84 Neurocritical Care

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KEY POINTS

- Critical care of the nervous system is based on control of cerebral and spinal cord physiology and the prevention of secondary insults. This goal, in turn, depends on the comprehensive maintenance and adequacy of physiologic parameters and organ function.
- Cerebral function is critically dependent on oxygen delivery matching metabolism.
- Increased intracranial volume beyond the capacity of compensatory mechanisms increases intracranial pressure (ICP) and may diminish perfusion adversely. The resulting cellular energy failure both initiates and propagates edema and inflammation.
- The resolution of cerebral edema depends on hydrostatic and osmolar forces applied to the blood-brain barrier. Excess perfusion pressure or intravascular hypotonicity worsens edema and must be avoided.
- Blood-brain barrier disruption varies over time and by pathologic process, and it affects the ability of hypertonic agents to exert a beneficial osmotic effect.
- Fever is frequently overlooked in the neurocritical care unit, but it significantly affects patient outcomes across a range of pathologic processes.
- Neurologic monitoring comprises placement of appropriate monitoring devices as well as prompt response and institution of therapy to the changes detected. The goal is to optimize the physiologic environment. Clinical examination of neurologic function remains a crucial part of monitoring and care.
- The main principle in the treatment of traumatic brain injury involves the control of physiologic parameters such as ICP to achieve an adequate cerebral perfusion pressure. No pharmacological intervention exists to minimize secondary brain damage.
- After the initial hemorrhage and early brain injury, mortality and morbidity from subarachnoid hemorrhage (SAH) arise from rebleeding and delayed cerebral ischemia. Early treatments of ruptured aneurysms, including medical and endovascular therapies, to improve cerebral perfusion, maintain blood volume, and optimize oxygen delivery have improved outcomes. SAH may be accompanied by significant pulmonary, cardiovascular, or endocrine effects.
- Successful therapy for ischemic stroke is contingent on a time window of viability. Urgent assessment and rapid treatment are crucial to a good outcome. Endovascular therapy, in conjunction with advances in imaging, has led to significant outcome benefits.
- Injury to the spinal cord necessitates careful evaluation of respiratory mechanics to assure adequate ventilation.
- Infections of the central nervous system demand an aggressive approach to volume resuscitation, cerebrospinal fluid sampling, and early empiric antibiotic therapy, similar to treatment for sepsis.

Critical care of the central nervous system (CNS) involves collaboration among several disciplines—neurosurgery, anesthesiology, neurology, neuroradiology, and electrophysiology. Each discipline offers unique contributions, which, in partnership, provide optimal care not only to the injured brain but also to the cardiopulmonary, endocrine, gastrointestinal, and renal systems that support cerebral physiology.[1] Integration of the complex goals of this care relies on the physician specializing in neurocritical care. The use of a neurocritical care team, rather than single specialty care, has been associated with reduced in-hospital mortality and the length of stay.[2] Although other specialists can train to be neurointensivists, anesthesiologists with training in neuroanesthesia and critical care are particularly well suited to demonstrate the combination of airway and cardiovascular support skills that, together with an understanding of the physiology and pharmacology of the nervous system, may improve the outcome.

Although the brain has certain preeminence among the organs of the body, it relies on a stable platform of organ function elsewhere to enable homeostatic control and mechanisms of repair and recovery. Injury to the brain is associated with and precipitates a wide spectrum of dysfunction of other organ systems (Box 84.1). Vice versa, brain function can also be perturbed by injury of the other organs. This mutual relationship is best described by the concept of organ crosstalk.[3-5]

Intracranial Physiology and Cerebrovascular Autoregulation

The cerebrovascular circulation is constrained by a rigid perimeter of bone (see also Chapter 11). After exhaustion of limited compensatory mechanisms, the bony confines of the

BOX 84.1 Potential Systemic Complications Associated With Serious Traumatic Brain Injury

Global	Pyrexia
	Inflammatory activation
Cardiovascular	Arrhythmia: bradycardia, tachycardia, atrial fibrillation
	Hypertension
	Hypotension
	Left ventricular dysfunction
Respiratory	Apnea
	Pneumonia: aspiration, hypostatic, ventilator associated
	Pulmonary edema
	Acute respiratory distress syndrome (ARDS)
Gastrointestinal	Gastric erosion
	Ileus
	Constipation
	Perforation
	Malabsorption
Renal	Dehydration
	Acute renal failure
	Urinary tract infection
Hematologic	Anemia
	Leukocytosis
	Coagulopathy, disseminated intravascular coagulation
	Deep venous thrombosis, pulmonary embolism
Metabolic or endocrine	Hyponatremia, hypernatremia
	Hypoglycemia, hyperglycemia,
	Hypokalemia, hyperkalemia
	Hypomagnesemia
	Hypophosphatemia
	Catabolic azotemia
	Rhabdomyolysis

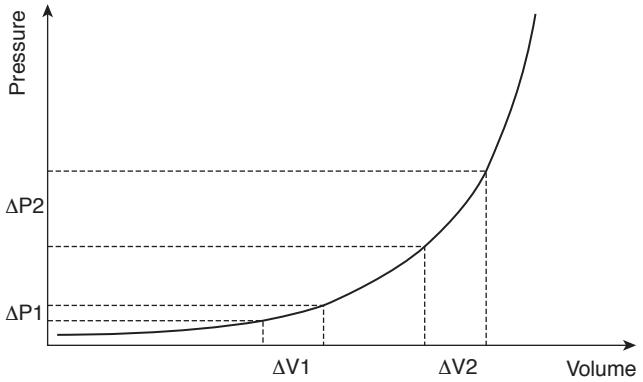

Fig. 84.1 Intracranial pressure-volume relationship: additional intracranial volume *(ΔV1)* is accommodated with minimal change in intracranial pressure *(ΔP1)*. Once this capacity is exhausted, the same increase in volume *(ΔV2)* leads to an exponential rise in intracranial pressure *(ΔP2)*.

skull mandate increasing intracranial pressure (ICP) consequent to increasing intracranial volume. The change in ICP with change in intracranial volume is often referred to as the intracranial compliance curve, but it is more appropriately termed the *intracranial elastance curve* (Fig. 84.1). The increase in elastance (i.e., changes in ICP as a function of changes in intracranial volume) implies poor compliance, and a small change in volume can lead to an inordinate increase in pressure. These changes in volume are due to the increase in intracranial tissue or fluid content (i.e., blood, interstitial fluid/edema, or cerebrospinal fluid [CSF]). Tissue content is relevant insofar as mass lesions influence intracerebral elastance and accentuate the effects of fluid changes. Small increases in volume can be accommodated by an outflow of CSF from the cranial cavity into the spinal canal, producing an exponential pressure-volume relationship (see Fig. 84.1).

The cranial vault is compartmentalized by the falx cerebri and tentorium cerebelli, which creates the possibility of internal pressure gradients (Fig. 84.2). Increased intracranial volume finally leads to herniation of brain tissue through the "apertures" of the compartments. Pressure gradients are initially hydraulically equilibrated, with CSF moving from the ventricular chambers to the extracranial spinal space. Brain herniation may also contribute to impedance of CSF drainage either by occlusion of the foramina of Monro in the case of lateral herniation or by occlusion of the third ventricle and aqueduct by supratentorial herniation through the tentorial gap. This situation typically gives rise to clinical features of midbrain compression. Unilateral pupillary dilation, ipsilateral or even contralateral paralysis (the Kernohan notch phenomenon), and abnormalities of respiration are apparent in the patient. If the herniation continues, it will result in cerebellar descent through the foramen magnum with consequent compression of the brainstem, thus producing bilateral papillary fixation, either tachycardia or bradycardia, and systemic hypertension.[6] Changes in cerebral mass secondary to increase in intracerebral venous blood volume also arise from venous drainage obstruction by compression of the easily susceptible bridging veins draining from cortex to venous sinuses. Once an individual threshold of elastance is crossed, changes in volume exert a mass effect on the draining veins, which act as Starling resistors. This effect decreases drainage, which, in turn, amplifies and prolongs pressure increases. Blood volume increases may be extravascular (i.e., hemorrhage) or intravascular (i.e., accumulation within a predominantly venous capacitance circulation). The other main fluid mass effect is through edema, either cytotoxic or vasogenic.[7] Cytotoxic edema results from hypoxia, with swelling of the intracellular compartment, whereas vasogenic edema in the interstitium usually develops from a breach of the blood-brain-barrier, often in response to high blood pressure.[8]

Changes in the control of cerebral blood volume (CBV) may have significant effects on ICP and, thereby, on cerebral perfusion pressure (CPP). The cerebral vasculature responds to increase in arterial partial pressure of carbon dioxide ($PaCO_2$), decrease of arterial partial pressure of oxygen (PaO_2), and reduced mean arterial pressure (MAP) by dynamically altering arteriolar caliber to maintain a constantly matched cerebral blood flow (CBF) sufficient to meet metabolic demands (Fig. 84.3). Carbon dioxide, as with hydrogen, potassium, calcium, nitric oxide, adenosine, and lactate, are among many purported metabolic mediators of flow.[9] A reduction in substrate delivery (i.e., oxygen and nutrients) to less than the threshold necessary to maintain

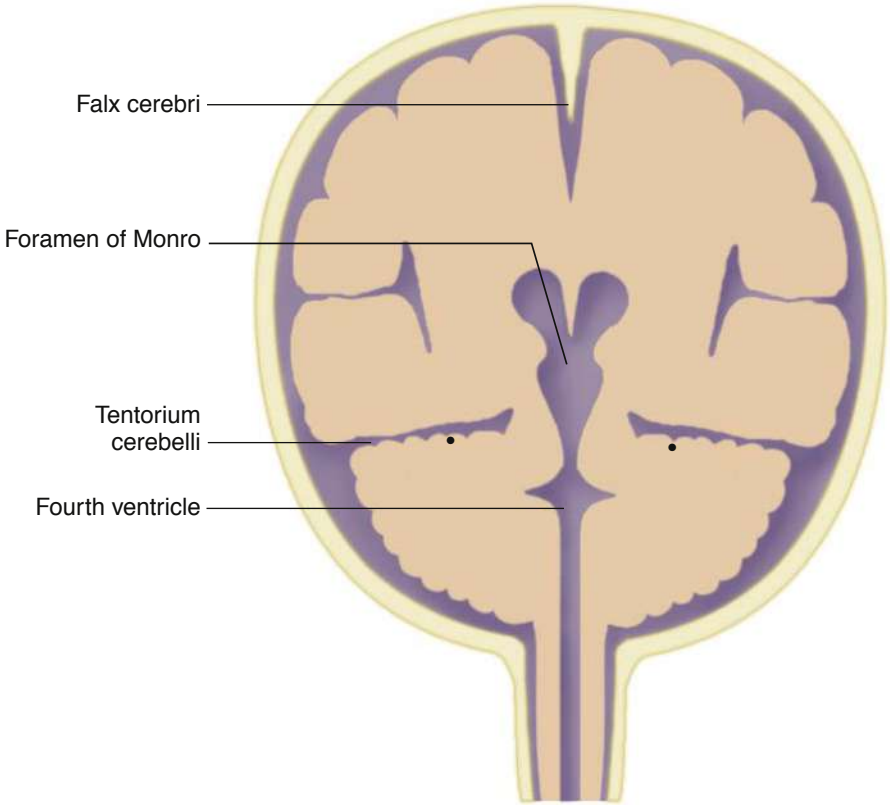

Fig. 84.2 Schematic of intracranial compartments: coronal section.

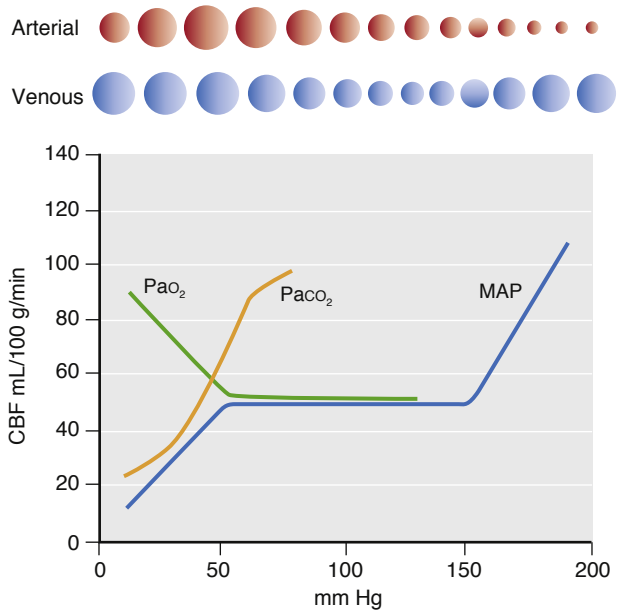

Fig. 84.3 The influence of changes in arterial partial pressure of oxygen *(PaO_2)*, arterial partial pressure of carbon dioxide *($PaCO_2$)*, and mean arterial pressure *(MAP)* upon vessel diameter and cerebral blood flow *(CBF)*.

cellular viability induces cell injury with consecutive cytokine and chemokine release. This inflammatory amplification expands the injury, disrupts the blood-brain barrier function, and may directly lead to apoptosis or necrosis.[10] The disruption of the blood-brain barrier creates vasogenic edema and allows serum proteins to cross into brain parenchyma with prolonged effects. This process is more evident in the high metabolically active gray matter than in white matter.

CBF control may be directly compromised by brain injury or by abnormalities of respiration and arterial blood pressure. Consequently, untoward changes in physiologic parameters, including arterial hypotension, hypoxia, hyper- and hypocapnia, hyper- and hypoglycemia, and fever, as well as seizures, produce what is termed a *secondary physiologic insult*. The *primary injury* is caused by the direct destruction of tissue during the initial trauma or ischemia, while the area of the *secondary injury* slowly extends into the intact tissue and induces further harm to the vulnerable brain and worsens outcome.[11] The control of the secondary brain injury is the target of the development of potential neuroprotection protocols.[12]

General Cardiopulmonary Considerations

Arterial hypotension, especially in combination with hypoxemia, is a well-documented source of cerebral morbidity.[13,14] Therefore, a reduction of cardiac output and CPP have to be avoided to prevent further deterioration of the level of consciousness, which in turn leads to airway compromise and hypercapnia and hypoxia. Hypercapnia, hypoxia, and arterial hypotension lead to autoregulatory cerebral vasodilation, which increases CBV and ICP and further diminishes CPP, perpetuating the vicious circle (Fig. 84.4).

