11 - 318 Nervous System Disorders in Critical Care

318 Nervous System Disorders in Critical Care

function and HF are at substantially elevated SCD risk, only ~20% of all SCDs occur in patients with poor left ventricular function. Most SCDs occur in individuals with preserved ventricular function who would not qualify for a primary prevention ICD. Although SCD rates are elevated compared to the general population, the absolute SCD risk in patients with CHD or HF who have an LVEF >35% is not high enough to warrant consideration of ICD therapy. While the incidence of SCD is lower in patients with preserved LVEF, SCD accounts for a greater proportion of cardiac deaths, and active efforts are being made to advance SCD risk stratification in this segment of the population. However, at present, SCD prevention primarily involves cardiac risk factor modification and standard medical therapy for the underlying condition.

Preventing Sudden Death in the General Population Only about one-half of men and one-third of women who suffer SCA are recognized to have heart disease prior to the event, and only half have warning symptoms prior to the event. SCD often occurs with out warning as the first manifestation of cardiac disease. In order to prevent these SCDs, preventive interventions would need to be employed broadly to the general population. Although several risk scores have recently been developed with the intent to stratify SCD risk in low-risk populations, the clinical utility to date is limited by the low absolute incidence of SCD, which is estimated to be only 50–90 per 100,000 in the general adult population. Therefore, cur rent efforts aimed at preventing SCD in general populations primar ily focus on modification of the SCD risk factors outlined previously. Individuals who adhere to a low-risk, healthy lifestyle that includes avoidance of smoking, maintaining a healthy body weight, par ticipating in moderate exercise, and a Mediterranean-type dietary pattern have markedly lower rates of SCD. A substantial number of SCDs are likely to be preventable through lifestyle modifications and treatment of risk factors. PART 8 Critical Care Medicine ■ ■FURTHER READING Al-Khatib SM et al: 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sud den cardiac death: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guide lines and the Heart Rhythm Society. J Am Coll Cardiol 72:e91, 2018. Callaway CW et al: Part 8: Post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resus citation and emergency cardiovascular care. Circulation 132:S465,

)15.
Dankiewicz J et al: Hypothermia versus normothermia after out-ofhospital cardiac arrest. N Engl J Med 384:2283, 2021. Deo R, Albert CM: Epidemiology and genetics of sudden cardiac death. Circulation 125:620, 2012. Marijon E et al: Lancet Commission to reduce the global burden of sudden cardiac death: A call for multidisciplinary action. Lancet 402:883, 2023. Merchant RM et al: Part 1: Executive summary: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 142:S337, 2020. Myerburg RJ et al: Pulseless electric activity: Definition, causes, mechanisms, management, and research priorities for the next decade: Report from a National Heart, Lung, and Blood Institute workshop. Circulation 128:2532, 2013. Perman SM et al: 2023 American Heart Association focused update on adult advanced cardiovascular life support: An update to the Ameri can Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 149:e254, 2024. Zeppenfeld K et al: 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 43:3997, 2022.

Section 3 Neurologic Critical Care J. Claude Hemphill, III, Wade S. Smith,

S. Andrew Josephson, Daryl R. Gress

Nervous System

Disorders in Critical Care Life-threatening neurologic illness may be caused by a primary disorder affecting any region of the neuraxis or may occur as a con sequence of a systemic disorder such as hepatic failure, multisystem organ failure, or cardiac arrest (Table 318-1). Neurologic critical care focuses on preservation of neurologic tissue and prevention of second ary brain injury caused by ischemia, hemorrhage, edema, herniation, and elevated intracranial pressure (ICP). Encephalopathy is a general term describing brain dysfunction that is diffuse, global, or multifocal. Severe acute encephalopathies represent a group of various disorders due to different neurologic or systemic etiologies but that share the common themes of primary and secondary brain injury. ■ ■PATHOPHYSIOLOGY Brain Edema Swelling, or edema, of brain tissue occurs with many types of brain injury. The two principal types of edema are vasogenic and cytotoxic. Vasogenic edema refers to the influx of fluid and solutes into the brain through an incompetent blood-brain barrier (BBB). In the normal cerebral vasculature, endothelial tight junctions associated with astrocytes create an impermeable barrier (the BBB), through which access into the brain interstitium is dependent upon specific transport mechanisms. The BBB may be compromised in ischemia, trauma, infection, and metabolic derangements, and typically devel ops rapidly following injury. Cytotoxic edema results from cellular swelling, membrane breakdown, and ultimately cell death. Clinically significant brain edema usually represents a combination of vasogenic and cytotoxic components. Edema can lead to increased ICP as well as tissue shifts and brain displacement or herniation from focal processes (Chap. 30). These tissue shifts can cause injury by mechanical disten tion and compression in addition to the ischemia of impaired perfusion consequent to the elevated ICP. Ischemic Cascade and Cellular Injury When delivery of sub strates, principally oxygen and glucose, is inadequate to sustain cel lular function, a series of interrelated biochemical reactions known as the ischemic cascade is initiated (see Fig. 437-2). The release of excitatory amino acids, especially glutamate, leads to influx of calcium and sodium ions, which disrupt cellular homeostasis. An increased intracellular calcium concentration may activate proteases and lipases,

which then lead to lipid peroxidation and free radical–mediated cell membrane injury. Cytotoxic edema ensues, and ultimately necrotic cell death and tissue infarction occur. This pathway to irreversible cell death is common to ischemic stroke, global cerebral ischemia, and traumatic brain injury. Penumbra refers to areas of ischemic brain tissue that have not yet undergone irreversible infarction, implying that these regions are potentially salvageable if ischemia can be reversed. Factors that may exacerbate ischemic brain injury include systemic hypotension and hypoxia, which further reduce substrate delivery to vulnerable brain tissue, and fever, seizures, and hyperglycemia, which can increase cellu lar metabolism, outstripping compensatory processes. Clinically, these events are known as secondary brain insults because they lead to exacer bation of the primary brain injury. Prevention, identification, and treat ment of secondary brain insults are fundamental goals of management. An alternative pathway of cellular injury is apoptosis. This process implies programmed cell death, which may occur in the setting of ischemic stroke, global cerebral ischemia, traumatic brain injury, and

TABLE 318-1 Neurologic Disorders in Critical Illness LOCALIZATION ALONG NEUROAXIS SYNDROME Central Nervous System Brain: Cerebral hemispheres Global encephalopathy Delirium Sepsis Organ failure—hepatic, renal Medication related—sedatives, hypnotics, analgesics, H2 blockers, antihypertensives Drug overdose Electrolyte disturbance—hyponatremia, hypoglycemia Hypotension/hypoperfusion Hypoxia Meningitis Subarachnoid hemorrhage Wernicke’s disease Seizure—postictal or nonconvulsive status epilepticus Hypertensive encephalopathy Hypothyroidism—myxedema Focal deficits Ischemic stroke Tumor Abscess, subdural empyema Intraparenchymal hemorrhage Subdural/epidural hematoma Brainstem/cerebellum Mass effect and compression Basilar artery thrombosis Intraparenchymal hemorrhage Central pontine myelinolysis Spinal cord Mass effect and compression Disk herniation Epidural hematoma Epidural abscess Ischemia—hypotension/embolic Trauma Myelitis Peripheral Nervous System Peripheral nerve Axonal Critical illness polyneuropathy Neuromuscular blocking agent complications Metabolic disturbances, uremia, hyperglycemia Medication effects—chemotherapeutic, antiretroviral Demyelinating Guillain-Barré syndrome Chronic inflammatory demyelinating polyneuropathy Neuromuscular junction Prolonged effect of neuromuscular blockade Medication effects—aminoglycosides Myasthenia gravis, Lambert-Eaton syndrome, botulism Muscle Critical illness myopathy Cachectic myopathy Acute necrotizing myopathy Thick-filament myopathy Electrolyte disturbances—hypokalemia/ hyperkalemia, hypophosphatemia Rhabdomyolysis

