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Series Editor: Daniel Tarsy

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Neurointensive Care Unit

Clinical Practice and Organization

Humana Press

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Preface

The field of neurocritical care is expanding. Presently, an understanding of its basic principles is essential for the appropriate care of patients requiring intensive care. In addition to understanding the basics of neurocritical care, it is also important to have an understanding of how a neurocritical care unit (NCCU) is structured and how the services paramount to its operation are accessed and organized. The goal of this book is to go beyond the management of neurocritical care-related illness by providing guidance to intensivists and providers from all backgrounds with regard to perspectives on how to organize and manage the challenging environment that is the NCCU. The first chapters in this book are dedicated to describing the current evidence-based management of key neurological emergencies, from beginning to end, across the timeline of care. We have included information about triaging decisions, from admission to discharge, as well as the use of pharmacologic agents unique to neurocritical care conditions. In the second section, we examine organizational principles of the NCCU including neurointensivists' training, telemedicine and telestroke, and the responsibilities of key personnel in the NCCU. This includes the special roles and training requirements of nurses, advanced practice providers, residents, fellows, and attendings. We further delve into the use of specialty services such as ultrasound, electroencephalography, angiography, and multimodal monitoring – all of which are necessary to support an NCCU. We also discuss the important issue of prognostication in neurocritical care patients. It is our goal to provide a textbook that is helpful to those aspiring to plan and build an NCCU as well as to those seeking a comprehensive review of neurocritical care management.

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Series Editor Introduction

Neurointensive Care Unit: Clinical Practice and Organization edited by Sarah Nelson and Paul Nyquist continues a tradition of books concerning neurocritical care that has appeared in Springer's "Current Clinical Neurology" series over the past 15 years. These include *Critical Care Neurology and Neurosurgery* edited by Jose Suarez and two editions of the *Handbook of Neurocritical Care* edited by A Bhardwaj, MA Mirski, et al. These volumes were designed to detail the array of patients with acute, life-threatening neurological and neurosurgical illnesses encountered in intensive care units. *Section 1* of this volume expands upon these conditions providing much information that has appeared in the past 15 years concerning newly described acute and severe neurological conditions and the scientific basis of many new treatments and interventions that have become available in this area. There are ample numbers of tables and figures throughout the book that very nicely illustrate the issues presented. *Section 2* contains a newer body of information that reflects the widespread growth of neurocritical care units as free-standing hospital facilities staffed by certified professionals with a primary interest in neurocritical care. Special training and certification of neurointensivists, remote diagnosis by the use of telemedicine and telestroke, and the utilization of physician extenders such as nurse practitioners, physician assistants, nurses, residents, and fellows have allowed for the increased growth of specialized neurointensive care units. These personnel have been increasingly assisted by sophisticated ancillary services such as multimodal neuromonitoring; brain metabolism, blood flow, and intracranial pressure monitoring; and ultrasound, which have become essential to support the care of patients in neurointensive care units. In the future, this will continue to be a rapidly growing field that is now very effectively brought up to date by this well-organized and instructive volume.

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Part I

Pathways for Intervention

Management of Elevated Intracranial Pressure

1

Aaron M. Gusdon, Paul A. Nyquist, and Sarah E. Nelson

Introduction

Intracranial pressure (ICP) is defined as the total pressure within the intracranial vault. Much of neurocritical care is focused on the diagnosis and management of increased ICP. Many of the patients admitted to the neurocritical care unit will have diagnoses associated with increased ICP such as intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), subdural hematoma (SDH), ischemic stroke, and hydrocephalus. Elevated ICP has been associated with poor outcomes. It is known from the TBI literature that survival is worse for patients with elevated ICP above 40 mmHg [1].

This chapter will outline the pathophysiology of increased ICP and will discuss the diagnosis and treatment of patients with sustained increases in ICP.

Intracranial Anatomy and Physiology

Anatomy

The contents of the intracranial vault represent a fixed volume, consisting of brain tissue (87%), cerebrospinal fluid (CSF) (9%), blood vessels (4%), and meninges (<1%) [2, 3].