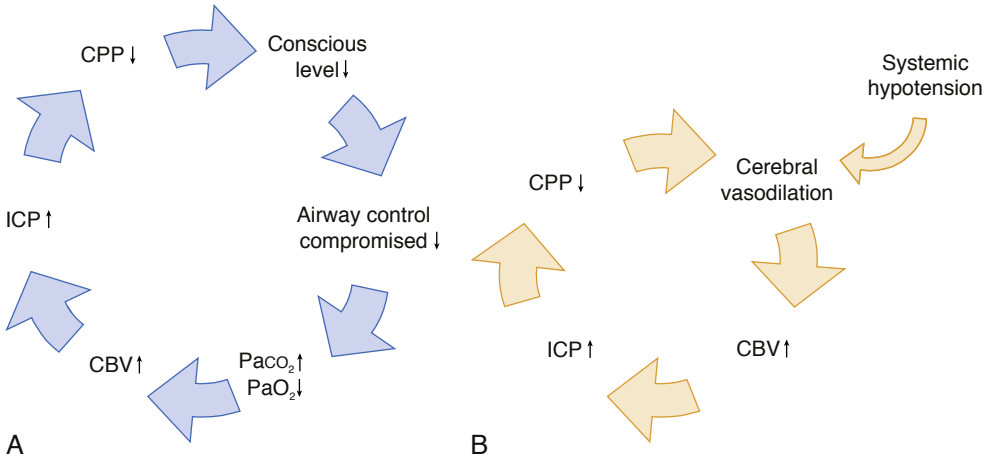

Fig. 84.4 (A) Ventilatory-neurologic circle of dysfunction. Induced changes in partial pressure of carbon dioxide *($PaCO_2$)* and partial pressure of oxygen *(PaO_2)* produce changes in cerebral blood volume *(CBV)*, intracranial pressure *(ICP)*, and cerebral perfusion pressure *(CPP)*. This, in turn, impairs ventilatory control. (B) Hemodynamic-neurologic circle of dysfunction. Similar to the diagram in **(A)**, systemic hypotension induces cerebral vasodilation, which increases CBV and ICP and reduces CPP, which, in turn, increases vasodilation.

Any deterioration in ventilatory efficacy adversely affects cerebral elastance through carbon dioxide-induced vasodilation and leads to hypoxemia, which can cause direct as well as indirect injury to the brain.[14] Arterial hypoxemia, less than 60 mm Hg, is a significant contributor to secondary insult from vasodilatory ICP effects, in addition to reduced oxygen delivery to the cell. Pulmonary compromise is often seen in neurologic patients with altered mental status due to impaired airway reflexes and repeated aspiration episodes, which culminate in a significant incidence of pneumonia, irrespective of the initiating pathologic process.[15,16] Another potential mechanism is the release of cytokines from the brain in response to the inflammatory process triggered by an injury. This release may be sufficient to induce acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS).[4,17] Conversely, ARDS can also trigger cerebral inflammation by releasing inflammatory mediators like cytokines.[4,17] The ventilatory treatment for ARDS may create a therapeutic dilemma in the presence of cerebral pathophysiology. However, the "open lung" concept (i.e., small tidal volumes, high frequencies, and high positive end-expiratory pressure [PEEP]) developed to minimize alveolar distention and reduce lung injury appears to be feasible in neurosurgical patients, despite theoretic concerns regarding adverse effects on ICP.[18] The use of PEEP up to 15 cm H_2O appears to improve brain tissue oxygen pressure and oxygen saturation without negative effects on ICP or CPP.[19].

Fluids, Electrolytes, and Nutrition

Normally, capillary fluid shift is a function of hydrostatic pressure pushing fluid out and the balance of osmotic forces retaining fluid within[20]:

$$Jv = Kf([Pc - Pi) - \sigma[\pi c - \pi i])$$

where Jv is the net fluid movement between compartments, Pc is the capillary hydrostatic pressure, Pi is the interstitial hydrostatic pressure, πc is the capillary osmotic pressure, πi is the interstitial osmotic pressure, Kf is the filtration coefficient (this is a product of surface area and hydraulic conductivity), and σ is the reflection coefficient (the membrane impermeability toward osmotically active particles).

In extracranial capillaries, these osmotic forces are derived from oncotic pressure because smaller solutes can cross the capillary basement membrane following concentration gradients and only large protein molecules remain to exert their effect. However, in the brain, because of the presence of tight junctions in the endothelium, the intact blood-brain barrier reflects smaller solutes (e.g., sodium and chloride ions), and this relative impermeability renders cerebral capillary fluid shift a function of hydrostatic and *total* osmolar forces, with the oncotic pressure being responsible for only 1 mOsmol/kg.[21] Therefore, the fluid shift in the cerebral capillaries is most dependent on the osmolar gradient. In the absence of externally administered osmotically active substances (e.g., mannitol), plasma osmolality is 280 to 300 mOsm/kg and is almost entirely determined by sodium concentration.

$$\text{Plasma osmolality} = [NA]_{serum} \times 2 + \text{glucose}/18 + \text{BUN}/2.8$$

where Na is sodium and BUN is blood urea nitrogen.

As a reduction of plasma osmolality of 4 to 5 mOsm/kg increases cerebral edema, hypotonic solutions must not be used in the neurosurgical patient. Table 84.1 shows that the mean measured osmolality is often lower than the calculated osmolarity.[21] Hence, intravascular fluid therapy must be carefully considered under circumstances of cerebral ischemia and inflammation. The brain exerts homeostatic control on metabolic and endocrine activity, and neurologic dysfunction can manifest as untoward changes in fluid and electrolyte balance. Diabetes insipidus is a florid example of this, with polyuria, subsequent hypovolemia, and, if the disorder is left untreated, systemic hypotension. Iatrogenic causes may include the use of osmotic diuretics. Sympathetic denervation stemming from brainstem or spinal cord injury (SCI) may also contribute to reductions in venous return due to increased vasodilation and peripheral venous pooling.[22]

TABLE 84.1 Osmolarity and Osmolality of Commonly Used Intravenous Fluids

Fluid	Mean Measured Osmolality (mOsm/kg)	Theoretical Osmolarity (mOsm/L)
Plasma	288 [280-300]	291
Isotonic saline 0.9%	285 [282-286]	308
Ringer´s lactate solution	257 [257-258]	276
Gelatin 4%	271 [270-272]	274
Human albumin (4%)	266 [266-267]	274.4

Nutritional deficits occur often in brain injured critically ill patients, and greater energy and protein deficits are associated with prolonged intensive care unit (ICU) and hospital stays.[23] According to the Brain Trauma Foundation (BTF), early enteral nutrition should be initiated at least by the fifth day and at most by the seventh day post injury.[24] It is possible that an even earlier start at day one after trauma can be beneficial in terms of better control of infection and overall complications.[25] For administration of enteral nutrition, a transgastric jejunal tube is recommended to reduce the incidences of ventilator-associated pneumonia.[24]

Stress-induced hyperglycemia is associated with higher morbidity and mortality in patients with neuronal injury,[26] but tight glycemic control, targeting plasma glucose levels of 80 to 120 mg/dL, increased the risk of hypoglycemia and did not improve outcomes compared to conventional therapy allowing a maximal glucose concentration of 150 mg/dL.[27] Therefore, moderate glycemic control with a target blood glucose level of 110 to 150 mg/dL is advocated.

Temperature Control

Fever occurs with an incidence of up to 70% in brain injured patients.[28] The degree and duration of early hyperthermia are closely correlated with a higher morbidity and mortality after neurologic injury.[29] The temperature threshold that produces progressive thermal injury to the metabolically active brain cells, blood-brain barrier, and vascular endothelium appears to be between 39°C and 40°C.[30] Hyperthermia, an often overlooked insult to the compromised brain, increases oxygen utilization and metabolic stress.[29,31] Patients in the ICU can have multiple risk factors for hyperthermia such as infection from indwelling catheters (e.g., arterial, venous, CSF) or lung injury.[31] However, in up to one-third of cases, the cause of the fever remains unexplained and often is classified as central fever.[28]

The concept of targeted temperature management in neurocritical care includes therapeutic mild hypothermia, controlled normothermia, and aggressive treatment of fever.[32] Although in head trauma patients, induced mild or moderate hypothermia failed to improve outcome, hypothermia did improve neurologic outcome in neonates with hypoxic-ischemic encephalopathy and in patients after out-of-hospital cardiac arrest.[33-35] To cool patients, gel pads or intravascular temperature-modulating devices with servo-controls should be used to minimize overshoot. Cold saline infusions are additionally recommended.[32] Core temperature should be monitored continuously using an esophageal temperature probe or a bladder temperature probe.[32] Shivering must be treated promptly with nonsedating interventions (e.g., acetaminophen) instead of narcotic analgesics, sedatives, or paralytics.

Monitoring

The avoidance or correction of secondary brain damage necessitates the use of physiologic monitors to guide individualized therapy. The most important neuromonitoring devices are shown in Fig. 84.5 (see Chapter 39).[36-39] Neuromonitoring does not obviate the need for regular neurologic clinical examination. Similarly, attention should be paid to the basics of volume status evaluation, cardiovascular stability, respiratory care, and metabolic consumption. Monitors (e.g., processed electrical activity, cerebral oxygenation, and ICP) are merely surrogates of actual integrity of brain tissue and cerebral function.

CLINICAL EXAMINATION

Comprehensive neurocritical care encompasses the ability to perform a competent neurologic examination. Reproducible and objective assessment of neurologic function is as important as some of the sophisticated technology mentioned later, with the advantage that it offers better insight into global nervous system function and allows integration of information in an inherently complex dynamic system. One of the most basic yet important examinations is the pupillary light reflex, the unilateral absence of which may indicate midbrain compression from uncal herniation, which is a neurologic emergency. Bilaterally absent pupillary reflexes signify imminent or established cerebellar herniation, but this may be reversible with rapid efficacious treatment.

Clinical scales have been devised for common neurologic settings. The Glasgow Coma Scale (GCS) is a well-known, universally applied scale (Table 84.2).[40] It relies on independent assessment of eye opening, speech, and best motor movement in response to progressive trials of command, voice, and noxious stimuli. Its accuracy is compromised by the use of sedatives/anesthetics. In clinical practice, duration of loss of consciousness, altered consciousness, and posttraumatic amnesia are also considered. The World Federation of Neurologic Surgeons (WFNS) scale is the preferred rating because it uses the more prevalent GCS but with a modifying component for focal deficit (Table 84.3). The Hunt and Hess Scale describes the severity of subarachnoid hemorrhages and is used as an outcome predictor (Table 84.4).[41,42] Knowing and using these scales are crucial to understanding the terminology and practice of neurocritical care.

INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE

Intracranial Pressure

Increased ICP after head trauma is an important and well-established indicator of secondary brain injury and is

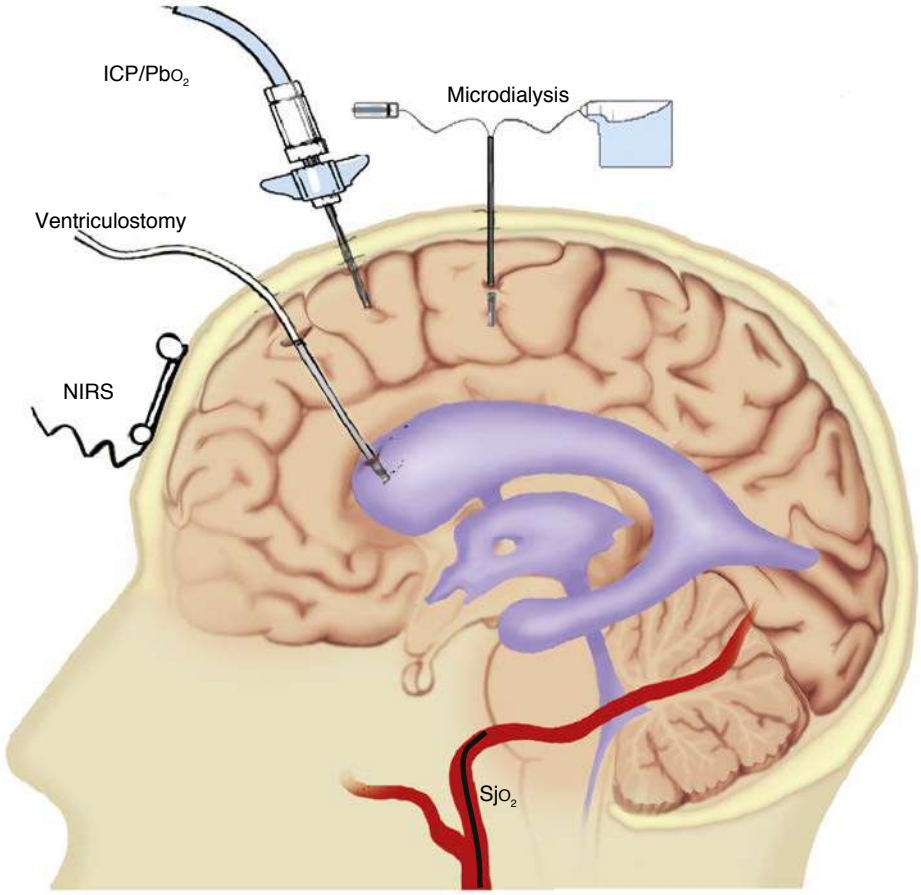

Fig. 84.5 Schematic of available intracranial monitoring, with near-infrared oximetry *(NIRS)*, intracranial pressure (*ICP*, either by ventriculostomy or parenchymal probe), brain tissue oximetry *(Pbo_2)*, microdialysis, and jugular venous oximetry *(Sjo_2)*.

