible neurological injury may be confined to the brain stem (pontine haemorrhage, basilar artery embolic stroke and gunshot wounds). In these cases, the rest of the brain may initially not be affected until obstructive hydrocephalus develops that in turn will cause increased intracranial pressure. More extended observation periods are recommended in these cases (German guidelines suggest 72 h of observation). The clinical confirmation is adequate. The use of ancillary tests may confuse the picture as cerebral blood flow may be maintained and EEG may show nonreactive alpha or spindle patterns.

### 23.6.3 Neuromuscular Disorders

There have been reported severe cases of Guillain–Barre syndrome that resemble brain stem death. It is essential to establish a clear cause of the irreversible damage to the brain before undertaking the clinical examination of the brainstem.

### 23.6.4 Pathophysiological Changes During Brain Stem Death

In high intracranial pressure states, herniation of the diencephalon compresses the pituitary stalk against the diaphragma sellae. If the pituitary gland itself is damaged, the posterior lobe is usually involved while the anterior lobe is

spared as it is protected within the sella turcica. Also, the anterior pituitary lobe of the basal part of the hypothalamus is normally perfused by extradural blood supply (cavernous portion of the carotid artery). These mechanisms explain why after coning, diabetes insipidus is observed in the majority of brain dead patients (65%) but not all and why the anterior part of the pituitary gland may still work despite the lack of intracranial blood flow. Diabetes insipidus causes sudden free water loss and results in intravascular depletion, hypernatremia, hypotension and cardiovascular instability.

In sharp increases of intracranial pressure, a massive outflow of catecholamines occurs. This catecholamine surge has an adverse effect on the myocardium. ECG changes vary from increased ST segments, inversion of T waves and widening of QRS complexes to QT interval prolongation. Echocardiographically, there is evidence of decreased ejection fraction and a plethora of wall motion abnormalities. These abnormalities may reflect reversible or irreversible myocardial injury.

The hypotension that follows the high catecholamine state of brain stem death is probably caused by the autonomic uncoupling leading to the loss of the baroreceptor sensitivity and the loss of the heart rate variability. In addition, loss of spinal cord sympathetic activity due to herniation through the foramen magnum causes vasodilatation.

Neurogenic pulmonary oedema has been observed after neurological catastrophes. The exact mechanism is not fully understood. It seems to be a combination of increased pulmonary vascular permeability and increased capillary hydrostatic pressure (Table 23.5).

Coagulation abnormalities are present few days after brain stem death either due to the release of plasminogen activator and thromboplastin from the injured/necrotic brain or the effect of the catecholamines on platelet function.

Because of the physiological instability that follows brain death, it is sometimes challenging to maintain the levels of homeostasis that is required to perform a valid clinical examination.

**Table 23.5** Theoretical mechanisms of neurogenic pulmonary oedema formation

| | |
|---|---|
| Pulmonary vascular permeability | • Increased protein pulmonary oedema fluid<br>• Neuropeptide Y, alpha adrenergic agonists, pulmonary microvascular injury from rapid increase of in pulmonary pressure and inflammatory mechanisms |
| Pulmonary hydrostatic pressure | • Pulmonary venous constriction<br>• Increased systemic venous constriction and increased venous return<br>• Failure of left ventricle (direct myocardial injury, myocardial stunning, increased systemic afterload and increased vagal tone) |

Some hospitals have introduced "catastrophic brain injury protocols" (Table 23.6) to maintain physiology until the brain stem tests are performed. Robust brain stem testing is essential as it eliminates all possible doubt about survivability while minimizes the suffering of the family as it confirms the diagnosis of death in a timely manner.

**Key Points**

- The definition of death should be considered as the irreversible loss of the capacity of consciousness combined with irreversible loss of the capacity to breathe.
- There are differences of the definition of death in different countries even when we apply neurological criteria.
- The underlying cause of the coma should be known and there should be no doubt that the damage is irreversible.
- Clinical examination should proceed only if the preconditions have been met and confounders have been carefully excluded.
- Ancillary tests can help confirm the findings of the clinical examination but cannot replace it.

**Table 23.6** Catastrophic brain injury pathway

| | | | |
|---|---|---|---|
| Catastrophic brain injury care pathway | | | |
| Do you suspect brain stem death? | | Yes/No | |
| Are pupils fixed and dilated and GCS 3/15? | | Yes/No | |
| Is the patient apnoeic (not triggering ventilator)? | | Yes/No | |
| Are cough and gag reflexes absent? | | Yes/No | |
| Has a decision to stop neuroprotection been made? | | Yes/No | |
| **If "Yes" to all of above questions, please commence the following checklist** | | | |
| **Time starting the protocol……** | | | |
| **Page specialist nurse on organ donation** ☐ **(time:……)** | | | |
| **Ventilation** | | | |
| Targets: $pO_2$ 8–14 kPa | | ☐ | |
| $pCO_2$ 5–6.5 kPa | | ☐ | |
| ***Additional actions*** | | | |
| ☐ Sit up the patient at an angle of approx. 30–45° and turn 3-hourly | | | |
| ☐ Recruitment manoeuvre by medical team to optimise lung ventilation (e.g., CPAP mode 25–40 cm $H_2O$ for 30–50 s) | | | |
| ☐ Set PEEP 8–10 cm $H_2O$ | | | |
| ☐ Lung protective ventilation ($V_T$ 6–8 mL/kg, peak pressure ≤ 30 cm $H_2O$) | | | |
| ☐ Repeat recruitment manoeuvre if $pO_2$ ≤ 10.0 kPa | | | |
| ☐ Review ventilation 2-hourly—repeat recruitment manoeuvre if deteriorating | | | |
| **Circulation** | | | |
| ☐ Insertion of central line | | | |
| ☐ Calibrated LiDCO (please record LiDCO machine number: ……..) | | | |
| ☐ Start cardiovascular algorithm (time:……) | | | |
| **Renal and electrolytes** | | | |
| Targets: Urine output 0.5–2.5 mL/kg/h | ☐ | Na 135–150 mmol/L | ☐ |
| Mg > 0.8 mmol/L | ☐ | K+ 4.0–5.5 mmol/L | ☐ |
| Ca ionised 1.0–1.3 mmol/L | ☐ | | |
| ***Additional actions*** | | | |
| ☐ If polyuria (>300 mL/h for 2 h), ensure adequate volume replacement | | | |
| ☐ If DI, bolus DDAVP 0.5 mcg—consider vasopressin infusion if not started | | | |
| ☐ If oliguria, despite optimisation of CVS, consider dobutamine/dopamine | | | |
| **Hormones and haematology** | | | |
| Targets: BM 4.0–9.0 mmol/L | | ☐ | |
| HB ≥8 g/dL, Plt > 50 × $10^9$/L | | ☐ | |
| INR <2.0, APTTR <1.5, Fib >2.0 g/L | | ☐ | |
| ***Additional actions*** | | | |
| ☐ Start insulin at one unit per hour and titrate to achieve BM control of 4–9 mmol/L. If hypoglycaemia, continue insulin and supplement with 20% dextrose—do not stop insulin altogether | | | |
| ☐ Continue enteral feed at low volume (10–30 mL/h) | | | |

Courtesy of Argyro Zoumprouli, St. George's University Hospitals NHS Foundation Trust, London, UK

## Suggested Readings


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# Organ Donation in Critical Care

# 24

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## 24.1 Introduction

Organ donation is considered the "gift of life" as a person donates one or more of their organs to people in need of those. Organ donation happens either after confirmation of death (with the assent of the next of kin) or while the person is alive (after obtaining consent).

For obvious reasons, living donation is limited either to one kidney only or part of the liver. Living donation can be *directed* (to someone we know, related or not) or *non-directed altruistic* when a living person anonymously donates one of their kidneys to a person they don't know. Sometimes, if a person is not a direct "match" for someone they wish to donate, they can donate to someone else, and another person can donate to their intended recipient. This is called paired/pooled donation and is part of the UK Living Kidney Sharing Schemes.

This chapter will focus on deceased donation practices and processes as they take place in intensive care units around the world after confirmation of death. Unfortunately, the need for organs for transplantation is greater than the number of the organs donated, resulting in people dying or experiencing poor quality of life while waiting for a transplant. For this reason, the interest of governments and professional medical bodies has increased in the last ten years. The aim is to make each country self-sufficient in donation and transplantation.

## 24.2 The "Dead Donor Rule"

The ethical platform of deceased organ donation is based on the "dead donor rule" which supports vital organs to be taken only from persons who are declared dead.

To meet this rule, deceased donation has been developed around two different programs: donation after death has been confirmed using neurological criteria (brain stem death or brain death—DBD) and donation after circulatory death (DCD) (Figs. 24.1 and 24.2). This generates the need for robust standards and practices for confirmation of death in a timely manner.

## 24.3 Donation After Brainstem or Brain Death

Although the incentive of diagnosing death using neurological criteria was derived by the need for defining futility in cases that the damage of the brain is irreversible, it allows organ donation to take place before apnea results in cardiac arrest. This

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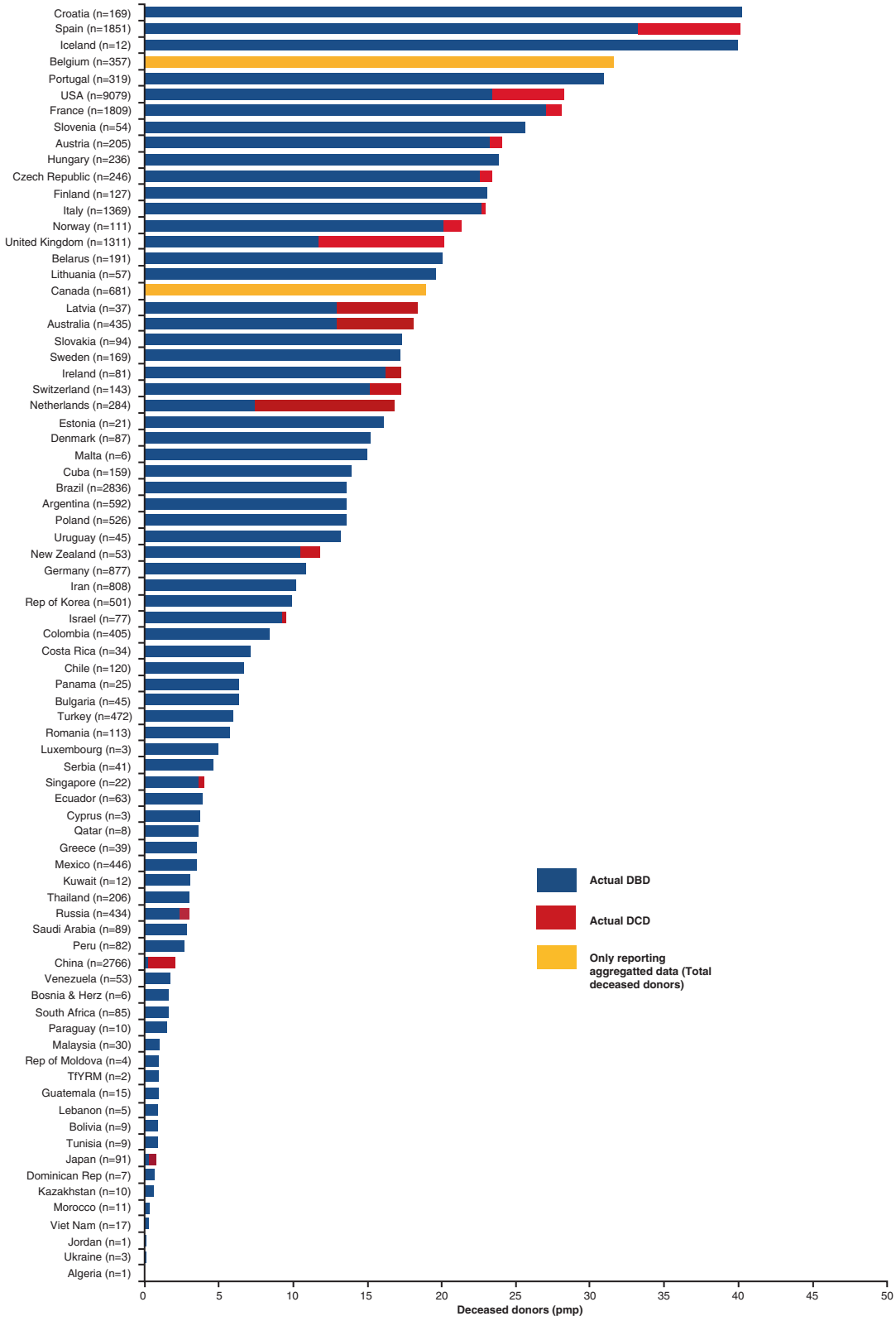



**Fig. 24.1** Donation from deceased persons. Absolute numbers and rates (per million of population of actual deceased donors in 2015). *Data of the WHO-ONT Global Observatory on Donation and Transplantation (2015)

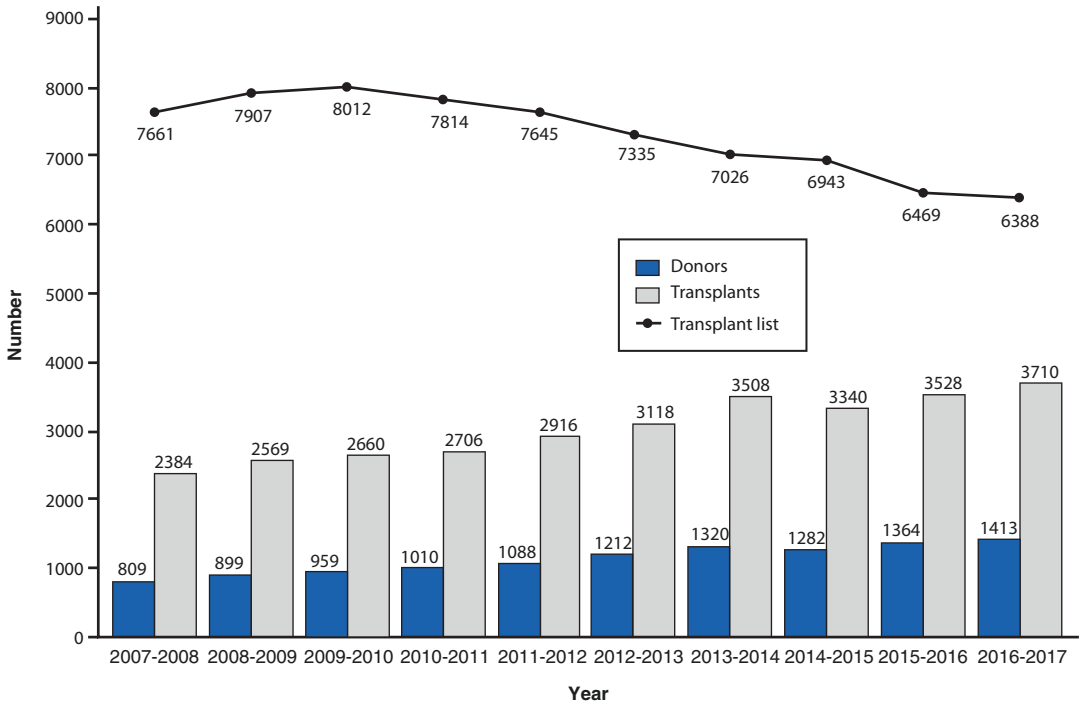



**Fig. 24.2** Number of deceased donors and transplants in the UK, 1 April 2007–31 March 2017 and patients on the active transplant list on 31st March. Source: Transplant activity in the UK, NHS Blood and Transplant. https://www.odt.nhs.uk/statistics-and-reports/

organ donation pathway is described as "donation after brain death" or "DBD" or "heart-beating donation". Compared to donation after circulatory death, it offers the opportunity to retrieve more organs (average DBD 3.7 vs DCD 2.8 organs/donor).

The organs that can be retrieved under these circumstances are kidneys (2), liver, heart, lungs (2), pancreas and small intestine. This means that there is the opportunity for eight different life-changing or lifesaving transplants. However, the physiological changes that occur during brain death present us with challenges to maintain the function of these organs.

### 24.3.1 Donor Optimization

The neuroprotective therapeutic goals in patients with devastating neurological injuries are sometimes harmful to other organs. Brain death is followed by a cascade of physiological changes that include catecholamine surge, myocardial injury, hormonal depletion, hypovolemia, cardiovascular instability, neurogenic pulmonary oedema and clotting abnormalities. In addition, very often, the injury is a result of trauma not necessarily isolated to the brain with injuries to the lungs and myocardium or injuries that cause excessive blood loss. This creates very challenging physiological conditions for the physician who aims to maintain the function of vital organs.

Different organizations worldwide have tried to standardize pathways of treatment for these donors. Although there is still a considerable variation of management but also of application of these protocols, the aims and physiological goals are similar.

Ethically, these interventions are supported on the basis that consent (via family's permission) for organ donation has been given and it is for patient's best overall interest to reach a successful donation.

The fundamental principles of organ donor management are based on the same monitoring and therapeutic tenets used in intensive care units worldwide when caring for the critically ill patient. Effectively after confirmation of brain

death, a therapeutic focus shift from neuroprotective to organ physiology restoration is required.

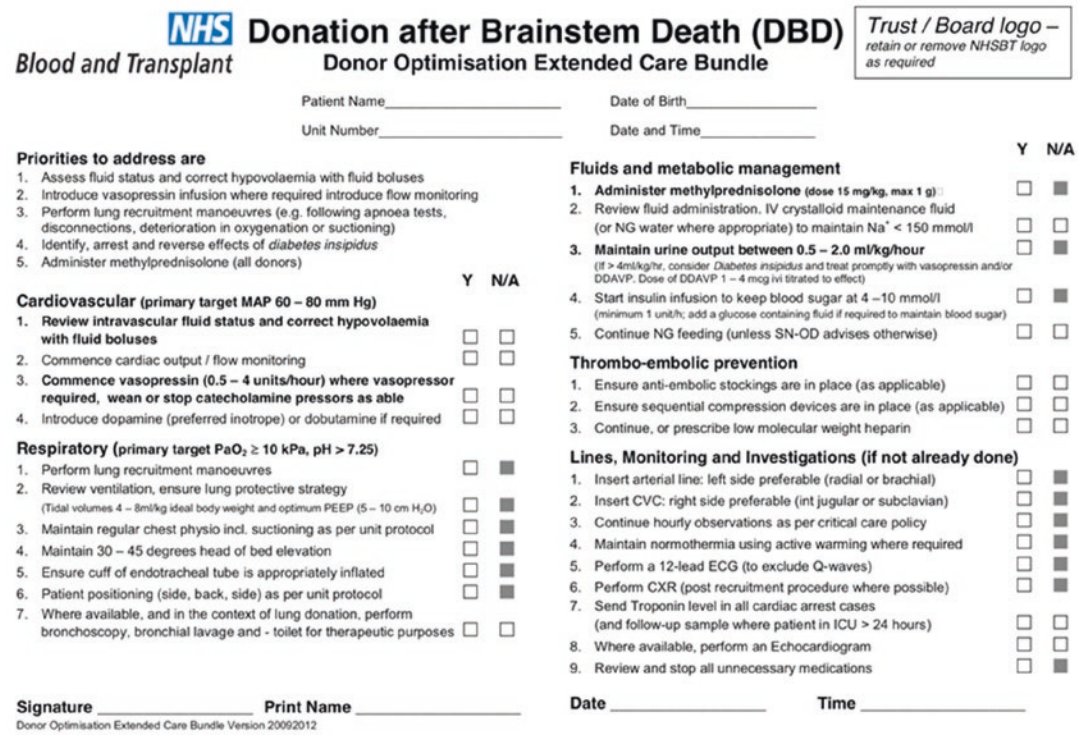
These donors should be looked after in an intensive care environment, where the nursing and medical care needs and support to the relatives can be facilitated.

The use of lung protective ventilation is advocated, with the use of tidal volumes 6–8 ml/kg of predicted body weight, ideal PEEP, the use of closed circuit for airway suction, apnea tests to be performed by using continuous positive airway pressure (CPAP) and recruitment manoeuvres. These simple management changes can increase lung procurement rates by 20%.

Cardiovascular management aims to achieve normovolemia with correction of hypovolemia and treatment of diabetes insipidus (DI) while avoiding excessive fluid administration at the same time. Unfortunately, these patients may have suffered a myocardial injury at the same time, and this combination makes their management a delicate balancing act. The minimum monitoring that is recommended is invasive arterial blood pressure measurement, central venous pressure measurement and hourly urine output. Most of the intensive care units though will try to optimize the cardiovascular system with the guidance of flow monitoring (invasive or non-invasive). The use of inotropes and vasopressors is common. Introduction of vasopressin and weaning of epinephrine or norepinephrine is advised. Hypernatremia is usually the manifestation of excessive free water loss and hypovolemia (DI) and should be avoided and corrected as it affects the survival of the transplanted liver graft.

Replacement of hormonal deficiencies will help to achieve homeostasis. Initial DI management may include the use of DDAVP. Insulin infusions and maintenance of glucose source are advocated. There is support for the use of methylprednisolone 15 mg/kg (max dose 1 g) every 12 h to attenuate the systemic inflammation of brain death by many organizations. Temperature >35 °C is also recommended.

An example of therapeutic goals is presented in Fig. 24.3, but other organizations have published similar "bundles" of donor management.



NHS Blood and Transplant

**Donation after Brainstem Death (DBD)**
**Donor Optimisation Extended Care Bundle**

*Trust / Board logo – retain or remove NHSBT logo as required*

Patient Name_____ Date of Birth_____

Unit Number_____ Date and Time_____

**Priorities to address are**

1. Assess fluid status and correct hypovolaemia with fluid boluses
2. Introduce vasopressin infusion where required introduce flow monitoring
3. Perform lung recruitment manoeuvres (e.g. following apnoea tests, disconnections, deterioration in oxygenation or suctioning)
4. Identify, arrest and reverse effects of *diabetes insipidus*
5. Administer methylprednisolone (all donors)

| | Y | N/A |
|---|---|---|
| **Cardiovascular (primary target MAP 60 – 80 mm Hg)** | | |
| 1. **Review intravascular fluid status and correct hypovolaemia with fluid boluses** | ☐ | ☐ |
| 2. Commence cardiac output / flow monitoring | ☐ | ☐ |
| 3. **Commence vasopressin (0.5 – 4 units/hour) where vasopressor required, wean or stop catecholamine pressors as able** | ☐ | ☐ |
| 4. Introduce dopamine (preferred inotrope) or dobutamine if required | ☐ | ☐ |
| **Respiratory (primary target $PaO_2 \geq 10$ kPa, pH > 7.25)** | | |
| 1. Perform lung recruitment manoeuvres | ☐ | ■ |
| 2. Review ventilation, ensure lung protective strategy (Tidal volumes 4 – 8ml/kg ideal body weight and optimum PEEP (5 – 10 cm $H_2O$) | ☐ | ■ |
| 3. Maintain regular chest physio incl. suctioning as per unit protocol | ☐ | ■ |
| 4. Maintain 30 – 45 degrees head of bed elevation | ☐ | ■ |
| 5. Ensure cuff of endotracheal tube is appropriately inflated | ☐ | ■ |
| 6. Patient positioning (side, back, side) as per unit protocol | ☐ | ■ |
| 7. Where available, and in the context of lung donation, perform bronchoscopy, bronchial lavage and - toilet for therapeutic purposes | ☐ | ☐ |

| | Y | N/A |
|---|---|---|
| **Fluids and metabolic management** | | |
| 1. **Administer methylprednisolone (dose 15 mg/kg, max 1 g)** | ☐ | ■ |
| 2. Review fluid administration. IV crystalloid maintenance fluid (or NG water where appropriate) to maintain $Na^+ < 150$ mmol/l | ☐ | ☐ |
| 3. **Maintain urine output between 0.5 – 2.0 ml/kg/hour** (If > 4ml/kg/hr, consider *Diabetes insipidus* and treat promptly with vasopressin and/or DDAVP. Dose of DDAVP 1 – 4 mcg ivi titrated to effect) | ☐ | ■ |
| 4. Start insulin infusion to keep blood sugar at 4 –10 mmol/l (minimum 1 unit/h; add a glucose containing fluid if required to maintain blood sugar) | ☐ | ■ |
| 5. Continue NG feeding (unless SN-OD advises otherwise) | ☐ | ☐ |
| **Thrombo-embolic prevention** | | |
| 1. Ensure anti-embolic stockings are in place (as applicable) | ☐ | ☐ |
| 2. Ensure sequential compression devices are in place (as applicable) | ☐ | ☐ |
| 3. Continue, or prescribe low molecular weight heparin | ☐ | ☐ |
| **Lines, Monitoring and Investigations (if not already done)** | | |
| 1. Insert arterial line: left side preferable (radial or brachial) | ☐ | ■ |
| 2. Insert CVC: right side preferable (int jugular or subclavian) | ☐ | ■ |
| 3. Continue hourly observations as per critical care policy | ☐ | ■ |
| 4. Maintain normothermia using active warming where required | ☐ | ■ |
| 5. Perform a 12-lead ECG (to exclude Q-waves) | ☐ | ■ |
| 6. Perform CXR (post recruitment procedure where possible) | ☐ | ■ |
| 7. Send Troponin level in all cardiac arrest cases (and follow-up sample where patient in ICU > 24 hours) | ☐ | ☐ |
| 8. Where available, perform an Echocardiogram | ☐ | ☐ |
| 9. Review and stop all unnecessary medications | ☐ | ■ |

**Signature** _____ **Print Name** _____

**Date** _____ **Time** _____

Donor Optimisation Extended Care Bundle Version 20092012

**Fig. 24.3** Donor optimisation extended care bundle. Source: NHS blood and transplant, UK. https://www.odt.nhs.uk/deceased-donation/best-practice-guidance/donation-after-brainstem-death

## 24.4 Donation After Circulatory Death

The number of potential DBD donors remains static (preventive medicine, improved therapeutic management, health and safety). At the same time, the need for organs is growing and the realization that transplanted kidneys retrieved from DCD donors have a similar outcome with those retrieved from DBD donors has driven in many countries the development of DCD programs (Fig. 24.4).

The DCD programs allow the donation and retrieval of organs from patients whose death has been confirmed using cardiorespiratory criteria and usually is referred as "non-heart-beating" organ donation. The Maastricht classification describes the clinical circumstances in which DCD can occur (Table 24.1). Most of the programs in the countries that support DCD are "controlled" with the Netherlands leading the way in uncontrolled programs. For obvious reasons, only countries that legally accept euthanasia allow category V DCD donation.

**Table 24.1** The modified Maastricht classification for donors after circulatory death—Paris 2013

| | | |
|---|---|---|
| Uncontrolled | Category I | Found dead *and have not been resuscitated*<br>*Ia: out-of-hospital*<br>*Ib: in-hospital* |
| Uncontrolled | Category II | Unexpected cardiac arrest—unsuccessful resuscitation<br>*IIa out-of-hospital*<br>*IIb in-hospital* |
| Controlled | Category III | Awaiting cardiac arrest after withdrawal of life-sustaining therapy/support |
| Controlled | Category IV | Cardiac arrest while brain dead<br>*IVa unexpected circulatory arrest in a brain-dead donor (uncontrolled)*<br>*IVb expected circulatory arrest in a brain-dead donor (highly controlled)* |
| Controlled | Category V | Euthanasia *(only in countries that legislation allows)*<br>*Va Medically assisted circulatory death in ICU*<br>*Vb Medically assisted circulatory death in operating theatre* |

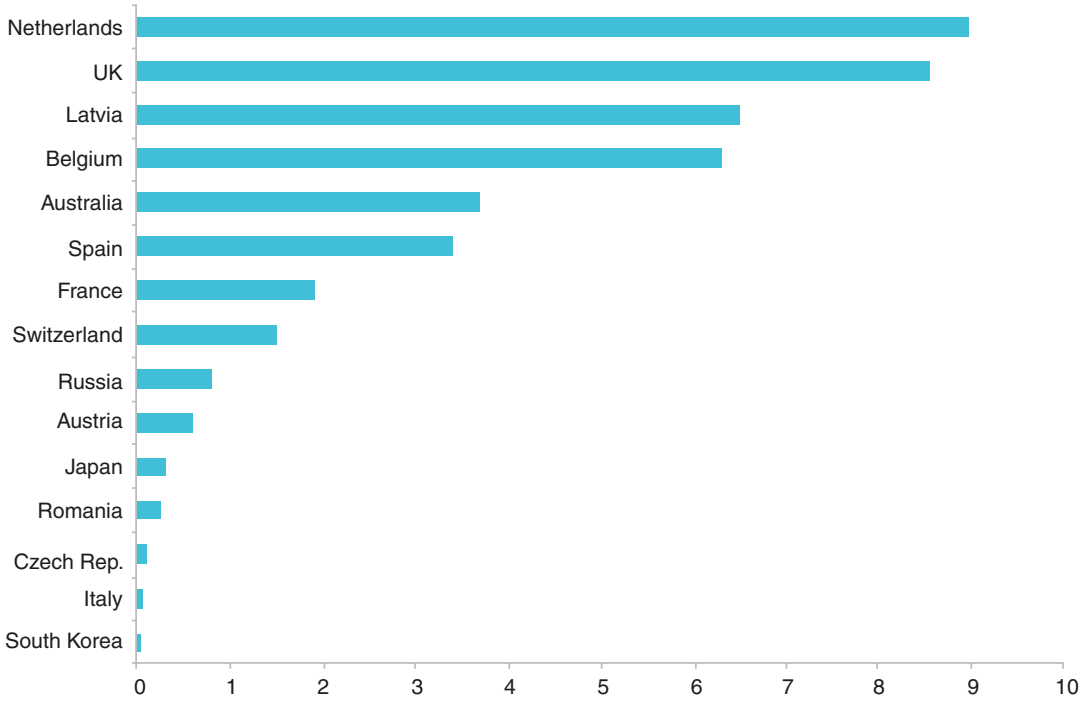



**Fig. 24.4** Worldwide DCD donor numbers (2013). Source: International Registry in Organ Donation and Transplantation (IRODaT), Free Database, http://www.irodat.org. Used with permission

Although DCD programs continue to increase the numbers of donors, clinicians in intensive care units are faced with challenges such as identification of potential donors, perceived conflicts between the decision to withdraw life-sustaining therapy (WLST) and DCD donation, safe diagnosis of death using cardiorespiratory criteria and ethical challenges around delayed WLST, to name few.

### 24.4.1 Confirmation of Death Following Cessation of Cardiorespiratory Function

Although brain death has generated a lot of controversy over the years, confirming death using cardiorespiratory criteria, it is not without challenges, and Lazarus phenomena have been reported after incorrect confirmation of death.

The accurate confirmation of death is crucial in cases that will proceed to organ donation as all donors should follow the "dead donor rule". Since death is a process that affects different organs at different timeframes, clinicians have to decide when the irreversible loss of life has occurred.

In most countries, absent arterial pulse, absent heart sounds, apnea and unresponsiveness are recommended as criteria to confirm death. The observation period varies worldwide ranging from 2 to 10 min with most common the 5-min period. In the UK, the confirmation of death can be made only if there is "absence of pupillary responses to light, of corneal reflexes and any motor response to supraorbital pressure", 5 min after continuous observation of cardiorespiratory arrest.

### 24.4.2 Warm Ischaemic Time

As the cardiovascular system collapses, during the dying process, the organs of DCD donors are exposed to longer warm ischaemic times than the organs retrieved from DBD donors. This phase starts before the asystole when the systolic blood pressure drops below 50 mmHg, or the arterial oxygen saturation decreases below 70% and stops when the retrieval teams initiate cold perfusion. This ischaemic injury increases primary and delayed graft function of the organs retrieved with liver (ischaemic cholangiopathy) and pancreas being more vulnerable.

There have been efforts to prevent or alter the effect of warm ischaemia to DCD organs:

- Withdrawal of treatment in the operating theatre suite
- Timely confirmation of death
- Normothermic regional perfusion (NRP)

### 24.4.3 Heart and Lung DCD Donation

Although the most significant contribution of DCD programs is to kidney transplantation, there are successful efforts to increase lung retrievals and recently heart procurement.

DCD lungs have not been exposed to the catecholamine storm during brain death or the excessive fluid administration that is usually observed in DBD donors. For successful lung donation after death confirmed using cardiorespiratory criteria, protection of the airway to prevent aspiration and early inflation of the lungs with oxygen is required. Since it is inappropriate to initiate any cardiopulmonary resuscitation after death has confirmed, strict adherence to protocols is paramount. In summary, there should be only one inflation manoeuvre of the lungs after a minimum of 10-min observation of circulatory arrest.

Although the first heart transplant by Barnard and colleagues was from a DCD donor, since the neurological criteria for confirming death were adopted, the primary source of transplanted hearts are the DBD donors. In 2008, surgeons from Denver, USA published a series of 3 heart transplants in infants from DCD donors. The 6-month survival was 100%. In 2014, the first adult series of successful DCD heart transplantation was published by an Australian group. The importance of this was that the donors were in different hospitals to the recipients. They used a portable, warm blood perfusion system to transfer the retrieved hearts. Since then, heart DCD donation programs have been introduced to the UK with great success, resulting in 17 successful heart retrievals in 2017 alone.

## 24.5 Successful Organ Donation Programs

There is significant variability of donation rates worldwide. Public surveys reveal that societies are supportive to organ donation. Most of the religions are also supportive although the views of different scholars may vary. Spain's success demonstrates that continuous increase of organ donation rates is not based only on investment or even availability of intensive care beds. Spain managed to increase the donation rates despite the economic struggle that the public sector of the country faced recently. The UK and other countries have adopted the Spanish model and adapted it to their needs with positive effects on their organ donation practices.

National organizations should be formed and should be responsible for setting up practices and structures to facilitate organ donation and transplantation in a transparent and fair way. Governments should assist and resolve legal, ethical and professional issues, to ensure that all professionals are supported by clear frameworks.

The process of organ donation should be viewed as an integral part of the end of life care provided and become a normal event in hospitals. Monitoring of donation and transplantation activity should be in place in hospitals and nationally. Training of all healthcare staff involved in organ donation should be mandatory (part of the professional curriculum), and hospitals should have access to specialist-trained personnel.