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The average total volume of the intracranial contents is 1700 mL, with brain tissue occupying 1200–1400 mL, CSF volume ranging from 70 to 160 mL, and blood occupying 150 mL. An additional 10–25 mL of CSF can be contained in the spinal subarachnoid space. The intracranial components are divided into several compartments by dural membranes. The two cerebral hemispheres are divided by the falx cerebri, the superior edge of which is attached to the superior sagittal sinus with the free edge attached to the inferior sagittal sinus. The supratentorial (cerebral hemispheres) and infratentorial (brainstem and cerebellum) fossae are separated by the tentorium cerebelli. These dural septa are fibrous and fairly rigid, with the tentorium cerebelli being significantly less flexible as about three-quarters of it are tethered in place [3]. Compression of brain tissue against these septa plays a key role in herniation syndromes (described in the next section).

The close proximity of several intracranial structures results in susceptibility to compression and injury, leading to distinct clinical findings. Among the cranial nerves, involvement of the oculomotor nerve is perhaps the best recognized and can aid in the diagnosis of herniation syndromes. The oculomotor nerve exits from the ventral surface of the midbrain where it travels between the superior cerebellar and poster cerebral arteries before running along the posterior communicating artery (PCOM) and finally penetrating the petroclinoid ligament to enter the cavernous sinus. The oculomotor nerve also courses directly inferior to the medial edge of the temporal lobe, putting it at risk of compression by a herniating uncus. Compression of the oculomotor nerve by either the uncus or PCOM can compress the pupillodilator fibers along the dorsal surface of the nerve leading to a unilateral dilated pupil. The abducens nerve exits the ventral surface of the pons and runs along the midbrain before also entering the cavernous sinus. While mass lesions usually do not result in compression of the abducens nerve unless affecting the cavernous sinus, abducens nerve paralysis is a sign of increased ICP (discussed below). The trochlear nerve is unique in that it exits the midbrain dor-

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sally just inferior to the inferior colliculi, courses ventrally near the oculomotor nerve, and passes through the petroclinoid ligament to enter the cavernous sinus. The trochlear nerve may be injured due to trauma, since displacement of the brainstem into the edge of the tentorium may result in superior cerebellar peduncle hemorrhage with involvement of the trochlear nerve nucleus or exiting fibers [4]. The basilar artery lies on the ventral surface, giving rise to the superior cerebellar arteries before the tentorial opening and then branches off into the posterior cerebral arteries (PCA). The PCAs run along the medial surface of the occipital lobe and are susceptible to compression when tissue herniates through the tentorium. The only opening in the skull through which brain tissue can exit is the foramen magnum, at the inferior end of the posterior fossa. This opening plays an important role in herniation, given the close proximity of the medulla, cerebellar tonsils, and vertebral arteries. Compression of the cerebellar tonsils against the foramen magnum can contribute to infarction and tissue edema [3].

Physiology

The choroid plexus is located on the floor of the lateral, third, and fourth ventricles and is the major site of CSF production. The average rate of CSF formation is 21–22 mL/hour, resulting in about 500 mL/day. After its formation, CSF flow is driven by arterial pulsations transmitted to the choroid plexus. CSF leaves the lateral ventricles and travels through the third ventricle, cerebral aqueduct, fourth ventricle, and then through the foramina of Magendie and Lushka. The CSF then fills the perimedullary space and travels around the brainstem rostrally into the basal cisterns, through the tentorial aperture and bathes the surfaces of the cerebral hemispheres where it is reabsorbed through the arachnoid villi [2].