possibly intracerebral hemorrhage. Apoptotic cell death can be distin guished histologically from the necrotic cell death of ischemia and is mediated through a different set of biochemical pathways; apoptotic cell death occurs without cerebral edema and therefore is often not seen on brain imaging. At present, interventions for prevention and treatment of apoptotic cell death remain less well defined than those for ischemia. Cerebral Perfusion and Autoregulation Brain tissue requires constant perfusion in order to ensure adequate delivery of substrate. The hemodynamic response of the brain has the capacity to preserve perfusion across a wide range of systemic blood pressures. Cerebral perfusion pressure (CPP), defined as the mean systemic arterial pres sure (MAP) minus the ICP, provides the driving force for circulation across the capillary beds of the brain. Autoregulation refers to the phys iologic response whereby cerebral blood flow (CBF) is regulated via alterations in cerebrovascular resistance in order to maintain perfusion over wide physiologic changes such as neuronal activation or changes in hemodynamic function. If systemic

blood pressure drops, cerebral perfusion is preserved through vasodilation of arterioles in the brain; likewise, arteriolar vasoconstriction occurs at high systemic pressures to prevent hyperperfusion, resulting in fairly constant perfusion across a wide range of systemic blood pressures (Fig. 318-1). At the extreme limits of MAP or CPP (high or low), flow becomes directly related to perfusion pressure. These autoregulatory changes occur in the micro circulation and are mediated by vessels below the resolution of those seen on angiography. CBF is also strongly influenced by pH and Paco2. CBF increases with hypercapnia and acidosis and decreases with hypo capnia and alkalosis because of pH-related changes in cerebral vascular resistance. This forms the basis for the use of hyperventilation to lower ICP, and this effect on ICP is mediated through a decrease in both CBF and intracranial blood volume. Cerebral autoregulation is a complex process critical to the normal homeostatic functioning of the brain, and this process may be disordered focally and unpredictably in disease states such as traumatic brain injury and severe focal cerebral ischemia.

CHAPTER 318 Nervous System Disorders in Critical Care Cerebrospinal Fluid (CSF) and ICP The cranial contents con sist essentially of brain, CSF, and blood. CSF is produced principally in the choroid plexus of each lateral ventricle, exits the brain via the foramens of Luschka and Magendie, and flows over the cortex to be absorbed into the venous system along the superior sagittal sinus. In adults, ~150 mL of CSF are contained within the ventricles and sur rounding the brain and spinal cord; the cerebral blood volume is also ~150 mL. The bony skull offers excellent protection for the brain but allows little tolerance for additional volume. Significant increases in volume eventually result in increased ICP. Obstruction of CSF out flow, edema of cerebral tissue, or increases in volume from tumor or hematoma may increase ICP. Elevated ICP diminishes cerebral perfusion and can lead to tissue ischemia. Ischemia in turn may lead to vasodilation via autoregulatory mechanisms designed to restore cerebral perfusion. However, vasodilation also increases cerebral blood volume, which in turn then increases ICP, lowers CPP, and provokes further ischemia. This vicious cycle is commonly seen in traumatic brain injury, massive intracerebral hemorrhage, and large hemispheric infarcts with significant tissue shifts. APPROACH TO THE PATIENT Severe Brain Dysfunction Critically ill patients with severe central nervous system (CNS) dysfunction require rapid evaluation and intervention in order to limit primary and secondary brain injury. Initial neurologic evalu ation should be performed concurrent with stabilization of basic respiratory, cardiac, and hemodynamic parameters. Significant barriers may exist to neurologic assessment in the critical care unit, including endotracheal intubation and the use of sedative or para lytic agents to facilitate procedures. An impaired level of consciousness is common in critically ill patients. The essential first task in assessment is to determine

Cerebral Blood Flow (CBF), mL/100 g/min

A Mean Arterial Pressure (MAP), mmHg PART 8 Critical Care Medicine Cerebral Blood Flow (CBF), mL/100 g/min

Mean Arterial Pressure (MAP), mmHg B FIGURE 318-1 Pressure autoregulation of cerebral blood flow. In the normal state where autoregulation is intact A, cerebral perfusion is constant over a wide range of systemic blood pressures (BP). This is mediated by dilation and constriction of small cerebral arterioles (round circles). Below the BP threshold for maximal dilation, cerebral blood flow becomes pressure-dependent and decreases, whereas above the threshold for maximum

constriction, cerebral blood flow increases with increasing systemic BP. In severe brain injury, autoregulatory mechanisms may be impaired and cerebral blood flow becomes pressure-dependent throughout (B). At the extremes of BP, there may be vascular collapse (very low BP) or forced vasodilation (very high BP). whether the cause of dysfunction is related to a diffuse, usually metabolic, process or whether a focal, usually structural, pro cess is implicated. Examples of diffuse processes include meta bolic encephalopathies related to organ failure, drug overdose, or hypoxia-ischemia. Focal processes include ischemic and hemor rhagic stroke and traumatic brain injury, especially with intracra nial hematomas. Because these two categories of disorders have fundamentally different causes, treatments, and prognoses, the initial focus is on making this distinction rapidly and accurately. The approach to the comatose patient is discussed in Chap. 30; etiologies are listed in Table 30-1. Minor focal deficits may be present on the neurologic examina tion in patients with metabolic encephalopathies. However, the finding of prominent focal signs such as pupillary asymmetry, hemiparesis, gaze palsy, or visual field deficit should suggest the possibility of a structural lesion. All patients with a decreased level of consciousness associated with focal findings should undergo an urgent neuroimaging procedure, as should all patients with coma of unknown etiology. Computed tomography (CT) scanning is usu ally the most appropriate initial study because it can be performed quickly in critically ill patients and demonstrates hemorrhage, hydrocephalus, and intracranial tissue shifts well. Magnetic reso nance imaging (MRI) may provide more specific information in some situations, such as acute ischemic stroke (diffusion-weighted imaging [DWI]). Any suggestion of trauma from the history or examination should alert the examiner to the possibility of cervi cal spine injury and prompt an imaging evaluation using CT or MRI. Neurovascular imaging using CT or MRI angiography or

venography is increasingly available and may suggest arterial occlu sion or cerebral venous thrombosis. Acute brainstem ischemia due to basilar artery thrombosis may cause brief episodes of spontaneous extensor posturing superficially resembling generalized seizures. Coma of sudden onset, accompa nied by these movements and cranial nerve abnormalities, neces sitates emergency imaging. A noncontrast CT scan of the brain may reveal a hyperdense basilar artery indicating thrombus in the vessel, and subsequent CT or MR angiography can assess basilar artery patency. Other diagnostic studies are best used in specific circumstances, usually when neuroimaging studies fail to reveal a structural lesion and the etiology of the altered mental state remains uncertain. Electroencephalography (EEG) can be important in the evaluation of critically ill patients with severe brain dysfunction. The EEG of metabolic encephalopathy typically reveals generalized slowing. One of the most important uses of EEG is to help exclude inappar ent seizures, especially nonconvulsive status epilepticus. Untreated continuous or frequently recurrent seizures may cause neuronal injury, making the diagnosis and treatment of seizures crucial in this patient group. Lumbar puncture (LP) may be necessary to exclude infectious or inflammatory processes, and an elevated opening pressure may be an important clue to cerebral venous sinus thrombosis. In patients with coma or profound encephalopathy, it is preferable to perform a neuroimaging study prior to LP. If bacterial meningitis is suspected, an LP may be performed urgently, but most often, it is prudent to administer antibiotics empirically before the diagnostic studies are completed. Standard laboratory evaluation of

critically ill patients should include assessment of serum electro lytes (especially sodium and calcium), glucose, renal and hepatic function, complete blood count, and coagulation. Serum or urine toxicology screens should be performed in patients with encepha lopathy of unknown cause.