The organ donation process should be seen as a continuum, and efforts to improve organ donation rates should focus on each step of the process.

**Identification and Referral** The process starts from the identification of the potential donor. Nowadays, the criteria are constantly changing, and transplants centres are accepting higher risk or marginal donors. In addition, assumptions based on religious beliefs or cultural background should not be made without exploring the person's/family's wishes. Improvement of identification and referral rates has been observed in systems that introduced "minimal identification criteria". A timely referral to the organ donation specialist (doctor or nurse) will ensure suitability checks and family support from trained professionals without delays.

**Consent** Clinicians are faced with a grieving family. At the same time, clinicians do not have adequate training about donation. Careful planning of the conversation about donation is paramount. The best model appears to be when clinicians are supported by organ donation specialists (collaborative approach). The process of breaking bad news and breaching the subject of donation should be decoupled. Families should be allowed time to understand the course of events that led to death. Discussion about organ donation should only happen after confirmation that the family has understood and accepted the death or the reasons for WLST. If the family has not come to terms with the inevitability of their loss, organ donation should not be mentioned. The person leading the conversation must have appropriate training and be able to answer any questions the family may have. Apologetic and negative language should be avoided as organ donation is a positive act and part of the care that the dying person may wish to receive.

The concept of brain death may be confusing for grieving families as artificial means still support the body. Families should be invited to witness the clinical examination that confirms death (brainstem death testing) as this improves understanding and trust.

**Organ Donor Management** Organ donor management could be challenging. Target-focused protocols help intensive care staff to maintain satisfactory organ function. Clinicians should be committed to provide the highest number of organs possible since the donor or their family have chosen organ donation as part of their end-of-life care. Failing to do so may be seen as not valuing their expressed wishes.

**Potential Organ Donors in Emergency Department (ED)** Patients die in ED departments. Involving ED personnel in the organ donation process is paramount. Although ED can

facilitate organ donation, it is advisable that the patient is admitted to ITU. Recent studies show that this is cost effective and also provides a better environment for the grieving family. It also protects clinicians from making incorrect early prognostication decisions.

**Key Points**

- The ethical platform of deceased organ donation is based on the "dead donor rule".
- Deceased donation has been developed around two different programs: donation after death has been confirmed using neurological criteria (DBD) and donation after death has confirmed with circulatory criteria (DCD).
- Caring for the donor: brain death is followed by a cascade of physiological changes that create very challenging physiological conditions for the physician who aims to maintain the good function of vital organs.
- Standardized protocols for organ donor management have been developed worldwide with similar physiological aims.
- The ischaemic injury during the dying process increases primary and delayed graft failure. There have been efforts to prevent or alter the effect of warm ischaemia to DCD organs.

## Suggested Readings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# Part VIII

# Near Misses in Intensive Care

# Ventilator-Associated Pneumonia

25

Richa Aggarwal

## 25.1 Introduction

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in mechanically ventilated patients and second most common infection in critical care units [1–3]. VAP is an important clinical identity that can influence morbidity and mortality of critically ill patients. The incidence of VAP varies depending on the criteria used for diagnosis and is reported to be approximately 9–27% of all mechanically ventilated patients [4]. Depending on the definition used, VAP rates range from 1.2 to 8.5 per 1000 ventilator days [5].

## 25.2 Definition

According to 2016 Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) guidelines, VAP is defined as pneumonia occurring more than 48 h after endotracheal intubation whereas hospital-acquired pneumonia (HAP) is defined as pneumonia not incubating at the time of admission to the hospital but occurring at 48 h or more after admission [6]. HCAP referred to as health care-associated pneumonia has been excluded from 2016 guidelines. HCAP was previously defined as pneumonia acquired in healthcare facilities like nursing homes, haemodialysis centres, rehabilitation centres, outpatient clinics and during hospitalization in previous 3 months. This term has been excluded from the guidelines now [6].

## 25.3 Epidemiology

According to the National Healthcare Safety Network (NHSN), there has been a steady decline in the VAP rates in the USA with reporting incidence varying from 0.0 to 5.8/1000 ventilator days [7]. However, recently published data showed that approximately 10% of patients on mechanical ventilation develop VAP [8, 9] and there is underreporting. The incidence of VAP in neurocritical care patients varies depending on the definition used. The VAP rates range from 4 to 31.3% according to different studies [10, 11], and development of VAP adversely affects the outcome. Neurological patients are at higher risk of developing pneumonia [10] due to decreased consciousness, impaired protective airway reflexes and dysphagia. The presence of neurological disease is an independent risk factor for the development of VAP and also for failure of VAP resolution with initial antibiotic therapy [12, 13]. NHSN reported incidence of VAP in neurocritical care units ranging from 2.1 (neurosurgical units) to 3.0

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(neurological units)/1000 ventilator days [14]. In neurocritical care unit, Glasgow coma score < 6, more severe brain injury and presence of cervical fracture with neurological deficit have a specificity of 97% for prediction of VAP.

VAP is associated with increased ICU stay, increased number of ventilator days and increased cost of care [15]. Recent data has revealed that the duration of mechanical ventilation increased from 7.6 to 11.5 days and hospital stay from 11.5 to 13.1 days in patients with VAP compared to patients without VAP [16, 17]. The risk of death also increases by 1.8—fourfold in patients with VAP. Mortality caused by VAP is defined as the percentage of deaths that would not have occurred in the absence of infection. It is difficult to determine attributable mortality to VAP as several cofactors affect mortality in ICU patients [16]. However, few studies have studied the attributable risk of death due to VAP and have reported as approximately 9–13% [18, 19], but this rate has decreased over time. This is not the same in neurocritical care patients. Few studies have shown no association between VAP and increased mortality in intubated NICU patients [10].

VAP is generally divided into early onset and late onset VAP. Early VAP is VAP that occurs within 5–7 days of mechanical ventilation, while late VAP is VAP that occurs more than 5–7 days [20, 21]. This distinction was made as early VAP was usually attributed to antibiotic sensitive pathogen and late onset VAP was more likely caused by multidrug-resistant pathogens [2, 4] but according to recent literature, the bacteriological difference has not been clear, and studies have found no relation between timing of VAP and risk of MDR organisms [22–24]. The difference in various studies has been in the timing of VAP (time zero of definition). Thus, differentiating VAP on the basis of timing may lead to undertreatment of patients with early onset VAP or delay in the starting of appropriate antibiotic therapy. The risk of VAP is approximately 1%/day, being higher in initial days, and this decreases as time passes to 3% in the first 5 days, then 2% between the fifth to tenth days, and then 1%/day of mechanical ventilation [25].

## 25.4 Pathogenesis

The main pathogenic mechanism in the development of VAP is the pulmonary aspiration of the colonized oropharyngeal secretions across the tracheal tube cuff. These days high-volume low-pressure cuffs (HVLP) are used in the endotracheal tubes. When these cuffs are inflated, folds appear along the cuff surface which cause micro- and macroaspiration of oropharyngeal secretions [26]. Another conduit of infection is through the tube itself [27]. The bacteria adhere to the internal surface of the tube forming a biofilm [28, 29] and translocate into the lungs with inspiration. Patients can be colonized either exogenously or endogenously, exogenously can be colonized from the hand, equipment, invasive devices and hospital environment or endogenously from the organisms present in the oropharynx, tracheal tube and gastrointestinal tract.

Impaired immune function of the body also plays a role [30]. In normal individuals, there are various defence mechanisms to prevent translocation of pathogen in the lower airways like epiglottis, adduction of true and false vocal cords, cough reflex and mucociliary clearance in the upper airways; however, these body defence mechanisms are impaired in intubated patients [2, 27]. Moreover, host factors like underlying disease, previous surgery and antibiotics are regarded as risk factors for VAP [4].

## 25.5 Microbiology

Common pathogens causing VAP include aerobic gram-negative bacilli, e.g. pseudomonas, *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Acinetobacter* and gram-positive cocci, e.g. *Staphylococcus aureus* and *Streptococcus* [31, 32]. The difference in the organisms depends on the hospital flora and the host factors. There is increased risk of VAP with *S. aureus*, *Haemophilus* and *Streptococcus pneumonia* infection in trauma and neurologic patients [33]. VAP can be polymicrobial also. Every hospital has its own data of the organism responsible for early and late onset VAP.

### 25.5.1 Risk Factors for MDR VAP Include [22, 23, 34, 35]

- Intravenous (IV) antibiotic use within the previous 90 days
- Septic shock at the time of VAP
- Acute respiratory distress syndrome (ARDS) preceding VAP
- ≥5 days of hospitalization prior to the occurrence of VAP
- Acute renal replacement therapy prior to VAP onset

However, coma present at the time of ICU admission is associated with lower risk of MDR VAP [36]. This may be that neurotrauma patients have an increased propensity to develop VAP early in ICU admission (which is due to sensitive organisms).

## 25.6 Diagnosis

The clinical diagnosis of VAP is difficult because clinical findings are non-specific. At present, there is no universally accepted gold standard criteria for VAP [37]. IDSA/ATS 2016 guidelines for management of VAP recommend clinical diagnosis of VAP based upon a new lung infiltrate PLUS clinical features suggesting infectious nature of the infiltrate like new onset of fever, purulent secretions, leukocytosis and decline in oxygenation [6].

Radiographic abnormalities of VAP include alveolar infiltrates, air bronchograms and silhouetting of adjacent solid organs. Diagnosis is confirmed when lower respiratory tract sampling identifies a pathogen. As there is increasing risk of MDR pathogens and risks associated with initial ineffective therapy, the cultures of respiratory secretions should be obtained from all the patients with suspected VAP [4]. Samples should be sent prior to initiation of antibiotics or change of antibiotic therapy as antibiotics reduce the sensitivity of both microscopic analysis and cultures [38, 39]. Whether to send blood culture of a patient with VAP depends on the clinical picture of the patient. Approximately, 15% of patients with VAP are bacteraemic [40, 41], and patients with bacteraemic VAP are at higher risk of morbidity and mortality than non-bacteraemic patients. Moreover, these positive blood cultures may indicate a non-pulmonary source of infection.

## 25.7 Sampling of the Respiratory Tract

There are two methods of sampling of the respiratory tract—invasive and non-invasive. Non-invasive sampling refers to endotracheal aspirates and invasive involves bronchoscopic bronchoalveolar lavage (BAL), protected specimen brushing (PSB) and blind bronchial sampling, i.e., miniBAL.

According to the IDSA/ATS guidelines, it is recommended that non-invasive sampling with semi-quantitative cultures be done to diagnose VAP rather than invasive sampling with quantitative cultures or non-invasive sampling with qualitative cultures. Rationale for non-invasive sampling is that it can be done more rapidly with fewer complications and resources, and studies have shown that there is no difference in mortality or length of stay in ICU whether sampling is done by either approach [42]. The threshold for quantitative cultures for different samples is as follows:

- For PSB > 1000 colony forming units/mL
- For BAL > 10,000 cfu/mL
- For endotracheal aspirates >1,000,000 cfu/mL

However, European Society of Intensive Care Medicine and European Society of Infectious Diseases suggest preference for invasive sampling method with quantitative cultures. Rationale behind this is that there would be less antibiotic exposure and good antibiotic stewardship with this approach [43]. The practice depends on the individual institution protocol. A positive microbiological sample in a patient with normal chest radiograph suggests tracheobronchitis.

There has been continuous search for a rapid identification of bacteria so that antibiotics can be

started early. Certain new automated microscopy methods such as ID/AST system using genomic and phenotypic techniques are in development [44].

## 25.8 Role of Biomarkers

IDSA 2016 guidelines recommend using clinical criteria alone for starting antibiotics in patients with suspected VAP and not on serum procalcitonin level plus clinical criteria. Evidence of PCT in patients with suspected VAP is not strong enough [45, 46]. Procalcitonin levels can be useful to stop/discontinue antibiotic therapy in patients with confirmed VAP and it can also be used as a prognostic marker [47, 48]. Other markers such as c reactive protein and soluble triggering receptor expressed on myeloid cells (sTREM-1) have minimal diagnostic value [49, 50].

Other diagnostic methods which have been in use to diagnose VAP include clinical pulmonary infection score, HELICS criteria and Johannson criteria.

## 25.9 Other diagnostic criteria

Clinical pulmonary infection score (CPIS) was developed by Pugin and colleagues to facilitate the diagnosis of VAP using clinical variables [51]. It gives a score of 0–2 for temperature, leucocytosis, $PaO_2/FiO_2$ ratio, chest radiography, tracheal secretions and culture of tracheal aspirate. The maximum score is 12 and a score > 6 is diagnostic of VAP. The limitation of CPIS was that there was a lot of interobserver variability in CPIS calculation hampering its routine use in clinical trials. The recent evidence suggests that CPIS can diagnose VAP with sensitivity and specificity of only 65% and 64%, respectively [52].

The HELICS [53] criteria are used for VAP surveillance in Europe. These rely on a combination of clinical, radiological and microbiological criteria and classify pneumonia from PN1 to PN5 based on microbiological method used.

The Johannson criteria diagnosed VAP with the presence of new/progressive infiltrates on chest X-ray associated with at least 2 of 3 clinical features—leucocytosis, purulent secretions and temperature greater than 38 °C. The sensitivity and specificity of these criteria are 69% and 75%, respectively [54].

The diagnosis of VAP is more problematic in neuro-ICU due to ubiquitous nature of clinical findings related to primary brain injury such as fever, leucocytosis and altered mental status. There is a huge variability in diagnosis and treatment of VAP in neurocritical care patients. According to a recent study, the clinical features significantly more prevalent in surveillance VAP as compared to clinical VAP were change in sputum character, tachypnea, oxygen desaturation, higher CPIS score and persistent infiltrate on chest X-ray but not positive sputum culture [11].

## 25.10 Ventilator-Associated Events

The United States Centre for Disease Control and Prevention (CDC) has adopted a new method of ICU surveillance employing ventilator-associated events (VAE) as a potential metric to assess quality of care in ICU. VAE include ventilator-associated complications (VAC) and infection-related ventilator-associated complications (IVAC) [55, 56]. These definitions are used for surveillance and quality improvement of the ICUs. These definitions fail to detect many patients with VAP and do not aid in management at the bedside level.

## 25.11 Differential Diagnosis

VAP has to be differentiated from many conditions that can have similar clinical or radiological findings. These are:

1. Ventilator-associated tracheobronchitis (VAT): VAT is characterized by signs of respiratory infection such as increase in volume and purulence of the secretions, fever, leukocytosis but no radiological infiltrates suggestive

of consolidation in chest X-ray. No antibiotic therapy is recommended for patients with VAT. It leads to more antibiotic resistance than benefits.
2. Aspiration pneumonitis: This can be differentiated from VAP by history and microscopic analysis of respiratory secretions. Aspiration pneumonitis can get secondarily infected with organisms leading to aspiration pneumonia.
3. Pulmonary embolism with infarction: The clinical features in embolism may suggest risk factors for embolism in these cases.
4. Acute respiratory distress syndrome (ARDS): The patients with ARDS will have negative cultures of respiratory secretions.
5. Pulmonary haemorrhage: There will be frank bleeding in cases of pulmonary haemorrhage and blood mixed with purulent secretions in VAP.
6. Lung contusion: The patient would have history of trauma along with negative cultures.

## 25.12 Treatment

Clinical suspicion of VAP mandates early antimicrobial therapy. Once VAP is suspected clinically, antibiotic therapy should be started as early as possible [6] and in cases of septic shock, should be started within an hour. Delay in treatment and inappropriate antibiotic are associated with higher mortality [57, 58].

All intensive care units should have a local antibiogram specific to their population. The regimens for empiric treatment of VAP should be based on local prevalence of pathogen and antimicrobial susceptibility [6].

## 25.13 Multidrug-/Pandrug-Resistant/Extensively Drug-Resistant Bacteria

Multidrug resistance in gram-negative bacilli is defined as acquired nonsusceptibility to at least one agent in three different antimicrobial classes [59]. Pan resistance refers to resistance to all antibiotics recommended for empiric treatment of VAP. Extensively drug-resistant bacteria are those bacilli resistant to atleast one agent in all but two antimicrobial classes.

Empiric therapy should include an agent with activity against *S. aureus*, Pseudomonas and other gram-negative bacilli. The treatment depends on whether the patient has risk factors for MDR VAP, *or* risk factors for MDR *Pseudomonas* and other gram-negative bacilli, *or* risk factors for MRSA. For patients with risk factors of MDR, empiric broad spectrum multidrug therapy is recommended. Once the culture reports are available, therapy should be deescalated according to the sensitivity pattern [60, 61]. If a patient is already on antibiotics, empiric therapy should be with a drug from a different class as the pathogen may be resistant to the initial class of antibiotic.

### 25.13.1 Risk Factors for MDR VAP Include [22, 23, 34, 35]

- Intravenous (IV) antibiotic use within the previous 90 days
- Septic shock at the time of VAP
- Acute respiratory distress syndrome (ARDS) preceding VAP
- ≥5 days of hospitalization prior to the occurrence of VAP
- Acute renal replacement therapy prior to VAP onset

### 25.13.2 Risk Factors for MDR *Pseudomonas* and Other Gram-Negative Bacilli Include

- Treatment in an ICU in which >10% of gram-negative bacilli are resistant to an agent being considered for monotherapy
- Treatment in an ICU in which local antimicrobial susceptibility rates among gram-negative bacilli are not known

### 25.13.3 Risk Factors for MRSA Include

- Treatment in a unit in which >10 to 20% of *S. aureus* isolates are methicillin resistant
- Treatment in a unit in which the prevalence of MRSA is not known

If no *MDR VAP* risk factors exist, and no risk factor for *MDR Pseudomonas and other gram-negative bacilli* exist, then either of the following antibiotics can be used:

Piperacillin–tazobactam 4.5 g IV every 6 h/Cefepime 2 g IV every 8 h/Levofloxacin 750 mg IV daily.

If *MDR VAP risk factors are present*, the patients should receive *two* agents with activity against *Pseudomonas aeruginosa* and other gram-negative bacilli and *one* agent with activity against MRSA:

Piperacillin–tazobactam 4.5 g IV every 6 h/Cefepime 2 g IV every 8 h/Ceftazidime 2 g IV every 8 h/Imipenem 500 mg IV every 6 h/Meropenem 1 g IV every 8 h/Aztreonam 2 g IV every 8 h.

*Plus* an aminoglycoside, which can be:

- Amikacin 15–20 mg/kg IV daily/Gentamicin 5–7 mg/kg IV daily/Tobramycin 5–7 mg/kg IV daily
- Or: An antipseudomonal fluoroquinolone such as ciprofloxacin (400 mg IV every 8 h) or levofloxacin (750 mg IV daily)
- Or: A polymyxin, IV colistin or polymyxin B, may be appropriate if highly resistant *Pseudomonas* spp., *Acinetobacter* spp. and Enterobacteriaceae (including *Klebsiella pneumoniae*) is suspected

*Plus*: Linezolid 600 mg IV every 12 h/Vancomycin 15 mg/kg.

If there are *no risk factors for MDR VAP but risk factors for MDR pseudomonas and gram-negative bacilli*, then *two* agents should be used for gram-negative bacilli. And, if the patient also has *MRSA risk factors*, then an MRSA agent should also be given.

Patients who *do not have risk factors for MDR gram-negative bacilli but do have risk factors for MRSA* should receive *one* agent with activity against *P. aeruginosa* and other gram-negative bacilli and *one* agent with activity against MRSA:

Piperacillin tazobactam/cefepime/ceftazidime/levofloxacin/ciprofloxacin/+ linezolid/vancomycin.

Once the culture reports are available, the antibiotic therapy should be deescalated according to the culture sensitivity report. The de-escalation to monotherapy can occur in most of the cases but if there is infection with pseudomonas and the patient is still in septic shock or at increased risk of death, then 2 antibiotics should be continued.

Aerosolized colistin, polymyxin or aminoglycosides can be used as adjunctive therapy (in combination with IV antibiotics) in patients with VAP caused by multidrug-resistant gram-negative bacilli, such as *Acinetobacter baumannii or P. aeruginosa* [62, 63]. This increases the antibiotic concentrations at the site of infection and is useful for treatment of organisms that have high MICs to systemic antimicrobial agents. If the patient improves clinically, *and* is able to take medications orally, intravenous antibiotics can be switched to oral.

Duration of therapy: The 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) recommend 7-day course of treatment and it can be prolonged or shortened based on the clinical response, and improvement in radiological and laboratory parameters. Serum levels of procalcitonin can be useful in decision to stop the antibiotic. With values <0.25 mcg/L or when there is decrease in the PCT value by more than 80%, antibiotics can be discontinued.

## 25.14 Prognosis

All-cause mortality associated with VAP ranges from 20 to 50% in different studies [6], but the attributable mortality is 9–13%. The factors associated with increased mortality are: bacteraemia, shock, coma, respiratory failure, ARDS,

severe underlying comorbid disease and infection with MDR organisms.

## 25.15 Prevention of VAP

The various modalities used to prevent VAP are as follows:

1. Head-up position: As aspiration of pathogens is the main cause of VAP, preventing aspiration in intubated patients must be a priority. There is evidence that patients in supine position have more chances of aspiration of gastric contents than patients in head-up position [64, 65]. The head end of the bed should be elevated to 30–45° [66].
2. Subglottic suction device: Endotracheal or tracheostomy tubes with subglottic suction tube should be used in patients who are expected to require more than 48 h of mechanical ventilation [66]. The secretions pooled over the cuff of the tube may get aspirated. Studies have shown that patients with these tubes have lesser VAP rate, reduced duration of mechanical ventilation and reduced ICU stay [67].
3. Oral care: Oral care with chlorhexidine mouthwash has proven its role in reducing VAP [68] and so should be used regularly in intubated patients.
4. Strict hand hygiene: The biofilm formation on the tube can be reduced by strict hand hygiene practices, closed suction systems and use of heat and moisture exchangers.
5. Reducing the duration of mechanical ventilation: This can be achieved by daily sedation vacation and spontaneous breathing trials and assessment of readiness to extubate.

Various studies have been conducted on other modalities but no conclusive results were presented. Selective decontamination of the digestive tract may increase the growth of resistant bacteria and so it is not widely practiced [69, 70]. Similarly, administration of probiotics and use of silver-coated endotracheal tubes have not shown promising results in the form of any significant decrease in the VAP rate or days on mechanical ventilation or hospital stay and are not recommended.

## 25.16 VAP Bundles

Implementation of various evidence-based interventions together to decrease the rate of VAP forms VAP bundle. There is no consensus which care processes to be included in these bundles but they have shown reduction in VAP rates in various studies [71] and should be implemented.

**Key Points**

- Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in mechanically ventilated patients and second most common infection in critical care units.
- Neurological patients are at higher risk of developing pneumonia due to decreased consciousness, impaired protective airway reflexes and dysphagia.
- VAP is associated with increased ICU stay, increased number of ventilator days and increased cost of care.
- There is increased risk of VAP with *S. aureus*, *Haemophilus* and *S. pneumonia* infection in neurologic patients.
- The diagnosis of VAP is more problematic in neuro-ICU due to ubiquitous nature of clinical findings related to primary brain injury such as fever, leucocytosis and altered mental status.
- The regimens for empiric treatment of VAP should be based on local prevalence of pathogen and antimicrobial susceptibility.
- For patients with risk factors of MDR, empiric broad spectrum multidrug therapy is recommended. Once the culture reports are available, therapy should be deescalated according to the sensitivity pattern.

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# Acute Respiratory Distress Syndrome

# 26

Fawaz Ahmad and Lauren Koffman

## 26.1 Introduction

In 1967, Ashbaugh and colleagues first described a respiratory distress syndrome in 12 patients with acute onset of tachypnea, refractory hypoxemia, loss of lung compliance, and diffuse alveolar infiltrates on chest X-ray (CXR) [1]. They noted that these patients had features similar to infantile respiratory distress syndrome, and that they did not respond to standard treatment. Over the years, many different definitions for Acute Respiratory Distress Syndrome (ARDS) have been proposed, with the American European Consensus Conference (AECC) most commonly used in the past and the Berlin definition (Table 26.1) being the most commonly used presently. The Berlin definition of ARDS was published in 2012 and was endorsed by the European Society of Intensive Care Medicine (ESICM), the American Thoracic Society (ATS), and the Society of Critical Care Medicine (SCCM) [2]. They defined ARDS as new or worsening respiratory symptoms within 1 week of clinical insult with bilateral opacities on CXR (Fig. 26.1) or computerized tomography (CT) scan (Fig. 26.2), not fully explained by cardiac failure or fluid overload. They further classified ARDS into three categories (Table 26.2) based on the arterial oxygen tension: fractional inspired oxygen ratio ($PaO_2/FiO_2$) and with a minimum positive end-expiratory pressure (PEEP) of 5. The Berlin definition is notably different from prior definitions in that it recognizes that a CT scan can be used in lieu of a chest radiograph, acknowledges that diagnosis can occur in the

**Table 26.1** ARDS definition comparisons

| | AECC | Berlin |
|---|---|---|
| Onset | Acute | Within a week of known clinical insult or new/worsening respiratory symptoms |
| Imaging | Bilateral infiltrates on CXR | Bilateral infiltrates on CXR or CT scan |
| Oxygenation | ALI—$PaO_2/FiO_2 \leq 300$ mmHg<br>ARDS—$PaO_2/FiO_2 \leq 200$ mmHg | Divided into mild, moderate, and severe as described in Table 26.2 |
| PAWP | <18 mmHg or no clinical evidence of left atrial hypertension | None |

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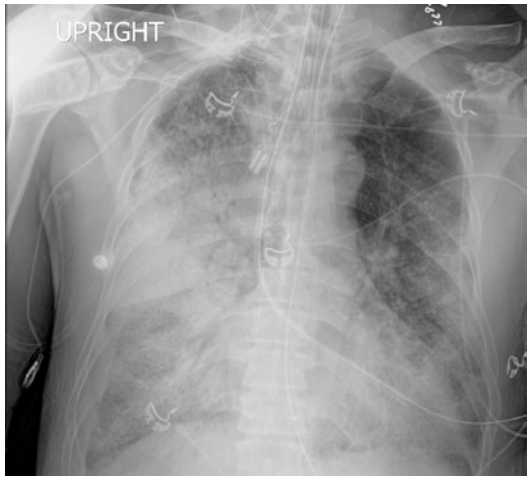


**Fig. 26.1** Chest X-ray of a patient showing bilateral lung opacities consistent with ARDS

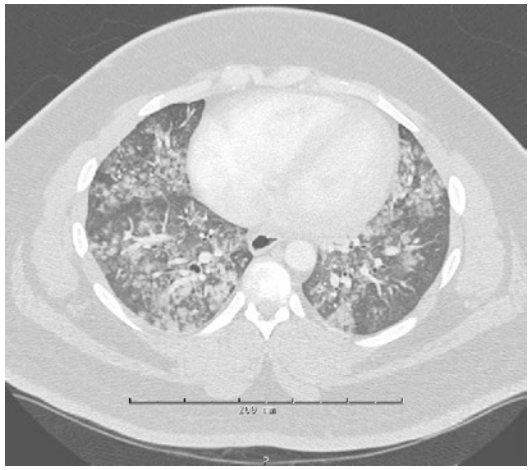

**Fig. 26.2** CT chest of a patient with ARDS showing diffuse extensive bilateral focal alveolar airspace opacities

**Table 26.2** Berlin definition categories for Acute Respiratory Distress Syndrome (ARDS)

| | |
|---|---|
| Mild | $PaO_2/FiO_2$ ratio 201–300 mmHg with PEEP or CPAP ≥5 cm $H_2O$ |
| Moderate | $PaO_2/FiO_2$ ratio 101–200 mmHg with PEEP ≥5 cm $H_2O$ |
| Severe | $PaO_2/FiO_2$ ratio ≤ 100 mmHg with PEEP ≥5 cm $H_2O$ |

presence of cardiac failure, and includes a minimum PEEP of 5 cm $H_2O$ (or CPAP for mild ARDS). The Berlin definition simplifies the prior definition by removing the classification of acute lung injury (ALI) and instead utilizing mild, moderate, and severe ARDS classifications. These classifications remain important to the definition of ARDS due to differences in mortality, as well as treatment options.

## 26.2 Epidemiology

Many studies have investigated the incidence of ARDS in acute respiratory failure. An internal report of the National Heart and Lung Institute from 1972 revealed an incidence of ARDS in the USA of 75/100,000 population/year. The Acute Lung Injury: Epidemiology and Natural history (ALIEN) study evaluated patient data from Spain and estimated an incidence of 7.2/100,000 population/year and an ICU mortality of 42% despite lung protective ventilation [3]. A broader study, which looked at 459 ICUs across 50 different countries, concluded that ARDS represented 10.4% of total ICU admissions and 23.4% of all patients on mechanical ventilation [4]. They also noted that ARDS continues to be underdiagnosed, with only 60% of patients qualifying for ARDS under the Berlin definition being recognized by clinicians.

Risk factors for ARDS include both direct and indirect lung injury. Direct lung injury can occur with pneumonia (bacterial, viral, fungal, and opportunistic), gastric content aspiration, pulmonary contusion, inhalation injury, and drowning. Indirect lung injury includes sepsis, trauma, pancreatitis, burns, drug overdose, and transfusion-related acute lung injury (TRALI) [2]. The majority of ARDS cases are related to pneumonia, gastric aspiration, and sepsis [5].

Aside from lung injury, it has been hypothesized that genetic predisposition may increase the risk for developing ARDS. Although no single gene has been identified as a culprit, over 40 genes have been associated with ARDS. These include angiotensin-converting enzyme (ACE), epidermal growth factor

(EGF), factor V, IL6, IL8, IL10, surfactant protein B, tumor necrosis factor-alpha (TNF), and Toll-like receptor 1 (TLR1) [6] among others. ACE has the clearest association with ARDS, which came into light when ACE2 was identified in in vitro studies as a potential receptor for the coronavirus that caused SARS [7]. This was confirmed by showing that ACE2 expression in cells that initially were not susceptible to the SARS infection would allow entry of the virus into the cell [8]. This has led to the possibility of recombinant ACE2 protein as a potential treatment for preventing the spread of SARS and protecting infected patients from worsening lung failure. Studies are also being conducted to better define the role of ACE2 in other emerging lung infections such as avian influenza A.

## 26.3 Pathophysiology

ARDS consists of three distinct phases: the exudative phase, the proliferative phase, and the fibrotic phase. The exudative phase occurs within 1–7 days after the initial insult to the lung. The initial insult may be a direct insult to the alveolar epithelium (pneumonia) or an indirect insult such as pancreatitis. This phase is characterized by immune cell-mediated damage of the alveolar capillary endothelial cells and alveolar epithelial cells. The result is a loss of the alveolar barrier and accumulation of protein-rich edema with the formation of a protein-rich hyaline membrane. Alveolar M1 macrophages secrete cytokines (IL-1, 6, 8, and 10), tumor necrosis factor-alpha, and lipid mediators. In response to these pro-inflammatory cytokines, neutrophils are recruited to the area [9] as well as activation of alveolar epithelial cells and effector T-cells, which leads to sustained inflammation and tissue injury [10]. The resulting inflammatory exudate directly affects type II alveolar cells, leading to inactivation of surfactant and impairment of alveolar function. This cascade of injuries and decreased pulmonary compliance leads to worsening gas exchange, increasing ventilation–perfusion mismatch, and refractory hypoxia which can be further worsened by mechanical stretch injury.

The proliferative phase of ARDS occurs from day 7 to 21 and attempts to repair the damages from the exudative phase. This occurs as M1 macrophages transition into M2 macrophages and help clear debris from the inflammatory process. This also leads to signaling type II alveolar cells which stimulate fibrin matrix scaffolds, synthesize surfactant, and differentiate into type I alveolar cells. As the epithelial lining recovers, protein channels and tight junctions are reestablished, which helps remove alveolar edema.

The final phase of ARDS, the fibrotic phase, does not consistently occur in all patients. This phase consists of extensive alveolar duct and interstitial fibrosis, and emphysema-like changes can be observed. Destruction of pulmonary vasculature and fibrosis leads to increased pulmonary hypertension. This phase is associated with a significant increase in mortality and may require long-term support on mechanical ventilation.

## 26.4 Treatment

Treatment of ARDS consists of identification and treatment of the underlying cause, while minimizing ventilator-induced lung injury and ensuring adequate gas exchange. This method of mechanical ventilation is termed “lung protective ventilation.” Noninvasive mechanical ventilation (NIV) is typically not used in patients with ARDS due to the high respiratory failure rates leading to intubation along with the concern for complications associated with delay in mechanical ventilation. A recent meta-analysis showed an intubation rate of up to 86% and a mortality rate ranging from 15 to 71% with NIV [11].

### 26.4.1 Mechanical Ventilation

The ARDS Network (ARDSnet) group was a network of 12 clinical sites initiated by the National Heart, Lung, and Blood Institute (NHLBI) and National Institutes of Health (NIH) which encompassed 20 years of research and included 5527 patients. This consortium was established to hasten

the development of therapy for ARDS, and includes numerous trials evaluating the use of fluids, statins, albuterol, steroids, and nutrition. One of the most influential studies, and one from which much of our current strategy for lung protective ventilation comes from, is the landmark ventilation with lower tidal volumes as compared to traditional tidal volumes for acute lung injury and ARDS (ARMA) study which was published by the ARDSnet group in 2000 [12].

The ARMA study looked at patients who were mechanically ventilated due to either acute lung injury or ARDS. Patients were randomized into receiving the higher tidal volume ventilation of 12 mL/kg of ideal body weight with plateau pressures <50 cm $H_2O$ or a low tidal volume ventilation of 6 mL/kg of ideal body weight and plateau pressures <30 cm $H_2O$. The study was stopped early due to an 8% reduction of mortality in the low tidal volume ventilation group (31% vs 38.8%). This led to the belief that higher tidal volume ventilation can lead to worsening pulmonary edema due to alveolar overdistention, which can cause additional damage to the endothelial and epithelial lining, and promote a pro-inflammatory cascade [13]. While the high tidal volume group in this study was significantly higher than typically used, this study offers evidence showing that mechanical ventilation with low tidal volumes has a reduction in mortality.

There is also much debate as to which mechanical ventilation mode is best suited for patients with ARDS. However, a Cochrane review of three randomized control trials that included 1089 patients showed that there was no evidence to suggest that there was an advantage of using pressure-controlled or volume-controlled ventilation [14].