associated with higher mortality and poor long-term outcome, especially when it is refractory to treatment.[36,43-46] However, the clinical benefit of ICP monitoring is still under discussion.[47-51] The indications for ICP monitoring (e.g., severe head trauma and abnormal computed tomography [CT] scan) and the recommended ICP threshold of 22 mm Hg given in the guidelines are more expert- than evidence-based.[24,52] The sole randomized clinical trial evaluating the potential benefit of ICP monitoring revealed that ICP monitoring does not influence long-term outcome after head trauma.[47] However, ICP-guided therapy in the context of duration of elevated ICP or in combination with information from other neuromonitoring devices may allow for individualized therapy of brain-injured patients and, thereby, improve outcome.[36] For example, the cumulative ICP-time burden with an ICP of 20 mm Hg for longer than 37 minutes diminishes outcome, whereas shorter periods had no adverse effects.[53] Impaired cerebrovascular autoregulation or a CPP below 50 mm Hg reduces the ability to tolerate an elevated ICP.[53]

In clinical practice, two different methods of monitoring ICP are used: microtransducer devices (strain gauge or fiberoptic types) and ventricular catheters.[54] Microtransducer systems are less invasive and easier to place, but they cannot drain CSF and may represent only the compartment pressure where they were placed (see Fig. 84.5).[55] The ventricular catheter is still the "gold standard" of measurement, as long as the ventricles are accessible, because they reflect global ICP and allow therapeutic drainage of CSF. However, they have an increased risk of complications, such as bleeding or infection.[54] Currently, noninvasive ICP measurements are not sufficiently reliable and cannot monitor the dynamics continuously, and, thus, are of research interest only.[36]

Cerebral Perfusion Pressure

The difference between MAP (zero reference point at the tragus of the ear) and the ICP describes the CPP. However, many interventions to decrease ICP, such as head elevation or barbiturate coma, suppress MAP and therefore, may also lower CPP. Most guidelines recommend CPP should be kept between 60 and 70 mm Hg, as higher or lower values worsen outcome after head trauma.[24,44] Recently, the concept of targeting an individualized optimal CPP was introduced, suggesting that an optimal CPP can be calculated for each patient, leading to a more favorable outcome compared with the standard threshold.[56]

CEREBRAL BLOOD FLOW

A constant, uninterrupted CBF is pivotal for the brain, as it has no storage for energy or oxygen. A decrease in CBF below 20 mL/100 g/min causes functional impairment (Table 84.5). Further reductions in CBF lead to structural damage of brain tissue. Modern imaging techniques such as CT perfusion or positron emission tomography (PET)

TABLE 84.2 Glasgow Coma Scale for Head Injury

Ability	Score
MOTOR RESPONSE	
Normal	**6**
Localized to pain (purposeful movement to side of pain)	**5**
Withdraws to pain	**4**
Abnormal flexion to pain *(an abnormal posture that can include rigidity, clenched fists, legs held straight out, and arms bent inward toward the body with the wrists and fingers bent and held on the chest)*	**3**
Abnormal extension to pain *(an abnormal posture that can include rigidity, arms and legs held straight out, toes pointed downward, and head and neck arched backward)*	**2**
None	**1**
VERBAL RESPONSE	
Normal conversation	**5**
Disoriented conversation	**4**
Words, but not coherent	**3**
No words, only sounds	**2**
None	**1**
EYE OPENING	
Spontaneous	**4**
To voice	**3**
To pain	**2**
None	**1**
SUM	3-15

TABLE 84.3 World Federation of Neurologic Surgeons Scale

Grade	Clinical Presentation
Grade 1	GCS score of 15, motor deficit absent
Grade 2	GCS score of 13-14, motor deficit absent
Grade 3	GCS score of 13-14, motor deficit present
Grade 4	GCS score of 7-12, motor deficit absent or present
Grade 5	GCS score of 3-6, motor deficit absent or present

GCS, Glasgow Coma Scale.

TABLE 84.4 Hunt and Hess Grading System

Grade	Clinical Presentation	Survival (%)
Grade 1	Asymptomatic or mild headache	70
Grade 2	Moderate to severe headache, nuchal rigidity, and no neurologic deficit other than possible cranial nerve palsy	60
Grade 3	Mild alteration in mental status (confusion, lethargy) and mild focal neurologic deficit	50
Grade 4	Stupor and/or hemiparesis	20
Grade 5	Comatose and/or decerebrate rigidity	10

TABLE 84.5 Functional Thresholds of Cerebral Blood Flow

CBF (mL/100 g/min)	Result
50	Normal
20	EEG slowing
15	Isoelectric EEG
6-15	Ischemic penumbra
<6	Neuronal death

CBF, Cerebral blood flow; *EEG*, electroencephalogram.

provide detailed information about cerebral hemodynamics, but cannot clinically be used for continuous monitoring of CBF.[36] Therefore, bedside solutions for continuous CBF measurement are necessary.

Thermal Diffusion Flowmetry

Thermal diffusion flowmetry is an invasive, continuous, and quantitative technique to measure local CBF. The thermal diffusion flowmetry catheter measures the temperature difference between a thermistor, which is heated some degrees above tissue temperature, and a temperature probe. The temperature difference can be converted to an absolute measurement of CBF in mL/100 g/min. The catheter is placed in areas at risk for hypoperfusion and can further help detect intracerebral vasospasm and assess cerebrovascular autoregulation.[57] However, there are still concerns about the validity of using thermal diffusion flowmetry long-term, as monitor dysfunctions secondary to placement errors and missing data during recalibration occur.[58]

Transcranial Doppler Monitoring

Transcranial Doppler monitoring is a noninvasive method that uses the Doppler shift effect to assess flow velocity in insonated cerebral arteries. Flow velocity has a linear relationship to CBF as long as the vessel's cross-sectional area and the angle of insonation remain constant.[59] This technique can continuously monitor flow velocity within the main components of the circle of Willis through the ophthalmic, temporal, and foramen magnum acoustic windows.[60] It has excellent temporal resolution and can detect inadequate CBF, assess pressure autoregulation and carbon dioxide reactivity, and can help predict outcome in patients with head trauma.[60,61] Changes in velocity can be used to assess alterations of vascular caliber (e.g., arterial vasospasm) or vascular stenosis.[60] High flow velocities in the middle cerebral artery (MCA) can be caused by vasospasm or hyperemia. This can be distinguished by calculating the ratio between the MCA and the extracranial carotid artery flow velocity (the Lindegaard index).[60]

CEREBROVASCULAR AUTOREGULATION AND VASOMOTOR REACTIVITY

Monitors of CBF can assess the response of the cerebral vasculature to changes in metabolism and blood pressure (i.e., cerebrovascular autoregulation).[62] Static cerebrovascular autoregulation can be determined with sustained blood pressure manipulation by using either a tilt test or a direct vasopressor, whereas dynamic cerebrovascular

autoregulation can be assessed using rapid deflation of thigh cuffs that have been inflated above systolic blood pressure (SBP). For continuous assessment of cerebrovascular autoregulation the pressure reactivity index is an established tool. Using the Pearson correlation coefficient the pressure curves of ICP and arterial blood pressure are correlated, calculating an index between -1 and +1.[56]

Instead of ICP other parameters like the CBF (measured by TCD), the brain tissue PO_2, or Near Infrared Spectroscopy (NIRS) derived variables can be used to calculate an autoregulatory index to assess the status of the cerebral autoregulation.[63-67] The presence or lack of autoregulation may guide subsequent treatment and prognosis because the loss of autoregulation is associated with a poor outcome frequently.[68]

CEREBRAL OXYGENATION

To assess the adequacy of cerebral perfusion, measurement of cerebral oxygenation is indicated, because it gives the balance between cerebral oxygen delivery and utilization.

Jugular Venous Oxygen Saturation

The Fick principle may be reversed to examine the venous oxygen saturation which, assuming a constant hematocrit and metabolism, can offer an assessment of the adequacy of CBF and associated oxygen delivery relative to cerebral oxygen consumption:

$$\text{If } AVDO_2 = (CMRO_2/CBF),$$
$$\text{then } CaO_2 - CjvO_2 = (CMRO_2/CBF)$$

Ignoring the contribution of dissolved oxygen, then:

$$(SaO_2 - SjvO_2) \times Hgb \times 1.34 = (CMRO_2/CBF)$$

where $AVDO_2$ is the arteriovenous oxygen content difference; $CMRO_2$ is the cerebral oxygen metabolic rate; CaO_2, $CjvO_2$, SaO_2, and $SjvO_2$ are the arterial oxygen and jugular venous oxygen contents and saturations, respectively; Hgb is the hemoglobin concentration; and 1.34 is the oxygen affinity constant.

In vivo, catheters to measure $SjvO_2$ are placed in retrograde fashion through the internal jugular vein to its jugular bulb at the foramen, or even beyond, to the large sinuses (Fig. 84.6). $SjvO_2$ can be measured intermittently by sampling venous blood from a catheter or continuously by fiberoptic measurement. The normal range of $SjvO_2$ lies between 55% and 75%. Both desaturation (<50%, suggesting inadequate delivery or excess consumption) and abnormally high saturation (>75%, suggesting hyperemia or stroke) have been associated with poor outcomes.[24,69] The arteriovenous oxygen content difference is possibly a more accurate assessment of the adequacy of flow and predictor of outcome.[70] Jugular venous oximetry is sometimes insensitive to focal changes because it reflects the averaged global cerebral venous oxygen saturation from the confluence of hemispheric venous drainage. Consequently, some authors have suggested using oxygen consumption in combination with the cerebral arteriovenous gradient of lactate to make stoichiometric assessments of aerobic versus anaerobic metabolism.[71] The idea is to base goal-directed therapy on metabolic indices ($SjvO_2$) rather than on hemodynamic indices (ICP and CPP).[72] However, due to technical problems (e.g., displacement of catheter) and its low sensitivity, the clinical use of jugular venous oximetry has decreased in favor of alternative monitoring methods for brain tissue oxygen monitoring.[73]

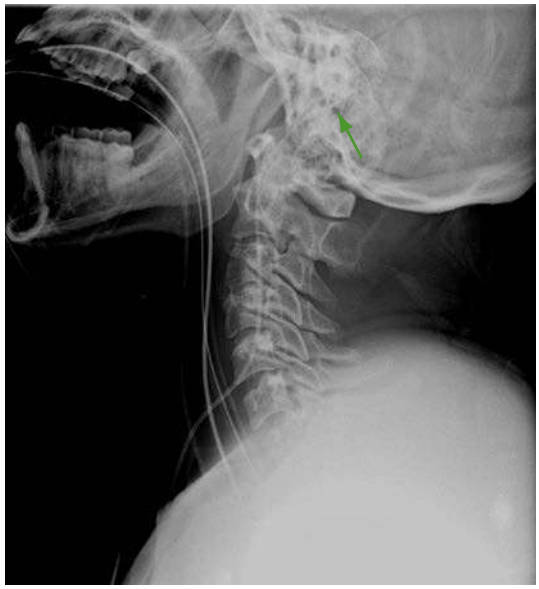

Fig. 84.6 Lateral cervical spine radiograph showing appropriate positioning of the jugular venous oximetry catheter above the lower border of the C1 vertebra (the *arrow tip* is actually within the jugular foramen).

Brain Tissue Oxygen Tension

Miniaturized Clark electrodes have been developed and combined with ICP catheters to provide simultaneous measurements of brain tissue oxygen tension (PbO_2) and ICP. The PbO_2 should be measured in the area of risk, which contains still viable subcortical white matter.[74]The normal range of PbO_2 lies between 20 and 45 mm Hg. In clinical settings, values less than 15 to 20 mm Hg are considered as cerebral ischemia and below 10 mm Hg as severe ischemia.[75] Several studies have demonstrated a correlation between low PbO_2 and poor outcome after traumatic brain injury (TBI). Therapy guided by combined ICP (<20 mm Hg) and CPP (60-70 mm Hg) and PbO_2 (> 20 mm Hg) was superior to ICP and CPP therapy alone.[76-78] To increase a low PbO_2 (<20 mm Hg), mechanical ventilator settings should be optimized. A challenge of 100% oxygen for 2 minutes (a temporary method to restore PbO_2 and to verify probe function) can be performed and CPP and ICP, hemoglobin, and sedation should be optimized.[79]

Near-Infrared Spectroscopy

Pulse oximetry for the brain relies on the principle of reflectance spectroscopy in which near-infrared light traverses bone. The light is scattered and reflected in a ratio that is inversely proportional to the concentration of light-absorbing materials in tissue (e.g., hemoglobin and oxyhemoglobin). The surface detector is constructed and calibrated to detect light that has traversed down to the cerebral cortex and back. An adjacent detector is positioned to detect a signal from superficial tissues, and both signals are then used in an algorithm to derive an estimated tissue saturation.[80]

NIRS is a noninvasive approach to continuously monitor a regional critical oxygen supply/demand mismatch. The normal range lies between 60% and 75%, but the lower threshold varies considerably among individual patients.[81] Unfortunately, the sensitivity to detect isolated cerebral hypoperfusion is low, and, therefore, high-quality data supporting the use of NIRS in patients with TBI, SAH, or stroke are missing.[36,66] In contrast, NIRS is an excellent trend monitor in patients with cerebral hypoperfusion caused by systemic changes, such as during cardiac surgery where a decreased NIRS compared to the awake baseline correlates with a poor outcome.[81-83]

BRAIN METABOLISM AND BIOCHEMISTRY—CEREBRAL MICRODIALYSIS

Cerebral microdialysis probes can assess the biochemical milieu of the brain. The probes are placed through a burr hole and cycle small volumes of dialysate through the catheter to an extracranial collection system. The tip of the catheter should be placed in at-risk brain tissue, which is most vulnerable to secondary brain damage.[84] A semipermeable membrane (molecular weight cutoff of 20 kDa) is incorporated in the tips of the probes through which various substances can diffuse along their concentration gradient (e.g., lactate, pyruvate, glucose, glycerol, and glutamate) into the dialysate for collection and analysis using a bedside high-pressure liquid chromatography device.[85] As these substances are associated with glucose metabolism, hypoxia/ischemia, and cellular energy failure, the cerebral microdialysis is used to guide individualized intensive care therapy to optimize substrate supply, cerebral perfusion, and oxygen transport.[86] An increased lactate:pyruvate ratio with a low pyruvate concentration in combination with a low-glucose concentration can indicate a profound reduction in energy substrate supply and is associated with poor outcome after brain injury.[87] In contrast, an increased lactate:pyruvate ratio with normal pyruvate and glucose concentrations is an indicator of a nonischemic cause (e.g., mitochondrial dysfunction).[88] Glutamate is a marker of excitotoxic brain damage and glycerol can indicate membrane breakdown of neurons.[89,90] Recently, probes with a high-molecular-weight cutoff membrane (100 kDa) have been used to detect biomarkers for neuronal damage like S100B or cytokines.[91,92] Despite promising results, the clinical utility of a therapy guided by cerebral microdialysis is still under discussion.