The cranium and dura form a rigid container, therefore a change in the volume of brain, blood, or CSF occurs at the expense of one of the other two in accordance with the Monro-Kellie doctrine. As mentioned above, only an additional 25 mL of CSF may be contained in the spinal subarachnoid space, therefore relatively small increases in brain parenchymal volume results in CSF displacement out of the intracranial space. The CSF space is in equilibrium with capillary and prevenous vasculature; however, changes in arterial pressure have minimal effect on ICP due to cerebral autoregulation [2]. Cerebral perfusion pressure (CPP) is dependent on ICP according to the following equation: CPP = MAP-ICP, where MAP = mean arterial pressure. Cerebral blood flow (CBF) is also directly proportional to CPP via the relationship CBF=CPP/CVR, where CVR = cerebrovascular resistance [5]. ICP is typically around 8 mmHg, and cerebrovascular autoregulation typically holds CBF relatively constant over a range of ICP and CPP values [2]. As CPP increases, CVR correspondingly increases, with the converse also being true. The brain also exerts tight control over MAP. The aortic depressor nerve (a branch of the vagus nerve) senses pressure at the aortic arch, while the carotid sinus nerve (a branch of the glassopharyngeal nerve) senses pressure at the carotid bifurcation. Both nerves terminate on the nucleus of the solitary tract, which provides input to the caudal ventrolateral medulla. The ventrolateral medulla provides inhibitor input to the tonic vasomotor neurons in the rostral ventrolateral medulla. The solitary tract also provides excitatory input to the cardiac decelerator neurons in the nucleus ambiguus. Thus, the brain is able to tightly regulate MAP and heart rate [6]. However, at MAP of 40 mmHg or lower or 150 mmHg or greater, autoregulation fails leading to a decrease or increase in CBF. Acute brain injury such as stroke, TBI, or hemorrhage can also impair the ability to autoregulate, given that it is an energy-dependent process requiring adenosine triphosphate (ATP) for arteriolar dilation or constriction [7]. Therefore, in neurocritically ill patients, CBF may linearly increase with CPP as autoregulation breaks down. On the other hand, autoregulation plays little role on the venous circulation such that increases in venous pressure lead to a relatively quick increase in ICP by increasing the volume of blood in cerebral veins and sinuses. This also explains the quick increases in ICP with maneuvers that increase intrathoracic pressure such as Valsalva, coughing, sneezing, and straining [8].

Diagnosis of Elevated ICP

Clinical Symptoms

Increases in ICP typically present with several early, relatively nonspecific clinical symptoms. The most consistently reported early symptoms include headache, nausea, and vomiting. While the exact mechanisms resulting in headache are unclear, it is likely that increased ICP activates pain receptors in the blood vessels and meninges [3]. Headache may be particularly prominent in patients who have increased ICP secondary to cerebral sinus thrombosis or other etiologies of cerebral venous obstruction. In this case, headache likely results from irritation of the sinus itself. The vomiting reflex is coordinated by neurons in the ventrolateral medullary tegmentum near the nucleus ambiguus. Increased ICP produces vomiting by causing pressure on the floor of the fourth ventricle. This commonly occurs due to the ICP pressure wave produced after the ictus of SAH [3].

Numerous other clinical symptoms have been reported to be associated with early signs of increased ICP. A notable complaint is a brief loss of vision upon standing, which has been termed visual obscurations. This occurs when perfusion

decreases, often after standing up, with a concomitant failure in autoregulation of the posterior circulation leading to brief occipital lobe ischemia. Other symptoms include, but are not limited to: confusion, agitation, air hunger, nasal itch, blurred vision, dysphagia, opsithotonus, facial twitching, pallor, sweating, thirst, salivation, yawning, hiccoughing, and urinary incontinence [3]. While none of these symptoms are specific for increased ICP, the treating provider should take into account the constellation of symptoms and evaluate for causes of elevated ICP as necessary. In patients whose ICP is not controlled, these symptoms often progress to confusion and disorientation followed by impaired level of consciousness. In patients with SAH, an immediate spike in ICP after aneurysmal rupture equilibrates ICP with MAP with a subsequent drop in CPP that may result in loss of consciousness. After the aneurysm tamponades and stops bleeding, ICP decreases, allowing CPP to return to normal levels with restoration of consciousness [3, 9].