### 26.4.2 PEEP

Ideal PEEP settings in ARDS are also controversial and likely vary by patient. While higher PEEP minimizes dead space and alveolar stretch, it can lead to decreased venous return. However, as the PEEP drops, atelectasis can worsen. It is recommended that a minimum PEEP of 5 cm $H_2O$ be used, with the goal of minimizing trauma induced by repetitive opening and closing of the alveoli. A meta-analysis of three randomized controlled trials showed that mortality was increased with lower values of PEEP in patients with moderate to severe ARDS [15].

Multiple methods have been suggested to determine the optimal PEEP. The most common method for titration is based on the $FiO_2$. The LOVS (Lung Open Ventilation to Decrease Mortality in the Acute Respiratory Distress Syndrome) study [16] compared patients who received conventional levels of PEEP to those receiving higher levels. The study did not show any significant difference in all-cause mortality or barotrauma in the two arms; however, the higher PEEP strategy did appear to improve some secondary end points. The ARDSnet protocol includes both a lower PEEP and a higher PEEP strategy, seen in Table 26.3. This is utilized to achieve an oxygenation goal on arterial blood gas ($PaO_2$) of 55–80 mmHg or an oxygen saturation ($SpO_2$) goal of 88–95%. When setting the ventilator to a lower tidal volume, it is often necessary to allow for permissive hypercapnia, often causing a respiratory acidosis.

Another method of PEEP selection is based on the Positive End-Expiratory Pressure Settings in Adults with Acute Lung Injury and Acute Respiratory Distress Syndrome (ExPress) trial, which increased PEEP in a stepwise manner while maintaining a constant tidal volume and an inspiratory plateau pressure between 28 and 30 cm $H_2O$ [17]. Subgroup meta-analysis of the ALVEOLI, ExPress, and LOVS trial suggested a survival benefit of using higher PEEP in patients with a $PaO_2/FiO_2$ ratio < 200.

**Table 26.3** ARDSnet PEEP/$FiO_2$ table

| *Lower PEEP/Higher $FiO_2$* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| $FiO_2$ | 0.3 | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.7 | 0.7 |
| PEEP | 5 | 5 | 8 | 8 | 10 | 10 | 10 | 12 |
| $FiO_2$ | 0.7 | 0.8 | 0.9 | 0.9 | 0.9 | 1.0 | | |
| PEEP | 14 | 14 | 14 | 16 | 18 | 18–24 | | |
| *Higher PEEP/Lower $FiO_2$* | | | | | | | | |
| $FiO_2$ | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.5 |
| PEEP | 5 | 8 | 10 | 12 | 14 | 14 | 16 | 16 |
| $FiO_2$ | 0.5 | 0.5–0.8 | 0.8 | 0.9 | 1.0 | 1.0 | | |
| PEEP | 18 | 20 | 22 | 22 | 22 | 24 | | |

The Esophageal Pressure-Guided Ventilation (EPVent) trial was conducted to determine the effects of transpulmonary pressure-directed controlled mechanical ventilation in relation to the ARDSnet 6 mL/kg tidal volume [18]. Although they weren't explicitly looking at PEEP, their trial resulted in patients within the control arm with higher levels of PEEP and better outcomes. A second EPVent2 trial is currently underway, which is evaluating similar effects against a higher PEEP strategy.

Further confusing the matter is the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) [19] published in 2017. This trial enrolled patients with a $PaO_2/FiO_2$ ratio < 200 and compared a low PEEP strategy (using the same low PEEP table as in the ALVEOLI and LOVS trial) to a stepwise titration in PEEP using recruitment maneuvers. Interestingly, this trial showed a higher rate of mortality in the experimental arm.

### 26.4.3 Baby Lung and Driving Pressures

Quantitative analysis of CT scan images of lungs in patients with ARDS [20] led to the concept of "baby lung." Analysis has shown that ARDS is not homogeneously distributed, but rather consists of portions of lung that is normally aerated and portions that are completely deprived of aeration. This results in a small portion of lung that must fulfill the ventilation requirements of the individual. Research by Amato and colleagues [21] uses this concept to suggest that tidal volumes based on ideal body weight (IBW) is a reflection of the lung volume of healthy individuals and does not take into account that the functional lung of a patient with ARDS is significantly reduced (baby lung). They suggest that taking into account the lower respiratory-system compliance ($C_{RS}$) of the functional lung as a ratio of the lung volume based on IBW ($V_T$) provides a better prediction for outcomes. They define this ratio as the driving pressure ($\Delta P = V_T/C_{RS}$), which can be calculated at the bedside as the plateau pressure minus positive end-expiratory pressure (Pplat − PEEP). They reviewed 3500 patients from nine different trials and concluded that there was a higher mortality rate associated with patients with higher driving pressures. They also noted that the protective benefits of higher PEEP were only seen when it was associated with lower driving pressures. Their analysis suggests that driving pressures above 15 cm $H_2O$ may increase mortality. There are ongoing trials evaluating the benefit of reduced driving pressures in ARDS patients.

### 26.4.4 Prone Positioning

The Proning Severe ARDS Patients (PROSEVA) trial [22], a multicenter RCT of 474 patients with severe ARDS ($PaO_2/FiO_2$ < 150 mm Hg with $FiO_2$ > 0.6), showed that when compared to supine positioning, there was a significant reduction in 28-day mortality with prone positioning (16% in prone vs 32% in supine). The trial utilized prone positioning for a minimum of 16 consecutive hours per day. Placing a patient in prone position reduces the pleural pressure gradient from nondependent to dependent regions and allows for a more homogeneous distribution of aeration and strain from dorsal to ventral areas of the lung, thus protecting the lung from ventilator-induced lung injury (VILI) and allowing for improved VQ matching. Absolute contraindications to prone positioning include, but are not limited to: pregnancy, spinal instability, increased intracranial pressure, shock, anterior burns, and chest tubes. Hemodynamic instability (MAP <65 mmHg) may be considered a relative contraindication.

Although prone positioning has become more common throughout critical care units, challenges still exist in implementation. One of the most important factors for successful implementation remains physician and nurse training in order to familiarize the process. Prone positioning can result in unintended endotracheal extubation. Oxygenation can transiently decrease with proning, in particular during the turning process. This does not reflect a failure in proning and is often a transient phenomenon. Additionally,

chest wall compliance can be significantly reduced in the prone position, which may be attributed to a decrease in compliance of the rib cage and diaphragmatic component of the chest wall [23].

### 26.4.5 Neuromuscular Blockade

Spontaneous breathing on mechanical ventilation, in particular with severe ARDS, can have negative consequences such as patient–ventilator dyssynchrony and generation of high transpulmonary pressures which may increase the risk of VILI. Use of paralytic agents can improve patient–ventilator synchrony and lower oxygen consumption by respiratory muscles. The ACURASYS trial [24] looked at the effects of cisatracurium, a neuromuscular blocking agent, for 48 h. The trial showed that when compared to placebo, there was significantly lowered adjusted 90-day mortality in the cisatracurium group, increased ventilator-free days, and decreased ICU days. The trial also showed that patients on cisatracurium had less barotrauma and pneumothoraces and had no significant difference of ICU-acquired paresis. Despite these studies, the Society of Critical Care Medicine has not commented on the use of neuromuscular blocking agents in the most recent ARDS guidelines.

### 26.4.6 Steroids

There has been much interest in studying the effects of corticosteroids in ARDS with the hope of reducing the inflammation process. Unfortunately, no study has shown clear evidence of benefit from steroids use. Meduri [25] showed that there may be a reduction in ICU mortality with the use of methylprednisolone in the early phase of ARDS. However, multiple subsequent studies have not been able to demonstrate any evidence supporting the efficacy and use of steroids in ARDS [26, 27]. The ARDSnet steroid study showed an increase in mortality in patients who were started on steroids more than 14 days after the onset of symptoms [26].

### 26.4.7 Fluids

The Fluid and Catheter Treatment Trial in ARDS (FACTT) [28] looked at outcomes in patients with ARDS who were resuscitated with either a conservative or liberal fluid regimen. Although this study did not show a difference in the 60-day mortality rate, patients receiving conservative fluid management had a reduction in the duration of mechanical ventilation and ICU days. Interestingly, this study also looked at the use of central venous pressure and pulmonary capillary wedge pressure (PCWP) for guiding fluid resuscitation. Like many other studies, they concluded that use of a pulmonary artery catheter did not improve outcomes.

### 26.4.8 ECMO

There has been great interest in utilizing venovenous extracorporeal membrane oxygenation (VV-ECMO) for patients with severe respiratory failure. VV-ECMO is a mode of ECMO that specifically provides support for the lungs by oxygenating blood and removing carbon dioxide externally. The efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial [29] looked at the utility of transferring patients with severe respiratory failure with a Murray score $\geq 3$ or uncompensated hypercapnia with a pH $< 7.2$ to an ECMO center. This study showed that when compared to conventional ventilator management, 6-month survival without severe disability was higher in patients who were transferred to an ECMO center (63% vs. 47%) but it did not show an increase in survival for those who received ECMO compared to those that did not. At the time of publication, there was insufficient evidence to make guideline recommendations for the use of ECMO in patients with ARDS.

### 26.4.9 Nutrition

Nutrition plays a vital role in the recovery of any critically ill patient. Aside from the obvious benefits of nutrition, enteral feeding has the advantages

of continuously stimulating the gut and reducing the risk of infection by bacterial translocation. The EDEN trial [30] conducted by the ARDSnet group looked at the difference between trophic and full enteral feeding for the first 6 days of treatment, after which all patients received full enteral feeding. Trophic, or trickle, feeding was defined by a rate of 20 kcal/h, whereas full enteral feeding was defined by a rate of 80 kcal/h. This study showed that there was no difference in outcomes (ventilator-free days, 60-day mortality, and infections) between the two groups. However, it was noted that the full enteral feeding group had higher incidences of gastrointestinal intolerance, resulting in emesis and higher gastric residuals. Patients enrolled in the EDEN trial were also initially concurrently enrolled in the OMEGA trial [31], looking at the benefits of omega 3-fatty acids. However, this trial was stopped early due to futility with interim analysis showing a 10% absolute increase in mortality in the treatment group (26.6% vs. 16.3%).

### 26.4.10 Other Treatment Considerations

There have been many studies looking at other treatment modalities in ARDS that have not shown to have much benefit or may cause harm. Once such modality is high-frequency oscillatory ventilation (HFOV). As more research has emerged regarding increased damage to the lung from overstretching or repetitive collapse of the alveoli, the thought was that patients may benefit from the extremely low tidal volumes provided by HFOV (1–2 mL/kg) at very high rates. A Cochrane review of 10 randomized controlled trials of HFOV in patients with moderate to severe ARDS [32] concluded that the use of high-frequency oscillation did not show any significant difference in hospital or 30-day mortality. One of the trials included in the review was terminated early after multiple in-trial analysis showed that the use of HFOV increased the mortality rate [33].

Inhaled nitric oxide (iNO) is a potent pulmonary vasodilator that is used in the treatment of pulmonary hypertension and was thought to improve oxygenation in patients with ARDS by improving blood flow to the healthy portion of lungs. Unfortunately, multiple trials, as summarized by a Cochrane review [34], did not show any evidence for improved survival with the use of iNO and exposed the patient to adverse effects such as hypotension and renal failure.

The Albuterol for the Treatment of ALI (ALTA) trial conducted by the ARDSnet group looked at the use of aerosolized albuterol [35]. Because beta-2 agonists had been shown to have anti-inflammatory effects in the lungs of experimental ALI, it was anticipated that the severity of lung injury would be reduced due to a reduction of permeability-induced lung injury. However, this trial was terminated early due to futility after showing no benefit in any of its end points. Similarly, another trial, the β-Agonist Lung Injury Trial (BALTI-II), was terminated early when interim analysis showed increased 28-day mortality [36].

While no broad clinical guidelines have been established regarding the treatment of ARDS, the ESICM, ATS, and SCCM did release a practice guideline statement in May, 2017 addressing mechanical ventilation in adult patients with ARDS [37]. Though limited, they strongly recommended the use of lung protective ventilation strategies utilizing low tidal volume and low plateau pressures and the use of prone positioning for >12 h/day in severe ARDS. Additionally, they recommended consideration for the use of higher PEEP and recruitment maneuvers in patients with moderate to severe ARDS. The practice guidelines recommended against the use of high-frequency oscillatory ventilation and were equivocal on the use of ECMO, stating that additional evidence was necessary to make a definitive recommendation.

## 26.5 Conclusion

Acute Respiratory Distress Syndrome is a complicated disease process and, despite advancements in medicine and technology, continues to have a high rate of mortality and utilizes significant resources. Furthermore, early identification

of patients with the diagnosis of ARDS continues to remain poor. The hallmark of ARDS management continues to be supportive care with treatment of the underlying process and low tidal volume ventilation. Despite numerous studies, few interventions have shown consistent mortality benefit. Therefore, it is important to remember that treatment should be personalized for each patient based on the clinical scenario and degree of disease severity.

**Key Points**

- Acute Respiratory Distress Syndrome results from direct or indirect insult to the alveolar epithelium resulting in damage to alveolar capillary cells.
- Acute Respiratory Distress Syndrome remains under-diagnosed and has an ICU mortality of up to 42%.
- The mainstay of treatment in Acute Respiratory Distress Syndrome is supportive care and lung protective mechanical ventilation.

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# 27 Deep Venous Thrombosis and Venous Thromboembolism Prevention in the Neurocritical Care Unit

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## 27.1 Introduction

Venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) is common and in some cases a life-threatening complication in neurosurgical and neurological patients cared for in a specialized neuroscience intensive care unit or in the general medical or surgical ICU. Deep venous thrombosis incidence in this population has been reported to be as high as 34% when prophylaxis was not given [1] with a mean of about 15% across several reports [2]. A previous report documented an incidence of 24.8% of PE in a consecutive autopsy series of 100 patients with neurological disease. Pulmonary embolism was the primary cause of death in almost 50% of these patients. A number of conditions place this subgroup of patients at a higher risk for VTE, such as delayed ambulation due to paralysis or coma, lengthy hospital stays, and length of neurosurgical procedures. Also, brain tumors, inflammatory diseases of the central or peripheral nervous system, and stroke (i.e., hemorrhagic or ischemic) can lead to vascular endothelium activation. There is a wide variability in clinical practice for VTE prophylaxis in these patients, partly due to paucity of data based on randomized clinical trials. Practice guidelines based on the available data have been published [3–5]. The lack of evidence has led to the development of evidence-based guideline incorporating the GRADE scale to reduce VTE and its complications. Randomized controlled studies were prioritized and meta-analyses were included. When such studies were not available, case series and retrospective studies were included in decision-making. Current evidence supports the use of mechanical and chemical VTE prophylaxis as beneficial in reducing the risk of developing DVT and PE; the risk of hemorrhagic complications upon initiating chemical prophylaxis for VTE prevention remains a serious concern for neurosurgeons and neurointensivists. The guidelines are also meant to be a point of reference for further research in the future.

Although information regarding the general critically ill neurological and neurosurgical population is important, it is even more useful to know the risk of DVT and PE in specific subpopulations of neurosurgery and neurology patients. For instance, spinal cord injury patients have been consistently reported to have higher incidence of VTE in the neurocritically ill population.

This chapter will describe especial circumstances for patients affected with the various neurological and neurosurgical conditions admitted to the intensive care unit. Every section will be

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followed by the current practice guidelines published and endorsed by the Neurocritical Care Society and the Society of Critical Care Medicine.

## 27.2 Thromboprophylaxis in Critically Ill Patients with Ischemic Stroke

Ischemic stroke is the second common cause of death and disability worldwide and is a major public health [6–8]. PE occurs in 2–3% of all ischemic stroke victims; DVT and PE have an incidence of 2.5 and 1.2%, respectively [9, 10]. The prevalence of institutionalized stroke survivors is expected to increase if stroke incidence and the mean length of poststroke survival do not decrease [6, 7], which in turn will increase the prevalence of VTE in the neurocritical care setting.

Ischemic stroke victims often present with preexisting comorbid conditions that require anticoagulation (i.e., atrial fibrillation, VTE, heart failure, cancer, etc.). It has been reported that patients who do not receive VTE prophylaxis after ischemic stroke have as high as a 75% likelihood of developing DVT and a 20% chance of developing PE in hemiplegic patients [11]. VTE is sometimes a chronic disorder with recurrence in one third of the patients over a 10-year period [12]. The American Heart Association and the American College of Chest Physicians have also published guidelines based on randomized trials [13, 14]. Many meta-analyses examine the use of pharmacologic VTE prophylaxis such as unfractionated heparin (UFH) as well as low-molecular-weight heparin (LMWH). Elastic compression stockings (CS) and intermittent venous compression stockings (IPC) have been studied in the setting of ischemic stroke [11, 15–17]. The results of these studies support the use of chemical prophylaxis with either LMWH or UFH with or without the use of IPC. There is a modest positive synergistic effect with the use of mechanical prophylaxis in addition to chemical prophylaxis [11, 15–17]. The use of compressive stockings carries a small risk for skin breakdown with an incidence ranging from 2 to 5% [11, 15–18]. It has also been reported that proximal DVT occurs more often in patients with stroke who wear below-knee stockings than in those who wear thigh-length stockings [18]. Skin breakdown is also slightly higher in patients who wear thigh-length stockings compared to those who wear below-knee stockings (3.9 vs 2.9%) [18]. CS and IPC use is ubiquitous; there is concern about inadvertent provocation of VTE dislodgement, particularly in immobile patients who have profound sensory changes prior to application.

The CLOTS (Clots in Legs Or sTockings after Stroke) 3 trial collaboration demonstrated a VTE absolute risk reduction of 3.6% (95% CI 1.4–5.8%) while using IPC in the first 3 days after suffering a stroke [17]. The PREVAIL (PREvention of VTE After Acute Ischemic Stroke With LMWH Enoxaparin) study suggested that in ischemic stroke, enoxaparin was preferable to unfractionated heparin for venous thromboembolism prophylaxis because of a better clinical benefit to risk ratio and increased convenience of once daily administration. Enoxaparin reduced the risk of venous thromboembolism by 43% compared with unfractionated heparin (68 [10%] vs 121 [18%]; relative risk 0.57, 95% CI 0.44–0.76, $p = 0.0001$; difference −7.9%, −11.6 to −4.2); this reduction was consistent for patients with an NIHSS score of 14 or more (26 [16%] vs 52 [30%]; $p = 0.0036$) or less than 14 (42 [8%] vs 69 [14%]; $p = 0.0044$) [11]. Serious hemorrhagic complications are estimated to be low in hospitalized patients with ischemic stroke treated with LMWH and UFH [19, 20].

In patients with MCA stroke who underwent decompressive hemicraniectomy (DH), the incidence of DVT (36%) and the need for placement of an IVC filter (25%) were not uncommon during the inpatient recovery period [21]. However, chemical prophylaxis for VTE prevention acutely after hemicraniectomy in the setting of the malignant MCA syndrome has not been studied [22].

The use of UFH and LMWH has both been considered to be safe in patients undergoing elective craniectomy [23–25]. Pharmacological and mechanical prophylaxis in this population is warranted due to a high risk of VTE in this subpopulation of patients. The use of UFH and LMWH in patients undergoing hemicraniectomy is safe in general. For patients undergoing endovascular

procedures, no clear data currently exists to guide practice although it is recognized that most protocols incorporate large doses of heparin during the procedure and often also incorporate rTPA. Waiting 24 h after the administration of rTPA or hemicraniectomy may be reasonable although not supported by strong clinical evidence.

### 27.2.1 Prophylaxis of Venous Thrombosis in Neurocritical Care Patients with Ischemic Stroke: Recommendations

1. Initiate VTE pharmacoprophylaxis immediately when feasible in all patients with acute ischemic stroke (strong recommendation and high-quality evidence).
2. In patients with acute ischemic stroke with restricted mobility, prophylactic-dose LMWH over prophylactic-dose UFH in concurrently with IPC (strong recommendation and high-quality evidence).
3. Due to insufficient evidence, no recommendation about the use of CS for VTE prophylaxis has been suggested. Presently their use does not appear to be harmful.
4. In stroke patients undergoing hemicraniectomy or endovascular intervention, the use of UFH, LMWH, and/or IPC for VTE prophylaxis is recommended in the acute postsurgical or endovascular epoch except when patients have received rTPA, in which case prophylaxis should be delayed 24 h (weak recommendation and low-quality evidence).

## 27.3 Thromboprophylaxis in Critically Ill Patients with Intracranial Hemorrhage

The risk of VTE is higher in patients with ICH compared with victims of ischemic strokes, possibly due to a higher incidence of need for mechanical ventilation, paresis or paralysis, and lengthier ICU stay. Patients who have suffered an ICH have a fourfold higher risk of developing a VTE when compared with the acute ischemic stroke population [5, 26, 27]. This higher risk is regarded to be boosted by lower utilization rates of chemical VTE prophylaxis [5]. Thus, despite an acute hemorrhagic insult, VTE prophylaxis is needed in this patient population. The prevalence of symptomatic DVT in ICH patients is reported to be 1–2% in retrospective studies [27–30]; nonetheless the FAST trial reported an incidence of 5% [31]. The incident radiological detection of DVT by venous ultrasonography was 20–40% in two prospective trials [32, 33]; both studies were conducted in Japan. The reported incidence of pulmonary embolism clinically relevant was reported to be 0.5–2% [26–34] with a consistent mortality rate of about 50%.

A prospective study where the authors randomly allocated patients with a documented ICH to compressive stockings alone or combined with IPC showed a significant reduction in the risk of asymptomatic DVT by day 10 by compression ultrasonography (4.7% CS + IPC vs 11% CS only) [35]. The CLOTS3 trial also supported these findings of the use of IPC for VTE prophylaxis in patients with ICH [17]. Earlier, the CLOTS trial 1 had reported that the use of CS alone did not prevent VTE and also caused skin breakdown [36].

A small prospective study examined the effect of heparin treatment in ICH patients beginning on the second, fourth, or tenth day. Early (day 2) low-dose heparin medication significantly lowered the incidence of pulmonary embolism, while an increase in the number of patients with rebleeding was not observed [37]. In another small randomized study using LMWH or CS starting on day 2 from intracranial bleed, no hematoma enlargement was observed at 72 h, 7 days, and 21 days in either group. Also, there was not any other systemic bleeding complication in LMWH group, while the incidence of VTE was not statistically significant between groups, proving to be safe in patients with ICH [38]. A larger meta-analysis demonstrated that in patients with hemorrhagic stroke, early anticoagulation is associated with significant reduction in PE, with minimal risk of increased hematoma enlargement [39]. The American College of Chest Physicians guidelines for antithrombotic therapy and prevention of thrombosis in its ninth edition [40] also implements the Grades of Recommendation, Assessment, Development,

and Evaluation (GRADE) system. It used indirect data from the ischemic stroke literature to estimate control rates for the incidence of VTE in patients with ICH and to estimate the effect of heparin on this incidence. It judged the indirectness to be insignificant and therefore did not rate down the quality of the evidence. It deemed heparin prophylaxis to be associated with 33 fewer symptomatic DVTs and 5 fewer PEs per 1000 patients treated. A recent small study compared the efficacy of fixed-dose enoxaparin and adjusted-dose unfractionated heparin in patients with cerebral venous thrombosis [41]. No significant differences in the incidence of expansion of preexisting intracerebral hematoma occurred.

### 27.3.1 Prophylaxis of Venous Thrombosis in Neurocritical Care Patients with Intracranial Hemorrhage: Recommendations

1. Using IPC and/or GCS for VTE prophylaxis as opposed no prophylaxis beginning at the time of hospital admission (strong recommendation and high-quality evidence).
2. Using prophylactic doses of subcutaneous UFH or LMWH directed to prevent VTE in patients with stable hematomas and no ongoing coagulopathy within 48 h of hospital admission (weak recommendation and low-quality evidence).
3. Maintain mechanical VTE prophylaxis with IPCs in patients in which pharmacologic prophylaxis has begun (weak recommendation and low-quality evidence).

## 27.4 Thromboprophylaxis for Critically Ill Patients with Aneurysmal Subarachnoid Hemorrhage

DVT is a common complication of aneurysmal subarachnoid hemorrhage (aSAH) associated with increased death and disability [1, 42–47]. Retrospective studies used screening ultrasound to estimate the incidence of DVT in aSAH to be 10–25% [45, 46]. A more recent prospective study found the incidence of DVT using repeated ultrasound screening to be 21% in a cohort of 198 patients [48] where 69% of the 42 cases of DVT were first detected between days 3 and 14. And the postrupture 5-day window of highest risk for DVT development was between days 5 and 9. During this time, chemoprophylaxis for DVT was not routinely used, in favor of mechanical prophylaxis with SCDs combined with frequent repeated ultrasound screening. Another study showed overall rates of VTE (DVT or PE), DVT, and PE to be 4.4%, 3.5%, and 1.2%, respectively [49], while also describing that patients who underwent clipping versus coiling had similar VTE rates. This has been the largest study evaluating the incidence and risk factors associated with the development of VTE after aSAH. It demonstrated that patients with VTE nearly double the mean length of stay ($p < 0.001$) and total inflation-adjusted hospital charges ($p < 0.001$).

Early mobilization programs for patients with aneurysmal SAH appear to be safe and feasible [50]; those programs help to reduce the incidence of VTE in patients who are able to participate. Compressive stocking use is ineffective in decreasing the incidence of DVT, and in turn its use increases the risk to develop skin breakdown. In a mixed neurosurgical population, ICDs were effective preventing VTE as compared to placebo [2]. Combining IPCs with anticoagulants could have additive effects in VTE prevention [2, 19].

Although the use of UFH decreases the incidence of DVT, there are no randomized controlled trials studying the safe dosing 10,000 vs 15,000 IUs. The higher dose has been regarded as posing a higher risk for intracranial hemorrhage, yet unproven [2]. LMWH has been associated with a trend toward higher rates of intracerebral hemorrhage and non-cerebral minor hemorrhage with low-molecular-weight heparin as compared with SCDs or UFH [51]. Low-dose LMWH use may outweigh risks in patients undergoing craniectomy when considering that disability and mortality resulting from SAH are 2–3 times greater when complicated by VTE [52].

Also, the timing of DVT prophylaxis in relationship with aneurysm occlusion is controversial. The norm is to withhold prophylactic medications until the aneurysm has been secured.

The risk of ventriculostomy-associated hemorrhage in patients with aneurysmal subarachnoid hemorrhage treated with anticoagulant thromboprophylaxis was also studied showing that the risk of VTE was reduced by more than half in patients receiving chemoprophylaxis, whereas ventriculostomy-associated hemorrhages were rare and minor [53].

### 27.4.1 Prophylaxis of Venous Thrombosis in Neurocritical Care Patients with Aneurysmal Subarachnoid Hemorrhage: Recommendations

1. VTE prophylaxis with UFH should be used in all patients with aSAH (strong recommendation and high-quality evidence) with the exception of those with unsecured ruptured aneurysms anticipated to undergo surgery (strong recommendation and low-quality evidence).
2. IPCs as VTE should be initiated as prophylaxis upon admission to the hospital in patients with aSAH (strong recommendation and moderate-quality evidence).
3. Begin VTE prophylaxis with UFH at least 24 h after securing an aneurysm by surgical approach or by coiling (strong recommendation and moderate-quality evidence).

## 27.5 Thromboprophylaxis for Critically Ill Patients with Traumatic Brain Injury (TBI)

Many controversies persist regarding the appropriate management for optimizing VTE prophylaxis in people critically ill with intracranial bleed resulting from traumatic brain injury, where physicians have to balance the risks of progressive hemorrhage in the brain against secondary thrombotic complications. A post hoc analysis of the erythropoietin in traumatic brain injury (EPO-TBI) trial showed that VTE occur [54] red in one out of every five patients with TBI treated in the ICU despite mechanical and pharmacological prophylaxis. Coagulopathy, both pro- and anticoagulatory abnormalities, has been described after TBI in about one third of the patients [55–57]. The presence of coagulation disorders after TBI has been associated with worse outcomes [57, 58]. Acute coagulopathy of trauma-shock results from widespread endothelial activation after hypoperfusion [59]. Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis [60].

A recent study showed substantial variation in VTE prevention practices in TBI patients in ICUs in more than 60 hospitals in Europe and Israel participating in the CENTER-TBI study. This was attributed to the lack of clear guidelines based on high-quality evidence [61]. The presence of limb trauma often limits the use of GCS and IPCs.

The Brain Trauma Foundation (BTF) guidelines for the management of severe traumatic brain injury (fourth edition) [62] provides level III recommendation for DVT prophylaxis based on low-quality body of evidence. In spite the high incidence of VTE in TBI patients, there are no randomized trials of early versus late chemoprophylaxis. In multi-trauma patients, a multicenter prospective cohort study evaluated clinical outcomes in adults with hemorrhagic shock after injury; it showed that delayed initiation of VTE prophylaxis (beyond day 4) was associated with a three times increased risk of developing DVT compared to starting chemoprophylaxis within 48 h from injury [63]. A systematic review evaluating the benefits and risks of anticoagulation following TBI suggested that VTE chemoprophylaxis appears to be safe among TBI patients with stabilized hemorrhagic patterns, that is, TBI patients presenting within 6 h of injury with small injury patterns and stabilized CT scans at 24 h were considered at a low risk, where 1% in the chemoprophylaxis group and 3% in the non-chemoprophylaxis group developed VTE [64].

There are no randomized controlled trials addressing regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis in TBI patients, specifically. In its fourth edition, the BTF guidelines in the management of TBI patients makes its recommendation based on four retrospective studies [65–68] stating that LMWH or low-dose UFH may be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage.

### 27.5.1 Prophylaxis of Venous Thrombosis in Neurocritical Care Patients with Traumatic Brain injury: Recommendations

1. Initiate IPC for VTE prophylaxis within 24 h of onset of TBI or within 24 h after treatment with a craniotomy, supported by evidence in ischemic stroke and postoperative craniotomy (weak recommendation and low-quality evidence).
2. Initiate LMWH or UFH for VTE prophylaxis concurrent to 24–48 h of presentation in TBI patients with ICH or within 24 h after craniotomy (weak recommendation and low-quality evidence).
3. Place mechanical devices including IPC for VTE prophylaxis in TBI patients, based on data from other neurological injuries such as ischemic stroke (weak recommendation and low-quality evidence).

## 27.6 Thromboprophylaxis for Critically Ill Patients with Brain Tumors

Patients with high-grade glioma (HGG; WHO grade III/IV) have an increased risk of venous thromboembolism (VTE). The occurrence of symptomatic VTE in patients with HGG has been reported to be around one in five patients in the postoperative period when received prophylaxis with LMWH [69]. Another meta-analysis reported that within 6 weeks after surgery, the incidence rate of deep venous thrombosis (DVT) ranged from 3% to 60% in patients with malignant glioma [70].

The use of LMWH in patients with HGG has been shown to decrease the risk of developing VTE, as only about 10% of the VTE events occurred during thrombosis prophylaxis with LMWH within the first postoperative days [69] with the risk again rapidly increasing after cessation of chemoprophylaxis for VTE, suggesting that thromboprophylactic regimens are sufficient, but their duration might be too short. A prior study reported that treating patients with prophylactic doses of LMWH (40 mg/day) or standard UFH (10,000 UI/day) in combination with intermittent pneumatic compression resulted in no symptomatic thromboembolic event within the first 9 postoperative days and relatively small incidence of asymptomatic VTE (9.3%) [71]. In both studies, the incidence of intracranial bleeding was not reported.

The ECOG (Eastern Cooperative Oncology Group) phase II trial examined the effect of dalteparin on thromboembolic events in patients with glioblastoma multiforme, suggesting that dalteparin reduces the incidence of VTE at a dose of 5000 UI/day; in their study there were no grade 3/4 bleeding or thrombocytopenic events, and no VTE events occurred while on dalteparin [72].

In two additional studies using low-molecular-weight heparins (dalteparin [73] and tinzaparin [74]) starting within 4 weeks of surgical resection and continued for up to 12 months, both showed reduced VTE, and increased intracranial bleeding was seen in the LMWH thromboprophylaxis groups. On the other hand, a retrospective analysis suggested that enoxaparin may decrease the incidence of postoperative VTE, while it did not increase the incidence of postoperative intracranial hemorrhage in patients with meningioma when received within 48 h after surgery. Though, due to study design and power, they were not able to demonstrate VTE reduction with statistical significance.

### 27.6.1 Prophylaxis of Venous Thrombosis in Neurocritical Care Patients with Brain Tumors: Recommendations

1. Initiate VTE prophylaxis with either LMWH or UFH when hospitalized for patients with brain tumors at low risk for major bleeding lacking signs of hemorrhagic conversion (strong recommendation and moderate-quality evidence).

## 27.7 Thromboprophylaxis for Critically Ill Patients with Spinal Cord Injury (SCI)

Venous thromboembolism remains the major complications in spinal cord injuries associated with motor complete or motor nonfunctional paralysis. The incidence is estimated to be three times higher than the general population [75]. Also, the occurrence of DVT and pulmonary embolism persists and recurs despite adequate anticoagulation [76]. SCI victims suffer changes in nerves, muscles, and blood vessels following the injury and paralysis. The incidence of DVT without prophylaxis in acute spinal cord injury patients is estimated to be between 50% and 80% [77]. Although the incidence is greatest acutely after the initial injury and decreases with time, over the following months, the risk never disappears completely [75, 78].

The role of GCS alone versus placebo after spinal cord injury has not been studied. A report using GCS plus IPCs and LMWH (nadroparin) combined showed an incidence of DVT of only 2%, and no PE developed when the protocol was started early within 72 h from injury. Those patients who were admitted after 8 days from the injury and not having received mechanical of prophylaxis, the incidence of DVT was 26% [78]. Two other studies showed that combined therapy, mechanical plus chemoprophylaxis using LMWH, was efficacious and safe in reducing the risk of VTE after SCI [79, 80].