NEUROPHYSIOLOGIC MONITORING

Clinical neurophysiology picks up the electrical activity of the central or peripheral nervous system.[93] It includes electroencephalography (EEG), evoked potentials (EP), and electroneuromyography and is very useful for diagnosis, prognosis, and follow-up of cerebral disorders.[93] However, clinical neurophysiology only evaluates the current functional brain status and cannot predict future complications.

Electroencephalography

The electroencephalogram (EEG) records spontaneous electrical activity of cortical neurons detected by appropriately placed electrodes in a radial and axial array as defined by the 10/20 system, an internationally standardized system of recording. The EEG is a surrogate parameter for functional metabolism of the cortical neurons and the integrity of the brain. The spectrum of component frequencies, together with amplitude and power, can be quantified and analyzed in a variety of fashions, and processed EEG monitors use these to assess the depth of anesthesia. In unconscious patients in the neurocritical care unit, EEG should be continuously used for the detection of nonconvulsive seizures, which can frequently occur and are associated with intracranial hypertension and cerebral metabolic derangements.[94,95] As the detection of nonconvulsive seizures is difficult, automatic monitoring systems have been developed.[96] Unfortunately, the current automatic detection of seizures is fraught with false negatives and false positives and cannot replace an EEG-trained neurologist.[96]

For prognosis after anoxic brain damage, poor outcome is associated with malignant EEG patterns like burst-suppression, α-coma, and low-voltage delta. In contrast, the persistence of EEG reactivity is an indicator of good outcome. Further development of intracranial electrocorticography, an invasive form of EEG monitoring, might allow the continuous detection of so-called spreading depolarizations, which occur in about half the patients with head trauma and can lead to secondary brain damage.[97,98]

Evoked Potentials

EPs measure changes in neuronal activity, which are triggered by sensory stimuli.[93] They reflect the passive response of the cerebral cortex or the brainstem to peripheral (acoustic, somatosensory, or visual) or central (transcranial magnetic stimulation) stimuli. In contrast to the EEG, where spontaneous cortical activity is recorded, the EPs monitor the integrity of central and peripheral tracts. The EP signals are quantified according to latency and amplitude. In the absence of peripheral or cervical dysfunction, the bilateral absence of the N_20 somatosensory EP response to median-nerve stimulation is the most reliable predictor of non-awakening in post-anoxic coma, whereas the preservation of cognitive evoked potentials (CEP) predicts awakening with a very high probability, irrespective of coma etiology.[93,99] After TBI, impairment of brainstem activity is the best predictor of bad outcome.[93]

MULTIMODALITY NEUROMONITORING

Multimodality monitoring uses a combination of parameters to identify, prevent, and treat the mechanisms of secondary brain damage and guide individualized therapy.[61,100] Various commercial systems are available to process and display multiple data streams.[101] The combination of ICP, cerebrovascular autoregulation, PbO_2, continuous EEG, and cerebral microdialysis offers the possibility to individualize care decisions in patients with severe brain injury.[39] In the future, the development of computational model interpretation of these complex multimodal data sets will provide summary outputs of patient-specific simulations of brain state to facilitate the interpretation and suggest individual therapies.[36,102]

RADIOGRAPHIC IMAGING

The most important diagnostic modalities for unconscious and brain-injured patients are CT, including

TABLE 84.6 Marshall Scale: Computed Tomography Categories for Head Injury

Category	Definition
Diffuse injury I	No visible intracranial pathologic process
Diffuse injury II	Cisterns are present with midline shift of 0-5 mm and/or lesion densities present; no high- or mixed-density lesions at >25 mL
Diffuse injury III	Cisterns compressed or absent, with midline shift of 0-5 mm; no high- or mixed-density lesions of >25 mL
Diffuse injury IV	Midline shift of >5 mm; no high- or mixed-density lesion of >25 mL
Evacuated mass lesion (V)	Any lesion surgically evacuated
Nonevacuated mass lesion (VI)	High- or mixed-density lesion of >25 mL; not surgically evacuated

TABLE 84.7 Classification of the Severity of Traumatic Brain Injury

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness	< 30 min	30 min to 24 h	>24 h
Posttraumatic amnesia	0-1 day	>1 and <7 days	>7 days
GCS (best available in 24 h)	13-15	9-12	3-8
Abbreviated injury scale score: Head	1-2	3	4-6

GCS, Glasgow Coma Scale.

CT-angiography, and magnetic resonance imaging (MRI). CT and CT-angiography are very efficient methods, while MRI is time consuming but more sensitive for brainstem lesions as well as for axonal injuries. These imaging techniques are used to diagnose damage after TBI (intracranial masses, cortical contusions, and neuronal/axonal injury), an epidural or subdural hematoma, subarachnoid hemorrhage (SAH), ischemic or hemorrhagic stroke, cerebral vein/sinus thrombosis, or postoperative complications such as brain edema or rebleeding.

It is important to standardize and categorize CT images for meaningful comparison of therapeutic modalities in clinical trials and for assessment of prognosis. For TBI, the novel Stockholm and Helsinki CT scores seem to give a more accurate outcome prediction compared to the Marshall CT classification and the Rotterdam CT score (Tables 84.6 and 84.7).[103] After SAH, the Hijdra sum score seems to be superior to the more commonly used modified Fisher scale in assessing the amount of subarachnoid blood and in predicting the occurrence and severity of cerebral vasospasm.[104,105] (Tables 84.8 and 84.9). For early assessment of neuronal damage after stroke, the Alberta Stroke Program Early CT Score (ASPECTS) uses signs of early ischemic lesions in regions M1 to M6 and the basal ganglia.[106,107]

TABLE 84.8 Fisher Scale (Computed Tomography Appearance)

Grade	Clinical Presentation
Grade 1	No blood detected
Grade 2	Diffuse deposition of subarachnoid blood, no clots, and no layers of blood <1 mm
Grade 3	Localized clots and/or vertical layers of blood ≥1 mm in thickness
Grade 4	Diffuse or no subarachnoid blood, but intracerebral or intraventricular clots present

TABLE 84.9 Modified Fisher Scale (Computed Tomography Appearance)

Grade	Clinical Presentation
Grade 0	No blood detected
Grade 1	Thin subarachnoid blood*, no intraventricular hemorrhage
Grade 2	Thin subarachnoid blood, with intraventricular hemorrhage
Grade 3	Thick subarachnoid blood, no intraventricular hemorrhage
Grade 4	Thick subarachnoid blood, with intraventricular hemorrhage

*Vertical thickness of 1 mm separates thin from thick subarachnoid hemorrhage.

Common Diseases in the Neurocritical Care Unit

TRAUMATIC BRAIN INJURY

Severe TBI is mainly a result of traffic accidents, assaults, falls, and domestic abuse. It is the leading cause of disability and death in young male adults.[108,109] Poor outcomes after TBI are correlated to older age and are worse after falls.[110,111] The primary injury, which is defined by the kinetic impact of the trauma, deforms the brain structure. The pattern of this damage covers a wide spectrum from localized contusion to diffusely scattered foci, lacerations, and hematomas varying with the circumstances of the incident and the architecture of the victim's brain. TBI is classified by whether it is via blunt or penetrating mechanism. Penetrating injury may again have widely varying consequences depending on site, depth, and energy, but is generally fatal if it bilaterally traverses the midbrain.[112] The GCS categorizes TBI into mild, moderate, and severe injury according to the patient's presenting clinical characteristics and correlates with outcome after TBI (see Table 84.2).[113] Additionally, the Abbreviated Injury Scale (AIS) score for the head and neck region classifies TBI by ranking injuries on a six-point scale based on mortality risk, with "1" indicating minor injury and "6" indicating a nonsurvivable injury. Both scores are comparable in predicting short-term mortality after severe TBI.[114]

The management of TBI in the ICU should include comprehensive examination and assessment using such principles as outlined in the Advanced Trauma and Life Support protocol because occult injuries can escape initial screening.

Pathophysiology

As the brain has no tolerance for hypoxia, TBI patients need immediate treatment according to current guidelines.[24] Unfortunately, the extent of the primary injury cannot be influenced by therapy and, therefore, prevention (e.g., by helmets or airbags) is the only way to avoid damage. The primary brain damage triggers a cascade of pathophysiologic changes, which then lead to secondary brain damage. During the first post-traumatic days, the aim of treatment is to minimize the growth of the secondary damage as much as possible in order to rescue salvageable brain tissue. Pathologic processes such as elevated ICP (due to edema, hemorrhage, obstruction of CSF flow), diminution of arterial inflow, and consequent reduction in CPP with resulting tissue hypoxia and loss of cerebrovascular autoregulation increase secondary brain damage. Inflammation, massive release of excitatory neurotransmitters, apoptotic cell death, high lactic acid concentrations due to anaerobic glycolysis, depleted adenosine triphosphate (ATP)-stores, increased intracellular Ca^{2+} concentrations, generation of free radicals and proteolysis are some of the identified contributors to secondary brain damage. Unfortunately, despite intense research and characterization of all these mechanisms, no drug has been identified that can improve outcome after TBI in randomized, prospective clinical trials. This is most likely related to the complex pathophysiology of brain damage, the heterogeneous patterns of damage, and various preexisting patient diseases. TBI also leads to disturbances in other systems such as: sympathetic discharge of the autonomic nervous system, inflammatory responses, endocrine dysfunctions, electrolyte imbalances, cardiovascular and respiratory disturbances, and coagulation impairments. These systemic effects must be monitored and immediately treated, as they also contribute to secondary brain damage.

Traumatic SAH (tSAH) occurs in up to 60% of admissions for TBI and influences outcome after TBI.[115-117] Approximately 20% of patients with tSAH may also develop vasospasm, which causes secondary ischemic insult.

Treatment

All therapeutic strategies focus on optimization of the delivery of oxygen and glucose to the brain cells. These strategies include maintaining adequate CPP, controlling ICP, and optimizing oxygenation. Therefore, in the critical care setting, the management of TBI patients should follow established protocols with close monitoring of parameters, including CPP, ICP, and oxygenation status.[118] Clinical assessments like continuous measurement of arterial blood pressure, heart rate, and pulse oximetry in combination with monitoring volume status, urine output, and GCS have to be performed.

Cerebral Perfusion Pressure. CPP results from the difference of MAP minus ICP and should be kept between 60 and 70 mm Hg.[24] Aggressive attempts to maintain CPP above 70 mm Hg with fluids and vasopressors should be avoided, as this treatment increases the risk of respiratory failure. Arterial hypotension with a SBP below 90 mm Hg is strongly correlated to poor outcome and has to be avoided in the management of TBI patients.[14,116] There exists a smooth U-shaped relationship between systolic or MAP and outcome without any evidence of an abrupt threshold effect. Therefore, while current recommendations are to maintain SBP above 100 mm Hg for patients 50 to 69 years old or at or above 110 mm Hg for patients 15 to 49 or over 70 years old, new data possibly suggest that an optimal SBP of 135 mm Hg should be the target.[24,119]

BOX 84.2 Management Checklist for the Treatment of Intracranial Hypertension

1. Keep physiological variables in normal range (normotension, normocapnia, normoxia, normothermia, normoglycemia, normovolemia)
2. Head position (30-degree elevation); avoid rotation of the head
3. CPP 60-70 mm Hg; massive fluid-therapy or high doses of vasoconstrictors should be avoided
4. Normocapnia ($PaCO_2$ = 35-40 mm Hg); if ICP >20-25 mm Hg, then induce short-term hyperventilation ($PaCO_2$ = 30-35 mm Hg)
5. Provide adequate sedation
6. CSF drainage if ventricles are still detectable
7. Consider mannitol or hypertonic saline
8. Consider barbiturate therapy (under EEG monitoring)
9. Fever control

CPP, Cerebral perfusion pressure; *CSF*, cerebral spinal fluid; *EEG*, electroencephalogram; *ICP*, increases intracranial pressure; *$PaCO_2$*, arterial partial pressure of carbon dioxide.

Intracranial Pressure. Elevated ICP above 22 mm Hg is associated with increased mortality and should be treated[24] with measures according to the checklist in Box 84.2. This includes optimizing patient position, osmotherapy, deep sedation with barbiturates or propofol, and ventricular drains.[120] Hyperventilation reduces CBV and ICP due to its vasoconstrictive effect, but at the same time hyperventilation leads to a mismatch between oxygen delivery and oxygen consumption.[121] Therefore, hyperventilation is only a temporizing measure until other ICP-lowering measures are available. Decompressive craniectomy has been a strategy to lower ICP, but unfortunately this intervention increases the number of patients surviving in a vegetative state or with severe brain damage.[122,123] Prophylactic mild hypothermia was also a promising intervention to reduce ICP; however, in prospective multicenter studies, this therapy was not superior to normothermia.[35] ICP control with high-dose steroids was shown to have an adverse effect on mortality and morbidity in a multicenter study of more than 10,000 patients with brain injury.[124] Therefore, steroids are not recommended for control of ICP after TBI.