EEG and LP are most useful when the mechanism of the altered level of consciousness is uncertain; they are not routinely performed for diagnosis in clear-cut cases of stroke or traumatic brain injury. Monitoring of ICP can be an important tool in selected patients. In general, patients who should be considered for ICP monitor ing are those with primary neurologic disorders, such as stroke or traumatic brain injury, who are at significant risk for secondary brain injury due to elevated ICP and decreased CPP. Included are patients with the following: severe traumatic brain injury (Glasgow Coma Scale [GCS] score ≤8 [see Table 454-1]); large tissue shifts from supratentorial ischemic or hemorrhagic stroke; or hydro cephalus from subarachnoid hemorrhage (SAH), intraventricular hemorrhage, or posterior fossa stroke. An additional disorder in which ICP monitoring can add important information is fulminant hepatic failure, in which elevated ICP may be treated with barbitu rates or, eventually, liver transplantation. In general, ventriculos tomy is preferable to ICP monitoring devices that are placed in the brain parenchyma, because ventriculostomy allows CSF drainage as a method of treating elevated ICP. However, parenchymal ICP monitoring is most appropriate for patients with diffuse edema and small ventricles (which may make ventriculostomy placement more difficult) or any degree of coagulopathy (in which ventriculostomy carries a higher risk of hemorrhagic complications) (Fig. 318-2). TREATMENT OF ELEVATED ICP Elevated ICP may occur in a wide range of disorders, including head trauma, intracerebral hemorrhage, SAH with hydrocephalus, and fulminant hepatic failure. Because CSF and blood volume can be redistributed initially, by the time elevated ICP occurs, intracranial compliance is severely impaired. At this point, any small increase in the volume of CSF, intravascular blood, edema, or a mass lesion may result in a significant increase in ICP and a decrease in cerebral perfusion. This is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general, ICP should be maintained at <20 mmHg and CPP should be maintained at ≥60 mmHg. Interventions to lower ICP are ideally based on the underlying mechanism responsible for the elevated ICP (Table 318-2). For example, in hydrocephalus from SAH, the principal cause of ele vated ICP is impairment of CSF drainage. In this setting, ventricular drainage of CSF is likely to be sufficient and most appropriate. In Lateral ventricle Brain tissue oxygen probe Ventriculostomy Fiberoptic intraparenchymal ICP monitor FIGURE 318-2 Intracranial pressure (ICP) and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fluid to treat elevated ICP. Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screwlike skull bolt. Cerebral blood flow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

TABLE 318-2 Stepwise Approach to Treatment of Elevated Intracranial Pressure (ICP)a Insert ICP monitor—ventriculostomy versus parenchymal device General goals: maintain ICP <20 mmHg and CPP ≥60 mmHg. For ICP

> “ 20–25 mmHg for >5 min:

1. Elevate head of the bed; midline head position
2. Drain CSF via ventriculostomy (if in place)
3. Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)

4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to Paco2 30–35 mmHg (short-term use or skip this step)
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain CHAPTER 318 adequate MAP to ensure CPP ≥60 mmHg (maintain euvolemia to minimize deleterious systemic effects of pressors). May adjust target CPP in individual patients based on autoregulation status.
8. Consider second-tier therapies for refractory elevated ICP a. Decompressive craniectomy b. High-dose barbiturate therapy (“pentobarb coma”) c. Hypothermia to 33°C Nervous System Disorders in Critical Care aThroughout ICP treatment algorithm, consider repeat head computed tomography to identify mass lesions amenable to surgical evacuation. May alter order of steps based on directed treatment to specific cause of elevated ICP. Abbreviations: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; MAP, mean arterial pressure; Paco2, arterial partial pressure of carbon dioxide. head trauma and stroke, cytotoxic edema may be most responsible, and the use of osmotic agents such as mannitol or hypertonic saline becomes an appropriate early step. As described above, elevated ICP may cause tissue ischemia, and, if cerebral autoregulation is intact, the resulting vasodilation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase MAP may actually lower ICP by improving perfusion, thereby allowing autoregulatory vasoconstriction as ischemia is relieved and ultimately decreasing intracranial blood volume. Early signs of elevated ICP include drowsiness and a diminished level of consciousness. Neuroimaging studies may reveal evidence of edema and mass effect. Hypotonic IV fluids should be avoided, and elevation of the head of the bed is recommended. Patients must be carefully observed for risk of aspiration and compromise of the airway as the level of alertness declines. Coma and unilateral pupillary changes are late signs and require immediate interven tion. Emergent treatment of elevated ICP is most quickly achieved by intubation and hyperventilation, which causes vasoconstric tion and reduces cerebral blood volume. To avoid provoking or worsening cerebral ischemia, hyperventilation, if used at all, is best administered only for short periods of time until a more definitive treatment can be instituted. Furthermore, the effects of hyperven tilation on ICP are short-lived, often lasting only for several hours because of the buffering capacity of the cerebral interstitium, and rebound elevations of ICP may accompany abrupt discontinuation of hyperventilation. As the level of consciousness declines to coma, the ability to follow the neurologic status of the patient by examina tion lessens and measurement of ICP assumes greater importance. If a ventriculostomy device is in place, direct drainage of CSF to reduce ICP is possible. Finally, high-dose barbiturates, decompres sive hemicraniectomy, and hypothermia are sometimes used for refractory elevations of ICP, although these have significant side effects and only decompressive hemicraniectomy has been shown to improve outcome in select patients. SECONDARY BRAIN INSULTS Patients with primary brain injuries, whether due to trauma or stroke, are at risk for ongoing secondary ischemic brain injury.

Because secondary brain injury can be a major determinant of a poor outcome, strategies for minimizing secondary brain insults are an integral part of the critical care of all patients. Although elevated ICP may lead to secondary ischemia, most secondary brain injury is mediated through other clinical events that exacerbate the ischemic cascade already initiated by the primary brain injury. Episodes of secondary brain insults are usually not associated with apparent neurologic worsening. Rather, they lead to cumulative injury limit ing eventual recovery, which manifests as a higher mortality rate or worsened long-term functional outcome. Thus, close monitoring of vital signs is important, as is early intervention to prevent sec ondary ischemia. Avoiding hypotension and hypoxia is critical, as significant hypotensive events (systolic blood pressure <90 mmHg) as short as 10 min in duration have been shown to adversely influ ence outcome after traumatic brain injury. Even in patients with stroke or head trauma who do not require ICP monitoring, close attention to adequate cerebral perfusion is warranted. Hypoxia (pulse oximetry saturation <90%), particularly in combination with hypotension, also leads to secondary brain injury. Likewise, fever and hyperglycemia both worsen experimental ischemia and have been associated with worsened clinical outcome after stroke and head trauma. Aggressive control of fever with a goal of normo thermia is warranted but may be difficult to achieve with antipyretic medications and cooling blankets. The value of newer surface or intravascular temperature control devices for the management of refractory fever is under investigation. The use of IV insulin infusion is encouraged for control of hyperglycemia because this allows better regulation of serum glucose levels than SC insulin. A reasonable goal is to maintain the serum glucose level at <10.0 mmol/L (<180 mg/dL), although episodes of hypoglycemia appear equally detrimental and the optimal targets remain uncertain. New cerebral monitoring tools that allow continuous evaluation of brain tissue oxygen tension, CBF, cortical spreading depolarizations, and cerebral metabolism (via microdialysis) may further improve the management of secondary brain injury. PART 8 Critical Care Medicine CRITICAL CARE DISORDERS OF THE CNS ■ ■HYPOXIC-ISCHEMIC BRAIN INJURY This occurs from lack of delivery of oxygen to the brain because of extreme hypotension (hypoxia-ischemia) or hypoxia due to respira tory failure. Causes include myocardial infarction, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxia may predominate. Carbon monoxide and cyanide poisoning are sometimes termed histotoxic hypoxia because they cause a direct impairment of the respiratory chain. Clinical Manifestations Mild degrees of pure hypoxia, such as occur at high altitudes, cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxiaischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but if hypoxia-ischemia lasts beyond 3–5 min, some degree of permanent cerebral damage often results. Except in extreme cases, it may be difficult to judge the precise degree of hypoxia-ischemia, and some patients make a relatively full recovery after even 10 min or more of global cerebral ischemia. The brain is more tolerant to pure hypoxia than it is to hypoxia-ischemia. For example, a Pao2 as low as 20 mmHg (2.7 kPa) can be well tolerated if it develops gradually and normal blood pressure is maintained, whereas short durations of very low or absent cerebral circulation may result in permanent impairment. Clinical examination at different time points after a hypoxicischemic insult (especially cardiac arrest) is useful in assessing prog nosis for long-term neurologic outcome. The prognosis is better for patients with intact brainstem function, as indicated by normal pupillary light responses and intact oculocephalic (doll’s eyes), ocu lovestibular (caloric), and corneal reflexes. Absence of these reflexes