SCI is often associated with major trauma and/or lower extremity injury and/or fracture which prevents the use of mechanical or chemoprophylaxis in the acute phase. The use of inferior vena cava (IVC) filter placement has been proposed. Although early reports of prophylactic placement of IVC filter in selected patients after SCI were safe and associated with effectively preventing both fatal and nonfatal PE [81–83], a more recent retrospective study demonstrated that the presence of prophylactic IVC filters in acute SCI patients may actually increase the risk of DVT [84]; the incidence of PE was not reported.

Both UFH and LMWH have been found to be effective reducing the incidence of DVT after sustaining SCI [80, 85, 86]. A retrospective cohort by Worley found no significant association ($p = 0.7054$) between the incidence of clinically evident VTE (7.78% overall) and type of prophylaxis received (low-dose UFH vs dalteparin) in acute traumatic spinal cord injury [87], further suggesting that adjusted-dose UFH is more cost-effective than enoxaparin 30 mg bid in a cost analysis in the same cohort.

Meanwhile, the American College of Chest Physicians Antithrombotic Guidelines and the Consortium for Spinal Medicine both recommend the use of UFH or LMWH in addition to IPCs after SCI for the prevention of VTE [14, 88].

The duration of DVT prophylaxis in patients following SCI has not been determined. The Consortium for Spinal Medicine recommends the duration of DVT prophylaxis be assessed based on the functional status, presence of other risk factors or medical conditions, etc. [89].

### 27.7.1 Prophylaxis of Venous Thrombosis in Neurocritical Care Patients with Spinal Cord Injury: Recommendations

1. Begin VTE prophylaxis as soon as possible, within 72 h of injury (strong recommendation and high-quality evidence).
2. Avoid using lone mechanical measures for VTE prophylaxis (weak recommendation and low-quality evidence).

3. Initiate LMWH or adjusted-dose UFH for VTE prophylaxis as immediately as bleeding is controlled (strong recommendation and moderate-quality evidence).
4. If VTE prophylaxis with LMWH or UFH is not possible, the use of mechanical prophylaxis with IPC is recommended (weak recommendation and low-quality evidence).

## 27.8 Thromboprophylaxis for Critically Ill Patients with Neuromuscular Disease

Patients with neuromuscular diseases (i.e., Guillain-Barre syndrome (GBS), amyotrophic lateral sclerosis (ALS), and myasthenia gravis (MG)) admitted to the intensive care unit share major risk factors for VTE development including sepsis, immobilization, and respiratory failure [90]. Increased incidence of VTE in patients with GBS is well documented and estimated to be around 2–8% [91–96]. Hence, VTE prophylaxis is required in the care of patient with neuromuscular diseases when hospitalized.

There are no randomized studies addressing VTE prophylaxis in this population subset, and the current practices are largely deduced from hospitalized and critically ill medical patients and patients with spinal cord injury where such data does exist. A retrospective study included 73 patients with GBS, 50 of which were anticoagulated. Anticoagulation was discontinued when they could walk independently. DVT developed in 7%, and almost half of those also had a pulmonary embolus despite prophylactic use of LMWH in patients admitted with major problems of mobility [91].

A number of meta-analyses analyze the utility of different forms of VTE prophylaxis in hospitalized and critically ill medical patients [90, 97–101]. The most recent by Kahn [90] include data from 4 to 8 clinical trials (5206–8605 patients) depending on the outcome (i.e., symptomatic DVT, PE, death from PE, major bleeding, heparin-induced thrombocytopenia). It recommended the use of LMWH or low-dose UFH for VTE chemoprophylaxis over no prophylaxis for critically ill patients without GI bleed. Grade 2C recommendation based on evidence (relative risk (RR) of 0.47 (95% CI 0.22–1) in symptomatic DVT, and RR 0.41 (95% CI 0.22–0.76) for fatal PE). There were no statistically significant differences in risk of PE, DVT, major bleeding, or mortality.

The ARTEMIS trial studied the efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients [102]; it included 849 medical patients aged 60 or more admitted to hospital. VTE was found in 5.6% of patients treated with fondaparinux and 10.5% of patients given placebo, with a relative risk reduction of 46.7% (95% CI 7.7% to 69.3%). The frequency of major bleeding was similar for both fondaparinux- and placebo-treated patients.

VTE prophylaxis using GCS or IPs is less well studied in critically ill medical patients. Though, GCS and IPC, when added to pharmacologic prophylaxis, are associated with a reduction in the risk of DVT but not PE in surgical patients [103, 104]. The Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT) examined the effects of chemoprophylaxis with dalteparin compared to UFH on VTE, bleeding, and other outcomes in critically ill patients showing that dalteparin was not superior to unfractionated heparin in decreasing the incidence of proximal DVT. However, the proportion of patients with PE was significantly lower with dalteparin (1.3%) than with unfractionated heparin (2.3%) (hazard ratio, 0.51; 95% CI, 0.30–0.88; $P = 0.01$), while there was no significant difference in the rates of major bleeding or death [105]. There is no data available addressing the optimal duration of VTE prophylaxis in and out of the hospital.

### 27.8.1 Prophylaxis of Venous Thrombosis in Neurocritical Care Patients with Neuromuscular Disease: Recommendations

1. Prophylactic dosing of UFH (bid or tid) LMWH or fondaparinux is the preferred method of VTE prophylaxis (strong recommendation and moderate-quality evidence).

2. IPC use for VTE prophylaxis in patients in whom bleeding risk is deemed too high for pharmacologic prophylaxis (strong recommendation and moderate-quality evidence).
3. Combined pharmacologic and mechanical VTE prophylaxis (with IPC) in neuromuscular patients is recommended (weak recommendation and low-quality evidence).
4. Use of GCS only for VTE prophylaxis in patients for whom neither pharmacologic prophylaxis nor IPC use is feasible (weak recommendation and low-quality evidence).
5. Continue VTE prophylaxis for extended periods, at a minimum for the duration of the acute hospitalization, or until able to ambulate returns (weak recommendation and very low-quality evidence).

## 27.9 Thromboprophylaxis in Critically Ill Patients Undergoing Neurosurgical and Neurovascular Interventions

VTE prophylaxis is paramount in the care of neurosurgical patients in the postoperative period. These populations of patients because of the procedures they undergo have a wide range of variability, ranging from an otherwise healthy individual undergoing an elective procedure to an emergent surgical case in a patient with a number of comorbidities. Thus, a highly variable incidence that ranges from 0 to 18% of VTE in neurosurgical patients is explained. Prolonged, extensive spinal procedures carrying the highest risk for DVT at 14% are revealed by noninvasive testing using color duplex Doppler imaging to rule out deep vein thrombosis 1 day before discharge [22, 106, 107]. Elective spinal procedures appear to carry a lower risk for DVT, around 2% as demonstrated by a systematic review of 25 studies, even when no chemoprophylaxis was utilized [108]. Another retrospective review was completed that included the three most common elective spinal procedures (lumbar microdiscectomy, anterior cervical discectomy and fusion, and lumbar stenosis decompression), encompassing more than 100,000 cases were included. Overall rates of PE, death due to PE, and DVT were 1.38, 0.34, and 1.18 per 1000 cases, respectively [109]. In patients with gliomas, there was a very high incidence of symptomatic VTE, particularly within 2 months of neurosurgery with a cumulative incidence of VTE of 7.5% [110]. A smaller series reported an incidence of VTE of 28% in patient with high-grade glioma [111]. Scarce data exists for patients undergoing neuroendovascular procedures. The vast majority of this patient population receives systemic anticoagulation during the neuroendovascular intervention, in all likelihood affecting the incidence of VTE. A recently published Guideline for the management of the emergent large vessel occlusion (ELVO) patient post-thrombectomy from the Society of NeuroInterventional Surgery failed to address VTE prophylaxis [112].

Various studies have aimed to examine the efficacy and risks associated with VTE prophylaxis in patients undergoing neurosurgical operations [1, 2, 25, 113–121]. A recent large study using the Nationwide Inpatient Sample (NIS) queried from 2002 to 2010 for hospital admissions for subarachnoid hemorrhage or intracerebral hemorrhage and either aneurysm clipping or coiling found that VTE was associated with pulmonary/cardiac complication (OR 2.8), infectious complication (OR 2.8), ventriculostomy (OR 1.8), and vasospasm (OR 1.3) [49]. The overall consensus is that the use of LWMH and ICP is generally equally safe and effective with a limited risk of ICH [122–128]. A study using low-dose perioperative UFH in neurosurgical patients suggests that such therapy is unlikely to be associated with increased morbidity when 5000 IU is administered subcutaneously twice a day, commencing before surgery and continuing until patients were ambulatory [129]. The largest prospective study assessing the risk of postoperative hemorrhage after intracranial surgery using early (<24 h) nadroparin administration supports its use for postoperative chemoprophylaxis in such patient. It reported an incidence of postoperative hemorrhages of only 1.5% in 2823 intracranial procedures [130], while intraoperative use of LMWH for the prevention of VTE in patients undergoing

craniectomy increases the risk for developing ICH [2, 51, 131, 132]. A small prospective, randomized, double-blind study using a small dose of 5000 IU of heparin in patients with brain tumors undergoing craniectomy starting 2 h before surgery and continuing until full mobilization or for 7 days was safe [133]. Combined therapy using IPCs plus either LMWH or UFH has been shown to be safe and beneficial in elective craniotomy surgery [71, 133] and in complicated spinal surgery [24, 115, 117, 129, 134–136].

A recent single institution retrospective study reported an incidence of 4% for VTE in endovascular neurosurgery patients [137]. While it has been demonstrated that heparinization for cerebral aneurysm coiling can be safely performed even after EVD placement within 24 h [138], conversely, the placement of EVD, ICP gauge, or combined EVD and ICP gauge within 48 h after cerebral aneurysm coiling and under different anticoagulation or antiplatelet regimens seemed to have no increased risk of hemorrhages [139].

### 27.9.1 Prophylaxis of Venous Thrombosis in Patients Undergoing Elective Spine Surgery

1. Ambulatory back surgery is associated with unique positioning strategies including prone or kneeling positioning and has been associated with zero rates of VTE; initiate IPC only for VTE prophylaxis in this population (weak recommendation and low-quality evidence).
2. In uncomplicated elective spine surgery, it is recommended to promote ambulation with mechanical VTE prophylaxis (GCS or IPC) singlely or combined with LMWH. In patients with a higher risk for VTE, begin combined therapy with ambulation, GCS or IPC, and LMWH (strong recommendation and moderate-quality evidence).
3. Because of the increased risk of bleeding, begin UFH only as alternative to other methods of VTE prophylaxis (strong recommendation and moderate-quality evidence).

### 27.9.2 Prophylaxis of Venous Thrombosis in Patients Undergoing Complicated Spinal Surgery

1. We suggest using IPC with LMWH or UFH (strong recommendation and moderate-quality evidence).
2. Avoid standard use of IVC filters in severe spinal cord injury or complicated spine surgery (weak recommendation and low-quality evidence).
3. Consider removing prophylactic IVC filters used as a temporary measure only in patients with PE and DVT or those with DVT at risk for PE who cannot be safely anticoagulated (weak recommendation and low-quality evidence).

### 27.9.3 Venous Thrombosis Prophylaxis in Patients Undergoing Elective Craniotomy

1. Initiate IPC with LMWH or UFH within 24 h after craniotomy (strong recommendation and moderate-quality evidence).
2. Initiate IPC with LMWH or UFH within 24 h after standard craniotomy for glioma resection (strong recommendation and moderate-quality evidence).

### 27.9.4 Prophylaxis of Venous Thrombosis in Patients Undergoing Elective Intracranial/Intra-arterial Procedures

1. Initiate CS and IPC until the patient is ambulatory (weak recommendation and low-quality evidence).

2. Initiate immediate prophylactic anticoagulation with LWMH or UFH (weak recommendation and low-quality evidence).

### 27.9.5 Prophylaxis of Venous Thrombosis in Patients Undergoing Intracranial Endovascular Procedures

1. Initiate chemoprophylaxis using UFH and/or mechanical VTE prophylaxis with IPC or CS for patients with hemiparesis from stroke or other neurological injury before 24 h if activated prothrombin time is monitored (weak recommendation and low-quality evidence). If during the procedure rTPA or other thrombolytics are used, then extra caution is advised, and delayed initiation of chemoprophylaxis for at least 24 h after the procedure should be considered (weak recommendation and low-quality evidence).
2. Patients undergoing elective procedures may benefit from early ambulation and/or mechanical prophylaxis with IPC or CS but may not require LMWH or UFH (weak recommendation and very-low-quality evidence).

**Key Points**

- Venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) is common and in some cases a life-threatening complication in critically ill neurological and neurosurgical patients.
- A number of conditions place this subgroup of patients at a higher risk for VTE, such as delayed ambulation due to paralysis or coma, lengthy hospital stays, and length of neurosurgical procedures.
- Brain tumors, inflammatory diseases of the central or peripheral nervous system, and stroke (i.e., hemorrhagic or ischemic) can lead to vascular endothelium activation.
- There is a wide variability in clinical practice for VTE prophylaxis in these patients, partly due to paucity of data based on randomized clinical trials.

## 27.10 Conclusions

The most common challenge is the paucity of randomized, double-blinded, and adequately powered clinical trials. Additional research is warranted to successfully address the countless issues surrounding VTE in the neurological and neurosurgical critically ill patient. Nonetheless, research of this type is challenging because of the complexity of the patients and the rarity of VTE.

All current recommendations need to be individualized in accorandance with individual patient need. They should evaluated judiciously by all the health-care providers involved when choosing the prophylactic therapy.

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# Fever in the Neuro-ICU

# 28

Marc-Alain Babi

## 28.1 Introduction

Normal body temperature varies during the day in healthy individuals, as it is closely regulated by the thermoregulatory centers of the hypothalamus [1]. The hypothalamic thermoregulatory centers tightly control the body temperature, hence, and under normal physiological conditions, the body is able to maintain a steady and tightly regulated temperature [2]. Excess heat productions are usually dissipated from the skin and lungs, whereas excess heat loss leads to peripheral vasoconstriction as well as shivering in an effort to preserve heat and produce energy, respectively [2]. The normal daily temperature variation is typically 0.5 °C (0.9–1.0 °F). However, in individuals who are acutely sick, recovering from an illness, or during ovulatory or post-ovulatory phases (women), temperature variation may be as high as 1.0 °C [2, 3].

Fever, hyperthermia, and hyperpyrexia are terms used to describe temperature pathogenesis. These terms however are not synonymous. Fever is regulated at the level of the hypothalamus, which is the thermostat that regulates the body temperature. This thermostat autoregulatory center shifts upwards during state of inflammation, in turn resulting in fever [4]. A rise in the levels of prostaglandin E2 in the hypothalamus is the key trigger for raising that set point [4]. Once the hypothalamic set point is raised, vasomotor neurons are activated, which set a vasoconstrictive response, and in turn, warm sensing neurons slow their firing rate. This in turn leads to an increase in peripheral heat production. However, this vasoconstrictive response produces a cold sensation in the hands and feet, as blood is shunted away from the periphery to the internal organs, essentially decreasing core body heat loss [5–7]. In addition, thermogenesis in either fat or muscle tissue contributes to an increase in core body temperature. At birth, the highly thermogenic brown fat is present and contributes to non-shivering thermogenesis. However, the brown fat decreases during the neonatal period [5, 6] and other methods of heat production and retention occur. Hyperpyrexia refers to very high fever (defined as >41.5 °C). This can be observed in certain pathological states, such as gram-negative sepsis, central nervous system (CNS) injuries, and disorder of metabolism [6–9].

## 28.2 Fever in the Context of Acute Nervous System Injury

Fever is fairly common in the neurocritical care ICU, with studies reporting fever to occur in 60–90% of patients admitted to a neurocritical care unit [10–12]. In the specific patients'

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population, the presence of fever, regardless of the etiology of the primary disease, is associated with an increase in mortality and morbidity of these patients [10–12].

One of the important mechanisms by which fever exacerbates neurological injury and may worsen outcome is by exacerbating inflammatory cascades and in turn increasing cerebral metabolism in an already diseased nervous system [12, 13]. Fever in post-traumatic brain injury has been shown to correlate with increased elevation in pro-inflammatory cytokines, increased accumulation of neutrophils, and increased systemic inflammatory markers [13, 14]. Numerous studies have also demonstrated an increase in neuronal excitotoxicity, with increase in free-radical production, increase in intracellular glutamate concentration, and potentiation of excitotoxic injuries [15–17]. In addition, fever in the context of acute brain injury has been associated with increased neural intracellular acidosis, increasing in the expression of heat-shock proteins as well as increase in receptor expression associated with glutamate neuro-transmission [15–19]. Studies have also demonstrated that fever directly induces nervous system injury. For example, persistent fever in the context of acute brain injuries results in profound abnormalities in the blood–brain barrier, as well as alteration in neuronal metabolism and change in cerebral blood flow. Fever may also result in increase in central intracranial pressure, which is deleterious in the acute phase of brain injury [17–21].

## 28.3 Fever in Specific Disease State

### 28.3.1 Cardiac Arrest

Secondary neurological injury following out of hospital cardiac arrest is the most common cause of death in post-cardiac arrest patients [22]. Numerous controlled and non-controlled trials have been published, asserting the effectiveness of mild to moderate therapeutic hypothermia, as well as normothermia in improving neurological outcome in post-cardiac arrest survivors [22–24]. Nonetheless, hyperthermia must be avoided in post-cardiac arrest, as failure to control the core's temperature has been associated with increased mortality and worsened neurological outcome [25, 26].

One study reported an increase in the rate of death for each degree over 37 °C during the first 48-h of post-cardiac arrest, with a worse outcome during the earlier onset of fever [25–27]. Hence, mild therapeutic hypothermia (32–34 °C) to normothermia (36 °C) has been implemented as standard of care in most neurological ICU across the world [24, 28, 29]. The method of delivering therapeutic hypothermia or achieving normothermia has not been correlated with difference in outcomes [4, 5, 30–32].

### 28.3.2 Stroke

Fever is well documented to occur in the setting of stroke and may contribute to increased brain injury in patients presenting with acute stroke. Clinical studies have demonstrated a strong direct correlation between fever and worsened stroke outcome, as well as fever and stroke severity [33–35]. Temperature modulation has long been a target of interest in stroke management. However, despite the strong literature correlating to worsened outcome in the setting of fever and stroke, there is no strong convincing evidence for the benefit of therapeutic hypothermia in stroke. The ICTus trial was an efficiency trial of mild hypothermia (33 °C) in post-stroke patients [36, 37]; however, this trial found no outcomes difference. Another follow-up trial, the ICTusS-L, which combined 24 h of endovascular cooling (33 °C) following systemic intravenous thrombolysis in acute ischemic stroke, reported no significant difference in the 3-month outcome [36]. The clinical and evidence of deleterious effect of hemorrhagic stroke in the setting of intracerebral hemorrhage is similar to that of acute ischemic stroke, with increase in mortality and morbidity associated with fever [36, 37]. In addition, studies demonstrated that persistent fever following intracerebral hemorrhage is detrimental, and is associated with worsened outcome, even after

accounting for measures of injury severity [34]. Therefore fever prevention is essential in all subtypes of stroke, regardless of the initial severity or magnitude.

### 28.3.3 Spinal Cord Injury

Fever is a common complication following spinal cord injury, both as a direct result of spinal cord injury, or as a complication of secondary systemic diseases ensuing spinal cord injuries. Similar to acute brain injury, patients' with spinal cord injury are known to develop thermoregulatory dysfunction, which may result in fever. Disrupted autonomic pathways lead to impaired vasomotor and sudomotor responses, which in turn lead to alteration in core body temperature in these affected patients [38]. In addition, common secondary complications following spinal cord injuries, such as urinary tract infection, deep venous thrombosis, pneumonia, and pulmonary emboli, all manifest with fever as a symptom. Studies have demonstrated that hyperthermia following acute spinal cord injury leads to increased tissue damage, and in turn, worsened clinical outcome [39–42].

### 28.3.4 Subarachnoid Hemorrhage

Fever is fairly common after subarachnoid hemorrhage, occurring in 50–80% of all patients within the first week following subarachnoid hemorrhage [34, 40, 43]. Studies have demonstrated that blood within the cerebrospinal fluid is a strong mediator of a febrile response [35]. In addition, some studies have demonstrated a direct correlation of fever and the development of cerebral vasospasm following subarachnoid hemorrhage [35, 44–47]. Fever has been demonstrated to independently correlate to increased morbidity and mortality in subarachnoid hemorrhage [44–48]. In addition, fever correlates with higher grade subarachnoid hemorrhage which in turn correlates with increase in mortality and morbidity [48–50]. Most recently, a case–control study found that the application of therapeutic normothermia for the first 2 weeks following subarachnoid hemorrhage was associated with improved 12-month outcome [48]. Another non-randomized study found that the use of external cooling devices in patients with subarachnoid hemorrhage resulted for fever prevention and control was associated with improved clinical outcomes [48, 49].

### 28.3.5 Traumatic Brain Injury

Fever has been well demonstrated to worsen outcome after traumatic brain injury [51, 52]. Nonetheless, studies demonstrated that fever in the first week after TBI is associated with increased intracranial pressure, prolonged ICU stay, and increased morbidity and mortality [53–55]. It is known that small physiological and hemodynamic variations play a crucial role in the pathogenesis of secondary neuronal injury following TBI. Small studies demonstrated that increase in body temperature resulted in worsened histopathology at the neuronal level, particularly the hippocampal CA1 neurons [52–57]. However, a large recent multicenter randomized control trial demonstrated that induced hypothermia over normothermia in moderate to severe TBI leads to increased mortality and morbidity in TBI [52, 53]. Therefore, and in conclusion, fever should be aggressively treated following TBI but hypothermia should be avoided.

## 28.4 Fever Treatment

### 28.4.1 Pharmacological Interventions

Endogenous pyrogens that are released in response to inflammation, drugs, blood products, or other stimuli induce the synthesis of prostaglandin E2 [55, 58]. This is the substrate in which cyclooxygenase and in turn arachidonic acid is released from the cell membrane [58]. Such reaction is the rate-limiting step in the synthesis of prostaglandin E2 [58] and anti-pyretic agents primarily work by blocking this process at the level

of cyclooxygenase-mediated prostaglandin synthesis in the brain [59]. Nonetheless, this process is dependent on the presence of an intact thermoregulatory center, which is not the case in most acute brain injuries.

Acetaminophen is a poor peripheral cyclooxygenase inhibitor that is oxidized in the brain by the p450 cytochrome system. This in turn inhibits cyclooxygenase activity [59, 60] and demonstrates strong anti-pyretic properties. It is hepatically metabolized and caution should be exercised in patient with underlying chronic or acute liver injury. Acetaminophen-induced liver injury is a well-recognized complication. Ibuprofen is a non-steroidal anti-inflammatory (NSAIDs) agent that is widely used in the neurocritical care population. It demonstrates strong fever reduction properties in adults' patients with acute brain injury. Similarly, aspirin is a direct COX-2 inhibitor and is effective in reducing fever. Finally, a small randomized study demonstrated that an infusion of diclofenac sodium was effective at reducing fever in patients with acute brain injury and without increase in adverse effects related to increasing hemorrhage rate [61]. However, studies have failed to demonstrate the superiority of one particular anti-pyretic agent over the other in reducing fever in the human population [60–63]. Nonetheless, one needs to tailor the use of a specific anti-pyretic according to the particular patient's characteristic.

### 28.4.2 Non-Pharmacological Intervention

#### 28.4.2.1 External Cooling

External cooling refers to the reduction of body temperature by means of enhancing core body temperature heat loss. Different means of heat loss are used to promote such heat exchange. This includes evaporation, conduction, convection, and radiation heat losses [30]. Often, combinations of both pharmacological and non-pharmacological methods are used to treat fever in the context of acute nervous system injuries. However, external cooling may result in reflex peripheral vasoconstrictive effect, as the body attempts to generate heat and counter the cooling process. This results in shivering which is counterproductive to external cooling.

Suppression of shivering by continuous infusion of sedative, analgesics, and anesthetic medications such as propofol, fentanyl, and midazolam may need to be used. However, treating clinicians should be aware of the potential complications associated with the above medication, particularly propofol infusion syndrome [31, 32]. The latter is a rare complication associated with prolonged and high doses of propofol, and may lead to cardiac arrhythmias (particularly bradyarrhythmias), hypotension, metabolic acidosis, renal failure, and cardiovascular hemodynamic collapse [31, 32, 56, 57, 64–67]. Meperidine which is an opioid-analgesic medication has also been used to suppress shivering; however, this drug can be associated with seizure, given its primary metabolic normeperidine. Dexmedetomidine has also been shown to suppress the shivering threshold, but its use may be limited by its side effects of bradycardia and hypotension [31].

#### 28.4.2.2 Internal Cooling

Internal cooling refers to the infusion of cold isotonic crystalloid to reduce the core temperature by directly lowering the core body temperature. Numerous studies have validated that the infusion of cold saline boluses in post-cardiac arrest patients is a safe and effective method to achieve normothermia and hypothermia [65]. Generally, intravenous infusion rates of 30 mL/kg of cold normal saline (4 °C) infused via a pressure bag over approximately 15 min may lead to a drop in core temperature by approximately 1 °C [31, 68]. However, patients with a history of cardiac disease, renal dysfunction, or signs of acute pulmonary edema should be closely monitored, as they are at risk of volume overload and secondary adverse side effects. Surface cooling measures may instead be implemented. However, there is no evidence demonstrating the superiority of a particular cooling method over the other.

In clinical practice, different combinations of cooling methods may be employed, and in turn, tailored to the specific patient's characteristic [31, 69–71]. As noted, shivering is fairly common during induction of therapeutic hypothermia. Shivering raises body temperature and therefore failure to suppress shivering results in delay in achieving body temperature [72–74]. Therefore, detection and treatment of shivering is essential to facilitate cooling.

## 28.5 Conclusion

Fever has long been established to be deleterious in the context of acute nervous system injury. Numerous studies and advance in temperature-modulating devices make it possible to treat fever and maintain normothermia for prolonged period of times. However, data on specific therapeutic markers, targets, clinical pathophysiology, therapeutic depth, and duration of fever control remain limited. While some studies support hypothermia in specific disease state, and other attest to the lack of benefits in others, it is well established that fever is deleterious. In summary, fever control and modulation remains enigmatic to the neuro-ICU population. Further work is needed to define such target and goal directed therapies.

**Key Points**

- Understand the pathogenesis of fever, hyperthermia, hyperpyrexia, and malignant hyperthermia.
- Become familiar of the pathophysiology of fever in the context of acute brain injury.
- Understand the deleterious effect of fever in specific acute brain injuries state: anoxic brain injury, traumatic brain injury, stroke, and intracerebral hemorrhage.
- Become familiar with the methods used to control fever.

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# Sepsis

# 29

Swagata Tripathy

## 29.1 Definition

When normally sterile areas of the body are invaded by pathogenic microbes, the resulting manifestation of systemic disease that ensues is commonly referred to as sepsis. The signs and symptoms of this entity may be difficult to separate from other non-infectious conditions such as acute pancreatitis. The principal reason for this is that diverse stimuli (infectious or not) may result in activation of the immune mechanism of the body releasing endogenous peptides and cytokines.

In recent history, the definitions of sepsis and the sepsis syndrome complex have been revised three times—in 1990 and 2001, sepsis was defined as the association of inflammatory responses with proof, or suspicion, of an infectious source. In the presence of at least single organ dysfunction, sepsis progressed to "severe sepsis" and when inflammation caused by infection resulted in hypotension requiring vasopressors, it was defined as "septic shock" [1, 2]. In the recent (third) consensus conference however, the term severe sepsis was removed from the triad, with sepsis being defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is a subset thereof in which profound abnormalities (cellular, circulatory, and metabolic) are observed, resulting in a greater risk of mortality [3].

In a clinical context, the presence of inflammatory response may be recognized by various clinical and laboratory parameters (like fever, tachycardia, tachypnoea, increased white cell counts, positive microbiological cultures, or serology). An increase in SOFA (sequential organ failure assessment) score by 2 or more points enables early recognition of organ dysfunction in patients with sepsis as per recent guidelines. New onset organ failure has been associated with an in-hospital mortality of 10% or more. Septic shock may be identified clinically when serum lactate level is >2 mmol/L or there is a need to supplement vasopressors in a patient who is adequately volume resuscitated, to maintain a mean arterial pressure >65 mmHg. A combination of sepsis and septic shock is associated with mortality rate >40%. The quick SOFA (qSOFA) has been suggested as a new bed side clinical score (at least 2 of—respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less) which may enable rapid identification of patients likely to have sepsis in out of ICU settings like the wards, emergency areas, etc.

## 29.2 Epidemiology of Sepsis

There has been a progressive rise in the incidence and prevalence of sepsis globally. Sepsis has been identified as the most common cause of

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readmission to the ICU. It has been referred to as the final common pathway from infection to death [4–10]. The reported incidence and prevalence of sepsis and septic shock varies according to the definitions used, patient population studied, and geographic location. The concern over the changing definitions of sepsis affecting the epidemiology of sepsis has been recently addressed by Shankar-Hari et al. [11]. The authors compared the incidence, outcomes, trend in outcomes, and predictive validity of patients classified according to the Sepsis 2 [2] versus the Sepsis 3 criteria [3]. They found an incidence of 101.8 and 19.3 per 100,000-person years for sepsis and septic shock, respectively, in 2015. Sepsis 2 severe sepsis and Sepsis 3 sepsis have similar incidence and mortality. The Sepsis 3 criteria identifies a similar sepsis population as the Sepsis 2 criteria (overlap of 92%); the septic shock population identified is smaller and sicker, with a higher predictive validity [11].

Sepsis after neurosurgery and in the neurointensive care unit occurs in up to 36% of patients admitted for more than 48 h [12, 13]. The most common infections are pneumonia, urinary tract infections (UTI), blood stream infections, and intracranial infections such as ventriculitis and meningitis.

## 29.3 Pathophysiology of Sepsis

A breach in the integrity of physical barriers of the human body such as skin, mucous membrane, gastrointestinal tract (GIT), and conjunctiva by microorganisms begins a process of localized inflammation. This localized inflammation may then spill over to generate systemic manifestations such as fever, tachycardia, tachypnea, and altered white cell counts. It was previously believed that a hyperactive host response to infection affects organ function due to widespread activation of inflammatory cascade via indigenous peptides such as cytokines, interleukins, and tumor necrosis factors. However, various studies have failed to show a consistent benefit of using antagonists of TNF or IL-1 (usually increased in serum of sepsis patients and believed to be the culprits) [14–16]. A meta-analysis of these pooled studies shows an overall improvement, however [17].

Another school of thought argued that septic patients may have a hypoactive response to infection; corroborating research shows that ICU patients have decreased expression of IL6 and TNF in response to endotoxin stimulation [18, 19]. Using granulocyte colony-stimulating factor to treat >700 patients with pneumonia and severe sepsis did not result in any improvement in survival [20].

The current thinking now is that the inflammatory response in patients with sepsis is complex and cannot be easily classified as enhanced or blunted. In some patients, blunting of the response may improve outcome, whereas in others a suppression may serve better. Bones has suggested that a treatment tailored to the individual patient with greater emphasis on identifying the cause than looking for a "magic bullet" may serve the "sepsis cause" better [21]. The coagulation pathway is also affected, with increased coagulability and decrease in fibrinolysis (Fig. 29.1). Alterations at the cellular level include leukocyte apoptosis, neutrophil hyperactivation, and endothelial cell failure. At a metabolic level, insulin resistance may result in hyperglycemia; a subset of patients with adrenal failure show better outcomes with steroid supplementation. High blood glucose levels have been shown to suppress polymorphonuclear neutrophils and decrease bactericidal activity; strict glycemic control may provide protection to endothelial cells [22–24].

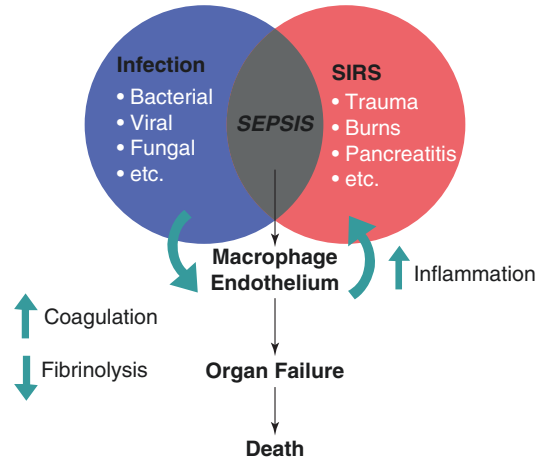


**Fig. 29.1** Pathophysiology of sepsis

## 29.4 Immune Dysregulation Following Neurotrauma

Evidence from animal and human studies shows that injury and ischemia in the brain tissue results in a dysregulated immune response consequential to a "brain injury induced immunosuppression syndrome." The systemic immunosuppression has been noted after stroke, trauma, surgery, spinal cord injury, or subarachnoid hemorrhage. An intense activation of the hypothalamo-pituitary axis and the sympathetic system resulting in an early (within 12 h) increased immune response followed by a phase of delayed suppression after 24 h (lasting up to several weeks) has been seen. Mediated by b2 receptors, this phenomenon has been associated with increased susceptibility to infections in patients with neurologic insult [25–28].

Studies have found that the size and site of the injury (most evidence coming from post-stroke patients) correlates with the magnitude of immunosuppression. Lesions in the orbitofrontal cortex, insular cortex, and putamen areas have a higher risk of pneumonia. Although no laterality predilection was observed, an overlap has been found in the correlates of dysphagia and pneumonia among these patients [29, 30]. Patients with intraventricular hemorrhage (IVH) show decreased baroreceptor sensitivity; this is an independent risk factor for increased infection and morbidity after IVH [31, 32].

## 29.5 Infections in the Neurocritical Care Unit

National Healthcare Safety Network (NHSN), Division of Healthcare Quality Promotion of the Centers for Disease Control and Prevention (CDC) for infections, includes three types of CNS infections in the acute care setting: intracranial such as brain abscess, subdural, or epidural infections and encephalitis; ventriculitis or meningitis and spinal abscess without meningitis [33].