Oxygenation and Ventilation. Patients with GCS scores of 8 or less should be intubated and ventilated with a target of PaO_2 above 80 mm Hg. If PEEP is necessary, levels up to 15 cm H_2O have been shown to increase brain tissue oxygen pressure and oxygen saturation without increase in ICP or decrease in CPP.[19]

Sedation. TBI patients should be sedated with drugs with a short context-sensitive half-life like propofol to facilitate daily examination of their neurologic condition. Care should be taken to screen patients for propofol infusion syndrome, which can occur when high-dose propofol is used over several days.[125] Most of the barbiturates and benzodiazepines have a longer half-life and are, therefore, less

suitable. Low-dose inhalational anesthetic can also be used. At higher concentrations, volatile anesthetics possess a direct vasodilatory effect, which increases CBV and, in turn, ICP. Ketamine was contraindicated in TBI patients due to perceived risks of causing intracranial hypertension, but in intubated and ventilated patients, ketamine has no adverse effect on ICP.[126] Ketamine has several favorable effects like reduced need of supplementary vasopressors and narcotics, activation of bowel movement, and bronchodilation.[127] Narcotics, like sufentanil, fentanyl, and remifentanil, have no negative effects on ICP as long as MAP is maintained. Muscle relaxants can be used in TBI patients, with the potential exception of succinylcholine, which possibly increases ICP. Nitrous oxide (N_2O) and etomidate should not be used in patients after severe TBI.

Additional Interventions. In TBI patients, enteral nutrition is recommended to attain basal caloric replacement between the fifth and the seventh day after TBI.[24] Enteral feeding using a transgastric jejunal tube should be started as soon as possible.[128-130] Early tracheotomy can facilitate the weaning of the patients and reduce mechanical ventilation days, but there is no evidence that it reduces mortality or the rate of nosocomial pneumonia. Up to 25% of patients with isolated TBI develop deep vein thrombosis (DVT) with the risk of pulmonary embolism.[131] Low-molecular-weight heparin or low-dose unfractionated heparin should be used in combination with mechanical prophylaxis, despite the increased risk of intracranial hemorrhage expansion.[24] The Parkland Protocol, which stratifies patients into different risk groups for spontaneous progression of hemorrhage, can help assess the optimal timing for the start of DVT prophylaxis.[132] The incidence of early posttraumatic seizures (during the first week after TBI) can be reduced by phenytoin.[24] As these early posttraumatic seizures do not influence outcome, this prevention is not obligatory. Late posttraumatic seizures are not susceptible to prophylactic interventions.

SPINAL CORD INJURY

In up to 5% of all major trauma cases, the spinal cord is injured and about 14% of these patients suffer from an unstable spine injury.[133] The American Spinal Injury Association (ASIA) has classified SCI into five categories, where ASIA A represents a complete impairment and ASIA E represents normal sensation and motor function (Table 84.10). Surgical decompression of the spinal cord should be performed within 24 hours after SCI and is associated with improved neurologic outcome.[134,135]

Damage to the sympathetic outflow to the heart and vasculature after SCI contributes to systemic hypotension and bradycardia due to unopposed vagal tone, commonly referred to as neurogenic shock.[136] Injuries above T7 have an 85% risk of serious cardiovascular instability.[137] To avoid secondary injury after SCI, the MAP should be kept above 85 to 90 mm Hg during the first 7 days after injury using fluid and vasopressor therapy.[138,139] Fluid therapy should be monitored by cardiac output monitoring devices and hypotonic solutions like dextrose 5% in water, Ringer´s lactate, and 0.45% sodium chloride should be avoided, as they worsen cord edema. Vasopressors should be inotropic, chronotropic, and vasoconstrictive like α_1- and β_1-agonists (dopamine, norepinephrine). Dobutamine has generally no indication because of its β_2-receptor activation and its vasodilatory effects. In cases with life-threatening bradycardia, a cardiac pacemaker placement can be considered.[140]

TABLE 84.10 ASIA Classification of Spinal Injury

Grade	Clinical Presentation
Grade A	Complete. No sensory or motor function is preserved in the sacral segments S4-S5
Grade B	Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5
Grade C	Incomplete. Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3 (Grades 0-2).
Grade D	Incomplete. Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade greater than or equal to 3
Grade E	Normal. Sensory and motor functions are normal.

The need for ventilatory support depends on the level of injury. The muscles contributing to respiration are the diaphragm (phrenic nerve, C 3-5), the intercostal muscles (thoracic nerves), and the accessory muscles, including the sternocleidomastoid (cranial nerve 11) and scalene muscles (cervical plexus). Respiratory failure secondary to abdominal and intercostal muscle paralysis can still occur even with injuries below C5 because these muscles significantly increase the efficiency of diaphragmatic contractions. The traumatic sympathectomy also leads to intestinal atony with subsequent abdominal distention, which further deteriorates the efficacy of the already compromised diaphragm. With complete cervical SCI, acute respiratory failure is common, secondary to the sudden loss of functional residual capacity and the inability of the sternocleidomastoid muscle to stabilize the chest wall. As hypoxia leads to poor outcome after SCI, patients who develop respiratory insufficiency should be intubated as soon as possible. Weaning should be started early and if it is complicated, the patient should receive a tracheostomy to reduce mechanical ventilation days, decrease the need for sedation, and facilitate pulmonary toilet.

Lower limb blood flow is reduced with increased arterial and venous pooling. This is associated with a higher incidence of thromboembolic disease, and early administration of venous thromboembolism prophylaxis within 72 hours after injury is recommended. Inferior vena cava filters are not suitable for prophylaxis.[138]

Many drugs have been tested for their potential neuroprotective effects; however, high-dose methylprednisolone, monosialotetrahexosylganglioside (GM-1), riluzole, fibroblast growth factor, minocycline, or magnesium have not improved outcome after SCI in prospective, randomized, multicenter studies.[141] Early mild hypothermia after SCI showed some promising results in clinical studies; however, they have to be validated by prospective, randomized, multicenter studies.[142]

Cerebrovascular Disease

Cerebrovascular diseases are the leading cause of death and disability worldwide.[143] Although clinical presentations and outcomes are highly variable, initial management often requires critical care resuscitation. Ischemic strokes are the most common (80%-90%) of stroke subtypes and are increasingly a larger proportion of post-procedural ICU management. Hemorrhagic strokes account for the remaining 10% to 20% of strokes, but are often the most medically complex and have the longest length of stay and highest morbidity and mortality in the ICU.[144] The following sections will provide an overview of the most common critical care management issues for SAH, ischemic stroke, and intracerebral hemorrhage (ICH).

SUBARACHNOID HEMORRHAGE

SAH is a neurologic emergency that requires critical care management. Accounting for less than 5% of all strokes worldwide, SAH is associated with severe morbidity and mortality. Most cases of SAH are aneurysmal in origin (aSAH). The incidence of aSAH per 100,000 person years is variable by ethnicity and geography—the lowest incidence being in China (2), followed by Central and South America (4.2), United States (8-15), and the highest being in Finland and Japan (19-23).[145,146] Women have a greater risk than men by a factor of 1.24, with a higher incidence among blacks and Hispanics compared to Caucasians. Most aneurysms occur between ages 40 and 60 years, with a mean age of 55 years.[145] Risk factors for aSAH include cigarette smoking, hypertension, heavy alcohol abuse, use of sympathomimetic agents, family history of SAH, and prior history of aSAH.[147] Between 10% and 15% of patients will die before hospitalization, and 25% will die within the first 48 hours. The initial hemorrhage is usually the primary cause of death, followed by rebleeding.[148] Case fatality rates had continued to decline in recent decades from 50% to 33% with the advent of endovascular treatment, microsurgical techniques, and improved ICU management.[149]

Early Brain Injury

The degree of neurologic abnormalities and the amount of bleeding are the strongest predictors of clinical outcome and complications after SAH. The Hunt and Hess grading system and World Federation of Neurological Surgeons Scale (WFNSS) are the most widely used (see Tables 84.3 and 84.4) with higher WFNSS and Hunt and Hess grades associated with worse clinical outcomes.[41,42] In the first 72 hours after the acute bleed, multiple mechanisms such as transient global ischemia, elevated intracranial pressures, and toxicity from SAH have been implicated in early brain injury. Subsequent effects on CBF, microcirculatory changes, cerebral edema, and sympathetic response can lead to both neurologic and systemic complications.[150,151] Acute management of blood pressure and oxygenation are critical in this period along with the prevention of early complications such as rebleeding, acute hydrocephalus, and elevated ICPs. Ideally, patients should be managed in high-volume facilities with dedicated neurocritical care units.[152]

Rebleeding. Rebleeding is a serious complication that significantly worsens outcomes and increases mortality as high as 70%.[153] The risk of rebleeding is the highest within the first 24 hours (4%-15%) after the initial bleed, remains elevated for the next 2 to 4 weeks (1%-2% per day), then eventually decreases to 2% to 4% annually after the first 6 months.[154-156] To reduce the risk of rebleeding, guidelines recommend securing the ruptured aneurysm by surgical clipping or endovascular coiling as soon as possible and ideally within the first 24 hours after symptom onset.[157-159] Since the publication of the International Subarachnoid Aneurysm Trial, endovascular coiling is the recommended treatment when the location, size, and morphology of aneurysm are favorable. Some aneurysms may be more suitable for surgical clipping. There should not be any delay in securing a ruptured aneurysm, regardless of the treatment modality chosen.[160,161] When surgical clipping or endovascular coiling are delayed, short-term (less than 72 hours) treatment with antifibrinolytic agents (aminocaproic acid or tranexamic acid) is recommended. In addition, seizure prophylaxis can be considered until the aneurysm is treated along with blood pressure control to normotensive goals.[158,162,163]

Acute Hydrocephalus. Acute hydrocephalus develops in 25% to 30% of patients after SAH, and emergency ventriculostomy may be lifesaving.[164] Patients with hydrocephalus can develop progressive deterioration leading to stupor and coma as well as more subtle clinical signs of gaze palsy, pupillary dysfunction, and cognitive slowing. Head CT showing ventricular dilation can be diagnostic and can facilitate early ventriculostomy placement. Hydrocephalus after SAH can be caused by obstruction of CSF outflow by blood products or by impaired CSF absorption by arachnoid granulations.[165] Most patients should have ventriculostomy drains removed when they no longer require external drainage and ICPs have stabilized. Some patients will develop delayed hydrocephalus (3-21 days after the onset), and 20% of patients will need ventriculoperitoneal (VP) shunt placement for chronic hydrocephalus.[157]

Neurogenic Cardiac and Pulmonary Disturbances. Cardiac and pulmonary disturbances are common after SAH and are thought to be secondary to a surge in catecholamine levels and sympathetic tone.[166,167] Significant autonomic nervous system disturbance after SAH can result in changes in the electrocardiogram and lead to myocardial dysfunction. Transient ECG abnormalities range from sinus tachycardia, peaked T-waves, T-wave inversions, and QT prolongation to ST segment depression or elevation.[168] Electrocardiographic changes are frequent but do not appear to relate to outcome.[169]

Cardiac dysfunction, however, can have a significant impact on management after SAH. Abnormal echocardiography has been described in up to 8% of SAH patients. Poor grade SAH patients can develop sudden hypoxemia and cardiogenic shock with or without pulmonary edema. This phenomenon of neurogenic stunned myocardium can cause severe limitation of cardiac contractility, which is reversible and associated with a good recovery profile. Patients with SAH have echocardiogram changes similar to takotsubo cardiomyopathy, which is also an acute transient dysfunction resulting from sympathetic overactivity.[170] Adrenoreceptor polymorphism has been implicated

BOX 84.3 Suggested Cardiovascular Management Strategies in Subarachnoid Hemorrhage

General

1. Manage hypertension in unsecured aneurysms (systolic BP < 140 mm Hg)
2. Maintain euvolemia prophylactically; no role for prophylactic hypervolemia.
3. Administer nimodipine.

Cardiovascular Instability

1. BP and cardiac output goals will alter as aneurysm is secured.
2. ECG

If abnormal (QTc prolongation, ST-segment changes): check troponins.

If troponins elevated: perform echocardiography.

3. Perform echocardiography if any hemodynamic lability or heart failure is suspected.
4. Monitor cardiac output.
5. Select vasopressors for cardiac output and blood pressure.
6. Consider aneurysm treatment as soon as practical.
7. Reserve coronary catheterization for isolated wall motion deficit and rising troponins (coil aneurysm first if possible).
8. Delayed cerebral ischemia: treat with euvolemia/mild hypervolemia, vasopressors, and cardiac output monitoring; adjust management based on perfusion targets when possible.
9. Transfusion: maintain hematocrit >25%.

BP, Blood pressure; *ECG,* electrocardiogram.

in myocardial stunning. Different receptor genotypes have an increased sensitivity to catecholamines and are associated with a 3- to 4.8-fold increased risk of cardiac injury and dysfunction.[171]

Troponins are frequently elevated in about 30% of patients after acute SAH. High serum levels are associated with increased hemorrhage, hemodynamic fluctuations, and worse outcomes.[172] Release of troponin can represent cardiac ischemia in patients with atherosclerotic heart disease or a "myocardial leak" from neurogenic injury.[172]

Cardiac dysfunction may complicate and limit the active treatment options for delayed cerebral ischemia (DCI) and increased ICP. A typical strategy for cardiovascular management is given in Box 84.3 based on comprehensive consensus guidelines.[157,158]

Pulmonary injury is a frequent complication after SAH, with nearly 17% of patients developing severe pulmonary dysfunction, including ARDS, which is associated with poor neurologic outcome.[173] In addition to acquired respiratory infections, common in ventilated ICU patients, neurogenic pulmonary edema caused by increased permeability of the pulmonary vasculature can occur in isolation or in combination with neurogenic cardiac problems.[174]

Secondary Brain Injury

Delayed Cerebral Ischemia. DCI is one of the most severe complications of SAH and is associated with worse outcomes. Although the exact mechanism of DCI is still unclear, multiple potential causes beyond cerebral vasospasm have been investigated, including microcirculatory dysfunction, microthrombosis, cortical spreading depolarization, and neuroinflammation.[175,176] About one-third of patients will develop symptoms from DCI as early as 3 to 5 days after the onset, with a peak frequency between 5 and 7 days, generally waning over 2 to 4 weeks. Seventy percent of patients will develop angiographic vasospasm, although only 30% to 40% of patients will become symptomatic. In addition, not all patients with DCI have evidence of vasospasm, suggesting vasospasm-independent mechanisms.[177]

Cerebral vasospasm is still considered as a cause of DCI, and most often the target of treatment interventions. Patients with a large amount of subarachnoid blood are at a higher risk for developing vasospasm. Radiographic tools such as the Hijdra sum score and Fisher score were developed to predict vasospasm (Table 84.8).[104,178] The modified Fisher score is the most commonly used to clinically prognosticate the risk of vasospasm (Table 84.9),[179] with the highest incidence of vasospasm observed in patients with modified Fisher grade 4.[180] Vasospasm monitoring is facilitated by serial clinical exams and the use of imaging modalities such as transcranial Doppler, CT with perfusion, and cerebral angiography.