and the presence of persistently dilated pupils that do not react to light are concerning prognostic signs. A lower likelihood of a favor able outcome from hypoxic-ischemic brain injury is suggested by an absent pupillary light reflex or extensor or absent motor response to pain 5–7 days following the injury, excluding patients with metabolic disturbances and those treated with high-dose sedative medications or hypothermia, which confound interpretation of these signs. Elec trophysiologically, the bilateral absence of the N20 component of the somatosensory evoked potential (SSEP) after several days also conveys a poor prognosis. Also, the presence of a burst-suppression pattern of myoclonic status epilepticus on EEG (Fig. 318-3) or a nonreactive EEG is associated with a lower likelihood of good functional outcome. A very elevated serum level (>60 µg/L) of the biochemical marker neuron-specific enolase (NSE) obtained during first 1–3 days follow ing injury is indicative of brain damage after resuscitation from cardiac arrest and is associated with worse outcome. Current approaches to prognostication after cardiac arrest encourage the use of a multimodal approach that includes these diagnostic tests, along with CT or MRI neuroimaging, in conjunction with clinical neurologic assessment. The administration of mild hypothermia after cardiac arrest (see “Treatment”) may affect the time points when these clinical and elec trophysiologic predictors become reliable in identifying patients with a very low likelihood of clinically meaningful recovery. For example, the false-positive rate for incorrect prediction of poor neurologic out come may be as high as 21% (95% confidence interval [CI] 8–43%) for patients treated with mild hypothermia who exhibit 3-day motor function no better than extensor posturing. Thus, sufficient time from injury is important to ensure accuracy of prognostic assessment and to avoid the self-fulfilling prophecy of poor outcome when withdrawal of life-sustaining therapy is undertaken in a patient who has the potential for recovery. The minimum observation period to ensure accuracy of prognostication remains unclarified, but some patients may awaken after a week or longer. Long-term consequences of hypoxic-ischemic encephalopathy include persistent coma or an unresponsive wakeful state (Chap. 30), dementia (Chap. 31), visual agnosia (Chap. 32), par kinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and an amnestic state, which may be a consequence of selective damage to the hippocampus. Pathology Principal histologic findings are extensive multifocal or diffuse laminar cortical injury (Fig. 318-4), with frequent involvement of the deep gray nuclei and hippocampus. The hippocampal CA1 neu rons are vulnerable to even brief episodes of hypoxia-ischemia, perhaps explaining why selective persistent memory deficits may occur after brief cardiac arrest. Scattered small areas of infarction or neuronal loss may be present in the basal ganglia, hypothalamus, or brainstem. In some cases, extensive bilateral thalamic scarring may affect pathways that mediate arousal, and this pathology may be responsible for the unresponsive wakeful state (previously known as the vegetative state). A specific form of hypoxic-ischemic brain injury, so-called watershed infarcts, occurs at the distal territories between the major cerebral arter ies and can cause cognitive deficits, including visual agnosia, and weak ness that is greater in proximal than in distal muscle groups. Diagnosis Diagnosis is based on the history of a hypoxic-ischemic event such as cardiac arrest. Blood pressure <70 mmHg systolic or Pao2 <40 mmHg is usually necessary, although both absolute levels and duration of exposure are important determinants of cellular injury. Carbon monoxide intoxication can be confirmed by measurement of carboxyhemoglobin and is suggested by a cherry red color of the venous blood and skin, although the latter is an inconsistent clinical finding. TREATMENT Hypoxic-Ischemic Brain Injury Treatment should be directed at restoration of normal cardiore spiratory function. This includes securing a clear airway, ensur ing adequate oxygenation and ventilation, and restoring cerebral

FIGURE 318-3 Electroencephalography (EEG) after cardiac arrest. A burst-suppression pattern is seen in a comatose patient with severe hypoxic-ischemic encephalopathy after cardiac arrest. In this patient, each burst on EEG was associated with a whole-body jerking movement leading to the clinical and electrophysiologic diagnosis of myoclonic status epilepticus. perfusion, whether by cardiopulmonary resuscitation, fluid, pres sors, or cardiac pacing. Hypothermia may target the neuronal cell injury cascade and has substantial neuroprotective properties in experimental models of brain injury. Several clinical trials found that mild hypothermia (33°C) administered for 12–24 h improved func tional outcome in patients who remained comatose after resuscita tion from cardiac arrest. These trials varied in the patients included, with some involving out-of-hospital arrest with a shockable cardiac FIGURE 318-4 Hypoxic-ischemic brain injury after cardiac arrest. Diffusionweighted magnetic resonance imaging shows reduced diffusion (bright signal) throughout the cerebral cortex as well as in the caudate, globus pallidus, and thalamus bilaterally.

 rhythm and others including in-hospital arrest and focusing on those with nonshockable rhythms. Two larger subsequent clinical trials that included patients with high rates of bystander cardiopul monary resuscitation and primary cardiac causes of arrest did not find hypothermia to 33°C as beneficial. In one, targeted temperature management (TTM) to 33 or 36°C resulted in similar outcomes, while in another, early treatment of fever (temperature ≥37.8°C) resulted in similar outcomes to those of patients treated with hypo thermia to 33°C. Given these heterogeneous findings from clinical trials, there exists variability in how clinicians treat patients with hypoxic-ischemic brain injury from cardiac arrest. Current guide lines recommend selecting and maintaining a constant temperature between 32 and 37.5°C during postarrest temperature control for patients who have no meaningful response to verbal commands after return of spontaneous circulation (ROSC). It is our current practice to target either 33 or 36°C. Fever should be avoided in all cases. Potential complications of hypothermia include systemic coagulopa thy and an increased risk of infection. Additional clinical trials have been conducted to assess whether targeting specific physiologic parameters that may impact cerebral blood flow and oxygen delivery after ROSC can improve outcome. A factorial design clinical trial tested both a higher mean arte rial blood pressure target (77 vs 63 mmHg) and a higher partial pressure of oxygen target (98–105 vs 68–75 mmHg) and found no differences in clinical outcome. Likewise, targeting early mild hypercapnia (Paco2 50–55 vs 35–45 mmHg) did not improve out come in a separate clinical trial. Anticonvulsants may be needed to control seizures, although these are not usually given prophylactically. Myoclonic status epi lepticus within 24 h after a primary circulatory arrest generally portends a poor prognosis, even if seizures are controlled. A clinical trial of complete suppression of rhythmic and periodic EEG activ ity for 48 h did not result in improved patient outcomes compared with standard care that included TTM, and therefore, this strategy should likely not be practiced. Posthypoxic myoclonus may respond

to oral administration of clonazepam at doses of 1.5–10 mg daily or valproate at doses of 300–1200 mg daily in divided doses.