### 29.5.1 Post-Craniotomy Infections

Four out of ten patients develop an infection after craniotomy [34]. Patients have a higher risk of developing pneumonia, ventilator associated infection, and urinary and intracranial infections [35–37]. The demarcation of infectious from inflammatory meningitis is difficult because the clinical signs and symptoms overlap. Intracerebral hemorrhage, inflammatory reactions to interventions, and immunosuppression can significantly change CSF profiles. Nosocomial meningitis may result in severe morbidity, need for repeated surgeries, prolonged LOS, and higher hospital costs. A recent study has proposed a prediction model for risk of developing nosocomial meningitis after neurosurgery. In it SAH, CRP $\geq$6 mg/dL, and CSF/serum glucose ratio $\leq$0.4 mmol/L get 1 point, whereas CSF leak and CSF PMN neutrophils $\geq$50% get 1.5 points and CSF lactate $\geq$4 mmol/L gets 4 points. The model has shown good calibration (Hosmer–Lemeshow goodness of fit = 0.71) and discrimination (area under the receiver operating characteristic curve = 0.94). A score $\geq$6 points suggests a high probability of neuroinfection, for which antibiotic treatment should be considered [38].

### 29.5.2 Device Related Infections

Devices in the central nervous system such as external ventricular drain (EVD), lumbar drain (LD), and intracranial pressure (ICP) monitors increase the risk of infections in neuropatients. Risk factors include duration of catheterization, frequency of EVD manipulation for CSF sampling or irrigation, presence of IVH, and insertion technique [39]. The signs and symptoms, diagnosis, and treatment of hospital acquired meningitis and ventriculitis have been clearly laid down by the infectious Diseases Society of America recently [40]. Tables 29.1 and 29.2 mention the clinical features and lab parameters for detecting or suspecting meningitis and/or ventriculitis of nosocomial origin—due to devices, neurosurgery, or trauma. Advanced tests for diagnosis as suggested by the society are—an increased CSF

**Table 29.1** Signs and symptoms of healthcare-associated meningitis and ventriculitis

| Condition | Signs and symptoms (grade of recommendation) with healthcare-associated ventriculitis and meningitis |
|---|---|
| CSF shunt or drain | • New onset headache, nausea, lethargy, and/or change in mental status suggest CSF shunt infection (strong, moderate)<br>• Erythema and tenderness over the subcutaneous shunt tubing suggest CSF shunt infection (strong, moderate)<br>• In the absence of another clear source of infection, fever could suggest CSF shunt infection (weak, low)<br>• Features of peritonitis or abdominal tenderness in patients with ventriculoperitoneal shunts, in the absence of another clear etiology, indicate CSF shunt infection (strong, moderate)<br>• Features of pleuritis in patients with ventriculopleural shunts, in the absence of another clear etiology, indicate CSF shunt infection (strong, moderate)<br>• Demonstration of bacteremia in a patient with a ventriculoatrial shunt, in the absence of another clear source of bacteremia, is evidence of CSF shunt infection (strong, moderate)<br>• Demonstration of glomerulonephritis in a patient with a ventriculoatrial shunt suggests CSF shunt infection (weak, low)<br>• New or worsening altered mental status in patients with external ventricular drains suggests infection (weak, low)<br>• New fever and increased CSF white blood cell count in patients with external ventricular drains could suggest infection (weak, low) |
| Neurosurgery or traumatic brain injury | • New headache, fever, meningeal irritation, seizures, and/or worsening mental status suggest ventriculitis or meningitis (strong, moderate)<br>• Fever, in the absence of another clear source of infection, suggests CNS infection (weak, low) |

**Table 29.2** Laboratory diagnosis of healthcare-associated ventriculitis and meningitis

| Variable | Healthcare-associated ventriculitis and meningitis—CSF findings (grade of recommendation) |
|---|---|
| Lab reports—cell count, glucose, and protein | • Abnormalities of CSF cell count, glucose, and/or protein may not be reliable indicators for the presence of infection in patients with healthcare-associated ventriculitis and meningitis (weak, moderate)<br>• Normal CSF cell count, glucose, and protein may not reliably exclude infection in patients with healthcare-associated ventriculitis and meningitis (weak, moderate)<br>• A negative CSF Gram stain does not exclude the presence of infection, especially in patients who have received previous antimicrobial therapy (strong, moderate) |
| Culture | • CSF cultures are the most important test to establish the diagnosis of healthcare-associated ventriculitis and meningitis (strong, high)<br>• If initial CSF cultures are negative in patients with CSF shunts or drains with suspected infection, it is recommended that cultures be held for at least 10 days in an attempt to identify organisms such as *Propionibacterium acnes* (strong, high)<br>• If a CSF shunt or drain is removed in patients suspected of having infection, cultures of shunt and drain components<br>are recommended (strong, moderate)<br>• If a CSF shunt or drain is removed for indications other than infection, cultures of shunt or drain components are not recommended (strong, moderate)<br>• Blood cultures are recommended in patients with suspected ventriculoatrial shunt infections (strong, high)<br>• Blood cultures may be considered in patients with ventriculoperitoneal and ventriculopleural shunts (weak, low)<br>• Single or multiple positive CSF cultures in patients with CSF pleocytosis and/or hypoglycorrhachia, or an increasing cell count, and<br>clinical symptoms suspicious<br>for ventriculitis or meningitis,<br>are indicative of CSF drain infection (strong, high)<br>• CSF and blood cultures in selected patients should be obtained before the administration of antimicrobial therapy; a negative CSF culture in the setting of previous antimicrobial therapy does not exclude healthcare-associated ventriculitis and meningitis (strong, moderate) |

procalcitonin or lactate to differentiate between bacterial infection or inflammatory CSF changes, detection of β–D-glucan and galactomannan in CSF for the diagnosis of fungal infection, and using nucleic acid amplification for early detection of infections. Magnetic resonance imaging with gadolinium enhancement and diffusion-weighted imaging for suspected meningitis/ventriculitis and CT scan or ultrasound abdomen for patients with infected VP shunt and abdominal symptoms is recommended for detecting abnormalities in patients with healthcare-associated ventriculitis and meningitis [40].

The recommendations for treatment of healthcare-associated meningitis or ventriculitis include single shot antibiotic prophylaxis with protocolized drain insertion (hair clipping and sterile field) in cases of indwelling catheters, prompt removal of catheters which are infected, and treatment according to sensitivity pattern (if available). Prolonged administration of antibiotics in patients with indwelling catheters has been seen to increase the risk of infections with multi drug resistant organisms; stopping long term prophylaxis may reduce other hospital associated infections [41, 42].

## 29.6 Systemic Infections

The incidence of nosocomial infections is very high in patients with neurologic injury. It varies from 20 to 40% in various conditions like TBI, ischemic stroke, intracranial hemorrhage, SAH, and status epilepticus [43–45].

The most common of these infections is ventilator associated pneumonia (VAP). This is associated with poor outcomes and longer periods of mechanical ventilation and hospital stay [46]. Patients at a particularly higher risk of nosocomial pneumonia are younger males with prolonged mechanical ventilation. Intubation at the scene or in the emergency department, lower Glasgow Coma Scale score, and higher injury scores, particularly thoracic injuries, also increase the risk of pneumonia [47].VAP may occur early (within 5 days) or late (after the fifth day) of intubation or mechanical ventilation. The causative organisms associated with the two are different, with more virulent, multi drug resistant organisms isolated in late onset VAP. Methicillin-sensitive *S. aureus*, *Haemophilus influenzae*, *Streptococcus* pneumonia, and Acinetobacter species are common pathogens in patients with VAP [48].

Urinary tract infections (UTI) occur commonly in the neuro-ICU. Rates range from 10 to 24%. Long duration of catheterization, frequent patient transport, and underlying immunosuppression may all contribute to the high rates of UTI. Independent risk factors for developing a urinary tract infection in a cohort of patients with SAH included older age, female sex, non-infectious complications, intracerebral hemorrhage, and diabetes [49].

Catheter related blood stream infections increase morbidity and length of stay in the neuro-ICU. Incidence may be as high as 30%, with gram positive organisms isolated more often. Prolonged duration, site of central line insertion, and nursing practices may influence the rates of infection [50, 51].

Surgical site infection rates vary from 1 to 15%. Independent predictive risk factors for infection are cerebrospinal fluid leakage, external shunt, longer operation time, craniotomy, dural substitute, staples in wound closure, and further neurosurgery [52, 53]. The rate of infection after spine surgery is as high as 18%. Diabetes, prolonged operative times (>3 h), obesity, posterior approach, and number of intervertebral levels (≥7) are associated with an increased risk of SSI after spinal surgery [54, 55].

Clostridium difficile infection is seen increasingly in ICUs. In neuro-ICUs the prevalence of 0.4–0.5% has been reported with an infection rate of 8.3 per 10,000 patient days [56, 57]. Prolonged hospitalization, use of antibiotics, and advanced age are the major risk factors associated with developing C diff. infections.

## 29.7 Prevention of Sepsis in the Neurointensive Care Unit

Measures to reduce infections and sepsis in the critical care unit by prior interventions have been studied. Antibiotic prophylaxis in post-stroke patients

and oral decontamination with povidone iodine in patients with TBI have not proven to be of any benefit—the rates of VAP have actually been seen to go up after using mouth care with povidone iodine [58, 59]. On the other hand, protocols to improve screening for swallowing difficulties have shown a reduction in the incidence of aspiration pneumonia [60]. The use of noninvasive ventilation where possible, early tracheostomy and protocolized early extubation, may reduce the days on mechanical ventilation and the rates of ventilator associated pneumonia [61, 62].

## 29.8 Management of Sepsis

The surviving Sepsis Campaign lays down the guidelines for quick recognition and management of sepsis. Details are out of the scope of the chapter, but the important points are highlighted.

### 29.8.1 Management of Infection

The SSC 2016 [63] has recommended administration of broad-spectrum antimicrobials within 1 h and rapid source control. Proper dosing of antibiotics according to the pharmacokinetic and pharmacodynamic profiles is needed. Recent studies indicate that continuous infusion of b-lactam antibiotics may result in better cure rates than intermittent bolus dosing [64, 65]. Procalcitonin levels may help to guide shorter antibiotic course and encourage the search for other causes of inflammatory response. A recent study has shown improved mortality in the group managed by procalcitonin levels [66].

### 29.8.2 Fluid Therapy

The guidelines recommend the administration of 30 mL/kg of intravenous crystalloid within the first 3 h. Further administration is to be guided by frequent assessment and application of fluid challenge techniques. With additional fluid based on frequent reassessment, dynamic indices of hemodynamic assessment are recommended; the application of a fluid challenge technique in which fluids should be continued as hemodynamic factors continues to improve with the use of crystalloids (balanced crystalloids or saline). Conservative resuscitation strategy may result in better pulmonary outcomes, as shown in a recent study [67]. The guidelines suggest that albumin may be considered as an alternate fluid if large volumes of crystalloids are to be infused. Although many studies do not show a mortality benefit of albumin over crystalloids, the ALBIOS trial has shown better mean arterial pressures at 6 h of resuscitation and lower total fluid balance in patients of septic shock resuscitated with albumin along with crystalloids [68].

### 29.8.3 Vasopressors

Guidelines recommend norepinephrine as the first-line vasopressor, being associated with lower adverse events rates such as arrhythmias than dopamine. Epinephrine and vasopressin may also be added to norepinephrine to reduce the requirement of norepinephrine—"relative vasopressin deficiency" has been described in patients with septic shock [63]. A recent meta-analysis however does not show any difference between noradrenaline and dopamine when administered to patients with hypotensive shock [69].

### 29.8.4 Steroids

A dose of up to 200 mg/day of intravenous hydrocortisone is recommended in patients in septic shock refractory to fluid and vasopressor resuscitation. A more recent study has not demonstrated any benefits (mortality or recovery from shock) of steroid administration in refractory septic shock [70].

### 29.8.5 Respiratory Failure

Respiratory failure is common in patients with sepsis, with ARDS being underrecognized in a majority of cases. Lung protective ventilation

with early proning for a minimum of 12 h is recommended in the guidelines [63]. Recent studies show beneficial role of statins in ARDS, use of high flow oxygen to reduce reintubation (and for early extubation), and that conservative oxygen therapy may improve outcomes as compared to conventional doses [71–74].

### 29.8.6 Kidney Dysfunction

The SSC guidelines recommend either continuous or intermittent RRT. CRRT may be preferred in hemodynamically unstable septic patients. The best time of initiation is still unclear as the two recent trials—AKIKI and ELAIN—have shown differing results: with AKIKI showing no difference in mortality and ELAIN showing improved mortality and renal function recovery with early onset on RRT [75, 76].

### 29.8.7 Transfusion

Restrictive practices are recommended, as per the SSC guidelines. These are based on the threshold for transfusion in a hemoglobin level <7 g/dL. The age of the RBC units to be transfused does not affect patient outcome [77, 78].

### 29.8.8 Nutrition

Adequate nutrition has an important role in patients in the neurocritical care unit. Current guidelines recommend early enteral nutrition over parenteral [63].

## 29.9 Conclusion

Infections and sepsis in the neurointensive care unit (neuro-ICU) are common. Different disease pathologies have different types of infections: pneumonia is most common. Craniotomy and devices place these patients at an increased risk for meningitis and ventriculitis. These patients are inherently more susceptible to infections due to dysregulated immune responses after acute brain injury. Preventive measures, early recognition, and prompt management may improve patient outcomes.

**Key Points**

- The signs and symptoms of sepsis may be difficult to separate from other non-infectious conditions.
- Sepsis after neurosurgery and in the neurointensive care unit occurs in up to 36% of patients admitted for more than 48 h.
- The most common infections are pneumonia, urinary tract infections (UTI), blood stream infections, and intracranial infections such as ventriculitis and meningitis.
- Craniotomy and devices place these patients at an increased risk for meningitis and ventriculitis.

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# Cerebral Resuscitation After Cardiac Arrest

30

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## 30.1 Introduction

Cardiac arrest (CA) is a sudden loss of heart function due to either a primary cardiac event such as myocardial event or secondary effect on the heart from neurological, respiratory, or metabolic causes. For out-of-hospital cardiac arrests (OHCA) patients, <10% survive to hospital discharge compared to 20–25% of in-hospital cardiac arrest (IHCA) patients that survive to hospital discharge [1, 2]. Eighty to Ninety percent of post-cardiac arrest survivors emerge with coma and severe long-term neurological deficits [3].

At the epicenter of the high mortality and morbidity from CA, is the post-cardiac arrest syndrome, which includes anoxic brain injury, myocardial dysfunction, and a systemic ischemia and reperfusion syndrome. Of these, perception of injury to the brain is the most common cause of death in two-thirds of patients with OHCA and a quarter of patients with IHCA [4]. The brain is prone to injury due to lack of significant intrinsic energy and nutrient stores, therefore highly dependent on a constant supply of oxygen and nutrients. Multiple factors play a role in the extent and pattern of brain injury post-cardiac arrest including the initial ischemic cascade, the reperfusion injury after return of spontaneous circulation (ROSC), the delay ischemia due to the no reflow phenomenon, and post-resuscitation variable such as pyrexia and hypoglycemia. We should also note that only 10% of these patients with brain injury progress to brain death [5].

This chapter will review the clinical manifestation of brain injury after a cardiac arrest, the pathophysiology of brain injury in this setting, the management post-CA, and neuroprognostication of patients post-CA.

## 30.2 Clinical Manifestations of Brain Injury After Cardiac Arrest

Certain neuronal populations in the brain are particularly susceptible to ischemia and tend to be prone to injury from hypoxia. Cortical pyramidal neurons, cerebellar Purkinje cells, and the CA-1 neurons of the hippocampus are the most vulnerable [6]. Areas of the brain that are phylogenetically more ancient such as the brainstem, the thalamus, and the hypothalamus tend to be more resistant to injury compared to the cortex [7, 8].

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The brainstem in particular is resistant to hypoxic injury, as manifested by the preservation of cranial nerve and sensory motor reflexes. Bilateral cortical or thalamocortical complex injuries result in dysfunction in arousal or consciousness [9]. Other areas affected by hypoxia include the basal ganglia and the cerebellum, which are responsible for movement disorders and the dyscoordination that is observed post-arrest.

### 30.2.1 Disorders of Arousal and Consciousness

Disorders of arousal are the most common presentations of hypoxic-ischemic injury after cardiac arrest. The ascending arousal system largely originates from a series of well-defined cell groups in the brainstem and is composed of two major pathways [10]. The first pathway ascends from the upper brainstem nuclei to the thalamus and activates the thalamic-relay nuclei and the thalamic reticular nucleus, with subsequent transmission to the cortex. The second pathway originates in the upper brainstem and caudal hypothalamus and bypasses the thalamus, and activates neurons in the lateral hypothalamus, basal forebrain, and throughout the cerebral cortex. Lesions anywhere along either of these arousal systems can cause a decrease in arousal.

If the pattern of injury involves the cortex but spares the brainstem and thalamus, one can observe a more vegetative state characterized with arousal and preservation of sleep-wake cycles, but a lack of awareness of self and purposeful response to the environment. However, involvement of these deeper structures including the thalamus, hypothalamus, and brainstem can result in a complete coma with no arousal and awareness.

### 30.2.2 Seizures

Damage to the cortex from hypoxic-ischemic injury can result in neuronal injury leading to seizures, which can present clinically as convulsive or non-convulsive. Incidence of seizure has increase over the last decade in part because of the increasing use of continuous EEG leading to better detection. One study that particularly looked at patients undergoing therapeutic hypothermia after cardiac arrest suggested that up to one in three patients had seizures, often non-convulsive, and this occurred despite the use of sedative medications [11]. In the targeted temperature management study (TTM), post-hoc analysis revealed a seizure incidence of 29% [12]. Seizures are potentially treatable complication that must not be used as a negative predictor until intractability to aggressive therapy is proven [13].

### 30.2.3 Post-Hypoxic Myoclonus

Myoclonus refers to brief, involuntary, and shock-like muscle contractions or lapses in muscle tone. Post-hypoxic myoclonus (PHM) can be distinguished into two fairly distinct clinical syndromes, acute post-hypoxic myoclonus that is generally self-limiting after a few days, and chronic post-hypoxic myoclonus, or Lance–Adams syndrome.

Acute post-hypoxic myoclonus is the most common form of myoclonus after cardiac arrest and often occurs within hours of hypoxic injury. It is poorly localized to the cortex, hippocampus, cerebellar Purkinje cell layer, the reticular thalamic nucleus, and the reticular formation of the medulla, based on animal and clinical studies [14]. Acute post-hypoxic myoclonus typically warrants an EEG evaluation to evaluate for seizures or myoclonic status epilepticus. There are no published guidelines of treatment of acute PHM, but if epileptiform discharges are present, clinicians can consider treatment with antiepileptic drugs.

Chronic post-hypoxic myoclonus, also known as Lance–Adams syndrome, develops days or weeks after the hypoxic episode and tends to persist. It is typically a multifocal action or intention myoclonus, which means that it is exacerbated during muscle activation or with intention in the setting of preserved consciousness.

Some antiseizure medications have been used successful to control this syndrome.

## 30.3 Pathophysiology of Brain Injury After Cardiac Arrest

Injury to the brain after cardiac arrest occurs in two distinct windows. Primary injury to the brain occurs during the hypoxia itself, whereas secondary injury occurs after return of spontaneous circulation. An appreciation of the mechanisms of injury provides the intensivist insight into the types of interventions that are available and future therapeutic options that are being explored to mitigate the extent of injury.

### 30.3.1 Primary Injury

Brain tissue is very sensitive to lack of oxygenation, and even brief ischemic periods of a few minutes can trigger a complex sequence of events leading to cell death. These mechanisms have been identified through study in various mammalian models. During hypoxia itself, the lack of oxygen in brain tissue causes cells to switch over to anaerobic respiration and this subsequently leads to a decrease in adenosine triphosphate (ATP) production. With diminished ATP supply, the sodium-potassium-ATPase pump on the cellular membrane no longer functions [15]. This results in accumulation of sodium ions inside cells, and subsequent cytotoxic edema. The lack of ATP also causes the cell to switch over to anaerobic respiration, resulting in cerebral lactate accumulation and intracellular acidosis [16]. The ischemia causes calcium influx through the cell, and release of glutamate, which serves an excitatory neurotransmitter. Glutamate binds to postsynaptic NMDA and AMPA receptors, resulting in downstream activation of degradative lipases and proteases that ultimately take neurons and other cells down a path to cellular death [17]. The immediate goal is to minimize the primary injury to the brain and systemic organs by providing prompt high quality cardiopulmonary resuscitation.

### 30.3.2 Secondary Injury After ROSC

The injury to the brain that occurs during hypoxia itself sets the stage for a maladaptive response of cells to reperfusion. This results in secondary injury that continues to cause cell death even after oxygen and blood flow have been re-established. The precise mechanisms of injury that occur during this phase are still under investigation, but multiple pathways of injury have been established.

Hypoxia during primary injury can be thought of as creating the pre-requisites for a maladaptive response. Terminal sequelae that ultimately result in death during secondary injury include direct cell death from formation of reactive oxygen species; cytotoxic edema and vasogenic edema that cause further ischemia and result in herniation; and finally, disorders of cerebral blood flow autoregulation that cause further hypoxic injury.

The hypoxia that occurs in primary injury causes significant mitochondrial dysfunction. After return of spontaneous circulation (ROSC), reactive oxygen species form in the mitochondria that then activate degradative enzymes, and damage the cellular structure, eventually leading to cell death. Furthermore, hypoxia during the initial lack of perfusion activates microglia that then initiate a pro-inflammatory cytokine release. There is also an associated increased migration of peripheral macrophages, monocytes, and neutrophils. Reperfusion results in the persistence and exacerbation of a cerebral inflammatory cascade, which results in damage to the endothelium. Endothelial dysfunction in turn leads to the formation of diffuse microthrombi in the cerebral vasculature [18]. Along with impaired vasodilation, there is an increased resistance to flow which decreases cerebral perfusion. The increased resistance to flow and the endothelial dysfunction also contribute to vasogenic edema, which in turn causes mass effect and further decreased flow to the area [19]. This increased edema also contributes to intracranial hypertension and resultant decrease in cerebral perfusion, eventually leading to transtentorial herniation and brain death.

There are various physiological factors that can further exacerbate the process of secondary injury. Hyperthermia can increase blood–brain barrier permeability, worsening cerebral edema, intracranial pressure (ICP), and ischemia [20]. Hyperthermia also increases glutamate production, which can cause further activation of degradative and harmful cellular enzymes. Significant anemia has been shown in animal studies to exacerbate secondary injury but data in human studies is limited. Both hypocapnia and hypercapnia can cause further injury. Hypocapnia can cause vasoconstriction, decreased cerebral blood flow, increased oxygen extraction, and result in ischemia. Hypercapnia can increase cerebral blood flow, which can cause hyperemia, increased intracranial pressure, excite-toxicity, and increased cerebral oxygen demand. While the optimal partial pressure of carbon dioxide in post-cardiac arrest patients is not known, the recommendation is to maintain carbon dioxide within the normal range.

## 30.4 Management Post-Cardiac Arrest

Post-cardiac arrest care is tailored toward identifying the cause of the arrest in individual patient along with management of ischemic reperfusion injury of multiple organ failure. This management focuses on cardiovascular care, targeted temperature management, respiratory care, and other neuroprotective measures in the ICU.

### 30.4.1 Cardiovascular Care

Per recent AHA guidelines, emergent coronary angiography should be performed in OHCA patients with suspected cardiac etiology of arrest and ST elevation on ECG, and reasonable in those patients without ST elevation. During the post-resuscitation, it is reasonable to avoid and immediately correct hypotension, defined as systolic blood pressure <90 mmHg or MAP <65 mmHg [21].

### 30.4.2 Therapeutic Hypothermia (TH) vs. Targeted Temperature Management (TTM)

Several studies have evaluated the effect of hypothermia on outcome post-cardiac arrest with different temperature goal, 32–34 °C in HACA study, 33 °C in the Bernard study, and recently a comparison of 33 °C vs. 36 °C in the Nielsen TTM study [22]. The 2015 AHA guidelines recommend that comatose adult patients with return of spontaneous circulation after cardiac arrest have a targeted temperature between 32 °C and 36 °C for both shockable and nonshockable rhythm and both OHCA and IHCA for at least 24 h with level of evidence B and C [21, 23]. However, the recent American Academy of Neurology practice guideline summary on post-cardiac arrest care has specific recommendation based on the scientific evidence and study designs. In OHCA patients with shockable rhythm, TH 32–34 °C for 24 h has a level A evidence for improving functional neurological outcome compared with TTM of 36 °C, which has a level B evidence. For nonshockable rhythm and patients, TH possibly leads to better survival and functional neurological status (level C evidence) [24]. Given this evidence, our temperature preference is 32–34 °C for post-cardiac arrest care. We should also note that temperature selection is based on individual patient characteristics, with lower temperature preferred in patients who may be at risk for seizure or brain edema, and higher temperature preferred in patients with risk of bleeding and hypotension. A period of normothermia of 72 h after TH/TTM is recommended. Following TH/TTM, the rewarming process should be gradual at a rate no faster than 0.25 °C/h to achieve normothermia and to avoid complications such as electrolytes abnormality, cerebral edema, and seizures [21]. Another key point in the AAN practice guideline is that prehospital cooling with intravenous chilled saline should not be offered, as it is unlikely to lead in improvement of functional neurological outcome with level A evidence [24].

Shivering is often encountered during TH/TTM, as it is the body's natural defense mechanism

against cold. Shivering can cause disruption of therapy by producing heat, thereby increasing body core temperature during the cooling process [25]. Shivering needs to be controlled. Most hospitals have a protocol for shivering, which include topical warming with warm blanket, and various pharmacological agents depending on the degree of shivering such as magnesium sulfate, buspirone, meperidine, sedatives, and paralytics.

### 30.4.3 Respiratory Care

It is important to note that with TH/TTM, reported $PaCO_2$ values might be higher than actual patient values. The goal is to maintain normocarbia (end-tidal $CO_2$ 30–40 mmHg or Pa $CO_2$ 35–45 mmHg) unless there are other patient's clinical factors that demand permissible hypercapnia (e.g., ARDS) or hypocapnia (e.g., hyperventilation in treating for cerebral edema) [21].

### 30.4.4 Cerebral Perfusion, Cerebral Edema, and Increased Intracranial Pressure

Hypotension, hypoxia, and hypercapnia may worsen cerebral damage and should be avoided [21]. Although, a MAP >65 mmHg has been suggested post-cardiac arrest, it is likely not sufficient for adequate cerebral perfusion. One study suggested that a MAP of 80–100 mmHg is beneficial, at least for the first 24 h after arrest [26]. In comatose patients with clinical signs of herniation, or cerebral edema on CT scan, ICP monitoring may be helpful to guide therapy in identifying optimum cerebral perfusion [27].

### 30.4.5 Fever Control

Fever is associated with poor neurological outcome as it may worsen secondary brain damage after cardiac arrest. Antipyretics and surface or invasive cooling measures should be used post-cooling to prevent fever and also used in patients not deemed candidate for TH/TTM [21, 23].

### 30.4.6 Glucose Control

Glucose management remains controversial in critically ill patients. Hyperglycemia has been linked to poor outcome after ischemic brain injury [28] and tightly controlled glucose leading to frequent hypoglycemia is known to be harmful. The target range for blood glucose is unknown post-cardiac arrest and current guidelines report the uncertainty of the benefit of any specific target range [21].

### 30.4.7 Seizure Control

Seizures, status epilepticus, and other epileptiform activity are common after cardiac arrest, with some features associated with poor neurological outcomes. Prophylactic antiepileptic drugs are not recommended post-cardiac arrest, but any patient noted to have seizure activity should be treated with standard antiepileptic medication. Any comatose patient after ROSC suspected of having seizure or not regaining consciousness should have an EEG promptly performed, interpreted, and monitored frequently or continuously [21].

These mechanisms of injury, and the physiological factors that can further exacerbate them, offer insights into the management post-cardiac arrest in the ICU. The next question following these management strategies is the prognostication of outcome.

## 30.5 Neuroprognostication

One of the challenges of neurointensivists is to determine the neurological outcome of post-cardiac arrest patients, which is time dependent, i.e., a patient with a cerebral performance category (CPC) score of 3 at discharge may improve to a better performance category at 3 months [29].

Most prognostications in acute brain injury are a prediction of poor outcome, which includes death, persistent coma, persistent vegetative state, or a state of temporary or permanent independence

[30, 31]. It is crucial to give the correct prognosis because too much optimism may lead to survival of neurologically devastated patients, whereas a pessimistic prediction may result in withdrawal of life-sustaining therapy (WLST) and death of a patient who would otherwise have favorable outcome [32, 33]. Several authors have noted that WLST in clinical practice is a self-fulfilling prophecy, because of the bias it introduces in both trials and observational studies, whereby as a consequence of a perceived poor outcome, treatment is limited or withdrawn, leading to realization of the predicted poor outcome [34].

Neuroprognostication is a multidisciplinary approach using a combination of clinical examination, neuroimaging, neurophysiological modalities, and biomarkers data. It is important to point out that most existing studies have limited reliability because of the lack of well designed, randomized, and blinded studies. In prognostication studies, the prevailing parameter is the false positive rate (FPR), which indirectly indicates the extent with which one can make mistake if using the particular parameter, i.e., the lower the FPR, the better the tool. Many studies provide FPR that is too high (FPR > 10); furthermore, the 95% confidence intervals of these studies are also very wide.

### 30.5.1 Clinical Examination

Clinical features used in prognostication post-cardiac arrest include: eyes findings, best motor response, and status myoclonus. After ROSC, the timing of prognostication is crucial and is influenced by the presence or absence of therapeutic hypothermia (TH). In the absence of TH, at least 72 h post-arrest is needed for a reliable exam [29, 35]. In patients treated with TH, the timing of an accurate neuroprognostication is much later because hypothermia reduces the clearance of sedatives and neuromuscular blockade drugs used during the cooling process [36–38]. Most clinicians will wait at least 72 h or longer after the patient has been rewarmed to prognosticate but some important considerations need to be made. In the TTM trial, the prognostication of resuscitated comatose patients was determined at a median of 118 h after cardiac arrest [22].

Ocular brainstem reflexes are important in prognostication. The absence of pupillary light reflex is the most accurate clinical predictor of poor outcome at 72 h or longer from ROSC [39]. Corneal reflex is less specific. Its absence is a poor prognostic sign with high FPR up to 5% [40, 41], because of the effect of muscle relaxants. In the 2015 AHA guidelines, absent pupillary light reflex post-cardiac arrest is a strong predictor of poor outcome with FPR of 0% in patients treated with or without TTM at 72 h, whereas absent corneal reflex at 24 h and 48 h post-arrest predicted a poor outcome, with FPR of 17% and 7%, respectively [21].

Regarding the motor response, an absence or extension response at 72 h or more after ROSC is a sensitive predictor of poor outcome, with low specificity and high FPR (10–40%) because of the effect of neuromuscular blockade and sedative [29, 41, 42]. It is a class III harm based on AHA 2015 guidelines and should not be used alone to predict poor outcome [21].

Evidence of early post-cardiac arrest status myoclonus, defined as continuous repetitive myoclonic jerks >30 min, is a sign of poor outcome with a FPR of 0% at 24 h post-arrest [21, 43, 44], whereas the presence of any simple myoclonus within 72 h after cardiac arrest has a 5% FPR, making it a non-reliable predictor of poor outcome [21].

It must be emphasized that the uncertainty in prognostication of poor outcome in comatose survivors becomes less over time [42]. While 72 h after rewarming seems to be favored, it should also be noted delayed recovery after 72 h of coma with favorable outcomes is being reported [5]. It's worthwhile highlighting that in the recent TTM study, prognostication of outcome was discouraged before 108 h [22].

### 30.5.2 Neuroimaging

After ROSC, a computer tomography (CT) or MRI of the brain is obtained to assess any evidence of brain injury and to help prognosticate.

Abnormal CT findings include intracranial hemorrhage, or evidence of early post-anoxic injury as diffuse brain edema, which can be quantified as the ratio between the densities of the gray matter and the white matter (GWR) at the level of the basal ganglia, within 1 h after ROSC [45]. An average GWR below 1.14 Hounsfield or a GWR below 1.22 Hounsfield predicted a poor neurological outcome with 100% specificity [45, 46].

On MRI studies, diffusion-weighed imaging (DWI) can detect neuronal cytotoxic edema. The presence of bilateral hippocampal hyperintensities on DWI and fluid-attenuated inversion recovery (FLAIR) sequences is a marker of poor prognostic sign according to one study [47]. Apparent diffusion coefficient (ADC) can quantify the severity of brain injury. Decrease ADC values correspond to area of diffusion restriction likely because of infarction. Normal values range between 700 and 800 × $10^{-6}$ $mm^2$ $s^{-1}$ [5], whereas ADC values <665 × $10^{-6}$ $mm^2$ $s^{-1}$ is a significant predictor for unfavorable neurological outcome [48, 49].

Although these neuroimaging techniques are promising, they are unfortunately not yet well validated and not practical, especially in the early acute phase when patients are critical.

### 30.5.3 Electrophysiological Studies

EEG patterns associated with poor neurological outcomes, with high sensitivity and specificity, include low voltage output pattern, burst suppression, alpha/theta coma, focal or generalized seizures, generalized periodic epileptiform discharges, status epilepticus, and background unreactivity [50]. A nonreactive EEG background at least 72 h post-cardiac arrest is incompatible with good neurologic recovery, with 100% specificity [50–53].

SSEPs are strong predictors of poor outcome in post-anoxic coma as determined by the bilateral absence of short latency (N20) SSEP response [54]. In the absence of therapeutic hypothermia, a bilateral absence of cortical N20 response is a reliable predictor of poor outcome as early as 24 h from ROSC with a false positive rate (FPR) of 0.7% [29, 31]. In patients treated with therapeutic hypothermia, a composite result of recent studies showed that bilateral absence of N20 SSEP response after rewarming is a reliable predictor of poor outcome with a FPR of 0.9% [41, 55, 56]. With comparison to EEG and clinical examination, SSEPs are better predictors of poor outcome post-cardiac arrest as they are less affected by sedation and temperature [21]. It is critical to note that though SSEPs are superior and promising, the above studies are still limited given the high rates of WLST and self-fulfilling prophecy; therefore, it is still better to wait at least 72 h to prognosticate.