Medical management of DCI centers on augmentation of arterial blood pressure with vasopressors, in the context of euvolemia rather than hypervolemia.[181] "Triple-H therapy," hypertension-hypervolemia-hemodilution, is no longer recommended because there was little evidence of benefit and potential harm shown in randomized control trials and meta-analyses.[182] The use of deliberate transfusion to increase oxygen delivery in the setting of DCI is controversial and needs to be balanced against the deleterious effects of transfusion. A prospective trial is awaited. Trials of endothelin antagonists and statins provided further evidence of some dissociation between vasospasm and clinical outcomes, as neither drug class showed any effect on outcome despite a decrease in the incidence of vasospasm.[183]

Nimodipine should be started for all patients as soon as possible after diagnosis for 21 days. Studies on the use of nimodipine provide the only level I evidence from randomized control trials in SAH that showed modest reduction in the incidence of ischemic deficit without any apparent effect on angiographic vasospasm.[184-187]

In patients who are refractory to medical therapy for DCI, the use of endovascular therapies can be considered.[188,189] Mechanical balloon dilation of blood vessels (angioplasty) can provide an effective treatment for vasospasm involving the larger arteries.[190,191] Intraarterial injection of vasodilator agents, most commonly calcium channel blockers such as nicardipine and verapamil, can be effective in smaller caliber vessels but are limited by the transient nature of their effects (<24 hours).[192]

Hyponatremia. Hyponatremia is observed in 30% to 40% of patients with SAH, and is most commonly the result of cerebral salt-wasting syndrome (CSWS) or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[193] Because these two conditions have different pathophysiology, correct diagnosis and management of hyponatremia is important, particularly when it precedes development of DCI and can worsen clinical outcome. In CSWS, sodium is actively excreted from the body in high concentration, and accompanying diuresis occurs, despite ongoing hyponatremia with hypovolemia.[194] Management of CSWS is the replacement of sodium with isotonic or hypertonic saline to restore volume depletion. Fludrocortisone is considered if diuresis is active and precludes the

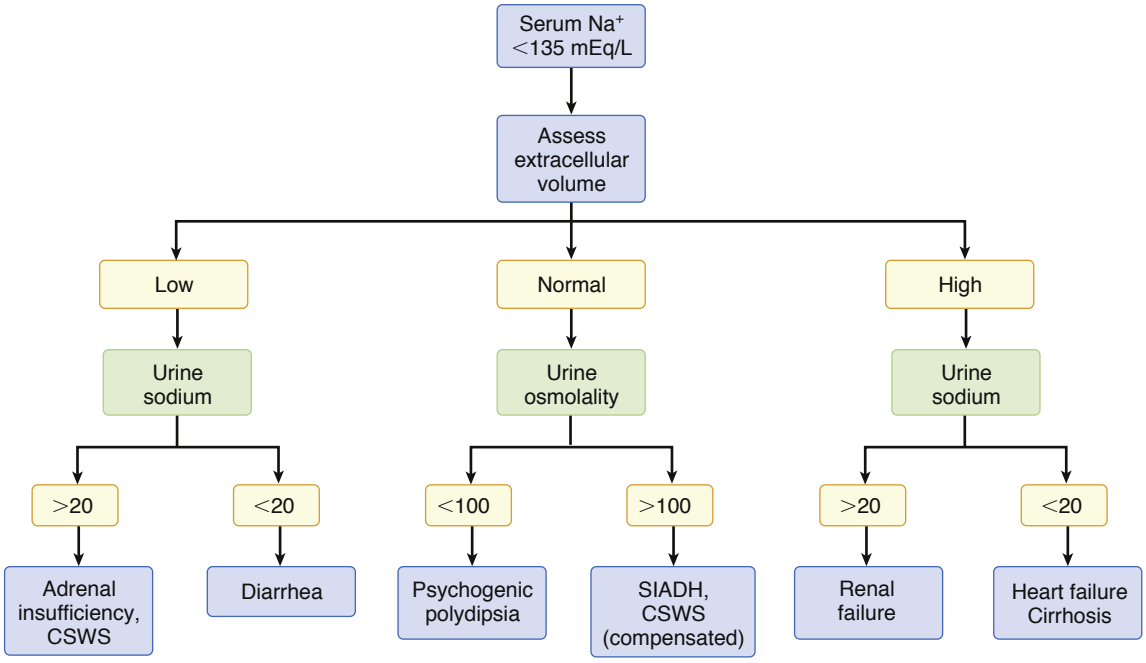

Fig. 84.7 Algorithm for the differential diagnosis of hyponatremia in the neurosurgical patient. *CSWS,* Cerebral salt-wasting syndrome; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone.

maintenance of adequate fluid balance.[157,158] Patients with SIADH are typically hypervolemic and are treated with fluid restriction to restore euvolemia and suppress antidiuretic hormone (ADH) release.[195] A suggested algorithm for resolving diagnostic uncertainty is given in Fig. 84.7.

ISCHEMIC STROKE

Stroke is the fifth leading cause of death in the United States and the second leading cause of death globally, accounting for nearly 12% of deaths worldwide with disproportionately higher mortality rates in lower income countries. Although mortality has declined in the United States, stroke remains a major source of disability.[196,197]

Acute ischemic stroke (AIS) is increasingly a treatable neurologic emergency. The deprivation of oxygen and nutrients to the brain beyond the combined thresholds of severity and time induces cellular death in neuronal tissue, resulting in ischemic infarction. The ischemic penumbra is potentially salvageable when factors such as collateral flow and residual perfusion blood flow to brain tissue yield a longer period before irreversible ischemic injury, thereby giving the opportunity for aggressive intervention with revascularization therapies such as thrombolysis and mechanical thrombectomy. Current guidelines recommend intravenous thrombolytics within 4.5 hours and embolectomy with modern thrombectomy devices for large vessel occlusion within 6 hours of symptom onset in eligible patients.[198-200] With current perfusion imaging tools, embolectomy in expanded time windows after stroke onset has shown efficacy in selected patients.[201] Vertebrobasilar occlusion may also benefit from the more recent techniques in even longer time windows.[202]

Successful management of AIS extends beyond the emergency treatment to reperfuse and recover threatened brain tissue. Ongoing management in the critical care setting is necessary to maintain adequate CBF to protect the ischemic penumbra and address factors that adversely affect vulnerable ischemic brain tissue such as fever and abnormal glucose. Early management of the potential complications of AIS, including postinfarction cerebral edema, hemorrhagic transformation, and reperfusion injury, are critical to improving patient outcomes.

Hypotension is uncommon after AIS but requires aggressive management. Neurologic deterioration, poor outcomes, and increased mortality have been reported with baseline blood pressures less than 100/70 mm Hg.[203] Common causes of arterial hypotension include hypovolemia, blood loss, decreased cardiac output, myocardial infarction, and arrhythmias. Neurocardiogenic injury has been described in particular with involvement of the right insula and may predispose to ECG changes and life-threatening arrhythmias.[204,205] The most common arrhythmia associated with AIS is atrial fibrillation.[206] Cardiac monitoring is recommended for at least the first 24 hours after stroke, with additional monitoring of cardiac function if there is evidence of symptomatic heart failure.

Elevated blood pressure should not be aggressively treated in the acute setting because the potential risk of lowering blood pressure may threaten penumbral perfusion and exacerbate brain ischemia. Urgent antihypertensive treatment may be needed for medical complications such as hypertensive encephalopathy, aortic dissection, and acute organ failure. Cautious lowering of blood pressure by 15% if it exceeds 220/120 mm Hg is indicated in certain clinical conditions. Because of the risk of hemorrhagic transformation with thrombolysis, blood pressure should be lowered to less than or equal to 185/110 mm Hg prior to treatment and maintained at less than 180/105 mm Hg for at least 24 hours. Similar blood pressure goals are recommended after revascularization procedures such as intraarterial thrombolysis and embolectomy.[198]

Hypoxia can also exacerbate ischemic injury. Poor airway control, hypoventilation, and aspiration pneumonia are most common after AIS. The patient's airway should be assessed, and tracheal intubation must be considered in stuporous or comatose patients. In addition, patients with brainstem involvement may be at high risk for aspiration. Although intubation and mechanical ventilation is associated with poor outcome and increased mortality, prevention of hypoxia and aspiration pneumonia should be considered.[198]

Changes in the patient examination after AIS may indicate a hemorrhagic complication, cerebral hyperperfusion, or cerebral edema and should prompt an emergent noncontrast CT. Thrombolysis bleeding should be treated with emergency administration of cryoprecipitate. Other rare events to monitor after alteplase administration include allergic reactions such as anaphylaxis and angioedema.[207,208] Attention should be paid to any signs of systemic hemorrhage such as lower abdominal pain, which may indicate retroperitoneal bleeding after embolectomy. Cerebral hyperperfusion is rare, but can also cause neurologic symptoms likely caused by sudden, rapid increase in CBF following revascularization. If severe, patients may develop headache, seizures, confusion, and potentially fatal cerebral edema and intracranial hemorrhage. Blood pressure should be monitored and lowered in patients with suspected hyperperfusion syndrome.[209]

Cerebral edema typically occurs during the first 3 to 5 days after AIS and subsides by 2 weeks. The overall risk of significant cerebral edema is low but tends to occur with distal carotid artery or MCA occlusion with complete MCA infarction. A subset of patients can have early (within 24 hours) malignant cerebral edema with brain herniation signs, which is associated with the highest mortality after AIS. Posterior fossa strokes are also associated with rapid neurologic deterioration from brain edema. Cerebellar infarctions may produce local edema that causes acute hydrocephalus with brainstem compression that can lead to rapid coma and sudden respiratory failure. Medical management using hyperosmolar therapies with mannitol and hypertonic saline and temporary hyperventilation may be helpful. Surgical interventions include management of hydrocephalus with external ventricular drainage and decompressive craniectomy. Early suboccipital craniectomy is potentially lifesaving with good clinical results.[210] Hemicraniectomy for anterior circulation stroke remains more controversial. In selected patients when performed early, outcomes may be better. Based on the combination of randomized trials in Europe, early decompressive hemicraniectomy is effective in decreasing mortality and improving clinical outcome in survivors.[211,212]

A standardized and systematic approach to stroke treatment provided by certified stroke centers has been shown to improve outcomes. Established protocols for all stroke patients including their ICU care have led to more uniform management of not only emergency delivery of care, but also supportive medical care such as glucose control, prevention of deep venous thrombosis, nutrition, and early rehabilitation.[213]

INTRACEREBRAL HEMORRHAGE

ICH has an overall incidence of 24.6 per 100,000 person years, with a high case fatality rate especially in low-income countries.[214,215] Nontraumatic ICH is often categorized as spontaneous or primary when associated with risk factors such as hypertension, tobacco, alcohol and substance use, antithrombotic medications, underlying coagulopathy, and amyloid angiopathy (especially in lobar hemorrhages). ICH may also arise from secondary causes such as ruptured aneurysm, ruptured vascular malformation, conversion from ischemic stroke, or tumor. This wide range of differential diagnoses can swiftly be refined by CT angiogram and assessment of pathophysiologic effect, with accompanying clinical signs aiding localization. Angiography may be required to further characterize any underlying vascular sources such as aneurysm, arteriovenous malformation, or dural fistula.

Management is important to avoid secondary insult by reducing the incidence of rebleeding, hypoxemia, hypercarbia, or cerebral edema. Initial care is directed toward the airway and circulation, with control of arterial blood pressure and early reversal of coagulopathy to decrease the risk of ICH volume expansion and rebleeding.[215,216] If the ICH is in the posterior fossa or midbrain, consideration should be given to the insertion of a ventriculostomy and early surgical decompression to reduce the risk of hydrocephalus and brainstem compression. Patients with lesions in these regions are prone to airway and respiratory problems and may need early tracheal intubation to protect their airway and prevent aspiration. The use of clinical severity scores such as NIH Stroke Scale and GCS with hourly neurologic assessments can detect early clinical deterioration prompting repeat imaging and aggressive management of cerebral edema or hematoma expansion. Medical management of volume status and sodium can be critical in patients with cerebral edema requiring hyperosmolar therapies.[216] The use of validated prognostic scores such as the ICH score for mortality and FUNC score for functional independence are additional tools that providers can use to communicate goals of care.[217,218]

Hypertension after ICH is common and associated with increased hematoma volumes and worse outcomes. Based on randomized controlled trials of aggressive blood pressure management, lowering SBP to a range of 120 to 140 mm Hg was safe, but did not improve outcomes when compared to lowering SBP to 140 to 160 mm Hg and is reflected in the American Heart Association guidelines.[215,219-221] If the initial CT or MRI appearance suggests aneurysm or arteriovenous malformation, then care should be taken to limit blood pressure to reduce the risk of rebleeding. The addition of ICP monitoring allows setting a CPP target and provides a more physiologic approach to the management of systemic blood pressure.