Severe acute carbon monoxide intoxication may be treated with hyperbaric oxygen. Carbon monoxide and cyanide intoxication can also cause a delayed encephalopathy. Little clinical impair ment is evident when the patient first regains consciousness, but a parkinsonian syndrome characterized by akinesia and rigidity without tremor may develop. Symptoms can worsen over months, accompanied by increasing evidence of damage in the basal ganglia as seen on both CT

and MRI. ■ ■POSTCARDIAC BYPASS BRAIN INJURY CNS injuries following open heart or coronary artery bypass graft ing (CABG) surgery are common and include acute encephalopathy, stroke, and a chronic syndrome of cognitive impairment. Hypoperfu sion and embolic disease are frequently involved in the pathogenesis of these syndromes, although multiple mechanisms may be involved in these critically ill patients who are at risk for various metabolic and polypharmaceutical complications. PART 8 Critical Care Medicine The frequency of hypoxic injury secondary to inadequate blood flow intraoperatively has been markedly decreased by modern surgical and anesthetic techniques. Despite these advances, some patients still expe rience neurologic complications from cerebral hypoperfusion or suffer focal ischemia from carotid or focal intracranial stenoses in the setting of regional hypoperfusion. Postoperative infarcts in the border zones between vascular territories are often attributed to systemic hypoten sion, although these infarcts can also result from embolic disease. Embolic disease is likely the predominant mechanism of cerebral injury during cardiac surgery as evidenced by diffusion-weighted MRI and intraoperative transcranial Doppler ultrasound studies. Thrombus in the heart itself as well as atheromas in the aortic arch can become dislodged during cardiac surgeries, releasing a shower of particulate matter into the cerebral circulation. Cross-clamping of the aorta, manipulation of the heart, extracorporeal circulation techniques (“bypass”), arrhythmias such as atrial fibrillation, and introduction of air through suctioning have all been implicated as potential sources of emboli. This shower of microemboli results in a number of clinical syn dromes. Occasionally, a single large embolus leads to an isolated largevessel stroke that presents with obvious clinical focal deficits. When there is a high burden of very small emboli, an acute encephalopathy can occur postoperatively, presenting as either a hyperactive or hypo active confusional state, the latter of which is frequently and incorrectly ascribed to depression or a sedative-induced delirium. When the bur den of microemboli is lower, no acute syndrome is recognized, but the patient may suffer a chronic cognitive deficit. ■ ■METABOLIC ENCEPHALOPATHIES Altered mental states, variously described as confusion, delirium, disorientation, and encephalopathy, are present in many patients with severe illness in an intensive care unit (ICU). Older patients are particularly vulnerable to delirium (Chap. 29), a confusional state characterized by disordered perception, frequent hallucinations, delu sions, and sleep disturbance. This is often attributed to medication effects, sleep deprivation, pain, and anxiety. The presence of delirium is associated with a worse outcome in critically ill patients, even in those without an identifiable CNS pathology such as stroke or brain trauma. In these patients, the cause of delirium is often multifactorial, resulting from organ dysfunction, sepsis, and especially the use of medications given to treat pain, agitation, or anxiety. Critically ill patients are often treated with a variety of sedative and analgesic medications, including opiates, benzodiazepines, neuroleptics, and sedative-anesthetic medi cations, such as propofol. In critically ill patients requiring sedation, use of the centrally acting α2 agonist dexmedetomidine may reduce delirium and shorten the duration of mechanical ventilation compared to the use of benzodiazepines such as lorazepam or midazolam. The presence of family members in the ICU may also help to calm and orient agitated patients, and in severe cases, low doses of neuroleptics

(e.g., haloperidol 0.5–1 mg) can be useful. Current strategies focus on limiting the use of sedative medications when this can be done safely. In the ICU setting, several metabolic causes of an altered level of consciousness predominate. Hypercarbic encephalopathy can present with headache, confusion, stupor, or coma. Hypoventilation syndrome occurs most frequently in patients with a history of chronic CO_2 reten tion who are receiving oxygen therapy for emphysema

or chronic pulmonary disease (Chap. 307). The elevated Paco2 leading to CO2 narcosis may have a direct anesthetic effect, and cerebral vasodilation from increased Paco2 can lead to increased ICP. Hepatic encephalopa thy is suggested by asterixis and can occur in chronic liver failure or acute fulminant hepatic failure. Both hyperglycemia and hypoglycemia can cause encephalopathy, as can hypernatremia and hyponatremia. Confusion, impairment of eye movements, and gait ataxia are the hall marks of acute Wernicke's disease (see below). ■ ■SEPSIS-ASSOCIATED ENCEPHALOPATHY Pathogenesis In patients with sepsis, the systemic response to infectious agents leads to the release of circulating inflammatory medi ators that appear to contribute to encephalopathy. Critical illness, in association with the systemic inflammatory response syndrome (SIRS), can lead to multisystem organ failure. This syndrome can occur in the setting of apparent sepsis, severe burns, or trauma, even without clear identification of an infectious agent. Many patients with critical illness, sepsis, or SIRS develop encephalopathy without obvious explanation. This condition is broadly termed sepsis-associated encephalopathy. Although the specific mediators leading to neurologic dysfunction remain uncertain, it is clear that the encephalopathy is not simply the result of metabolic derangements of multiorgan failure. The cytokines tumor necrosis factor, interleukin (IL) 1, IL-2, and IL-6 are thought to play a role in this syndrome. Diagnosis Sepsis-associated encephalopathy presents clinically as a diffuse dysfunction of the brain without prominent focal findings. Confusion, disorientation, agitation, and fluctuations in level of alert ness are typical. In more profound cases, especially with hemodynamic compromise, the decrease in level of alertness can be more prominent, at times resulting in coma. Hyperreflexia and frontal release signs such as a grasp or snout reflex (Chap. 32) can be seen. Abnormal movements such as myoclonus, tremor, or asterixis can occur. Sepsisassociated encephalopathy is quite common, occurring in the majority of patients with sepsis and multisystem organ failure. Diagnosis is often difficult because of the multiple potential causes of neurologic dysfunc tion in critically ill patients and requires exclusion of structural, meta bolic, toxic, and infectious (e.g., meningitis or encephalitis) causes. The mortality rate of patients with sepsis-associated encephalopathy severe enough to produce coma approaches 50%, although this principally reflects the severity of the underlying critical illness and is generally not a direct result of the encephalopathy. Patients dying from severe sepsis or septic shock may have elevated levels of the serum brain injury biomarker S-100β and neuropathologic findings of neuronal apoptosis and cerebral ischemic injury. Successful treatment of the underlying critical illness almost always results in substantial improve ment of the encephalopathy. However, although severe disability to the level of chronic unresponsive wakeful or minimally conscious states is uncommon, long-term cognitive dysfunction clinically similar to dementia is being increasingly recognized in some survivors, especially in older patients. ■ ■OSMOTIC DEMYELINATION SYNDROME (CENTRAL PONTINE MYELINOLYSIS) This disorder often presents in a devastating fashion as quadriplegia and pseudobulbar palsy, although less severe presentations may occur. Predisposing factors include severe underlying medical illness or nutritional deficiency; most cases are associated with rapid correction of hyponatremia or with hyperosmolar states, and clinical symptoms are usually identified a few days after sodium correction. Previously termed central pontine myelinolysis, the more accurate term osmotic demyelination syndrome is now preferred. The pathology consists of

FIGURE 318-5 Osmotic demyelination syndrome. Axial T2-weighted magnetic resonance scan through the pons reveals a symmetric area of abnormal pontine high signal intensity that characteristically involves transverse pontine fibers and spares the descending corticospinal tracts. (Image courtesy of Dr. Jared Narvid, Department of Radiology & Biomedical Imaging, University of