### 30.5.4 Biomarkers

Two most common biomarkers used in post-cardiac arrest are neuron specific enolase (NSE), derived from neuron, and the S100B protein, derived from astrocyte and Schwann cells [39]. Higher levels of these biomarkers correlate with a higher extent of brain injury and therefore poor outcome [39], whereas patients with good outcomes have lower S100B levels and lower NSE levels on day 1 and 3 post-arrest ($p < 0.0083$) [57]. However, there are several limitations of these biomarkers, including extra central nervous system sources (from hemolysis, neuroendocrine tumors, muscles, and adipose tissue breakdown), lack of laboratory standards between centers, and false positive results from hemolysis [21], which make them not a good prognosticator tool, but rather a confirmatory tool.

In summary, a combination of absent pupillary light reflex at 72 h after rewarming, absent bilateral SSEPs response, malignant EEG patterns, and abnormal neuroimaging are prognostic factors of poor outcome.

## 30.6 Future Directions

Neurological outcome after cerebral resuscitation post-cardiac arrest is highly dependent on the prompt administration of high quality CPR leading to ROSC and the management post-ROSC, with

strong evidence for mild therapeutic hypothermia (32–34 °C) for 24 h. Clinicians must use a multidisciplinary approach by combining experience with available clinical, neuroimaging, neurophysiological, and biomarkers data to counsel family regarding the prognosis of their loved ones. Timing is key in prognostication as there are many confounding factors in early prognosis, such as evolving disease, pharmacological agents, and reversibility of injury [58], so when in doubt, one should wait. There is a need for better studies that are blinded, with proper sample calculation, without bias, and a better understanding of patients' outcome, not only functional status, but also cognition and integration back into society.

**Key Points**

- At the epicenter of the high mortality and morbidity from cardiac arrest, is the post-cardiac arrest syndrome, which includes anoxic brain injury, myocardial dysfunction, and a systemic ischemia and reperfusion syndrome.
- The brain is prone to injury due to lack of significant intrinsic energy and nutrient stores, therefore highly dependent on a constant supply of oxygen and nutrients.
- Multiple factors play a role in the extent and pattern of brain injury post-cardiac arrest including the initial ischemic cascade, the reperfusion injury after return of spontaneous circulation (ROSC), the delay ischemia due to the no reflow phenomenon, and post-resuscitation variable such as pyrexia and hypoglycemia.
- Clinicians must use a multidisciplinary approach by combining experience with available clinical, neuroimaging, neurophysiological, and biomarkers data to counsel family regarding the prognosis of their loved ones.
- Timing is key in prognostication as there are many confounding factors in early prognosis.

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# Part IX

# Recent Advances

# Therapeutic Hypothermia in Neurologic Diseases

31

Ankur Khandelwal

## 31.1 Introduction

In the last two decades, therapeutic hypothermia (TH) or induced hypothermia (IH) has emerged as a powerful neuroprotective modality in improving outcomes in patients sustaining cardiac arrest and hypoxic-ischemic encephalopathy [1, 2]. It is defined as the deliberate decrease of core body temperature to 32–35 °C [3]. The term TH was replaced with "targeted temperature management (TTM)" based on recommendations of the five international critical care societies in 2011 [4]. However, in the face of current literature, the conventional terms (TH and IH) are still used widely.

In a wide range of systemic diseases, primary injury or the initial impact is followed immediately by secondary injury that aggravates the disease pathology as a result of complex pathological cascade. This secondary injury may last for hours and even days or months and contributes to worsening of clinical state and overall outcome. The potential effect of TH on these mechanisms can be utilized depending on the timing of the therapy. When applied during the initial hours of the injury TH optimizes the potential for neuroprotection by working primarily at the cellular level to arrest pathologic processes that play a significant role in secondary injury. As injury progresses, TH is administered mainly with the aim of reducing cerebral edema and mass effect that the primary injury has on uninjured areas of the brain [5, 6]. Thus, TH can be applied both for neuroprotection and neurorescue in the neurocritical care unit (NCCU).

## 31.2 Neurophysiology and Hypothermia

Cerebral metabolism is a major determinant of brain temperature. Significant changes in neural metabolism can result even with minor changes in brain temperature. Change in per degree Celsius of brain temperature is accompanied by 6–8% change in cerebral metabolism [7, 8]. Innumerable studies have clearly demonstrated that fever alone is associated with unfavorable neurological outcome. In a meta-analysis of more than 14,000 patients, Greer et al. found that fever alone was a significant and independent predictor of morbidity and mortality across different conditions such as ischemic stroke, hemorrhagic stroke, and traumatic brain injury (TBI) [9]. The pathophysiological mechanisms by which fever worsens neurological outcome include increase of cerebral metabolic rate of oxygen consumption ($CMRO_2$), production of free radicals, local thermopooling, disruption of the blood–brain barrier (BBB), intracranial

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pressure (ICP) elevation, increased enzymatic inhibition of protein kinases, and worsened cytoskeletal proteolysis [10, 11].

Tight regulation of core body temperature in patients with brain injury is critical for optimal brain function. A broad range of beneficial effects of TH have been well described, including effects on many cellular and molecular processes from microRNA responses to differential gene expression [12, 13]. The protective mechanisms of mild hypothermia are illustrated in Table 31.1.

In a systematic review (2009) involving 11 prospective RCTs that compared ICP levels with hypothermia versus normothermia and six prospective cohort studies that provided ICP data before and during hypothermia, the authors found a mean ICP reduction of 10 mmHg with TH; this effect was lowest with ICP reduction of 6 mmHg for hyperventilation, 8 mmHg for mannitol and barbiturates, 15 mmHg for hypertonic saline and cerebrospinal fluid (CSF) drainage, and highest with 19 mmHg for decompressive craniectomy [14]. In another systematic review (2012) involving 13 RCTs and five observational studies, the authors observed that ICP in the TH group (32–34 °C) was significantly lower than ICP in the normothermia group [15].

**Table 31.1** Protective effects of therapeutic hypothermia

| |
|---|
| 1. Decreases oxygen and energy consumption secondary to decrease in metabolism |
| 2. Reduces inflammation and immune reactions |
| 3. Reduces neuro-excitatory cascade by reducing excessive calcium influx, glutamate receptor activation, and neuronal hyperexcitability |
| 4. Reduces mitochondrial injury and dysfunction |
| 5. Reduces intracellular acidosis |
| 6. Upregulates expression of cold shock proteins (CSP) and thus cytoprotection |
| 7. Inhibition of apoptotic/necrotic processes |
| 8. Decreases free radical formation |
| 9. Stabilizes blood brain barrier |
| 10. Decreases vascular permeability and cerebral edema |
| 11. Reduces cerebral thermo-pooling and local hyperthermia |
| 12. Improved tolerance for ischemia |
| 13. Suppression of epileptic activity and seizures |
| 14. Reduces reperfusion injury |

## 31.3 Therapeutic Hypothermia and Neurological Conditions

Whether TH or TTM improves patient outcome in varied other neurological conditions apart from cerebral hypoxia post-cardiac arrest is still not clear. This chapter is mainly confined to the application of TH in various neurological conditions. Various existing literatures and current evidences have been incorporated for better understanding of advantages, disadvantages, and potential limitations of TH in various neurological diseases.

### 31.3.1 Traumatic Brain Injury (TBI)

The application of TH after TBI can have variable effects depending on the type and severity of injury in addition to timing, depth, and duration of cooling. Appropriate patient selection is pivotal for obtaining maximum therapeutic benefits. Mild hypothermia can be administered either early after injury and prior to ICP elevation or as a resort for refractory intracranial hypertension. Although positive results of TH have been observed in experimental models of TBI [16], human studies have clearly shown inconsistent results.

The National Acute Brain Injury Study: Hypothermia II (NABIS: H II) trial failed to demonstrate any outcome difference of prophylactic (within 2.5 h of injury) hypothermia (33–35 °C for 48 h) versus normothermia (37 °C) in patients with severe TBI [17]. Similarly, the results of Eurotherm3235 Trial demonstrated that TH plus standard care to reduce ICP (>20 mmHg) resulted in worse outcomes as compared to standard care alone in patients with TBI [18]. The recent Brain Trauma Foundation (BTF) Guidelines (2016) have also clearly given recommendations against the early (within 2.5 h) or short-term (48 h post-injury) prophylactic hypothermia to improve outcomes in patients with diffuse brain injury [19]. The ongoing long-term mild hypothermia for severe TBI (LTH-1) trial will further throw light on the effect of long-term (5 days) mild hypothermia (34–35 °C) on neurological outcome in

severe TBI patients unlike the existing studies which have focused on short-term cooling (24–48 h) [20].

In a post hoc analysis of two clinical trials (NABIS: H I and NABIS: H II), it was observed that initiation of hypothermia to 35 °C before or soon after craniotomy with maintenance at 33 °C for 48 h improved outcome of patients with hematomas and severe TBI [21]. One explanation could be due to different pathophysiology of hematomas as compared to diffuse brain injury. Hematomas when removed surgically have a higher incidence of raised ICP due to reperfusion injury-related spreading depolarizations [22]. The reasons for improvement after application of TH in such a subpopulation probably depend on the suppressive effect of hypothermia on reperfusion injury [23]. Moreover, the risk of rebound increase in ICP is probably curtailed due to absence of bone flaps [17]. In a recent study by Tang et al., a total of 60 adults with ICP of more than 20 mmHg after decompressive craniectomy were randomly assigned to standard care (control group) or hypothermia (32–35 °C) plus standard care. A significant difference in ICP and cerebral perfusion pressure (CPP) was observed between the two groups. Favorable outcomes occurred in 12 (40.0%) patients of hypothermia group as compared to seven (36.5%) patients of control group ($P$ = 0.267). There was a marked difference in survival between the hypothermia and control group ($P$ = 0.032). However, patients in hypothermia group had higher incidence of pulmonary infection and dyselectrolytemia as compared to control groups ($P$ = 0.038 and 0.033, respectively) [24]. The ongoing randomized, prospective, multicentric HOPES trial will further add evidence on the effect of mild hypothermia on surgically evacuated TBI patients (ClinicalTrials.gov Identifier:NCT02064959).

### 31.3.2 Intracerebral Hemorrhage (ICH)

Despite high incidence of ICH and its significant impact on morbidity and mortality, no specific treatment is currently available. Optimal management of patients with ICH remains elusive till date. Perihemorrhagic edema (PHE) that develops after ICH has been implicated as a contributing factor for delayed neurologic deterioration. In various animal models of spontaneous ICH, hypothermia has been observed to reduce PHE, inflammation, and thrombin-induced injury along with preservation of BBB integrity [25–27]. However, there is very little evidence to suggest the beneficial effect of TH after spontaneous ICH in humans.

In one of a large case series reported by Staykov et al., patients ($n$ = 25) with large supratentorial ICH (volume > 25 mL) were subjected to mild TH of 35 °C for 8–10 days. The authors observed that patients in the hypothermia group had stable PHE unlike the control group ($n$ = 25) where PHE continuously increased up to day 10. The most frequent complications during TH were shivering (36%) and pneumonia (96%) but could be treated effectively. Mortality rate after 3 months and 1 year was higher in the control group (16.7% and 44%) as compared to TH (8.3% and 28%) [28].

Currently, no data exist about the optimal timing and duration of TH in ICH. In a retrospective, case control study, Volbers et al. grouped 33 ICH patients treated with hypothermia (35 °C) based on timing of initiation of TH (early: days 1–2 and late: days 4–5 after admission) and duration of hypothermia (short: 4–8 days and long: 9–15 days). Patients with ICH matched for age, ICH volume, ICH localization, and intraventricular hemorrhage (IVH) were identified as controls ($n$ = 37). Early initiation of hypothermia led to relative decrease in PHE between admission and day 3, whereas median relative PHE increased in control patients and patients with late hypothermia initiation. However, after day 3, relative PHE showed an increase in all groups without difference. Neurological outcome scale (Modified Rankin scale) did not show any difference between patients treated with hypothermia and controls at day 90 [29].

The impact of TTM on functional outcome is far more controversial. In a recent systematic review, Fischer et al. identified 11 experimental studies that investigated the effects of TTM on

functional outcome using neurobehavioral testing. The authors observed little or no beneficial effect of temperature modulation on overall outcome [30]. The impact of non-surgical intervention on neurobehavioral outcome in experimental ICH was also addressed in a meta-analysis by Frantzias et al. Analyzing six controlled trials they found no improvement in functional outcome through TTM [31]. However, certain factors such as paucity of data on long-term outcome in animals and a relatively less lethal injury in experimental models as compared with human ICH should be taken into accountability. In a recent systematic review and meta-analysis in human ICH, TH exhibited no advantage in reducing mortality and poor outcomes [32].

Thus, even though clinical studies have shown substantial effect of TH in reducing PHE, the net effect on mortality and neurological outcome remains unchanged. Controversies regarding the initiation, optimal target temperature, duration, and method of cooling along with speed of rewarming for patients with ICH need to be addressed in future randomized studies.

### 31.3.3 Acute Ischemic Stroke (AIS)

The use of TH in AIS is supported by robust data from experimental models that have been validated impressively by a recent meta-analysis using rigorous statistical approaches warranting consideration of TH in larger clinical trials of AIS [33, 34].

In the Intravascular Cooling in the Treatment of Stroke 2 (ICTuS) trial, 120 patients were enrolled out of the targeted 1600 before the study was terminated. In this study, patients who were treated within 3 h of symptom onset with intravenous recombinant tissue plasminogen activator (rtPA) either received endovascular maintained hypothermia ($n$ = 63) targeted to 33 °C (over 24 h) or normothermia ($n$ = 57). The primary outcome of 90-day mRS 0,1 occurred in 33% hypothermia and 38% normothermia subjects, odds ratio (95% CI) of 0.81 (0.36–1.85). Serious side effects occurred equally in both the groups. Mortality rate was higher in hypothermia group (15.9%) as compared to normothermia (8.8%) subjects, odds ratio (95% CI) of 1.95 (0.56–7.79). Occurrence of pneumonia was higher in hypothermia (19%) versus normothermia (10.5%) subjects, odds ratio (95% CI) of 1.99 (0.63–6.98). No significant difference was found in the respective outcome between the treatment groups [35]. Although the cooling rates and adherence to target temperature were in accordance to protocol, the published results have to be interpreted with great caution, as the statistical analysis plan was calculated based on the enrolment of 1600 patients.

Hong et al. studied the effects of mild TH (34.5 °C) in adequately sedated intubated patients during a period of 48 h of cooling and 48 h of rewarming versus normothermia after successful recanalization therapy in anterior circulation ischemic stroke. Patients in hypothermia group ($n$ = 39) had less hemorrhagic transformation ($P$ = 0.016) and cerebral edema ($P$ = 0.001) and better outcome ($P$ = 0.017) compared with the normothermia group ($n$ = 36). Factors such as implementation of TH only in angiographically proven recanalization, controlled and slow rate of rewarming (over 48 h), and intubation and deep sedation in all patients to prevent pneumonia and shivering need to be considered for the reproducibility of the results [36]. In AIS, surface cooling is feasible to 35.0 °C in awake patients but is associated with increased risk of pneumonia. This was observed in the recent Cooling for Ischemic Stroke Trial (COOLIST) [37]. Similar results were also observed in the study by Piironen et al. in thrombolyzed, spontaneously breathing patients with stroke [38].

More research is the need of the hour to better understand the underlying principles and mechanisms of TH and to overcome potential barriers which seem to impede the routine use of TH in stroke. Moreover, selective cooling can potentially reduce the systemic complications associated with systemic hypothermia. The results of the multicentric, randomized, Euro-HYP-1 clinical trial will further throw light on the effect of TH on outcome (mRS) at 91 days after AIS. In this study, patients randomized to hypothermia group are subjected to a target body temperature

of 34–35 °C within 6 h after symptom onset and maintained for 24 h [39].

### 31.3.4 Aneurysmal Subarachnoid Hemorrhage (aSAH)

One of the known complications following surgery of intracranial aneurysm is the development of post-operative neurologic deficits. The application of TH in aSAH has produced variable results. The landmark randomized, multicentric IHAST (Intraoperative Hypothermia for Aneurysm Surgery Trial) investigators recruited a total of 1001 patients with a preoperative World Federation of Neurological Surgeons (WFNS) score of I, II, or III ("good-grade patients"), who had aSAH no more than 14 days before planned surgical aneurysm clipping. The patients were randomly assigned to intraoperative hypothermia ($n$ = 499, $T$ = 32.5–33.5 °C) or normothermia ($n$ = 501, $T$ = 36–37 °C). The duration of stay in the ICU, the total length of hospitalization, the rates of death at follow-up (6% in both groups), or the destination at discharge (home or another hospital, among surviving patients) were comparable between the two groups. At the final follow-up, 329 of 499 patients in the hypothermia group had a Glasgow Outcome Score (GOS) of 1 (good outcome), as compared with 314 of 501 patients in the normothermia group (66% vs. 63%; odds ratio, 1.14; 95 percent CI, 0.88–1.48; $P$ = 0.32). However, patients in normothermia group had less post-operative bacteremia as compared to hypothermia group (3% vs. 5%, $P$ = 0.05) [40]. Thus, the IHAST trial failed to show any improvement in mortality and functional or cognitive outcome. This could be due to the fact that most subjects were in good clinical condition without acute brain injury [41].

A recently published systematic review of three studies (Hindman et al. [42], Todd et al. [40], and Chouhan et al. [43]) involving 1158 patients of both ruptured or unruptured intracranial aneurysms compared intraoperative mild hypothermia ($n$ = 577, $T$ = 32–35 °C) with normothermia ($n$ = 581). About 93.8% of the patients had good-grade aSAH. Death or dependency at 3 months was less in patients who received hypothermia (13.1% vs. 16.0%; RR 0.82; 95% CI 0.62–1.09; RD −0.03; 95% CI −0.07 to 0.01, moderate-quality evidence). Unfavorable outcomes were comparable between the two groups. Decompressive craniectomy or corticectomy was not reported in any patient. Infarction and clinical vasospasm were noted in 36 (6.2%) and 34 (6%) patients, respectively, in hypothermia group as compared to 40 (6.9%) and 32 (5.5%) patients without hypothermia. None of the study mentioned about duration of hospital stay. Only one study which included 112 participants reported discharge destinations: 43 of 55 (78.2%) participants in hypothermia group were discharged home as compared to 39 of 57 (68.4%) participants in the control group. Incidence of infection and cardiac arrhythmias was almost similar between the two groups. Due to outcomes being reported in a variety of ways, the authors failed to gather any concrete evidence regarding the benefits of the routine use of intraoperative mild hypothermia in aSAH [44].

In the light of current evidence, there are only few studies on the effect of hypothermia in poor-grade SAH. Kuramatsu et al. conducted an observational matched controlled study that included 36 poor-grade (Hunt and Hess Scale >3 and WFNS >3) SAH patients. Twelve patients received early TH (<48 h after ictus), mild (35 °C), and prolonged (7 ± 1 days) and were matched to 24 patients from the prospective SAH database. 71% of the patients had angiographic vasospasm. TH reduced the degree of macrovascular spasm as well as peak spastic velocities ($P$ < 0.05) despite no effect on occurrence or duration of vasospasm Delayed cerebral ischemia (DCI) was observed in 50% of patients in hypothermia group as compared to 87.5% of the patients in control group. Statistically, this resulted in a relative risk reduction by 43% and preventive risk ratio of 0.33 (95% CI 0.14–0.77, $P$ = 0.036). Functional outcome was far more favorable in TH-treated patients [66.7% vs. 33.3% of non-TH ($P$ = 0.06)] [45].

In a recent pilot study conducted on 22 poor-grade aSAH patients (Hunt & Hess Scale 4, 5 and modified Fisher Scale 3, 4), Choi et al. observed

less incidence of symptomatic vasospasms (18.1% vs. 36.4%) and DCI (36.3% vs. 45.6%) in the TH group ($n$ = 11) when compared to control group ($n$ = 11). However, these differences did not result in statistical significance. At 3 months, good-to-moderate functional outcome was observed in 54.5% patients in the TH group (0–3 on the mRS) as compared to 9.0% patients in the control group ($P$ = 0.089). At 1 month, mortality was 0.0% in the TH group as compared to 36.3% in the control group ($P$ = 0.090) [46].

Mild TH is feasible and can be safely used in patients with poor-grade SAH. In addition, it may reduce the risk of vasospasm and DCI, improve functional outcomes, and reduce mortality. However, further larger randomized controlled trials (RCTs) are warranted.

### 31.3.5 Status Epilepticus (SE)

Antiepileptic property of hypothermia has been demonstrated in multiple animal studies [47, 48]. The probable mechanisms that have been implicated include reducing Na+ exchange, decreasing K+ conductance, regulating glutamatergic synaptic transmission, reducing the release of presynaptic vesicle, and disrupting the synchronism of discharges [49].

In humans, literature on the positive impact of TH on SE is limited to few case reports and case series [50]. In a systematic review, application of TH in patients with refractory SE did not show convincing evidence to support its use as adjuvant therapy for seizure control or for the achievement of a burst-suppression EEG pattern [51].

In the multicentric HYBERNATUS (Hypothermia for Brain Enhancement Recovery by Neuroprotective and Anticonvulsivant Action after Convulsive Status Epilepticus) trial, 270 patients of convulsive SE who were critically ill and receiving mechanical ventilation were enrolled to receive hypothermia (32–34 °C for 24 h) in addition to standard care or to standard care alone. Application of hypothermia lowered the rate of progression to EEG-confirmed SE on the first day as compared to the control group (11% vs. 22%; odds ratio, 0.40; 95% CI, 0.20–0.79; $P$ = 0.009). However, no significant differences in 90-day functional impairment and mortality were seen between the two groups. The overall length of ICU and hospital stay was similar between the two groups despite more frequent adverse events in the hypothermia group. Thus, the results of this trial do not support a beneficial effect of TH as compared with standard care alone in patients with convulsive SE [52].

While there is limited evidence, and some risks associated with therapeutic hypothermia, it can be considered as a reasonable and potentially effective treatment option for refractory SE.

### 31.3.6 Central Nervous System (CNS) Infections

CNS infections may provoke excitotoxic cascade, thus leading to overt or subtle epileptic seizures, thereby deteriorating the prognosis of these patients. In an experimental study conducted on rabbits, Irazuzta et al. demonstrated that moderate hypothermia (32–34 °C) significantly decreased the levels of excitatory neurotransmitters in bacterial meningitis, thus attenuating neuronal stress [53].

Clinical trials of TH in CNS infections have been more commonly investigated in children than adults. In a retrospective analysis, 27 out of 43 children who had been subjected to mild hypothermia as management strategy for acute encephalopathy/encephalitis had variable outcome. Early initiation (≤12 h) of cooling was related to favorable outcome, whereas delayed cooling (>12 h) produced worse outcome. However, outcome with delayed cooling was statistically invariant with normothermic children [54].

In the light of current evidence, very less is known about the effects of TTM or TH in adults with CNS infections. Only few case reports and case series have thrown light on this aspect. In a case series of 11 patients suffering from severe meningoencephalitis (median GCS 8 and APACHE score 24) and subjected to mild hypothermia (32–34 °C), only one patient died, three patients recovered fully, whereas others

recovered with residual impairment [55]. The same Croatian group had previously observed a neuroprotective effect of induced hypothermia in adult community-acquired bacterial meningitis [56]. However, the authors did not mention about induction of hypothermia and the duration including rewarming. Moreover, since majority of patients had pneumococcal infection, concomitant administration of steroid, if any, was also not mentioned. Dexamethasone, a glucocorticoid, has shown to improve outcome as adjuvant in bacterial meningitis [57]. The results of this case series should be interpreted with caution and further large randomized trials are needed to establish the effectiveness of TH in meningitis/meningoencephalitis.

### 31.3.7 Spinal Cord Injury (SCI)

Over the years, various animal studies have reliably shown a consistent benefit of systemic hypothermia in acute SCI [58, 59].

Initiation of TH in humans with acute SCI differs greatly from animal models. This may be attributed to the delay in hospitalization of the patient, lack of prompt diagnosis, inappropriate planning, and substandard preparation. Despite these limitations, few clinical trials have successfully demonstrated the effectiveness of systemic hypothermia initiated within 6 h of injury and sustained for 48 h [60, 61]. Levi et al. demonstrated that out of 8 patients at 1 year follow-up, 3 patients improved to American Spinal Injury Association (AIS) B, 2 patients improved to AIS C, and 1 patient improved to AIS D from complete cervical SCI (AIS A) following 48 h of modest (33 ° C) intravascular hypothermia [60]. In a case-controlled study conducted by Dididze et al., 35 patients of acute cervical cord injury were subjected to systemic hypothermia (33 °C) for 48 h. International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) scale developed by the American Spinal Injury Association was used for assessment of neurological outcome. All patients were complete ISNCSCI A on admission, but four converted to ISNCSCI B in <24 h post-injury. The mean time to initiate hypothermia from the time of injury was 5.76 (±0.45) h. At around 10 months follow-up, 15 (43%) patients showed improved in ISNCSCI by at least one grade. After excluding four patients who converted to ISNCSCI B within 24 h, 11patients out of remaining 31 (35.5%) improved at least one ISNCSCI grade. Respiratory complications were similar in both prospective ($n$ = 21) and retrospective group ($n$ = 14). The overall risk of any thromboembolic complication was 14.2% [61]. Collectively, these results suggest that early and rapid initiation of systemic cooling, maintenance for at least 48 h, and followed by gradual rewarming are effective in improving patient outcomes. The use of this technique for SCI should move into large-scale RCTs for further concrete evidence.

The first convincing clinical evidence of the benefit of local hypothermia in acute SCI came from the study by Hansebout and Hansebout. In this study, institution of local hypothermia (6 °C) in 20 patients was done within 7.1 h of their injury. The mean duration of hypothermia was 7.1 h. In addition, all patients underwent decompressive surgery and received corticosteroids. Initially, all patients were classified as ASIA grade A impairment. At final follow-up, an improvement in motor and sensory index scores was observed to be 63% and 88%, respectively. The investigators concluded that recovery profile is better with application of local hypothermia as compared to systemic hypothermia [62]. Further RCTs are needed to draw definitive conclusions about its effectiveness.

## 31.4 Neurocritical Care Challenges

### 31.4.1 Phases of TH

The mild TH procedure can be divided into three phases: induction, maintenance, and rewarming.

During induction phase, process of cooling should be as rapid as possible to achieve the target temperature. If a patient is cooled too slowly, the therapeutic effect is lost. Avoidance of delay in cooling (“earlier is better” strategy) has been

shown to improve neurological outcome [63]. One of the most important caveats of induction phase is the occurrence of shivering which in turn leads to increased metabolism, greater oxygen demand, and heat generation. The threshold for this defense mechanism of the thermoregulatory system is around ±35.5 °C (1 °C below the vasoconstriction threshold) [64]. Thus, a reasonable justification is to overcome this threshold as quickly as possible. The simplest method of avoiding shivering is to keep hands and feet warm by application of gloves and socks, respectively. In addition, shivering can be treated with pharmacological measures such as acetaminophen, opioids, dexmedetomidine, propofol, and magnesium sulfate [65]. Buspirone is an anxiolytic that functions by binding to serotonin and dopamine receptors in the brain. This increases norepinephrine metabolism in the brain, which reduces the shivering threshold [66]. Muscle paralysis should be practiced only in refractory cases. Severity of shivering is commonly done based on the Bedside Shivering Assessment Scale (BSAS) [67]. It is a 4-level tool that uses observation and palpation to score shivering. It is classified as: Score 0 (none)—no shivering noted on palpation of the masseter, neck, or chest wall; Score 1 (mild)—shivering localized to the neck and/or thorax only; Score 2 (moderate)—shivering involves gross movement of the upper extremities in addition to neck and thorax; and Score 3 (severe)—shivering involves gross movements of the trunk and upper and lower extremities.

During the maintenance period, core body temperature can be maintained using advanced cooling technology with only minor fluctuations (±0.5 °C). Clinical infection is unusual during hypothermic induction. However, it is not uncommon during maintenance phase. Increased temperature of the circulating water in the cooling device may indicate a febrile response and thus may be used as a surrogate marker of infection [68]. In addition, dyselectrolytemia due to intracellular shifts is very commonly observed during maintenance period and thus requires frequent replacement. The most critical and challenging phase of hypothermia management is the period of rewarming. Therapeutic effects of cooling can be lost with large fluctuations in temperature resulting from reperfusion injury. Rapid rewarming is associated with secondary brain injury which manifests as impaired cerebrovascular reactivity, cerebral edema, and rebound intracranial hypertension [69–72]. A gradual, controlled rewarming (0.1–0.2 °C/h) should be used to reduce the risk of intracranial sequelae.

### 31.4.2 Cooling Methods

The cooling techniques and devices can be separated into two main groups: surface cooling and intravascular cooling. Surface cooling systems consist of pads or blankets that circulates forced cold air or fluid when applied to the skin of patients. In endovascular technique, cooling is done by placement of heat exchange catheters in large central veins (femoral, subclavian, and internal jugular) and circulating temperature-adjusted saline in a closed-loop system through the catheter's balloon. Each technique has its own limitations despite being equally effective for induction and maintenance of hypothermia [73, 74]. As such, these techniques when combined with automatic computer processed feedback device is a good and safe solution. In clinical practice, the simplest and least expensive method of cooling is by infusing cold intravenous fluids (4 °C normal saline or lactated ringers at 30–40 mL/kg over 1 h) and application of ice packs [74, 75].

### 31.4.3 Temperature Monitoring

Continuous and accurate monitoring of core temperature is recommended in all critical settings particularly in patients with brain injury [76]. The pulmonary artery blood temperature is considered to best reflect core temperature. An integrated sensor (thermistor) located in the distal tip of the endovascular catheters (e.g., InnerCool RTx Endovascular System) directly records temperature without a lag period inherent in rectal and bladder sensors. Other sites for core temperature measurement are tympanic membrane, rectum, bladder, nasopharynx, and esophagus. Axillary temperature approximates

rectal temperature in an environment with stable ambient temperatures (e.g., neonatal units) [77].

### 31.4.4 Side Effects and Complications of TH

Despite multiple therapeutic effects of deliberate hypothermia, a wide range of side effects limits its application in clinical practice. These may be attributed to side effects of hypothermia per se, failure to maintain constant temperature levels and unregulated rewarming. Discussion of individual side effects is beyond the scope of this chapter. All the known and potential side effects have been enlisted in Table 31.2.

## 31.5 Conclusion

Therapeutic hypothermia or targeted temperature management is one of the most encouraging tools for neuroprotection in acute brain injury. This therapeutic tool provides reliable ICP reductive action. Hypothermia inhibits multiple pathological processes simultaneously unlike pharmacotherapy that tends to antagonize a single neurochemical process. On the other hand, beneficial effects of mild hypothermia might be outweighed by side effects, limitations, or complications. Current literature is limited and is largely representative of meta-analyses, systematic reviews, and case studies. There are certainly potential benefits to TH in neurocritical care; however, the limitations of current findings highlight the need for further research to be conducted to provide clarity. Safe and effective application of TH includes rapid induction, smooth maintenance, and slow rewarming. Presently, there are no formal guidelines that dictate when TH should be implemented, the specific patient populations that may benefit, and precise temperature or duration. Strict vigilance should be ensured to detect infectious manifestations during the application of TH. Prophylactic administration of antibiotics is not recommended. Despite lack of convincing evidence, antibiotics may be considered in case of suspected infections. Future prospective trials must address this issue. Implementation of TH should be guided by clearly defined clinical targets and monitoring thresholds. Application of advanced neuromonitoring techniques seems reasonable considering the complex pathophysiological cascade during hypothermia and rewarming. Maximal benefit can be obtained by utilizing multimodal neuromonitoring techniques.

**Table 31.2** Harmful effects of systemic hypothermia

| |
|---|
| 1. Increases cerebral energy consumption and metabolic demand secondary to shivering |
| 2. Electrolyte imbalance (low magnesium, phosphate, and potassium levels due to intracellular shifts) |
| 3. Prolonged drug action (due to decreased drug metabolism) |
| 4. Immunosuppression and risk of infections |
| 5. Hyperglycemia (hypothermia decreases insulin secretion and induces insulin resistance) |
| 6. Bedsores and surgical wound infections (secondary to hypothermia induced cutaneous vasoconstriction) |
| 7. Coagulopathy, platelet dysfunction, and thrombocytopenia |
| 8. Transient renal dysfunction |
| 9. Hemodynamic disturbances and arrhythmias (particularly at core temperature <32 °C) |
| 10. Rewarming injuries (infections, rebound increase in ICP due to vasodilatation, abrupt increase in electrolyte levels particularly potassium, and increased insulin sensitivity leading to hypoglycemia) |
| 11. Endovascular catheter related complications |

**Key Points**

- Therapeutic hypothermia (TH) is one of the most promising tools for neuroprotection in cardiac arrest and ischemic encephalopathy.
- TH inhibits multiple pathological processes simultaneously. Various beneficial effects of TH include reduction of intracranial pressure, antiepileptic effect, stabilization of blood brain barrier, scavenging of free radicals, reducing reperfusion injury, and improving tolerance to ischemia.

- TH has also been investigated in various neurological disorders comprising intracranial hypertension, traumatic brain injury, intracerebral hemorrhage, acute ischemic stroke, status epilepticus, central nervous system infections, and spinal cord injury. However, the results have not shown consistent benefit in reducing morbidity and mortality.
- Potential side effects of TH include immunosuppression and risk of infections, coagulopathy, shivering, hemodynamic perturbations, hyperglycemia, and decreased drug metabolism.
- Challenges in the safe and effective application of TH include fast induction, smooth maintenance, and slow rewarming. Its application requires specialized critical care units.

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# Research in Neuroscience

# 32

Chanannait Paisansathan

## 32.1 Introduction

It seems that every day there is an explosion of new information in neuroscience and an associated enhancement of technological advancements. More than ever neuroscientists are generating substantive collective knowledge regarding the interconnections within the brain, its connectivity, and function. These research data are increasing our understanding of the brain in the healthy and diseased states. The effects of anesthesia in protecting or injuring cerebral functions are widely discussed, with controversial conclusions. This chapter includes data from the past 5 years of recent developments in anesthesia and neurocritical care research.