Coagulopathy increases the severity of ICH, with significant hematoma expansion. Acute management with rapid reversal of coagulopathy is warranted.[222] In the setting of vitamin K antagonists, use of prothrombin complex concentrates (PCCs) is advocated. In a prospective, randomized trial of PCC compared to fresh frozen plasma (FFP), PCCs had significantly faster international normalized ratio correction, decreased hematoma expansion, and decreased mortality.[223] There were no significant differences with thrombotic complications, and PCCs avoided the risk of volume overload and

transfusion reactions associated with FFP. In patients with known recent thrombotic events, PCCs should be used with caution. With increasing use of the novel oral anticoagulants (NOACs), there is a rising need for rapid reversal agents for NOAC-associated ICH. Idarucizumab is a monoclonal antibody that can bind to dabigatran and rapidly correct coagulopathy in the setting of life-threatening bleed. Andexanet alfa was recently approved by the FDA for reversal of factor Xa inhibitors.[222] In ICH patients on antiplatelet therapy, the use of platelet transfusions to reduce the risk of hematoma expansion and improve outcomes are more controversial. In a prospective, randomized trial of platelet transfusion within 6 hours compared to standard medical therapy in a nonsurgical ICH population, there was no benefit to transfusion, and an increase in mortality and higher disability.[224] Platelet transfusion prior to surgical intervention has not been well studied.

Other neuroprotection strategies remain unproven. Unlike SAH, nimodipine does not have an established role in ICH. Corticosteroids are also not indicated. Statins may be beneficial in ICH when continued in current users. However, starting statins in acute ICH has not been proven beneficial. The role of long-term statin and increased risk of recurrent bleed is also controversial.[215,225] Newer agents such as the iron chelator, deferoxamine, are currently in clinical trials. Large trials of surgical hematoma evacuation have not shown benefit.[226] However, in patients with cerebellar hemorrhage and brainstem compression or in those showing acute neurologic deterioration or obstructive hydrocephalus, surgical evacuation may be indicated.[215] The use of thrombolytics in intraventricular hemorrhage was shown in a randomized, controlled trial to improve mortality, but not functional outcome.[227] There are several ongoing trials testing the benefit of decompressive surgery without hematoma evacuation, minimally invasive surgery, catheter-based hematoma aspiration with thrombolysis (phase 3 trial), and new endoscopic devices.

STATUS EPILEPTICUS

Status epilepticus is a medical and neurologic emergency that is associated with significant morbidity and mortality. Defined as continuous or rapid sequential seizure activity without recovery between attacks, or more strictly, continuous seizure lasting at least 30 minutes, this condition affects both children and adults with an estimated annual incidence of 12.6 per 100,000 worldwide.[228] Although all types of seizures may present status epilepticus, there are two main classifications: convulsive (typically generalized tonic-clonic activity) and nonconvulsive. In addition, psychogenic or nonepileptic seizures can mimic status epilepticus and present their own particular diagnostic challenges.[229] In comatose critically ill patients, obtain an EEG if there are no other explanations for the comatose state.

Seizure activity may arise from multiple etiologies, including any major insult affecting the cerebral cortex (e.g.,vascular, infectious, mechanical, metabolic, or toxic). Even mild insults may provoke status epilepticus if the seizure threshold is reduced by preexisting parenchymal disease or comorbidity (e.g., alcohol withdrawal). Given the previously outlined emphasis on the avoidance and termination of secondary insult to the brain, management of status epilepticus is focused on acute stabilization, rapid control of seizures, and timely identification and treatment of the underlying etiology. Management guidelines have been published that address the important phases of management.[230] Initial goals in the first 5 minutes of treatment include stabilization of the patient's airway, breathing, and circulation with rapid assessment of any neurologic disability. The subsequent treatment phases are focused on seizure termination and prevention of recurrence. Prompt treatment of seizure in the first 5 to 10 minutes should be instituted because a seizure lasting beyond 5 minutes is unlikely to stop spontaneously. Recommended agents include midazolam, lorazepam, and diazepam. If seizures persist, second phase treatments include loading doses of anticonvulsants such as fosphenytoin, valproic acid, levetiracetam, or phenobarbital (if other agents are not available). Ongoing seizures beyond 40 minutes involve third-phase therapies, which include repeating second-line agents or moving to anesthetic doses of thiopental, midazolam, pentobarbital, or propofol. This approach would likely require intubation and ventilation. Paralytic agents should be avoided for the long-term due to fear of masking ongoing or recurrent seizures. Continuous EEG is highly recommended. In patients refractory to treatment, alternative options such as inhaled anesthetics and electroconvulsive therapies have been used with success, but evidence supporting the routine use is lacking.[231,232]

Status epilepticus is also associated with numerous systemic complications that can be related directly to the neurologic injury or associated with the treatments. Early management of acute hypoxic respiratory failure and associated acid-base imbalance can prevent secondary injury. Treatment of glucose abnormalities and early detection and treatment of infection can also prevent seizure recurrence. Myocardial depression from cardiotoxicity of seizure treatments may require additional cardiac monitoring and vasopressor support. Traumatic injury, rhabdomyolysis, and renal dysfunction should be monitored in patients with prolonged convulsions. Many of the antiepileptic medications can cause ileus, hypomotility, and potentially gut ischemia.[233]

Neuromuscular Disease

Neuromuscular diseases involving the muscle, nerve, and neuromuscular junction can pose unique challenges for the anesthesiologist in the ICU. We will review two common diseases that may require critical care management.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is a common cause of acute, severe neuropathy occurring at a rate of 1 to 2 cases per 100,000 persons per year worldwide. The incidence increases with age and is more prevalent in men. Because of the associated complications, including respiratory failure, GBS is one of the neurologic causes of admission to critical care units. Although GBS is associated with low overall mortality (6.9%), mortality increases with the need for mechanical ventilation (14.3%). These patients tend to have a higher incidence of cardiorespiratory arrest before ICU admission, prolonged ICU length of stay, and higher severity of illness scores.[234-236]

Several distinct clinical variants are associated with the syndrome, including acute inflammatory demyelinating

polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), and Miller-Fisher syndrome (MFS). The classic and most common variant of GBS is AIDP that typically manifests as a relatively symmetric, ascending muscle weakness that can progressively lead to severe flaccid paralysis and respiratory failure affecting 20% to 30% of cases. More than half the patients have a recent history of bacterial or viral infection. *Campylobacter jejuni* is the most frequently observed pathogen, along with cytomegalovirus, Epstein-Barr virus, and herpes simplex virus.[237] Regional variation has been associated with higher rates of infectious exposures, including recent association with the Zika and chikungunya viral epidemics.[238] GBS may also display sensory and autonomic features, depending on the subtype, and variation in speed of onset and offset. The AMAN variant is usually associated with *C. jejuni* infections, and the severe limb weakness is related to the autoimmune antibody response against GM1 and GD1a gangliosides. Similarly, with the MFS variant, anti-GQ1b antibodies can cause symptoms affecting the cranial nerves resulting in the clinical triad of ophthalmoplegia, ataxia, and areflexia.[235]

Commonly, the preceding infection or other immune response triggers an autoimmune reaction to peripheral nerves and spinal roots. Within 1 to 2 weeks after exposure, symptoms progress over several days to reach their peak at 2 to 4 weeks, with a plateau thereafter. In approximately 5% of patients, GBS progresses more rapidly, with maximal loss of function within 72 hours of symptom onset. At 4 weeks, most patients have progressed to the limit of their symptoms, and improvement is observed to start soon thereafter. However, recovery may be protracted for months to years depending on the extent of nerve injury.[239,240]

Investigations should include electrocardiography, CSF protein (for acellular protein elevation), electrophysiologic studies (axonal degeneration is associated with poorer recovery), and antibody status or screening for possible causative pathogens as well as prognosis. GM1 antibody is associated with worse recovery.[240]

Loss of ventilatory efficacy is often the main reason for admission to the ICU. A forced vital capacity of less than 20 mL/kg is a sensitive indicator of need for observation, and 15 mL/kg for probable intubation, along with maximal inspiratory pressure (MIP) less than -30 cm H_2O and clinical signs of fatigue and airway compromise. Hypercarbia is a relatively late sign, and the clinician should not rely on it. The Erasmus GBS Respiratory Insufficiency Score (EGRIS) is a validated tool to assist in prediction of which patients may benefit from early admission to the ICU based on severity of weakness, timing of symptoms, and bulbar symptoms.[241] Similarly, predicting successful weaning occurs in younger patients with milder symptoms and evidence of rapid improvement. Early tracheostomy in identifiably prolonged respiratory failure cases is appropriate.[242]

Dysautonomia is seen in up to 20% of patients and is a source of morbidity.[240] ICU level monitoring should also be considered for GBS patients with autonomic nervous system involvement that can cause cardiac arrhythmia, blood pressure lability, uncontrolled sweating, temperature dysregulation, ileus, and bladder dysfunction.

Supportive care in the ICU is important for patient outcomes, including DVT prophylaxis, early mobilization and rehabilitation, nutrition, and psychosocial support. Specific challenges to management are the problems of deafferentation pain and psychiatric depression. The pain can be severe, is truncal in distribution, and may respond to anticonvulsants more than opiates. It certainly contributes to the frequently observed depression. This pain is often magnified by immobility, boredom, and the limited ability of busy staff to engage actively with a cognitively intact patient.[240]

Both symptom limitation and recovery from GBS have been improved with the use of plasmapheresis or intravenous immune globulin (IVIG). No advantage is seen with one treatment approach over the other or in combination. However, many physicians try them sequentially in cases of treatment failure. In patients with acute respiratory failure, persistence of lack of foot flexion at the conclusion of immunotherapy is an indicator of prolonged mechanical ventilation.[243] Neither interferon nor corticosteroid use has been shown to improve outcome, either alone or in combination with immunotherapy, but newer immune modulation drugs are currently in clinical trials.[244]

MYASTHENIA GRAVIS

Several disorders affecting the neuromuscular junction, including toxins and immune-mediated and genetic syndromes, can cause skeletal muscle weakness. Myasthenia gravis (MG) is the most common of these disorders. Although the majority of patients with MG have autoantibodies against the muscle nicotinic acetylcholine receptor (AChR-Ab), some patients will have autoantibodies to muscle-specific tyrosine kinase (MuSK-Ab) or lipoprotein-related protein 4 (LRP4). Myasthenia itself has a strong association with various autoimmune conditions (e.g., thyroid disease, pernicious anemia, and rheumatoid arthritis), as well as being linked to women with certain human leukocyte antigen types.[245,246]

Although MG is a relatively rare disease (incidence of 4 to 12 per million person years and prevalence of 40 to 180 per million worldwide), it is relevant to neurocritical care in that patients can present acutely in myasthenic crisis with rapid deterioration of muscle function and ventilatory failure. Typical of autoimmune diseases, MG occurs in young adult women, with a mean age of 30. There is also a late onset presentation in men with mean age over 50 years. Modern management with immunosuppression and supportive treatment has led to improved prognosis with overall mortality rates of 2.2% to 4.5%, including recent lower ICU mortality rates of 5.3%.[247,248]

The myasthenic crisis can be precipitated by a progression in severity of the disease state or often by amplification by another factor. This factor can include infection, recent surgery, or interruption of immunosuppressants. Many drugs can exacerbate myasthenic crisis, including aminoglycosides, fluoroquinolones, anticonvulsants (including phenytoin), steroids, β-blockers, calcium channel antagonists, ketamine, lidocaine, neuromuscular blockers, and anticholinergic agents.[249]

The diagnosis should be suspected in patients with variable weakness, including respiratory, ocular, and bulbar muscles. Diagnostic workup is often to exclude GBS, brainstem stroke, organophosphate poisoning, and botulism. Tests should include electrophysiologic studies (helpful in

seronegative cases), CSF protein, edrophonium response (less commonly used), and autoantibody testing to AChR and MUSK and LRP4. Subtyping by autoantibody type is increasingly important for diagnosis and management.[245]

The presentation is typically that of acutely worsening weakness of the respiratory or pharyngeal muscles. The patient should be observed closely for signs of impending respiratory failure. Forced vital capacity is useful, with 15 mL/kg being a useful trigger for intubation.[250]

Symptomatic treatment with acetylcholinesterase inhibitors is often diagnostic as well as therapeutic, balancing improvement in weakness with side effects from cholinergic stimulation. The other mainstay of therapy is immunomodulation. Typically, IVIG or plasmapheresis is started quickly to limit progression of severe generalized symptoms and avert frank crisis. Corticosteroids do have a role in establishing longer-term control of immunosuppression because IVIG and plasmapheresis have limited duration of efficacy. Corticosteroids alone are associated with a transient worsening of symptoms, before improvement, so they are best used concurrently with or immediately after plasmapheresis or IVIG. Chronic management typically involves tapering to low doses of prednisone with addition of a glucocorticoid-sparing immunomodulating agent (azathioprine, mycophenolate mofetil, cyclosporine, or tacrolimus) if necessary. Newer immunosuppression agents, including complement inhibition, are potentially new strategies.[251]

Central Nervous System Infection

Meningitis and encephalitis can be life threatening neurologic emergencies that require critical care management. Inflammation of the meninges and/or the brain can have multiple etiologies with CNS infections being the most common and having significant morbidity and mortality. Early recognition and treatment particularly of bacterial meningitis and herpes encephalitis can improve patient outcomes. The global burden of CNS infection disproportionately impacts lower-income countries. For bacterial meningitis, there are an estimated 3 million cases each year with the highest incidence of 85 cases per 100,000 persons in low income versus 6 cases per 100,000 persons in higher income countries.[252]

MENINGITIS

Meningitis is a serious condition producing inflammation of the leptomeninges covering the CNS. The causative pathogens differ among different patient populations. Community infections are frequently caused by *Streptococcus pneumoniae, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis,* and group B streptococci. *N. meningitidis* is particularly evident in teenagers. Since the advent of childhood vaccination programs, meningitis has become quite rare in high-income countries, with the highest incidence in children under the age of 1. In low-income countries, poverty and poor access to health care have led to persistently high rates of infection with regional differences in the pathogens reported. In the United States, *H. influenzae* affects mainly adults, but other organisms tend to affect all age groups. Worldwide, *S. pneumonia* and *N. meningitidis* are the most common pathogens in adults. Viral infections typically have a more subacute presentation. Fungal meningitis should be considered in immunocompromised patients. Nosocomial infection, in contrast, predominantly arises in the neurosurgical patient, especially with the use of ventricular devices, and the pathogens here comprise gram-negative rods and staphylococci.[253]

Initial assessment should include basic resuscitation, attention to airway management in patients with low GCS, and assessment of sepsis. Diagnostic features include fever, almost invariably with the classic nuchal rigidity and change in mental status; less often, photophobia, papilledema, and new-onset seizures may be seen. A rash is typical of meningococcal infection. Tests should include CSF cell count, protein, glucose, Gram stain, and culture, but any previous antibiotic dosing can diminish sensitivity, although polymerase chain reaction (PCR) testing using amplification may be able to identify small amounts of DNA in a sample. Viral PCR, immunoglobulin, fungal antigens, and cultures can also be considered. Opening pressure should always be recorded when possible. A CT scan should delay the lumbar puncture only when the patient's history suggests a previous mass lesion, stroke, or focal infection, recent seizures, or immunocompromised state.[254] Similarly, signs of papilledema, depressed level of consciousness, or focal deficit indicate a need for a CT examination to avoid herniation. Cerebral edema can develop in patients with meningitis and can lead to acute deterioration in mental status. ICP monitoring may be indicated.[255]

Treatment should be instituted quickly, delaying only to obtain emergency samples for Gram stain and culture. If no identification is possible on Gram stain, empiric antibiotic therapy should be delivered with third-generation cephalosporins (e.g., ceftriaxone or cefotaxime), along with vancomycin, until organism identification and sensitivities are obtained. This approach covers many of the community-acquired pathogens but should be tailored to individual patients and other potential pathogens. Nosocomial or trauma-associated infections may need broader spectrum antibiotic coverage. Steroids are useful adjuncts in bacterial meningitis and have been shown to reduce complications but not overall mortality.[256,257] The outcome of meningitis is a function of patient-related factors, the pathogenicity of the organism, and the time to effective treatment.