California, San Francisco.) occasional acute cases and atrophy of the mammillary bodies in most chronic cases. There is frequently endothelial proliferation, demyelin ation, and some neuronal loss. These changes may be detected by MRI (Fig. 318-6). The amnestic defect is related to lesions in the dorsal medial nuclei of the thalamus. Pathogenesis Thiamine is a cofactor of several enzymes, including transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehydro genase. Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage. Glutamate accumulates due to impairment of α-ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage. demyelination without inflammation in the base of the pons, with rela tive sparing of axons and nerve cells. MRI is useful in establishing the diagnosis (Fig. 318-5) and may also identify partial forms that present as confusion, dysarthria, and/or disturbances of conjugate gaze with out quadriplegia. Occasional cases present with lesions outside of the brainstem. Therapy for the restoration of severe hyponatremia should aim for gradual correction, i.e., by ≤8 mmol/L (8 meq/L) within 24 h and 15 mmol/L (15 meq/L) within 48 h. ■ ■WERNICKE'S DISEASE Wernicke's disease is a common and preventable disorder due to a defi ciency of thiamine (Chap. 344). In the United States, alcoholics account for most cases, but patients with malnutrition due to hyperemesis, star vation, renal dialysis, cancer, HIV/AIDS, or rarely gastric surgery are also at risk. The characteristic clinical triad is ophthalmoplegia, ataxia, and global confusion. However, only one-third of patients with acute Wernicke's disease present with the classic clinical triad. Most patients are profoundly disoriented, indifferent, and inattentive, although rarely they have an agitated delirium related to ethanol withdrawal. If the dis ease is not treated, stupor, coma, and death may ensue. Ocular motor abnormalities include horizontal nystagmus on lateral gaze, lateral rectus palsy (usually bilateral), conjugate gaze palsies, and rarely ptosis. Gait ataxia probably results from a combination of polyneuropathy, cerebellar involvement, and vestibular paresis. The pupils are usually spared, but they may become miotic with advanced disease. Wernicke's disease is usually associated with other manifestations of nutritional disease, such as polyneuropathy. Rarely, amblyopia or myelopathy occurs. Tachycardia and postural hypotension may be related to impaired function of the autonomic nervous system or to the coexistence of cardiovascular beriberi. Patients who recover show improvement in ocular palsies within hours after the administration of thiamine, but horizontal nystagmus may persist. Ataxia improves more slowly than the ocular motor abnormalities. Approximately half recover incompletely and are left with a slow, shuffling, wide-based gait and an inability to tandem walk. Apathy, drowsiness, and confusion improve more gradually. As these symptoms recede, an amnestic state with impairment in recent memory and learning may become more apparent (Korsakoff's psychosis). Korsakoff's psychosis is frequently persistent; the residual mental state is characterized by gaps in memory, confabulation, and disordered temporal sequencing. Pathology Periventricular lesions surround the third ventri cle, aqueduct, and fourth ventricle, with petechial hemorrhages in

CHAPTER 318 FIGURE 318-6 Wernicke's disease. Coronal T1-weighted postcontrast magnetic resonance imaging reveals abnormal enhancement of the mammillary bodies (arrows), typical of acute Wernicke's encephalopathy. Nervous System Disorders in Critical Care TREATMENT Wernicke's Disease Wernicke's disease is a medical emergency and requires immediate administration of high-dose thiamine, in a dose of 500 mg IV. The dose should be begun prior to treatment with IV glucose solutions and continued three times daily for 2–3 days. Thiamine may then be given in a dose of 250 mg IV or IM daily for 5 more days (in conjunction with other B vitamins), with oral thiamine then contin ued at 100 mg daily until the patient is no longer

considered at risk. Glucose infusions may precipitate Wernicke’s disease in a previously unaffected patient or cause a rapid worsening of an early form of the disease. For this reason, thiamine should be administered to all alcoholic patients requiring parenteral glucose. ■ ■HYPERPERFUSION DISORDERS (POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME) Several seemingly diverse syndromes including hypertensive encepha lopathy, eclampsia, postcarotid endarterectomy syndrome, and toxicity from calcineurin inhibitor and other medications share the common pathogenesis of hyperperfusion likely due to endothelial dysfunction. Vasogenic edema is typically the primary process leading to neurologic dysfunction, and this is thought to result from one of two mechanisms: exceeding the cerebral autoregulatory threshold leading to increased CBF and capillary leakage into the interstitium, or direct impairment of the BBB itself. The predilection of all of the hyperperfusion disorders to affect the posterior rather than anterior portions of the brain may be due to a lower threshold for autoregulatory breakthrough in the posterior circulation or a vasculopathy that is more common in these blood vessels.

TABLE 318-3 Common Etiologies of Posterior Reversible Encephalopathy Syndrome Disorders in which increased capillary pressure dominates the pathophysiology Hypertensive encephalopathy, including secondary causes such as renovascular hypertension, pheochromocytoma, cocaine use, etc. Postcarotid endarterectomy syndrome Preeclampsia/eclampsia Disorders in which endothelial dysfunction dominates the pathophysiology Calcineurin inhibitor toxicity (e.g., cyclosporine, tacrolimus) Chemotherapeutic agent toxicity (e.g., cytarabine, azathioprine, 5-fluorouracil, cisplatin, methotrexate, tumor necrosis factor α antagonists) HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count) Hemolytic-uremic syndrome (HUS) These disorders of hyperperfusion can be divided into those caused primarily by increased pressure and those due to endothelial dysfunc tion from a toxic or autoimmune etiology (Table 318-3). In reality, both of these processes likely play some role in each of these disorders. The clinical presentation of all of the hyperperfusion syndromes is sim ilar with prominent headaches, seizures, or focal neurologic deficits. Headaches have no specific characteristics, range from mild to severe, and may be accompanied by alterations in consciousness ranging from confusion to coma. Seizures may be present, and these can be of mul tiple types depending on the severity and location of the edema. Non convulsive seizures have been described; therefore, a low threshold for obtaining an electroencephalogram (EEG) should be maintained. The typical focal deficit in hyperperfusion states is cortical visual loss, given the tendency of the process to involve the occipital lobes. However, any focal deficit can occur depending on the area affected, as evidenced by patients who, after carotid endarterectomy, exhibit neurologic dysfunc tion referable to the ipsilateral newly reperfused hemisphere. It appears as if the rapidity of rise, rather than the absolute value of pressure, is the most important risk factor. PART 8 Critical Care Medicine MRI classically exhibits the high T2 signal of edema primarily in the posterior occipital lobes, not respecting any single vascular terri tory (Fig. 318-7). CT is less sensitive but may show a pattern of patchy hypodensity in the involved territory. The term posterior reversible encephalopathy syndrome (PRES) is often used to describe these condi tions; however, the clinical syndrome is not always reversible or limited just to the posterior brain regions. Vessel imaging may demonstrate narrowing of the cerebral vasculature, especially in the posterior circu lation; whether this noninflammatory vasculopathy is a primary cause of the edema or occurs as a secondary phenomenon remains unclear. FIGURE 318-7 Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the brain in a patient taking cyclosporine after liver transplantation, who presented with seizures, headache, and cortical blindness. Increased signal is seen bilaterally in the occipital lobes predominantly

involving the white matter, consistent with a hyperperfusion state secondary to calcineurin inhibitor exposure.