This first section discusses the perplexity of electrical brain circuits and their associated connectivity. The effects of various anesthetic drugs on brain function and circuitry connectivity are described. The complicated transition from consciousness to unconsciousness is presented along with the various monitors used to track these transitions. The electroencephalogram is frequently used in both laboratory and clinical research efforts; however, this presents a problem because different anesthetic drugs present with different EEG signal changes, further complicating the problem of identifying EEG indicators of unconsciousness.

The next section discusses the interaction between anesthesia/surgery and the potential for neurodevelopmental and behavioral changes in pediatric patients. The strengths and weaknesses of animal research are discussed along with the conflicting data from clinical studies. The limitations of transferring animal research data to the human infant are substantial. This section is followed by a discussion of neural dysfunction associated with anesthesia in the elderly patient population. The literature regarding postoperative cognitive dysfunction (POCD) and delirium is confusing, as retrospective studies are incomplete and diagnostic tools are inconsistent. The use and effectiveness of potential monitoring modalities are discussed along with the lack of tools with good sensitivity and specificity.

The ability of physicians to decrease the serious neurologic injuries associated with cerebral ischemia is one of the positive improvements in the care of stroke patients. This chapter concludes with a discussion of the controversy regarding the use of general anesthesia versus conscious sedation. It describes the need for further laboratory and clinical research studies to improve the outcome of our stroke patients. Adequately designed research evaluations are needed to translate preclinical work into the clinical environment.

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## 32.2 Anesthesia-Induced Unconsciousness

General anesthesia is a neurophysiologic state that consists of unconsciousness, amnesia, analgesia, and immobility along with maintenance of bodily functions. Although rapid advancement in neuroimaging modalities and mathematical modeling computation [1] has helped progress our understanding of how brain networks generate consciousness, accurately measuring the neural correlates of consciousness remains a significant challenge for neuroscience.

In earlier investigation in the 1980s and 1990s, research in the anesthetic mechanism of action was focused on biophysiology of the neurotransmitter receptors and ion channels interaction to various anesthetics and their molecular structures. In the early 2000s, it was found that several anesthetics metabolically activate sleep-promoting regions while simultaneously suppressing arousal-promoting areas [2]. The anesthetic-induced unconsciousness mechanism was proposed to work via two opposite pathways: bottom-up and top-down mechanisms.

### 32.2.1 Bottom-Up Mechanism

The sleep-wake cycle is neurally mediated by subcortical nuclei in the hypothalamus and brainstem, with the ventrolateral preoptic nucleus (VLPO) as the key role in sleep generation. The halogenated inhalational agent isoflurane was shown to activate VLOP neurons. Dexmedetomidine was shown to activate hypothalamic α2-adrenergic receptors. Accumulatively, there is strong evidence that supports the role of thalamus as an essential center in both sleep- and anesthetic-induced unconsciousness. The thalamus has rich interconnectivity to the cortex and is believed to be the hub of sensory input and part of ascending arousal system. Suppression of thalamic activity can result in altered cortical and thalamocortical oscillation and disrupt information processing. Intravenous anesthetic agents (except ketamine) suppress thalamus activity, supporting the bottom-up mechanism.

### 32.2.2 Top-Down Mechanism

The primary sensory cortex and higher-order association areas (frontoparietal cortex) [3] connectivity play important roles in the proposed top-down mechanism of consciousness. Interrelated structural and functional connections between these areas orchestrate an integration of neural information and processing of perception. Functional MRI (fMRI) and electroencephalographic studies of propofol, sevoflurane, and ketamine show a functional breakdown in frontal-parietal connectivity and information transfer, supporting the top-down mechanism.

### 32.2.3 Effects of Anesthetic Drugs

Arousal and conscious processes have been linked to thalamocortical electroencephalographic rhythms in gamma (30–80 Hz) and high-gamma (80–200 Hz) ranges. Isoflurane causes a dose-dependent attenuation of the power in the 30–200 Hz range, and this effect is greater for the thalamus than for the cortex [4].

Propofol, 2,6-di-isopropyl-phenol, acts as an agonist at GABAa receptor and results in hyperpolarization of the post-synaptic cell producing neuronal inhibition. The pattern of behavioral EEG oscillation and model computation of propofol consistently shows five pattern of response. The paradoxical excitation at low dose concentration is EEG manifested by an elevated power in the beta (12.5–25 Hz) frequency band. At deeper levels of propofol, a transition to an unconsciousness states is associated with both the appearance of low-frequency delta (1–4 Hz) activity and a highly coherent alpha (9–13 Hz) rhythm in the frontal cortex [5]. Simultaneously, while the frontal alpha emerges, the posterior occipital alpha is lessened. Together, this phenomenon has been described as the anteriorization [6]. At the deep level of propofol, the EEG dynamic demonstrates the burst suppression pattern.

Dexmedetomidine acts as an α2-adrenergic receptor agonist. Dexmedetomidine is associated with a substantial drop in the capacity for

information transfer in functional neuronal networks. These changes result from reduction in the strength of connectivity and also manifest as reduced within and between resting-state network connectivity both locally and globally [7].

### 32.2.4 Transition to Unconsciousness

Developing reliable brain measures to track the transition to loss of consciousness is still hindered by individual variability and susceptibility to anesthetics. Observation shows that even at stable sedation doses, patients are sometimes intermittently responsive to verbal commands during states of light sedation. During these periods, prominent anesthesia-induced neural oscillations such as slow-delta (0.1–4 Hz) oscillations are markedly absent. Pavone et al. recently reported that the decrease in eyes-closed, awake-alpha (8–12 Hz) oscillation power is associated with lack of responsiveness during sevoflurane effect-onset and -offset during light sedation. They concluded that awake-alpha oscillation, which was previously thought to be an idling rhythm, is associated with responsiveness to behavioral stimuli during light sedation [8].

Thus, the mounting evidence suggests that anesthetic agents disrupt the integration and sensory processing leading to unconsciousness. A true unconscious state, in which a patient transits from sedation to unawareness, still does not seem to manifest a consistent EEG signature across anesthetic agents. An appearance of alpha oscillation anteriorization or lack of does not reliably predict the unconsciousness [9]. Brain connectivity or data processing in various pathological physiology or even age-related different functionality and anesthetic sensitivity is largely unknown. The obvious question about multianesthesia agents used in the operating room to maintain unconsciousness state and the different neuronal activation or suppression results in different frequency oscillation and produces a combination of variable frequencies. Is the frontal cortex the best target to monitor unconsciousness? Once we understand the brain electrical pattern produced by various anesthetic combination that correlates with unconsciousness, can we identify the pathological electroencephalogram that occurred in high risk patients?

Even though there is much progress in our understanding of how anesthesia affects the neuronal activity locally and globally in the past 10 years, yet the precise state of anesthesia-induced unconsciousness and unawareness need to be elucidated. Unconsciousness does not seem to reliably predict unawareness. The question remains whether the electroencephalogram is the best tool to identify unawareness when there are many variables that can affect the interpretation. This area of research remains a major focus in neuroscience.

## 32.3 Anesthesia and Neurodevelopmental and Behavioral-Cognitive Function

The process of neurogenesis starts at the early stages of the gestation. Migration and neuroapoptosis occur rapidly from 24 weeks' gestation until 4 weeks after birth. The proliferation of neuronal synapses begins around the 20th week of gestation at a fast pace and reaches a peaking number of synapse at around 1–2 years old. Myelination begins by the end of the second trimester and continues at a slower rate throughout childhood.

The γ-aminobutyric acid (GABA) and glutamate neurotransmitter and receptor systems play an important role in neuronal connection and communication. Without neuronal transmission and binding of GABA and glutamate, neurons undergo neuroapoptosis. All the anesthetics that are currently used in clinical setting bind to either GABA or NMDA receptors (Table 32.1). The interference of neurotransmission and its receptor system potentially affect the neurogenesis and synaptosis for the developing brain [10, 11]. It is plausible that repeated exposure to anesthetics at the early gestational age or during childhood will have an impact on neurodevelopment and contribute to behavioral-cognitive dysfunction in the adult.

**Table 32.1** Common anesthetic agents and receptors

| Agent | GABA | NMDA | Alpha 2 agonist |
|---|---|---|---|
| Halogenated anesthetics (sevoflurane, isoflurane, desflurane) | Agonist | Antagonist (only sevoflurane and high dose isoflurane) | |
| Nitrous oxide | | Antagonist | |
| Benzodiazepine | Agonist | | |
| Propofol | Agonist | | |
| Etomidate | Agonist | | |
| Ketamine | | Antagonist | |
| Dexmedetomidine | | | Agonist |

Several experimental animal studies demonstrated that early exposure to a single or a combination of drugs commonly used in pediatric anesthesia (midazolam, nitrous oxide, and isoflurane) for 4 h or longer causes widespread apoptotic neurodegeneration in the developing brain, deficits in hippocampal synaptic function, and persistent memory/learning impairments [12, 13].

The notion of anesthetics and sedatives that are commonly used in modern surgery, potentially can cause neuroapoptosis and other neurodegenerative changes in the developing mammalian brain in animal studies, have triggered the warning of using anesthesia in the pediatric population. Earlier retrospective studies in human and experimental animal studies have reported an association between exposure to general anesthesia as an infant and later neurobehavioral problems in childhood [14–16].

Because of the potential health epidemic hazard association with anesthesia for children, multiple studies attempt to explore this complex question. The General Anesthesia compared to Spinal anesthesia (GAS) trial [17] and Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) trial [18] are well-designed clinical prospective observational trials. They showed cautious optimistic results. Both trials suggest that there is no significant neurocognitive deficit for short anesthetic exposure early in life.

However, in the PANDA trial, the high socioeconomic status and advanced education of the household yield a higher IQ than the general population. This confounding factor may alter the threshold of susceptibility or be a source of environmental enhancement which allows the subjects to overcome the insult. Additionally, both trials had mean anesthetic exposure of less than 2 h which likely leads to lessening cognitive insult, and neither study specifically assessed recognition memory, which was previously reported to be impaired after a 2-h exposure early in life [19]. However, the report from the primary outcome from the GAS trial still has not been available.

Another large population based study investigated the cohort of 33,514 Swedish children with one anesthesia and surgery exposure before the age of four and no subsequent hospitalization were compared to 159,619 matched unexposed control children. They also evaluated 3640 children with multiple surgical procedures. The research reported that exposure to anesthesia and surgery before 4 years old has a small association with later academic or cognitive performance at the age of 16 [20]. These large trial results encourage optimism regarding the minimal effect on neurodevelopmental and cognition to short anesthetic exposure in early childhood.

However, a recent small retrospective report investigated children who had short exposure to anesthetics before the fourth birthday coming for non-cardiac surgeries showed interesting findings. They did not find overall a difference in cognitive scores between the exposed and controlled groups. However, one finding that worth mentioning was the decrease in listening comprehension and performance IQ that were associated with lower gray matter density in the occipital cortex and cerebellum. Even though this study cannot identify the causation of this finding, it demonstrated the first structural assessment of human brain after exposure to surgery and anesthesia early in life in otherwise healthy children [21].

The evidence of ongoing animal research continues to suggest that not only the early exposure to anesthetics might cause the impaired neurodevelopment and cognitive functions, but also exposure to anesthetics intrautero or during the delivery time might result in neurobehavioral problems such as anxiety-depression, attention deficit, and psychiatric disorder such as schizophrenia. Exposure to ketamine during the second trimester in rats resulted in offspring that manifested disinhibition and hyperactive behavior at puberty. Later, during adulthood, animals displayed phenotyping of schizophrenia-like behavior, including social withdrawal, spatial memory impairments, hyperagitation, stereotypic behavior, anxiety, depression, and aggressive-like behaviors [22].

In humans, there are conflicting reports that exposure to anesthesia early in childhood increases the risk of being subsequently diagnosed with developmental and behavioral disorders [23–25]. A study by DiMaggio et al. showed that children who were enrolled in a state Medicaid program and underwent surgery when they were younger than 3 years old had 60% greater chance of behavioral problems than a similar group of siblings who did not have surgery [23]. On the contrary, another group of researcher from Puerto Rico studied children diagnosed with an autistic spectrum disorder and anesthetic exposure. They reported that children with exposure to anesthesia in the uterus and during the first 2 years of life are not more likely to develop neither autistic spectrum disorder nor a severe form of the spectrum [24].

There is clear evidence from animal studies that exposure to anesthesia in the clinical range dose can cause neuroapoptosis and can affect the neurodevelopment. So far clinically we understand that a single short exposure to anesthesia in healthy children might not cause significant impairment of intellect. However, multiple exposures to anesthesia and vulnerable children who require multiple surgeries during their childhood are still at risk. Research on neurotoxicity to developing brain needs to continue, including the investigation of susceptibility factors and searching for biomolecular molecular targets. Such research is needed for developing strategies to protect those vulnerable children who are exposed to multiple anesthetics. Another question that researchers might seek to answer is the anesthetic effect on children with a diagnosis of autistic spectrum disorder. Do these children response to anesthesia in a dose-related manner or are they more at risk for the neuronal injury as compared to the otherwise healthy pediatric population?

## 32.4 Anesthesia and Neurotoxicity Postoperative Cognitive Decline in Elderly Patients

The precise pathogenesis of postoperative cognitive decline (POCD) is not known and may involve perioperative as well as patient-related factors. The role of anesthetics in the POCD's genesis in humans is debated. A huge number of preclinical studies have been conducted on the topic, and many mechanisms have been proposed to explain the potential neurodegenerative effects of anesthesia [26].

However, similarly, with research in neurocognitive dysfunction in children, the evidence of an anesthesia-induced cognitive decline in elderly is inconclusive. Early studies reported the incidence of POCD in cardiac surgery. Later POCD studies also showed increased POCD incidence with noncardiac procedures at 1 week but a decreased incidence at 3 months after the surgery [27, 28].

Evered et al. found that the early PODC at 7 days postoperatively was higher in coronary artery bypass grafting (CABG) surgery but the association dissipated at 3 months when compared to patients who underwent other surgeries [29]. The same author reported that in the large Australian population, there was an increase in the prevalence of dementia 7.5 years after CABG surgery as compared to general population. Dementia was associated with preexisting cognitive impairment and peripheral vascular disease [30]. On the contrary, another epidemiology study reported the prospective investigation in elderly age over 65 years old with no preexisting

diagnosis of cognitive dysfunction showed no association between recent anesthesia exposure and dementia or Alzheimer disease [31]. Another group of investigators examined the incidence of postoperative delirium and POCD in patients aged 60 years or older undergoing non-cardiac surgery. A secondary analysis of the randomized controlled Surgery Depth of Anesthesia and Cognitive outcome (SuDoCo) trial did not see convincing evidence of postoperative delirium associated with POCD at 3 months [32].

Researchers attempt to identify factors that will predict which individual is susceptible to postoperative delirium and possible to develop a POCD. A neurophysiological EEG measurement study suggests that failure to undergo anteriorization or to show significant frontal alpha power (lower alpha power) while under general anesthesia is an intraoperative marker of poorer preoperative cognitive status [33]. Surprisingly an association between cerebral blood flow and autoregulation using the autoregulation index and tissue oxygenation index calculation with POCD was not found [34]. Altered resting-state functional connectivity (RSFC) in regions of the posterior cingulate cortex and right superior frontal gyrus, that is an anatomical and functional location of the brain's default mode network (DMN), is positively correlated with global cognitive change 6 weeks after cardiac surgery. This finding suggests that DMN activity and connectivity possibly can be used as diagnostic markers of POCD [35].

So far there are limited prospective studies on neuroimaging or functional neuroimaging investigating the gray matter of patients with and without POCD. It will be interesting to see if there are structural changes, especially frontal/occipital area, in patients and the correlation with the diagnosis of POCD or dementia after surgery.

### 32.4.1 Intraoperative Monitoring

Intraoperative EEG is suggested to be used as an adjunct monitor for elderly patients by some investigators. However, the median bispectral index (BIS) value for patients who developed POCD was similar to patients who did not. Unexpectedly, patients who developed POCD spent less time with bispectral index <45 and time in burst suppression [36]. On the contrary, another study showed lighter BIS-guided plane of anesthesia is associated with less incidence of POCD in elderly patients [37]. Another separate study showed BIS-guided anesthesia reduced anesthetic exposure and decreased the risk of POCD at 3 months after surgery. They estimated that for every 1000 elderly patients undergoing major surgery, anesthetic delivery titrated to a range of BIS between 40 and 60 would prevent 23 patients from POCD and 83 patients from delirium [38]. There is a report that perioperative cerebral oxygen saturation (ScO2) of patients with POCD is lower than patients without POCD. Absolute value and percentage decrease of ScO2 is less in patients with POCD. Thus, it is suggested that ScO2 can be used as a reliable intraoperative predictor of POCD [39].

### 32.4.2 Biomarkers

There are several reports of serum and CSF biomarkers that have been associated with POCD and Alzheimer disease. The majority of the markers are released during the exaggerated inflammation state including specific markers for neuroinflammation. Plasma IL-1 beta, TNF-alpha, Il-10, and IL-6, serum S100A, S100B are commonly reported to be elevated in patients with POCD [40, 41]. A low CSF A(1–420) could be used as a predictor of POCD at 3 months [42]. The identification of a biomarker with high sensitivity/specificity that can be used as the screening tool for a susceptible individual is essential to attenuate the incidence of POCD after surgery in elderly.

### 32.4.3 Perioperative Medications and POCD

Choice of anesthesia agents also is the subject of investigation in this topic. Propofol is proposed to have a more favorable outcome

regarding biological markers in POCD as compared to inhalation agents (sevoflurane is worse than isoflurane) [43]. Intraoperative administration of steroids has been associated with lessen biomarkers and POCD [44–46]. Single dose administration of 8 mg dexamethasone was found to reduce the incidence of POCD in elderly patients undergoing surgery, especially when associated with BIS 46–55 [47]. Dexmedetomidine is associated with improved cognitive function in aged animal and elderly patients [48, 49].

Research in this area is ongoing. The association of anesthetic exposure to POCD and a developing of Alzheimer–dementia disorder is unclear. Are the perioperative events such as neuroinflammation associated with the cardiac bypass a main culprit for elderly to develop POCD? Is there a role of peripheral inflammation? Identification of the screening tool by biomarkers or the use of neuroimaging may help to identify an individual at risk. Do postoperative management and behavioral therapy help? Because the world population is aging, research in this area is essential to address one of the population health concerns globally.

## 32.5 A Recent Update in Stroke Research

Mechanical thrombectomy has seen an explosive growth in recent years. Two randomized multicenter trials demonstrated that in patients with an acute ischemic stroke (AIS) caused by a proximal intracranial occlusion of the anterior circulation, an intraarterial treatment administered within 6 h and up to 8 h after stroke onset was effective and provided benefit to eligible patients [50, 51]. However, much debate was the issue of choice of anesthesia administered during the procedure specifically the superiority of conscious sedation over general anesthesia. Several retrospective observational studies report the benefit of conscious sedation over general anesthesia. Thus, collectively these studies provide level II evidence [52–56]. However, these studies had some limitations of confounding factors and bias.

Since then, three single-center prospective randomized clinical trials have investigated the use of general anesthesia versus conscious sedation during the intraarterial procedure for AIS. The AnStroke Trial (Anesthesia During Stroke) reported no difference of anesthesia choice on neurological outcome at 3 months after the procedure [57, 58]. General anesthesia is associated with more intraprocedural hypotension [59]. The Sedation versus Intubation for Endovascular Stroke Treatment (SIESTA) trial did not find a greater improvement in neurological status at 24 h comparing conscious sedation versus general anesthesia. The time from groin puncture to final angiographic result was shorter with patients under general anesthesia than those with patients under conscious sedation [60, 61]. The General or Local Anesthesia in Intra Arterial Therapy (GOLIATH) trial examined the infarct growth and clinical outcomes. The investigators reported successful reperfusion was significantly higher in the general anesthesia than in the conscious sedation groups but did not result in a difference in the volume of infarct growth. There was a shift toward better clinical outcomes in the general anesthesia group [62]. A recent meta-analysis on this topic reported a better outcome with conscious sedation as compared to general anesthesia [63], but the analysis did not include the latest data from GOLIATH trial in their analysis.

So what is missing in this area of research? Obviously, there is accumulation of level two evidence that conscious sedation provides a better neurological outcome for patients undergoing the endovascular procedure for acute ischemic stroke in the anterior circulation. Conversely, all recent level I evidence research which emphasizes on strict blood pressure control during the procedure did not support the notion of better neurological outcome associated with conscious sedation. However, all the prospective randomized control trials are a single center. The result might not be generalized to all populations. We are still in need of a multicenter prospective randomized controlled trial to answer this important question.

### 32.5.1 Animal Study

Preclinical study remains an intense focus on stroke research. Experimental stroke research in animal consistently yields the neuroprotective effects of various agents. The main mechanism was the demonstration of the attenuation of neuroinflammation associated with an ischemic-reperfusion injury via various pathways. However, earlier promising results from a preclinical study have not translated into a therapeutic modality in humans. Why can't we develop a magic bullet, since we have abundant choices from all positive results in animal studies and therefore have a better outcome in stroke patients? Recent meta-analysis in experimental stroke research using the filament model in rodent suggests that exposure to anesthesia before ischemia produces a baseline protective effect, thus potentially produces a bias toward protection. Approximately only 70% of studies were adequately powered, few studies were performed in female animals and the neuroprotective effect disappeared in animals with co-morbidity. An error in sample size calculation in preclinical studies might derive from referencing earlier research that showed benefit when using a small sample size [64]. Future preclinical research should select an adequate sample size to clarify the real clinical benefits. The study should include both male and female animals to reflect the same composition in human. The animal co-morbidity should be one of the considerations before an interpretation of a true or lack of a neuroprotective effect. The animal with preexisting co-morbidity model can be used to mimic the human conditions.

In summary, research in neuroscience has progressed substantially over the past several years. Recent advances in technology enhance our understanding of the mechanism of neuronal functions, protection, and injury. Many more advances are expected in the near future. Transition from animal research to clinical application of new knowledge will improve our ability to treat patients.

**Key Points**

- The anesthetic-induced unconsciousness mechanism was proposed to work via two opposite pathways: bottom-up and top-down mechanisms. The thalamus or the switch is proposed as a center in both sleep- and anesthetic-induced unconsciousness in a bottom-up pathway. The primary sensory cortex and higher-order association areas (frontoparietal cortex) connectivity play important roles in the proposed top-down mechanism of consciousness.
- There is an ongoing debate in neurocognition and neurobehavioral effects of anesthesia in children. However, the current evidence in humans shows optimism suggesting no association between early short exposure to anesthesia and neurotoxicity in children.
- Currently, there is no conclusive evidence of anesthesia and surgery causing neurocognitive decline and the development of dementia or Alzheimer disease in elderly patients.
- Anesthesia choice between conscious sedation versus general anesthesia during intraarterial treatment for stroke patients shows conflicting results between large retrospective data and recent prospective randomized trials. Accumulative report from several retrospective studies suggests the better clinical outcome of stroke patients when undergoing conscious sedation. However, results from recent prospective randomized control trials do not support the previous notion.

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# 33 Evidence-Based Practice of Neuroanesthesia and Neurointensive Care

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## 33.1 Introduction

Advent of anesthesia and evidence-based medicine (EBM) are two of the 15 landmark milestones in medical history [1]. The first public demonstration of anesthesia on 16th October 1846 and its subsequent publication a month later in the Boston Medical and Surgical Journal (the current New England Journal of Medicine) [2] suggests the early integration of EBM into anesthesia practice. With publication of high-quality studies over the last few decades from across the world, practice of neuroanesthesia and neurocritical care is moving from experience and eminence-based practice to evidence-based clinical practice (EBCP). This chapter provides an overview about EBM and discusses relevant aspects of the current best evidence in certain important clinical domains of neuroanesthesia and neurocritical care. More details and explanations regarding these EBCP guidelines are available in the cited references.

## 33.2 Evidence-Based Medicine and Evidence-Based Clinical Practice

EBM is a systematic approach to clinical problem-solving that allows integration of the best available research evidence with clinical expertise and patient values [3]. EBCP overcomes deficiencies in patient care that is largely based on expert opinions or inappropriate use of available evidence and provides in its place a structured framework for assessment and application of the current available evidence to inform patient care decisions [4].

### 33.2.1 Step-Wise Approach to Evidence-Based Clinical Practice

A scientific and structured approach to a clinical problem is a pre-requisite for EBCP. The 5A technique describes the process of using medical literature to guide patient care and involves the following steps: asking a structured question, acquiring relevant evidence, appraising the evidence (distinguishing the more from the less trustworthy), evaluating the applicability of findings to a given patient, and acting on the evidence by taking into consideration clinician expertise and patient preference [5]. The 6th "A" involves "*A*ssessing" the patient performance at conclusion of this process [4].

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### 33.2.2 Finding the Current Best Evidence

Finding current best evidence is critical to inform effective implementation of evidence for patient care at bedside. With >2000 articles being indexed with PubMed daily [6], identifying current best evidence quickly becomes extremely difficult. For example, a PubMed search on "cerebral vasospasm" provides more than 7000 citations (including guidelines, reviews, randomized trials, cohort studies, experimental studies, and case reports) making selection of relevant evidence for applying into healthcare practice, challenging. Pre-appraised evidence-based resources provide quick and efficient way of finding answers for clinically important questions and facilitate optimal implementation into patient care. In this regard, high-quality recommendations consisting of good evidence summaries using grading of recommendation, assessment, development, and evaluation (GRADE) become important resources for direct clinical application. GRADE framework provides transparent method to evaluate quality of evidence for various outcomes in systematic reviews [7].

In the hierarchy of EBM resources for finding answers to research or clinical questions, systems and guidelines form the top of the pyramid, pre-appraised research (synopses and systematic reviews) is placed at the mid-level, and non-pre-appraised research (case reports and cohort or controlled studies) occupy the bottom of the pyramid. The 5s model provides information about the hierarchy of levels of evidence for identifying, informing, and implementing clinical care decisions [8].

### 33.2.3 Application of EBM in Neuroanesthesia and Neurocritical Care Practice

With increasing publication of high-quality studies in neuroanesthesia and neurocritical care, pre-appraised evidence-based tools such as practice guidelines are now available for most of the common clinical conditions. Guidelines makes it easier for clinicians to directly implement care decisions for their patients without having to go through the laborious exercise of searching for the evidence and appraising the quality of evidence before using them for patient care. The pre-appraised guidelines inform various aspects of patient care for a particular clinical condition. Where evidence is poor or absent, guidelines provide practice framework for implementing clinical care decisions. This chapter informs certain important recommendations in the management of neurological conditions such as traumatic brain injury (TBI), stroke, aneurysmal subarachnoid hemorrhage (aSAH) and provides overview of management principles based on current evidence where guidelines are lacking.

## 33.3 Traumatic Brain Injury

TBI encompasses a broad range of pathologic injuries to the brain of varying clinical severity that result from head trauma. The management of patients with TBI is largely based on the guidelines provided by the Brain Trauma Foundation (BTF) [9], and the key practice recommendations are listed in Table 33.1. A three-level system is used to rate individual studies during synthesis of evidence and accordingly, well-designed randomized controlled trials (RCTs) and meta-analyses of RCTs are rated as level I evidence, poor quality RCTs and prospective cohort studies are designated as level II evidence, and case-control studies, case reports, or expert opinion are classified as level III evidence.

## 33.4 Acute Ischemic Stroke (AIS)

Stroke is one of the commonest causes of disability and death worldwide. Early diagnosis and prompt neurological and systemic management have shown to improve outcomes after AIS. The

**Table 33.1** Management of patients with acute traumatic brain injury: current recommendations for treatment, monitoring, and thresholds based on BTF guidelines

| Topic | Level of evidence | Recommendation |
|---|---|---|
| Decompressive craniectomy (DC) | Level IIA | a. Bifrontal DC is not recommended to improve outcomes (as measured by the GOS-E score at 6 months after severe TBI) in patients with diffuse injury and with ICP values >20 mmHg for more than 15 min within a 1-h period that are refractory to first-tier therapies. However, this procedure reduces ICP and minimizes days in the ICU<br>b. A large fronto-temporo-parietal DC is recommended for improving survival and neurological outcomes<br>c. RESCUEicp trial showed that DC in patients with TBI and raised ICP was associated with lower mortality than medical management. However, more survivors in surgical group were functionally dependent (finding after BTF guidelines) |
| Prophylactic hypothermia | Level IIB | Early (<2.5 h), short-duration (<48 h) prophylactic hypothermia is not recommended for diffuse injury |
| Hyperosmolar therapy | Level I, II, III | Though hyperosmolar therapy lowers ICP, there is inadequate evidence with regard to patient outcomes to support a particular recommendation, or a specific agent, for severe TBI |
| Cerebrospinal fluid (CSF) removal | Level III | a. Continuous rather than intermittent CSF drainage may be considered to reduce ICP<br>b. CSF removal to reduce ICP may be considered when GCS is <6 during the 1st 12 h after TBI |
| Ventilation strategies | Level IIB | Long-term prophylactic hyperventilation to $PaCO_2$ of ≤25 mmHg is not recommended |
| Anesthetics, analgesics, and sedatives | Level IIB | a. Prophylactic barbiturates to achieve burst suppression for intracranial hypertension is not recommended<br>b. High-dose barbiturate is recommended for controlling raised ICP refractory to maximal medical and surgical management subject to hemodynamic stability<br>c. Propofol is recommended for controlling raised ICP but not for improving outcomes. High-dose propofol can result in significant morbidity |
| Steroids | Level I | Steroids are not recommended for improving outcome or reducing ICP |
| Nutrition | Level IIA<br>Level IIB | Feeding patients to achieve basal caloric requirement by day five to day seven after TBI is recommended to decrease mortality<br>Transgastric jejunal feeding is recommended to minimize occurrence of ventilator-associated pneumonia |
| Infection prophylaxis | Level IIA<br>Level III | a. Early tracheostomy is recommended to reduce ventilator days but this does not reduce mortality or nosocomial pneumonia<br>b. Povidone-iodine oral care is not recommended to reduce ventilator-associated pneumonia<br>Antimicrobial-impregnated catheter may be considered to prevent external ventricular drainage-related infection |
| Deep vein thrombosis (DVT) prophylaxis | Level III | a. LMWH or unfractionated heparin may be used in combination with mechanical prophylaxis. However, risk for expansion of intracranial hemorrhage exists<br>b. Current evidence does not support recommendations for choice of agent, dose, or timing of pharmacologic prophylaxis |

(continued)

**Table 33.1** (continued)

| Topic | Level of evidence | Recommendation |
|---|---|---|
| Seizure prophylaxis | Level IIA | a. Prophylactic phenytoin or valproate is not recommended to prevent late-onset PTS<br>b. Phenytoin is recommended to decrease early PTS (<7 days)<br>c. Evidence is insufficient to recommend levetiracetam over phenytoin |
| Intracranial pressure monitoring | Level IIB | Management of severe TBI patients guided by ICP monitoring is recommended to minimize in-hospital and 2-week post-TBI mortality |
| Cerebral perfusion pressure monitoring | Level IIB | Management of severe TBI using CPP monitoring is recommended to reduce 2-week mortality |
| Advanced cerebral monitoring | Level III | $AVDO_2$ monitoring from jugular bulb may be considered to decrease mortality and improve outcomes at 3 and 6 months after TBI |
| Blood pressure thresholds | Level III | Maintaining SBP ≥100 mmHg, for patients aged 50–69 years old or ≥110 mmHg for patients aged 15–49 years or aged >70 years may be considered to reduce mortality and improve outcome |
| Intracranial pressure threshold | Level IIB | ICP >22 mmHg should be treated as this is associated with increased mortality |
| Cerebral perfusion pressure threshold | Level IIB<br>Level III | a. The CPP value between 60 and 70 mmHg is recommended to improve outcomes. The CPP threshold within this range depends on patient's autoregulatory status<br>b. Aggressive maintenance of CPP >70 mmHg with fluids and vasopressors should be avoided |
| Advanced cerebral monitoring thresholds | Level III | Jugular venous saturation of <50% may be avoided to reduce mortality and improve outcomes |

*TBI* traumatic brain injury, *ICP* intracranial pressure, *ICU* intensive care unit, *BTF* brain trauma foundation, $PaCO_2$ arterial partial pressure of carbon dioxide, *CBF* cerebral blood flow, $SjvO_2$ jugular venous oxygen saturation, $PbtO_2$ partial pressure of brain tissue oxygen, *EEG* electroencephalogram, *LMWH* low molecular weight heparin, *PTS* post-traumatic seizures, $AVDO_2$ arterio-venous oxygen difference, *CPP* cerebral perfusion pressure, *SBP* systolic blood pressure, *CT* computed tomography

recent guidelines from the American Heart Association/American Stroke Association (AHA/ASA) provide comprehensive set of recommendations for clinicians caring for adult patients with AIS. The strength of recommendation is classified as I (strong; benefit >>> risk), IIa (moderate; benefit >> risk), IIb (weak; benefit ≥ risk), III-No benefit (moderate; benefit = risk), and III-Harm (strong; risk > benefit) based on the level of evidence (A = well-designed RCTs and meta-analyses of RCTs; B = randomized and non-randomized studies and meta-analyses of such studies; C = observational or registry studies with limited data or consensus of expert opinion). The key recommendations particularly relevant to neuroanesthesiologists and neurointensivists are summarized in Table 33.2, and the readers are advised to go through the detailed guidelines here [10].

## 33.5 Intracerebral Hemorrhage (ICH)

ICH is the second most common cause for stroke and is associated with high mortality and morbidity. The initial management goals include preventing expansion of hematoma, and detection and control of raised intracranial pressure (ICP) apart from treatment of associated complications.

### 33.5.1 General Management Issues

As per the AHA/ASA guidelines, patients with ICH should be monitored and managed in an intensive care unit [11] with the availability of neurosurgical care within the hospital. Evidence suggests that vigilant monitoring and management in a stroke unit results in improved outcomes after ICH [12].