ENCEPHALITIS

Encephalitis manifests with fever, headache, and alteration of consciousness. Patients may also have delirium, focal deficit, and, commonly, seizures. Nuchal rigidity may be present in a mixed meningoencephalitis picture but should be absent in isolated encephalitis. Accompanying identifiers may be a vesicular rash associated with herpes zoster (although its absence does not remove zoster from the differential diagnosis), bilateral paralysis typical of West Nile disease, parotitis if mumps is suspected, and, of course, the hyperactivity, hydrophobia, and pharyngeal spasm of rabies.[253,258]

Many nonviral and noninfectious causes of encephalitis may confound the diagnosis. These include an expanding group of autoimmune encephalitis, vasculitis, systemic lupus erythematosus, stroke, rickettsial and parasitic infection, and drug-induced meningitis. Careful examination of clinical features, history, and laboratory data is necessary. CSF should

be drawn for viral DNA PCR as well as the routine biochemistry, culture, and cell count. MRI with contrast is useful in identifying the demyelination and edema that can be difficult to see on CT. Serum serology is helpful for the diagnosis of Epstein-Barr virus, mumps, and West Nile disease as sources of encephalitis. Paired samples are recommended to allow later comparison if CSF PCR is unhelpful. Brain biopsy was considered the gold standard but is now a last option, after CSF PCR, culture, and serology have proven negative.[259]

Herpes simplex type 1 infection carries a very poor outlook if it is not treated expeditiously, and a course of empiric intravenous acyclovir is recommended until herpes infection has been excluded. Treatment for other viral etiologies is mainly supportive, including respiratory care and seizure management.[255] Other mosquito-borne viral infections such as West Nile and Zika have been increasing globally.

The pathogen mostly remains unidentified, and outcome usually then depends on classification of the clinical features, with intractable seizure and cerebral edema carrying a poor prognosis. Self-limiting seizure usually indicates a swift recovery. The advent of high-throughput DNA sequencing has advanced the ability to detect viral pathogens and potentially virus discovery in cases of unexplained meningitis and encephalitis.[260]

Postoperative Neurosurgical Care

Many neurosurgical procedures are lengthy and involve significant insult to the brain. Thus, postoperative ICU admission is necessary to avoid secondary insult and monitor postoperative complications like intracranial rebleeding, cerebral edema, or seizures. The incidence of post-craniotomy bleeding of 0.5% is associated with increased blood pressure during and after surgery (SBP >160 mm Hg; MAP >110 mm Hg) and mainly occurs during the first 24 hours.[261]

The patient should be extubated immediately after surgery if possible because a full clinical and neurologic evaluation of the awake patient is the best way to detect post-craniotomy complications. Exceptions are possibly extremely long operations, low preoperative GCS, major surgery in the posterior cranial fossa or close to the brain stem, or a high risk for the development of cerebral edema. The incidence for postoperative complications is higher in patients with intraventricular tumors.[262] Early extubation in combination with close neurologic monitoring is safe and omits the need for routine postoperative CT.[263] In patients where a planned extubation cannot be performed within 1 hour after surgery, an immediate CT should be performed, as these patients have a high risk for postoperative complications and may need emergency neurosurgical interventions.[263]

Pain is often underestimated after craniotomy and narcotics are avoided due to the fear of hypoventilation, which might increase ICP.[264] Therefore, a careful evaluation of pain using the visual analog scale and adequate therapy with nonsteroidal antiinflammatory drugs and opioids must be initiated. A scalp block with local anesthetics also reduces postoperative pain.

Patients after craniotomy have a high risk for postoperative nausea and vomiting. As retching and vomiting are extremely unpleasant for the patient and additionally increase the risk of rebleeding, pharmacologic prevention with selective serotonin antagonists (e.g., ondansetron and granisetron) in combination with low-dose corticosteroids should be used.[265]

DVT and pulmonary embolism occur in 3% of the patients up to 30 days after craniotomy with a peak at the third postoperative day. Prophylaxis with heparin can be initiated in most cases 1 day after surgery.[266,267]

BRAIN DEATH

The diagnosis of brain death remains one of the most challenging and controversial areas of neurocritical care. Physicians must have adequate training and understanding of the principles of brain death declaration and be able to apply them assiduously and without compromise (see Chapter 83).

Declaration of brain death was originally codified by the Harvard criteria in 1968, with subsequent modification to allow separation of cerebral death from death of the entire nervous system, including the spinal cord.[268,269] The diagnosis is built on a thorough clinical examination of nervous system function, involving evaluation of the reflex response of the brain and cranial nerves to hypercarbia, pain, light, temperature change, attitudinal change of the middle ear, and detection of the blink, cough, and gag reflexes. The mechanisms for the irreversible cause of neurologic dysfunction should be clear. The examination must be done in circumstances of adequate systemic oxygenation and perfusion. Confounders, such as hypothermia, metabolic or endocrine compromise, and persistent sedative or neuromuscular drugs, must be corrected. One of the tests should include an appropriately conducted apnea trial in the presence of the responsible physician, with confirmation of adequate changes in $PaCO_2$. If for any reason any test cannot be completed in a safe manner or to the satisfaction of the responsible physician(s), then an ancillary test should be performed based on standard policies. The hospital should have an institutionally approved protocol for brain death declaration and the conduct of any ancillary tests. In addition, mechanisms for regular review and quality improvement are essential.

Proper training and knowledge of administrative and legal policies are essential, as there may be differences across hospitals, regions, and countries. Guidelines on the examination and examiner may be different in adult versus pediatric cases).[270,271] In addition, physician qualifications may vary by training in neurology, neurosurgery, or neurocritical care. Perhaps more important than the diagnosis of brain death is communicating with the care team and the family.

Ethical Considerations

Ethical issues are frequently encountered in a neurocritical care unit (see Chapter 8). Unfortunately, significant life-altering morbidity can occur, to the extent that many patients and families would not prefer aggressive therapy.[272] This can be a difficult concept to accept for the physician, whose aim is to heal and preserve life. However, the ethical imperative in Western culture is to preserve the autonomy of the individual (along with the principles of nonmaleficence, beneficence, and justice), and this has been extended to health care decision making. This situation may lead to uncomfortable choices and communication within the health care team, whose members may

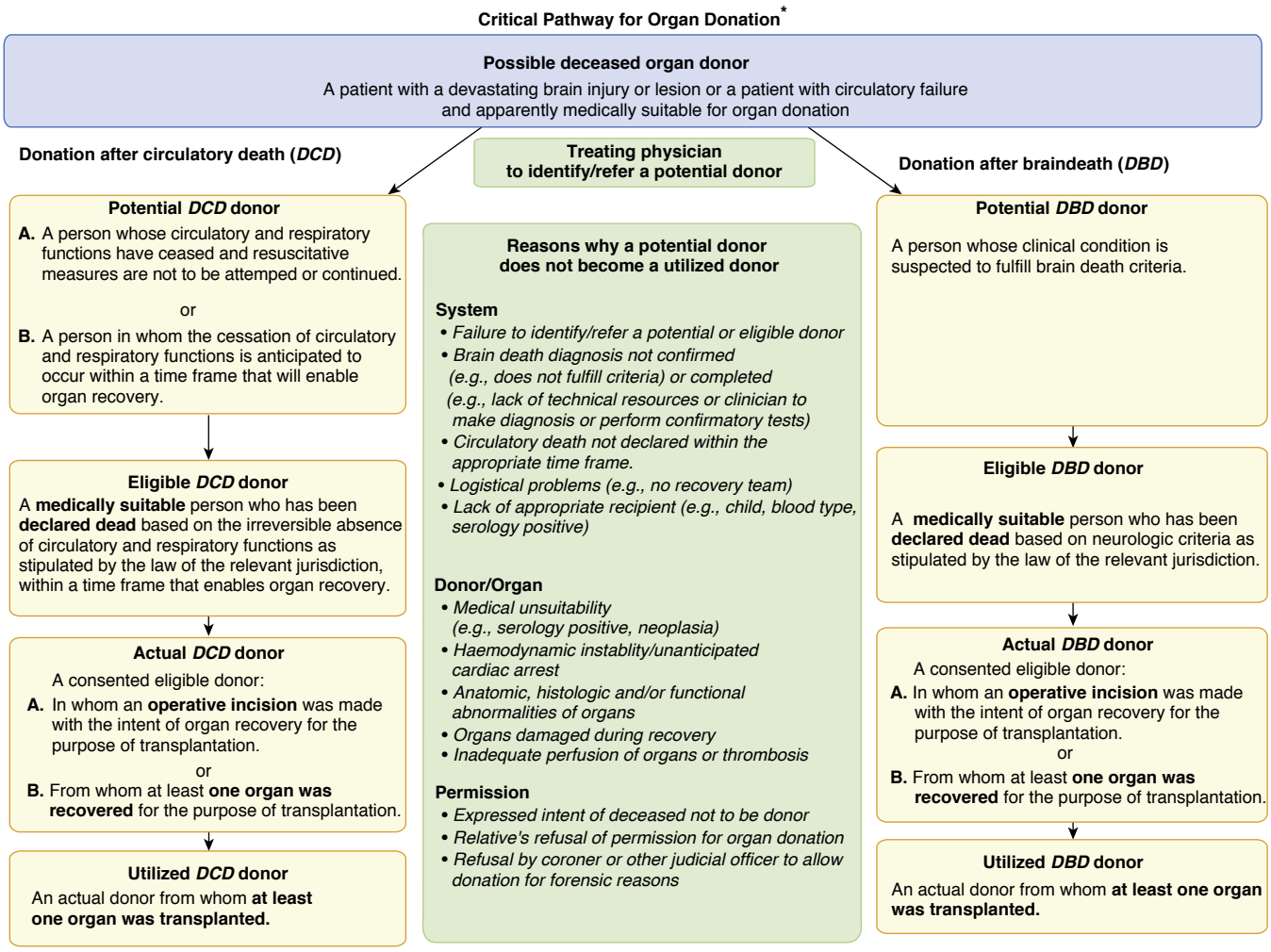

Fig. 84.8 The critical pathways for organ donation after brain death and donation after circulatory death, as published by the World Health Organization. (From Dominguez-Gil B, Delmonico FL, Shaheen FAM, et al. The critical pathway for deceased donation: reportable uniformity in the approach to deceased donation. *Transplant Int.* 2011;24:373.)

have differing opinions on goals as well as the patient and relatives, who, again, may think very differently.

Certain strategies can avoid or minimize these difficulties:

- Prognosis should be made based on the best available evidence. This may involve planning and discussion among the team members in advance of family meetings. Personal anecdotes should be avoided, even if solicited.
- The relationship within the team should be open and collegial, with mutual respect given to the principle of open discussion. This approach avoids misperception of goals and attitudes and enables more consistent communication with families, who often find dissonance among members of the ICU team disturbing.
- The presence of an advance directive offers major benefits, and the neurocritical care unit should have an admissions protocol that includes asking all competent, conscious patients to consider making their attitudes or wishes known.
- Regular family and patient conferences allow communication of prognosis and offer the opportunity for correction of any misconceptions, as well as progressive education of the family members to anticipated problems.
- Internal institutional mechanisms for raising concerns and conducting reviews should be in place. This is often facilitated by the presence of an institutional ethics committee, whose members can examine the issues, promote educational discussion, and help achieve consensus.
- All decision making should be documented carefully and completely.
- Orders for limitation or withdrawal of therapy should be written explicitly, and institutional protocols should be used wherever possible.

Other important areas of possible conflict exist that are not possible to address within the confines of this text, but readers are advised to educate themselves on these and include the following:

- The issues surrounding organ donation from the brain dead and the non-heart-beating donor (Fig. 84.8)
- Withdrawal of care for the incompetent patient without family
- Hospital bylaws and state legislation on the certification of death, whether that be by neurologic or cardiovascular criteria

Conclusion

Neurocritical care demands a thorough comprehension of the physiology, pharmacology, and pathology of the nervous system as well as for the organ systems supporting it. The best care is provided in circumstances that allow multidisciplinary collaboration and appropriate attention to detail of often complex and demanding pathologic processes but integrating them optimally under the direction of the critical care physician.

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