Other ancillary studies such as CSF analysis often yield nonspecific results. Many of the substances that have been implicated, such as cyclosporine, can cause this syndrome even at low doses or after years of treatment. Therefore, normal serum levels of these medications do not exclude them as inciting agents. Treatment involves judicious lowering of the blood pressure with IV agents such as labetalol or nicardipine, removal of the offending medication, and treatment of an underlying medical condition such as eclampsia. If the blood pressure is very elevated, it is reasonable to lower the MAP by ~20% initially, as further lowering of the pressure may cause secondary ischemia and possibly infarction as pressure drops below the lower range of the patient's autoregulatory capability. Seizures must be identified and controlled, often necessitating continu ous EEG monitoring. Anticonvulsants are effective when seizure activ ity is identified, but in the special case of eclampsia, there is evidence to support the use of magnesium sulfate for seizure control. ■ ■POST–SOLID ORGAN TRANSPLANT BRAIN INJURY Immunosuppressive medications are administered in high doses to patients after solid organ transplant, and many of these compounds have well-described neurologic complications. In patients with head ache, seizures, or focal neurologic deficits taking calcineurin inhibitors, the diagnosis of hyperperfusion syndrome should be considered, as discussed above. This neurotoxicity occurs mainly with cyclosporine and tacrolimus and can present even in the setting of normal serum drug levels. Treatment primarily involves lowering the drug dosage or discontinuing the drug. Sirolimus has very few recorded cases of neurotoxicity and may be a reasonable alternative for some patients. Another example of an immunosuppressive medication with neuro logic complications is the leukoencephalopathy seen with methotrex ate, especially when it is administered intrathecally or with concurrent radiotherapy. In any solid organ transplant patient with neurologic complaints, a careful examination of the medication list is required to search for these possible drug effects. Cerebrovascular complications of solid organ transplant are often first recognized in the immediate postoperative period. Border zone territory infarctions can occur, especially in the setting of systemic hypotension during cardiac transplant surgery. Embolic infarctions classically complicate cardiac transplantation, but all solid organ trans plant procedures place patients at risk for systemic emboli. When cere bral embolization accompanies renal or liver transplantation surgery, a careful search for right-to-left shunting should include evaluation of the heart with agitated saline echocardiography (i.e., "bubble study"), as well as looking for intrapulmonary shunting. Renal and some car diac transplant patients often have advanced atherosclerosis, provid ing a risk for stroke. Imaging with CT or MRI should be done when cerebrovascular complications are suspected to confirm the diagnosis and to exclude intracerebral hemorrhage, which most often occurs in the setting of coagulopathy secondary to liver failure or after cardiac bypass procedures. Given that patients with solid organ transplants are chronically immunosuppressed, infections are a common concern (Chap. 148). In any transplant patient with new CNS signs or symptoms such as seizure, confusion, or focal deficit, the diagnosis of a CNS infection should be considered and evaluated through imaging (usually MRI) and possibly LP. The most common pathogens responsible for CNS infections in these patients vary based on time since transplant. In the first month posttransplant, common pathogens include the usual bacterial organisms associated with surgical procedures and indwelling catheters. Starting in the second month posttransplant, opportunistic infections of the CNS become more common, including Nocardia and Toxoplasma species as well as fungal infections such as aspergillosis. Viral infections that can affect the brain of the immunosuppressed

patient, such as herpes simplex virus, cytomegalovirus, human herpes virus type 6 (HHV-6), and varicella, also become more common after the first month posttransplant. Beyond 6 months, immunosuppressed posttransplant patients still remain at risk for these opportunistic bac terial, fungal, and viral infections but can also suffer late CNS infectious complications such as progressive multifocal leukoencephalopathy

(PML) associated with JC virus (Chap. 142) and Epstein-Barr virus– driven clonal expansions of B cells resulting in posttransplant lympho proliferative disorder or CNS lymphoma (Chap. 95). CNS COMPLICATIONS OF CHECKPOINT INHIBITOR AND CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY Cancer immunotherapy is now a widely used treatment for both solid tumors and hematologic malignances. Two types of this immunother apy, checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell (CAR-T) therapy, can carry significant neurologic toxicity that may manifest as encephalopathy, cerebral edema, or white matter demy elination. These complications may be severe and require neurocritical care evaluation and intervention. Immune checkpoint inhibitors are monoclonal antibodies that bind to normally occurring checkpoint proteins such as PD-1, PD-L1, and CTLA-4, thereby freeing T cells to attack cancerous cells. Currently available checkpoint inhibitors include pembrolizumab, nivolumab, cemiplimab, atezolizumab, avelumab, durvalumab, and ipilimumab. Common side effects are diarrhea, rash, and pneumonitis. Neurologic side effects occur in ~5% of patients treated with monotherapy and ~10% undergoing combination therapy, presumably as a result of shared antigens between tumor cells and self, leading to an autoimmune process (Chap. 99). CNS adverse events include limbic encephalitis, cerebellitis, and myelitis. A clinical syndrome of encephalopathy, memory distur bances, and seizures may occur. Peripheral nervous system complica tions such as myasthenia gravis, myositis, and neuropathy have also been described and may be even more common than CNS manifestations. Patients who develop CNS neurologic symptoms while on check point inhibitor treatment should undergo MRI studies of the brain or spinal cord, based on clinical symptoms. Mesial temporal lobe hyper intensities and a lymphocytic CSF pleocytosis may be present. EEG may be appropriate to evaluate for subclinical seizures. Various auto antibodies such as anti-Ma2, anti-GFAP, anti-Hu, and anti-CASPR2 have been described but are not required for diagnosis. Treatment consists of discontinuing the checkpoint inhibitor and administering high-dose glucocorticoids. Intravenous immunoglobulins and plasma pheresis have been used in severe cases. For mild cases, restarting the checkpoint inhibitor may be considered; however, relapse with fatal necrotizing encephalitis has been described. Given that checkpoint inhibitor–treated patients are immunocompromised, before check point inhibitor–related neurotoxicity is diagnosed, it is imperative to rule out an alternative diagnosis such as cerebral metastases, infection, or stroke. CAR-T therapy for leukemia or lymphoma involves removing a patient’s T cells and genetically engineering them using a disarmed virus to produce surface chimeric antigen receptors that, when given back to the patient, recognize antigens on tumor cells. CAR-T therapy is frequently associated with significant side effects, which usually occur as either cytokine release syndrome (CRS) or neurotoxicity. These two types of CAR-T side effects are distinct but often occur in the same patient, and both occur within days of initiation of CAR-T treatment. CRS is a clinical syndrome of hypotension, fever, and hypoxia, which may have associated multiorgan dysfunction. CRS occurs in 80–100% of CAR-T–treated patients and is due to widespread release of proin flammatory cytokines. Treatment is with the IL-6 receptor pathway blocker tocilizumab, which can alleviate CRS symptoms without impairing the antitumor efficacy of the CAR-T cells; glucocorticoids may also be administered. CAR-T neurotoxicity is less common but still occurs in more than half of treated patients. Clinical manifestations may include headache,

encephalopathy, aphasia, seizures, tremors, and life-threatening cere bral edema. Predictors of occurrence of neurotoxicity include earlier and more severe CRS, fever, elevated C-reactive protein and serum ferritin, and older patient age. Treatment of CAR-T neurotoxicity also involves administration of tocilizumab (as most of these patients also have CRS) and glucocorticoids. In addition to these treatments, patients with CAR-T neurotoxicity should also undergo brain imaging

and EEG if indicated based on symptoms, with concurrent treatment of cerebral edema and seizures if present.