**Table 33.2** Management of patients with acute ischemic stroke: current recommendations based on the AHA/ASA guidelines

| Topic | Class of recommendation; level of evidence (LOE) | Recommendation |
|---|---|---|
| Emergency triage and initial evaluation | Class I; B | Clinical assessment and neurological evaluation by an acute stroke team. Administer intravenous alteplase ≤60 min of arrival in the ED in ≥50% of patients<br>Use stroke rating scale, preferably the NIHSS<br>Mandatorily assess blood glucose. Electrocardiogram recommended but should not delay alteplase |
| | Class IIb; B | Usefulness of chest radiographs in the absence of evidence of acute cardio-pulmonary disease is not known<br>Telestroke consultation guided IV alteplase may be safe and beneficial |
| Early diagnosis: cerebro-vascular imaging | Class I; B | Brain imaging <20 min of ED arrival in ≥50% of patients who may be candidates for alteplase and/or mechanical thrombectomy |
| | Class I; A | Non-contrast CT to exclude ICH<br>Noninvasive vascular study during initial imaging evaluation if intra-arterial fibrinolysis or thrombectomy is contemplated<br>CT perfusion, DW-MRI, or MRI perfusion for anterior circulation AIS <6–24 h of last known normal |
| | Class III; B | CT hyperdense MCA sign, and hypoattenuation or ischemic changes should not lead to withholding of IV alteplase<br>Routine MRI before alteplase is not recommended. Multimodal imaging should not delay alteplase use<br>CT and MRI perfusion, and diffusion imaging for mechanical thrombectomy <6 h is not recommended |
| | Class II; B | CT angiography in patients without history of renal impairment if large vessel occlusion is suspected |
| | Class IIa; C | For mechanical thrombectomy, imaging of both intracranial and extracranial vessels |
| | Class I; C | Brain imaging interpretation <45 min of patient arrival to the ED |
| General care and treatment of complications | Class I; B | Cardiac monitoring for at least first 24 h for potentially serious cardiac arrhythmias<br>Systolic BP should be <185 mmHg and diastolic BP <110 mmHg before fibrinolytic therapy is initiated and maintained <180/105 mmHg for ≥ first 24 h after intravenous alteplase |
| | Class I; C | Airway and ventilatory support to patients who have bulbar dysfunction<br>Oxygen to maintain oxygen saturation >94%<br>Sources of hyperthermia be identified and treated<br>In patients who do not receive fibrinolysis, BP should be lowered by 15% during first 24 h after stroke<br>Medications should be withheld unless systolic BP is >220 mmHg or diastolic BP is >120 mmHg<br>Hypovolemia corrected with normal saline, and arrhythmias reducing cardiac output be corrected<br>Blood glucose <60 mg/dL should be treated |
| | Class IIa; B | Restarting antihypertensive medications after first 24 h for preexisting hypertension and are stable neurologically |
| | Class IIa; C | No data to recommend BP lowering drugs<br>Achieve blood glucose levels of 140–180 mg/dL and closely monitor to prevent hypoglycemia |
| | Class IIb; C | Data to guide recommendations for treatment of hypertension in patients not undergoing reperfusion strategies are inconclusive or conflicting |
| | Class III; C | Supplemental oxygen not recommended in non-hypoxic patients |

(continued)

**Table 33.2** (continued)

| Topic | Class of recommendation; level of evidence (LOE) | Recommendation |
|---|---|---|
| Intravenous fibrinolysis | Class I; A | Intravenous alteplase (0.9 mg/kg, maximum 90 mg with 10% as bolus over 1 min) patients who may be treated <3 h of AIS<br>Door-to-needle time <60 min from arrival |
| | Class I; B | Exclusion for alteplase administration in the time period of 3–4.5 h after stroke onset—age >80 y, oral anticoagulants, baseline NIHSS score >25, imaging suggestive of ischemic injury involving >1/3 of MCA territory and history of both stroke and diabetes mellitus<br>Promptly manage side effects of iv alteplase (bleeding and angioedema) |
| | Class IIa; B | In patients with 1–10 microbleeds on brain MRI, IV alteplase is reasonable<br>IV alteplase may be beneficial for AIS with known sickle cell disease |
| | Class IIb; B | In patients with >10 microbleeds on MRI, alteplase may increase risk of ICH |
| | Class III; B | Abciximab and alteplase should not be administered concurrently |
| | Class IIa; C | Seizure is not a contraindication for iv alteplase |
| | Class IIb; C | Fibrinolysis may be considered in patients with mild stroke deficits, rapidly improving stroke symptoms, major surgery in preceding 3 months and recent MI, weighing the risks and benefits |
| | Class III; A | Streptokinase for stroke treatment not recommended |
| | Class IIb; B | Tenecteplase 0.4 mg/kg bolus is an alternative to alteplase in patients with minor neurological impairment without major occlusion |
| | Class III; B | Sonothrombolysis is not recommended with IV thrombolysis |
| Endovascular interventions | Class I; A | Patients eligible must be administered iv alteplase despite considering intra-arterial treatments. Mechanical thrombectomy with stent retriever be considered if following criteria are met: (1) pre-stroke mRS score of 0 or 1; (2) occlusion of ICA or MCA segment; (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated <6 h of symptom onset |
| | Class I; B | Intra-arterial fibrinolysis benefits patients with major AIS of <6 h duration from MCA occlusion who are ineligible for iv alteplase |
| | Class IIb; B | Though stent retrievers remain the first choice other mechanical thrombectomy devices may be considered |
| | Class IIb; C | Rescue intra-arterial fibrinolysis or mechanical thrombectomy are reasonable for large-artery occlusion not responding to intravenous fibrinolysis |
| | Class IIa, B | For minor stroke, dual antiplatelet therapy started <24 h and continued for 21 days can benefit in early secondary stroke prevention for 90 days |
| | Class III; B | Ticagrelor is not recommended for acute treatment of minor stroke |
| Mechanical flow augmentation | Class I; C | Vasopressors may be considered in patients with systemic hypotension resulting in neurological sequelae, close monitoring is recommended when drug-induced hypertension is used |
| | Class IIb; B | Role of high-dose albumin is not clear |
| | Class III; A | Hemodilution by volume expansion is not recommended |
| | Class III; A | Pentoxifylline is not recommended |

**Table 33.2** (continued)

| Topic | Class of recommendation; level of evidence (LOE) | Recommendation |
|---|---|---|
| Neuroprotective agents | Class IIa; B | Continue statin therapy if already taking |
| | Class IIb; B | Induced hypothermia for AIS is not well established |
| | Class III; A | Neuroprotective pharmacological agents are not efficacious in improving outcomes after ischemic stroke |
| Surgical interventions | Class IIb; B | Urgent CEA for AIS is not established |
| General stroke care | Class I; A | Patients with pneumonia or UTIs should receive appropriate antibiotics |
| | Class I; B | Enteral feeding should be initiated <7 days of admission<br>Patients who cannot take feed orally should receive nasogastric, nasoduodenal, or PEG tube feedings |
| | Class IIa; A | Aspirin is reasonable when anticoagulants are contraindicated for DVT prophylaxis |
| | Class IIa; B | Consider nutritional supplements if malnourished |
| | Class IIa; C | Assessment of swallowing before patient begins oral intake is recommended<br>NG tube feeding preferred for 2–3 weeks after stroke |
| | Class IIb; B | Oral hygiene reduces risk of pneumonia |
| | Class III; B | Compression stockings and routine prophylactic antibiotics are not beneficial |
| | Class III; C | Routine bladder catheters not recommended |
| | Class IIa; C | Patients and families with stroke should be referred to palliative care if applicable |
| Treatment of acute neurological complications | Class I; B | Decompressive surgery of space-occupying cerebellar infarction and for malignant edema of cerebral hemisphere is effective and lifesaving |
| | Class I; C | Ventricular drain is useful for acute hydrocephalus |
| | Class IIa; C | Brief hyperventilation ($PCO_2$ 30–34 mmHg) may be considered during acute neurological deterioration from brain swelling |
| | Class III; A | Corticosteroids are not recommended for cerebral edema and raised ICP |
| | Class III; C | Prophylactic anticonvulsants are not recommended |

*ED* emergency department, *NIHSS* National Institute of Health Stroke Scale, *CT* computed tomography, *ICH* intracranial hemorrhage, *DW-MRI* diffusion weighted magnetic resonance imaging, *AIS* acute ischemic stroke, *MCA* middle cerebral artery, *BP* blood pressure, *mRS* modified Rankin score, *ASPECTS* Alberta Stroke Program Early CT Score, *CEA* carotid endarterectomy, *UTIs* urinary tract infections, *PEG* percutaneous endoscopic gastrostomy, *DVT* deep vein thrombosis, *NG* nasogastric, $PaCO_2$ arterial partial pressure of carbon dioxide

### 33.5.2 Specific Recommended Interventions [11]

1. *Fever management*: Sources of fever should be treated, and antipyretic medications should be used to achieve normothermia in febrile patients with stroke.
2. *Glucose management*: Hyperglycemia during the initial 24 h after stroke contributes to adverse outcomes; insulin treatment should target serum glucose level between 140 and 180 mg/dL. Hypoglycemia should be avoided.
3. *Venous thromboembolism (VTE) management*: Intermittent pneumatic compression is the mainstay for prevention of VTE in patients with acute ICH.
4. *Fluid management*: Normal saline should be used for maintenance and replacement; hypotonic fluids and hypervolemia are avoided as they exacerbate cerebral edema and ICP [12].
5. *Aspiration pneumonia*: Dysphagia is common and is a major risk factor for developing aspiration pneumonia. Prevention of

aspiration includes initial nil-per-oral status until swallowing function is evaluated.

6. *Reversal of anticoagulation*: The summary of recommendations for reversal of antithrombotic agents in patients with ICH is detailed in Table 33.3 and details are available here [13].
7. *Blood pressure (BP)*: For patients with systolic BP >200 mmHg or mean BP >150 mmHg, aggressive reduction of BP with intravenous infusion of medication accompanied by frequent (every 5 min) BP monitoring is considered. For patients with systolic BP >180 mmHg or mean BP >130 mmHg and evidence or suspicion of elevated ICP, monitoring ICP and reducing BP using intravenous medication to keep cerebral perfusion pressure (CPP) between 60 to 80 mmHg should be considered. For patients with systolic BP >180 mmHg or mean BP >130 mmHg and no evidence or suspicion of elevated ICP, reduction of BP (target mean BP of 110 mmHg or BP of 160/90 mmHg) using intravenous medication is considered, and patient is clinically re-examined every 15 min. In patients presenting with systolic BP of 150–200 mmHg, lowering to 140 mmHg is probably safe.
8. *Seizure prophylaxis and treatment*: Seizures are more common in lobar as compared to deep hemorrhage [14]. If seizures occur, use intravenous fosphenytoin or phenytoin. The 2010 guidelines recommend against prophylactic use of antiepileptic drugs.
9. *Intracranial pressure*: Increased ICP can result from hematoma or edema, and may contribute to brain injury and neurologic deterioration. Current guidelines recommend head of the bed elevation by 30° once hypovolemia is excluded, along with analgesia and sedation, particularly in intubated patients. Mild hypernatremia should be tolerated. Glucocorticoids should not be used to lower the ICP. Invasive monitoring and treatment of ICP should be considered for patients with GCS <8. Intravenous mannitol is the treatment of choice to lower increased ICP. The goal of therapy is to achieve plasma hyperosmolarity (300–310 mosmol/kg) while maintaining adequate plasma volume. Barbiturate anesthesia can be used if mannitol fails to lower ICP to an acceptable range. Hyperventilation ($PaCO_2$ 25–30 mmHg) causes rapid lowering of ICP. CSF drainage by intraventricular catheter is effective for lowering the ICP.
10. *Surgery*

*Cerebellar hemorrhage*: Surgical removal of hematoma with cerebellar decompression should be performed for cerebellar hemorrhages >3 cm in diameter who are deteriorating, or have brainstem compression and/or hydrocephalus [12].

*Supratentorial hemorrhage*: Craniotomy only for those with lobar clots >30 mL within

**Table 33.3** Reversal of antithrombotic agents in intracranial hemorrhage

| Antithrombotic agent | Reversal drug |
|---|---|
| Vitamin K antagonist | For INR >1.4, intravenous vitamin K 10 mg + 3–4 PCC or FFP 10–15 ml/kg if PCC unavailable |
| Factor Xa inhibitor | Activated charcoal (50 g) within 2 h, PCC 50 U/kg |
| Direct thrombin inhibitor | For dabigatran-activated charcoal (50 g) within 2 h and idarucizumab 5 g. Hemodialysis or repeat idarucizumab if persistent bleeding |
| Unfractionated heparin | Protamine 1 mg for every 100 U of heparin given in last 2–3 h |
| LMWH | Enoxaparin dosed >8 h—protamine 1 mg IV for every 1 mg enoxaparin, for 8–12 h—0.5 mg for every 1 mg of enoxaparin Dalteparin, nadroparin, and tinzaparin dosed within 3–5 half lives of LMWH protamine 1 mg/100 anti Xa U of LMWH or recombinant factor VIIa (rFVIIa) 90 mcg/kg |
| Thrombolytic agents | Cryoprecipitate 10 U or tranexamic acid 10–15 mg/kg over 20 min or epsilon aminocaproic acid 4–5 g |
| Antiplatelet agent | DDAVP (desmopressin) 0.4 mcg/kg IV or platelet transfusion (one apheresis unit) if neurosurgical intervention is planned |

*PCC* prothrombin complex concentrate, *FFP* fresh frozen plasma, *INR* international normalized ratio, *rFVIIa* recombinant factor VIIa, *LMWH* low molecular weight heparin

1 cm of the surface. No other patient group is recommended for surgery. The routine evacuation of supratentorial ICH in the first 96 h is not recommended.

*Intraventricular hemorrhage*: Patients with intraventricular extension of ICH are at risk for hydrocephalus, especially if third and fourth ventricles are involved. Such patients should be closely monitored.

11. *Hemostatic therapy*: Hemostatic therapy stops ongoing hemorrhage and prevents hemorrhage enlargement; however, trials demonstrate mixed results. Recombinant factor VIIa for acute ICH that is not associated with warfarin should not be used.
12. *Resumption of antiplatelet therapy*: Aspirin therapy can be resumed after acute phase of ICH, provided BP is well controlled and indication for antiplatelet treatment is strong (potential benefit outweighs the increased risk of recurrent ICH).
13. *Resumption of anticoagulation*: For patients who require anticoagulation soon after ICH, the AHA/ASA guidelines conclude that intravenous heparin may be safer than oral anticoagulation. Oral anticoagulants may be resumed 3–4 weeks after the onset of ICH with rigorous monitoring and maintenance of international normalized ratio (INR) in lower end of therapeutic range.
14. *Treatment of hypertension*: This is the most important step to reduce the risk of ICH, and its recurrence. Cessation of smoking, alcohol, and cocaine is also recommended.

## 33.6 Aneurysmal Subarachnoid Hemorrhage

The classic presentation of aSAH is as follows: Abrupt onset of a sudden, severe headache which might be associated with neck pain, nausea and vomiting, transient loss consciousness, or coma. Examination should include Glasgow Coma Scale (GCS) score, pupil evaluation, fundoscopy for retinal hemorrhages, and neck examination for meningismus. Clinical severity of aSAH can be determined using World Federation of Neurological Surgeons or Hunt and Hess Scale. Once aSAH is diagnosed, bed rest is advised (Class 2B). Pre-operative laboratory evaluation includes complete blood count, platelets, coagulation parameters, electrolytes, blood urea and serum creatinine, cardiac enzymes, and 12-lead electrocardiogram. Nimodipine 60 mg per oral or via nasogastric tube every 4 h (watch for hypotension) should be started within 4 days of ictus and continued for 21 days. Antiepileptic drug is administered until the aneurysm is secured (Class 2B). However, phenytoin use has been associated with worse cognitive outcomes. When aSAH patients present with coagulopathy, platelets should be administered for platelet count $<50 \times 10^9$/L [15].

### 33.6.1 Anesthetic Management of aSAH

Patients with aSAH may exhibit physiologic derangements that affect anesthetic management, including neurologic dysfunction, cardiac abnormalities, electrolyte disturbances, anemia, and seizures. The goals during anesthesia for surgery or coiling are hemodynamic stability, avoiding hypertension and aneurysm rupture, and maintaining cerebral perfusion. An arterial catheter, placed prior to induction of anesthesia, allows continuous BP monitoring. Precise guidelines for BP management do not exist [16]. In patients with unruptured aneurysm or ruptured aneurysm with normal ICP, systolic BP should be maintained $\leq$140 mmHg with mean BP $\geq$60 mmHg. Short acting, titratable medications such as labetalol or nicardipine are recommended for BP control. However, over-zealous treatment of BP can lead to brain ischemia (especially if hydrocephalus is present). For ruptured aneurysm with suspected or known intracranial hypertension, passive hypertension should not be actively treated. Hypertension in response to noxious stimulation and iatrogenic hypertension should be avoided, and CPP of 50–60 mmHg should be maintained. A temporary clip may be placed on

a feeding vessel to facilitate dissection and permanent clipping. If neuromonitoring (somatosensory evoked potentials) shows ischemic changes during temporary clipping, increasing mean BP by 10–20% may be appropriate. The administration of anesthetic drugs for neuroprotection during temporary clipping is controversial, and practice varies. Induced hypothermia has been shown not to improve outcomes for patients who undergo aneurysm clipping [16]. Adenosine, 0.4–0.6 mg/kg IV, may be administered to induce temporary bradycardia or cardiac arrest to reduce or suspend flow through the aneurysm or in the event of intraoperative aneurysm rupture [17].

Intraoperative aneurysm rupture occurs most commonly during aneurysm dissection and clipping. Goals for management are to rapidly create a bloodless field to facilitate clipping, and to protect the brain. Esmolol 10–20 mg intravenously may be used to induce hypotension targeted to a mean BP of 50–60 mmHg. Propofol 20–60 mg IV followed by >125 mcg/kg/min infusion may be used to maintain reduced cerebral metabolic rate. If electroencephalogram (EEG) monitoring is used, propofol can be titrated to burst suppression. After aneurysm clipping, IV fluids and blood products are administered to achieve euvolemia and hemoglobin ≥8 g/dL. The guidelines provided by Neurocritical Care Society [18], American Heart Association [15], and European Stroke Organization [19] regarding perioperative management of aSAH are summarized here [20].

## 33.7 Stupor and Coma

Stupor and coma reflect impaired or absent responsiveness to external stimulation and present as difficulty in arousal necessitating prompt intervention to preserve life and brain function. Most often, patients present to an emergency department following trauma, cerebrovascular disease, intoxications, infections, and metabolic derangements [21].

### 33.7.1 Management

Basic care should be administered based on the clinical findings and laboratory investigations. Patients with a GCS ≤8 require intubation to protect the airway. Intubation is also necessary if hypoxemia (peripheral oxygen saturation of <90%), vomiting, or poor cough/gag reflex are present. Hypotension (mean BP <70 mmHg) is managed with intravenous fluids or vasopressors or both. Dextrose bolus 25 g (as 50 mL of a 50% solution) should be administered while awaiting blood reports to identify cause of coma. Thiamine 100 mg should be administered in malnourished patients to manage potential Wernicke's encephalopathy. Naloxone (0.4–2.0 mg IV) and flumazenil are appropriate for known or suspected drug toxicity [22]. Gastric lavage and activated charcoal are considered in suspected toxic or drug ingestions. If cerebral herniation is evident on clinical examination or imaging, urgent treatment is recommended. Hyperthermia (>38.5 °C) can aggravate brain damage; antipyretics and/or cooling blankets should be promptly instituted. Empiric therapy is recommended for bacterial meningitis [23] (e.g., ceftriaxone 2 g IV twice daily and vancomycin 2 g/day IV 6 hourly) or viral encephalitis [24] (acyclovir 10 mg/kg IV thrice a day) until these conditions are excluded. Phenytoin or fosphenytoin (15–20 mg/kg) is recommended for seizure management. If non-convulsive seizures are suspected and EEG is unavailable, phenytoin or lorazepam (1–2 mg IV) may be considered [25]. Definitive therapy should be considered after a confirmatory diagnosis. Patients with coma either recover or progress to brain death, persistent vegetative state, or minimally conscious state.

## 33.8 Meningitis and Encephalitis

Patients having hyper-acute (hours) and acute (hours to days) onset of headache with altered mentation should be suspected of having meningitis or encephalitis. Other signs such as

meningismus, fever, rash, focal neurological deficits, or seizure significantly increase the possibility of central nervous system (CNS) infection. Patients with altered mental status should be monitored for needing airway management. Similarly, patients with bacterial meningitis are likely to have lung or bloodstream infections with the same pathogen, hence cardio-respiratory parameters should be monitored closely to diagnose sepsis. Bacterial meningitis and herpes encephalitis should be recognized early (< 1st hour), as prompt treatment can improve the outcome.

If the patient develops systemic inflammatory response syndrome, 20–30 ml/kg of intravenous crystalloids should be administered over 20–30 min and vital signs, mental status, and airway should be reassessed frequently during this treatment. Dexamethasone 10 mg should be administered 15 min before antibiotic therapy particularly in *Streptococcus pneumoniae* meningitis [26]. Selection of antibiotics/antivirals is based on (a) course of CNS infection, (b) age, and (c) other infectious risk factors [27]. Children <3 months are susceptible for group B streptococci, *Escherichia coli*, *Listeria monocytogenes, Streptococcus pneumonia, and Neisseria meningitidis;* ampicillin, gentamycin, and cefotaxime should be used. In children >3 months, causes include *Streptococcus pneumoniae*, *Neisseria meningitides,* and *Haemophilus influenzae*. Vancomycin with either cefotaxime or ceftriaxone is the preferred antibiotic choice in this population. Broader empiric antibiotics should be considered in children with immune deficiency, recent neurosurgery, penetrating head trauma, or anatomic defects. Young patients suspected of bacterial meningitis from *Haemophilus influenza, Neisseria meningitidis,* and *Streptococcus pneumoniae* should receive CNS doses of third-generation cephalosporin and vancomycin. Adults are at risk of *Streptococcus pneumoniae* infection while the elderly and immunosuppressed are at risk for *Streptococcus pneumoniae* and *Listeria monocytogenes* and should be treated with CNS doses of ampicillin, a third-generation cephalosporin and vancomycin. Vancomycin and trimethoprim-sulfamethoxazole are alternatives in patients with penicillin allergy. For suspected CNS infections that evolve over days, Herpes simplex encephalitis should be considered, and treatment begun with thrice a day acyclovir 10 mg/kg. Adequate hydration with intravenous fluids avoids acyclovir-associated renal failure. In immunosuppressed patients with CNS infections that evolve over days, fungal meningitis should be considered and empiric Amphotericin B can be administered. A lumbar puncture (LP) establishes diagnosis and helps in tailoring the therapy.

## 33.9 Convulsive Status Epilepticus

Generalized convulsive status epilepticus is a medical emergency that requires prompt evaluation and treatment [28, 29]. The assessment and treatment in status epilepticus should proceed simultaneously. Initial treatment with a benzodiazepine (Grade 1A) is recommended with hemodynamic and respiratory monitoring to avoid side effects of therapy. When intravenous access is available, lorazepam is preferred (Grade 2C). The loading dose is 0.1 mg/kg infused at ≤2 mg/min, allowing 1 min for assessing the effect before deciding additional doses. Alternatively, 4 mg fixed dose may be administered in adults. In addition to benzodiazepines, a loading dose of a longer-acting anti-seizure drug is recommended to control seizures (Grade 1B). Fosphenytoin (20 mg/kg phenytoin equivalents [PE]) is the preferred anti-seizure drug (Grade 2C). Valproic acid (20–40 mg/kg IV) and levetiracetam (40–60 mg/kg) are alternatives in patients with phenytoin hypersensitivity or history of primary generalized epilepsy. In patients who are actively seizing despite two doses of benzodiazepine, a midazolam or propofol infusion should administered simultaneously with fosphenytoin, valproic acid, or levetiracetam, since the primary role of non-benzodiazepine anti-seizure drug is to prevent recurrence rather than to terminate the seizures.

Most patients begin to recover responsiveness within 10–20 min after generalized convulsions, but there is a broad range. The two most common reasons for prolonged post-ictal recovery are sedation due to medications and continuation of (non-convulsive) seizures. All patients who do not attain consciousness after initial treatment should be monitored by EEG to determine ongoing seizure and adequacy of treatment. Following recovery, a full neurologic examination and head imaging should be performed to look for underlying etiology. A LP is warranted if the clinical presentation is suggestive of CNS infection or if the patient has a history of a malignancy with possible metastasis to the meninges.

The optimal duration of treatment for refractory status epilepticus is not well established. In general, infusions are continued for 24 h of clinical and EEG seizure suppression and then gradually tapered over 12–24 h. The prognosis depends on the underlying etiology, but there is some evidence that status epilepticus is independently associated with mortality and neurologic sequelae.

## 33.10 Acute Non-traumatic Weakness

Weakness is a common, nonspecific complaint arising from both neurologic and non-neurologic diseases. A structured approach involving detailed history, physical examination, and if necessary, imaging studies is needed to arrive at a diagnosis of acute non-traumatic weakness arising from neurologic and neuromuscular processes. The intensivist's first responsibility is to rule out life-threatening or permanently disabling causes of weakness that require urgent treatment. The immediate life threats from acute neuromuscular weakness include inability to protect or maintain the airway, respiratory failure from thoracic and diaphragmatic muscle weakness, and circulatory collapse from autonomic instability. Once life-threatening problems have been addressed or ruled out, the clinician should approach the patient with objective weakness in a systematic manner. The first important step in this approach is to determine whether the weakness is unilateral (asymmetric) or bilateral (symmetric), and to look closely for signs of central neurologic involvement. When assessing acute weakness, it is helpful to begin cephalad and centrally and then progress caudal and peripherally. This approach provides a reliable framework for neuroanatomic localization and accurate diagnosis. If unilateral weakness is identified, signs suggestive of cortical, subcortical (lacunar), or brainstem lesions should be searched. If these are absent, a peripheral process (radiculopathy or peripheral nerve injury) most likely accounts for the patient's symptoms. If bilateral weakness is identified, patient's mental status and signs of upper or lower motor neuron lesions and associated abnormalities should be evaluated. The constellation of examination findings should allow approximate identification of the site of the lesion and determination of the need for imaging studies, specialist consultation, and treatment [30].

## 33.11 Cervical Spine Injury

Spinal injury should be suspected after trauma, especially following motor vehicle collisions, assaults, falls, and sports-related injuries. Immobilization of the spine using backboard, rigid cervical collar, and lateral head supports should begin at the scene, and maintained until instability related spine injury is excluded [31]. Unstable lesions above C3 may cause immediate respiratory paralysis while lower cervical lesions may cause delayed respiratory distress. In the obtunded adult patient, flexion-extension imaging should not be used to assess for a possible isolated ligamentous injury or spinal cord injury without radiographic abnormality of the cervical spine. In cases of less severe trauma, the history, physical examination, and clinical decision rules are used to determine if spinal imaging is necessary. Both the National Emergency X-Radiography Utilization Study (NEXUS) low-risk criteria and the Canadian C-spine rule are well validated and sensitive. Conservative treatment of cervical fractures

**Table 33.4** Electrophysiological monitoring for surgery of spinal column and spinal cord

| Recommendation | Level of evidence |
|---|---|
| MIOM, SSEPs, and MEPs during spinal cord/spinal column surgery are a reliable and valid diagnostic adjunct to assess spinal cord integrity | Level I |
| MEP recordings are superior to SSEP recordings | Level I |
| SSEP recordings during spinal cord/spinal column surgery are reliable and valid diagnostic adjuncts to describe spinal cord integrity | Level II |
| MIOM, including SSEPs and MEP recording, during spinal cord/spinal column surgery does not improve gross total tumor resection or improve neurological outcome, when utilized during intramedullary tumor resection procedures | Level II |

*MIOM* multimodality intraoperative monitoring, *SSEPs* somatosensory evoked potentials, *MEPs* motor evoked potentials

consists of closed reduction under fluoroscopic guidance and halo-vest immobilization. If plain radiographs or computed tomography demonstrate minor spinal fracture patterns and there is no neurologic deficit, then outpatient management may be possible. Unstable fractures should be surgically fixed. The summary of recommendations for electrophysiological monitoring during surgery for spinal column or cord is listed in Table 33.4, and further details are available here [32].

## 33.12 Prophylaxis for Venous Thromboembolism in Neurocritical Care

The risk of VTE and its consequences including death is high in patients cared in the neurointensive care unit necessitating prophylaxis. The increased risk is due to venous stasis from paralysis and increased endothelial activation in this population. The risk of bleeding from prophylaxis in these patients is also high. The Neurocritical Care Society has provided guidelines regarding prophylaxis for VTE in neurocritical care setting [33], and the summary is provided in Table 33.5.

## 33.13 Temperature Management in Neurointensive Care

Targeted temperature management (TTM) is often used to minimize secondary injury and improve outcome in neurocritical care. Though the evidence is strong for neonatal hypoxic-ischemic encephalopathy and out-of-hospital cardiac arrest, its use for patients with TBI and stroke is increasingly evaluated. Key aspects of the guidelines for TTM provided by Neurocritical Care Society [34] are described in Table 33.6.

## 33.14 Conclusions

The application of EBM in neuroanesthesia and neurocritical care practice enhances possibility of optimal patient diagnosis and management and is likely to improve patient outcomes. Neuroanesthesiologists and neurointensivists should acquire knowledge and necessary skills regarding searching for good quality evidence, critical appraisal of current available evidence and identifying and implementing pre-appraised evidence such as practice guidelines to better inform clinical care decisions for improving outcomes in neurological patients.

**Key Points**

- Evidence-based practice of neuroanesthesia and neurocritical care improves quality of care and outcomes in patients with neurological illness.
- Neuroanesthesiologists and neurointensivists should use pre-appraised evidence such as guidelines to deliver standardized and transparent care for patients.
- Where these are not available, structured approach to finding best current evidence and integrating this evidence with clinician experience and patient values is desirable.

**Table 33.5** Prophylaxis for venous thrombosis in neurocritical care patients

| Diagnosis | Recommendation and level of evidence | Recommendation |
|---|---|---|
| Ischemic stroke | Strong; high-quality evidence<br><br><br>Weak; low-quality evidence | a. VTE pharmaco-prophylaxis should be performed as soon as is feasible<br>b. LMWH over prophylactic-dose UFH in combination with intermittent pneumatic compression<br>c. When patients have received rTPA, VTE prophylaxis should be delayed for 24 h |
| Intracranial hemorrhage | Strong; high-quality evidence<br><br><br>Weak; low-quality evidence | a. IPC and/or graduated compression stocking for over no prophylaxis beginning at admission<br>b. UFH or LMWH in patients with stable hematomas and no ongoing coagulopathy beginning <48 h of admission. IPCs in patients on pharmacologic prophylaxis |
| Aneurysmal subarachnoid hemorrhage (aSAH) | Strong; low-quality evidence<br><br>Strong; moderate-quality evidence<br>Strong; moderate-quality evidence | a. UFH in all patients with aSAH except unsecured ruptured aneurysms<br>b. IPCs at hospital admission<br>c. UFH at least 24 h after securing of aneurysm |
| Traumatic brain injury (TBI) | Weak; low-quality evidence | IPC <24 h of TBI or <24 h after craniotomy |
| Brain tumors | Strong; moderate-quality evidence | LMWH or UFH upon hospitalization who are at low risk for major bleeding and who lack signs of hemorrhagic conversion |
| Spinal cord injury | Strong; high-quality evidence<br><br>Weak; low-quality evidence | a. VTE prophylaxis at the earliest, <72 h of injury<br>b. No mechanical measures alone<br>c. IPC if LMWH or UFH is not possible |
| Neuromuscular disease | Strong; moderate-quality evidence<br><br>Weak; very low-quality evidence | a. UFH, LMWH, or fondaparinux preferred<br>b. Continuing VTE prophylaxis at least for duration of hospitalization, or until ambulation |
| Complicated spinal surgery | Strong; moderate-quality evidence<br>Weak; low-quality evidence | a. IPC with LMWH or UFH<br>b. No routine use of IVC filters<br>c. Prophylactic IVC filter as a temporary measure only in patients with PE and DVT or those with DVT at risk for PE who cannot be anticoagulated |

*VTE* venous thromboembolism, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin, *rTPA* recombinant tissue plasminogen activator, *IPC* intermittent pneumatic compression, *DVT* deep vein thrombosis

**Table 33.6** Targeted temperature management (TTM) in neurointensive care

| Intervention | Recommendation | Quality of evidence |
|---|---|---|
| Initiation of cooling | No recommendation on timing of TTM initiation | Moderate |
| | Use controlled normothermia to reduce fever burden | Moderate |
| Duration of cooling | At least 24 h of cooling in OHCA | Moderate |
| | No longer than >72 h or <32 °C in HIE | Moderate |
| | Long duration for ICP control in severe TBI | Low |
| Method of cooling to achieve fastest cooling | Nasal, skin or intravascular temperature modulating devices and/or cold saline infusions preferred to air blankets, cooling fans or packs for faster target temperature achievement, improving likelihood of reaching the target and minimizing overshoot | High |
| | Surface cooling devices preferred to passive air cooling/ice packs to achieve target temperature in HIE | High |
| Measurement site | Use continuous esophageal temperature probe; if not appropriate/available, use bladder probe | Low |
| Shivering assessment and treatment | Use bedside sedation assessment scale to assess shivering | Moderate |
| | Use stepwise approach prioritizing non-sedating interventions over narcotics, sedatives, or paralytics | |
| | Metabolic support based on disease state and estimation of metabolism, enteral nutrition <24–48 h | |
| Complication prevention/management | No additional interventions for gastric intolerance | Low |
| | Follow standard critical care guidelines for monitoring infection | Low |
| | Maintain serum potassium levels of 3.0–3.5 mmol/L | High |
| | Temperature-corrected ABG measurements, monitoring similar to critically ill, consider impact of drugs | |
| | Similar ICU care with respect to monitoring for bleeding | High |
| | Thromboelastometry helpful in measuring coagulation | Low |
| | Closely monitor for skin breakdown during surface cooling | Low |
| | Recommend cardiac monitoring during TTM | High |

*OHCA* out of hospital cardiac arrest, *HIE* hypoxic ischemic encephalopathy, *TBI* traumatic brain injury, *ICP* intracranial pressure, *ABG* arterial blood gas

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