CRITICAL CARE DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM Critical illness with disorders of the peripheral nervous system (PNS) arises in two contexts: (1) primary neurologic diseases that require critical care interventions such as intubation and mechanical ventila tion, and (2) secondary PNS manifestations of systemic critical illness, often involving multisystem organ failure. The former include acute polyneuropathies such as Guillain-Barré syndrome (Chap. 458), neuromuscular junction disorders including myasthenia gravis (Chap. 459) and botulism (Chap. 158), and primary muscle disorders such as polymyositis (Chap. 377). The latter result either from the sys temic disease itself or as a consequence of interventions and as a group are often referred to as ICU-acquired weakness (ICUAW). CHAPTER 318 General principles of respiratory evaluation in patients with PNS involvement, regardless of cause, include assessment of pulmonary mechanics, such as maximal inspiratory force (MIF) and vital capacity (VC), and evaluation of strength of bulbar muscles. Regardless of the cause of weakness, endotracheal intubation should be considered when the MIF falls to below –25 cmH2O or the VC is <1 L. Also, patients with severe palatal weakness may require endotracheal intubation in order to prevent acute upper airway obstruction or recurrent aspira tion. Arterial blood gases and oxygen saturation from pulse oximetry are used to follow patients with potential respiratory compromise from PNS dysfunction. However, intubation and mechanical ventila tion should be undertaken based on clinical assessment rather than waiting until oxygen saturation drops or CO2 retention develops from hypoventilation. Noninvasive mechanical ventilation may be consid ered initially in lieu of endotracheal intubation in myasthenia gravis but is generally insufficient in patients with severe bulbar weakness or ventilatory failure with hypercarbia. Principles of mechanical ventila tion are discussed in Chap. 313. Nervous System Disorders in Critical Care ■ ■NEUROPATHY Although encephalopathy may be the most obvious neurologic dys function in critically ill patients, dysfunction of the PNS is also quite common. It is typically present in patients with prolonged critical illnesses lasting several weeks and involving sepsis; clinical suspicion is aroused when there is failure to wean from mechanical ventilation despite improvement of the underlying sepsis and critical illness. Critical illness polyneuropathy refers to the most common PNS complication related to critical illness; it is seen in the setting of prolonged criti cal illness, sepsis, and multisystem organ failure. Neurologic findings include diffuse weakness, decreased reflexes, and distal sensory loss. Electrophysiologic studies demonstrate a diffuse, symmetric, distal axonal sensorimotor neuropathy, and pathologic studies have con firmed axonal degeneration. The precise mechanism of critical illness polyneuropathy remains unclear, but circulating factors such as cyto kines, which are associated with sepsis and SIRS, are thought to play a role. It has been reported that up to 70% of patients with the sepsis syndrome have some degree of neuropathy, although far fewer have a clinical syndrome profound enough to cause severe respiratory muscle weakness requiring prolonged mechanical ventilation or resulting in failure to wean. Aggressive glycemic control with insulin infusions appears to decrease the risk of critical illness polyneuropathy. Treat ment is

otherwise supportive, with specific intervention directed at treating the underlying illness. Although spontaneous recovery is usu ally seen, the time course may extend over weeks to months and neces sitate long-term ventilatory support and care even after the underlying critical illness has resolved. ■ ■DISORDERS OF NEUROMUSCULAR TRANSMISSION A defect in neuromuscular transmission may be a source of weakness in critically ill patients. Botulism (Chap. 158) may be acquired by ingest ing botulinum toxin from improperly stored food or may arise from an anaerobic abscess from Clostridium botulinum (wound botulism). Infants

can present with generalized weakness from gut-derived Clostridium infection, especially if they are fed honey. Diplopia and dysphagia are early signs of food-borne botulism. Treatment is mostly supportive, although use of antitoxin early in the course may limit the duration of the neuromuscular blockade. General ICU care is similar to patients with Guillain-Barré syndrome or myasthenia gravis with focused care to avoid ulcer formation at pressure points, deep venous thromboprophylaxis, and infection prevention. Public health officers should be rapidly informed when the diagnosis is made to prevent further exposure to others from the tainted food or source of wound botulism (such as injection drug use).

Undiagnosed myasthenia gravis (Chap. 459) may be a consider ation in weak ICU patients; however, persistent weakness secondary to impaired neuromuscular junction transmission is almost always due to administration of drugs. A number of medications impair neu romuscular transmission; these include antibiotics, especially amino glycosides, and beta-blocking agents. In the ICU, the nondepolarizing neuromuscular blocking agents (nd-NMBAs), also known as muscle relaxants, are most commonly responsible. Included in this group of drugs are such agents as pancuronium, vecuronium, rocuronium, and cisatracurium. They are often used to facilitate mechanical ventilation or other critical care procedures, but with prolonged use, persistent neuromuscular blockade may result in weakness even after discon tinuation of these agents hours or days earlier. Risk factors for this prolonged action of neuromuscular blocking agents include female sex, metabolic acidosis, and renal failure. PART 8 Critical Care Medicine Prolonged neuromuscular blockade does not appear to produce permanent damage to the PNS. Once the offending medications are discontinued, full strength is restored, although this may take days. In general, the lowest dose of neuromuscular blocking agent should be used to achieve the desired result, and when these agents are used in the ICU, a peripheral nerve stimulator should be used to monitor neuromuscular junction function. ■ ■MYOPATHY Critically ill patients, especially those with sepsis, frequently develop muscle weakness and wasting, often in the face of seemingly adequate nutritional support. Critical illness myopathy is an overall term that describes several different discrete muscle disorders that may occur in critically ill patients. The assumption has been that a catabolic myopa thy may develop as a result of multiple factors, including elevated corti sol and catecholamine release and other circulating factors induced by the SIRS. In this syndrome, known as cachectic myopathy, serum cre atine kinase levels and electromyography (EMG) are normal. Muscle biopsy shows type II fiber atrophy. Panfascicular muscle fiber necrosis may also occur in the setting of profound sepsis. This less common acute necrotizing intensive care myopathy is characterized clinically by weakness progressing to a profound level over just a few days. There may be associated elevations in serum creatine kinase and urine myo globin. Both EMG and muscle biopsy may be normal initially but even tually show abnormal spontaneous activity and panfascicular necrosis with an accompanying inflammatory reaction. Acute rhabdomyolysis can occur from alcohol ingestion or from compartment syndromes.

A thick-filament myopathy may occur in the setting of glucocorti coid and nd-NMBA use. The most frequent scenario in which this is encountered is the asthmatic patient who requires high-dose glucocor ticoids and nd-NMBA to facilitate mechanical ventilation. This muscle disorder is not due to prolonged action of nd-NMBAs at the neuromus cular junction but, rather, is an actual myopathy with muscle damage; it has occasionally been described with high-dose glucocorticoid use or sepsis alone. Clinically this syndrome is most often recognized when a patient fails to wean from mechanical ventilation despite resolution of the primary pulmonary process. Pathologically, there may be loss of thick (myosin) filaments. Thick-filament critical illness myopathy has a good prognosis. If patients survive their underlying critical illness, the myopathy invariably improves and most patients return to nor mal. However, because this syndrome is a result of true muscle dam age, not just prolonged blockade at the neuromuscular junction, this process may take weeks or months, and tracheotomy with prolonged ventilatory support may be necessary. Some patients do have residual long-term weakness, with atrophy and fatigue limiting ambulation. At present, it is unclear how to prevent this myopathic complication, except by avoiding use of nd-NMBAs, a strategy not always possible. Monitoring with a peripheral nerve stimulator can help to avoid the overuse of these agents. However, this is more likely to prevent the complication of prolonged neuromuscular junction blockade than it is to prevent this myopathy. ■ ■FURTHER READING Cook AM et al: Guidelines for the acute treatment of cerebral edema in neurocritical care patients. Neurocrit Care 32:647, 2020. Dhar R: Neurologic complications of transplantation. Handb Clin Neurol 141:545, 2017. Donnelly J et al: Regulation of the cerebral circulation: Bedside assessment and clinical implications. Crit Care 20:129, 2016. Nolan JP et al: European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: Post-resuscitation care. Intensive Care Med 47:369, 2021. Perman SM et al: 2023 American Heart Association Focused Update on Adult Advanced Cardiovascular Life Support: An update to the American Heart Association Guidelines for Cardiopulmonary Resus citation and Emergency Cardiovascular Care. Circulation 149:e254, 2024. Posner JB et al: Plum and Posner’s Diagnosis and Treatment of Stupor and Coma, 5th ed. New York, Oxford University Press, 2019. Quillinan N et al: Neuropathophysiology of brain injury. Anesthesiol Clin 34:453, 2016. Rubin D et al: Clinical predictors of neurotoxicity after chimeric anti gen receptor T-cell therapy. JAMA Neurol 77:1, 2020. Ruijter BJ et al: Treating rhythmic and periodic EEG patterns in comatose survivors of cardiac arrest. N Engl J Med 386:724, 2022. Toledano M, Fugate JE: Posterior reversible encephalopathy in the intensive care unit. Handb Clin Neurol 141:467, 2017. Vanhorebeek I et al: ICU-acquired weakness. Intensive Care Med 46:637, 2020.

Revision #1
Created 2026-01-06 16:34:17 UTC by Omar Ayman
Updated 2026-01-06 16:34:17 UTC by Omar Ayman