Physical Examination Findings and Herniation Syndromes

Several physical examination findings should raise concern for elevated ICP in the appropriate clinical situation. Papilledema occurs in the setting of ICP elevation due to a pressure differential across the optic nerve. The optic nerve is surrounded by dura and arachnoid sheaths putting the exterior of the nerve in communication with the CSF and subarachnoid space [10]. However, the retinal ganglion cells are subject to intraocular pressure. Thus, patients with increased ICP are exposed to a pressure differential across the optic nerve. A high-pressure gradient leads to axoplasmic flow stasis and swelling of the optic nerve fibers with subsequent leakage of fluid into the extracellular space [10].

The abducens nerve is often affected early due to elevated ICP. As mentioned above, it emerges from the ventral surface of the pons and enters the subarachnoid space, penetrating the dura to enter Dorello's canal before coursing along the midbrain and entering the cavernous sinus. The abducens nerve is susceptible to compression due to increased ICP while it passes through the osteofibrous Dorello's canal [11].

As a mass lesion increases causing ICP to rise, CSF is displaced into the lumbar cistern in order to compensate. When little CSF is left to be displaced, compliance becomes very poor, such that small increases in the size of a mass may lead to substantial increases in ICP. Herniation occurs when there is little or no CSF volume left to displace, and part of the brain parenchyma is displaced into a neighboring compartment with lower pressure. Seven primary patterns of herniation occur: subfalcine herniation, lateral displacement of the diencephalon, uncal herniation, central transtentorial herniation, rostrocaudal brainstem deterioration, tonsillar herniation, and upward brainstem herniation [3].

When a hemispheric mass lesion compresses the cerebral hemisphere medially against the falx, subfalcine herniation occurs. The medial wall of the cerebral hemisphere may develop ischemia due to compression of the pericallosal and callosomargial arteries against or underneath the falx. Compression of the anterior cerebral artery can also occur. Lateral displacement of the diencephalon can be monitored by displacement of the pineal gland, and correlates well with the degree of impairment in consciousness (0–3 mm results in alertness, 3–5 mm in drowsiness, 6–8 mm with stupor, and 9–13 mm with coma) [12].

With uncal herniation, a lesion located relatively laterally in the cerebral hemisphere displaces the medial edge of the temporal lobe over the free tentorial edge into the tentorial notch. As the dorsal surface of the oculomotor nerve is compressed by the herniating uncus, the ipsilateral pupil becomes dilated and may become fixed. Eye movement abnormalities also occur due to third nerve compression and may be elicited by examining oculocephalic responses, as the patient may not be sufficiently awake to be able to follow commands. Impaired consciousness is almost always present by the time a fixed and dilated pupil has occurred. Consciousness can be affected by distortion of the ascending arousal systems passing through the midbrain or compression of the diencephalon. Hemiparesis also occurs as the uncus compresses the cerebral peduncle. Paresis can be either ipsilateral or contralateral. Contralateral paresis occurs when the uncus compresses the adjacent cerebral peduncle, while ipsilateral paresis occurs when the contralateral cerebral peduncle is compressed against Kernohan's notch [13]. The posterior cerebral artery is often compressed in the tentorial notch and can lead to occipital lobe infarction [3, 14].

Central transtentorial herniation results from pressure on the diencephalon. As vessels of the circle of Willis are stretched and compressed, coma results due to ischemia of the ascending arousal system as it passes through the diencephalon. Ischemia results in edema and a cycle of more shift and compromise of blood supply. As shift becomes severe enough, the pituitary stalk may be sheared, leading to diabetes insipidus, a finding usually occurring late in herniation near brain death. A particular pattern of herniation termed Parinaud's syndrome occurs when a mass compresses the dorsal aspect of the midbrain. The syndrome consists of impaired upgaze, impaired convergence, and retractory nystagmus [3].

Rostrocaudal deterioration occurs when the brainstem is displaced, causing impaired vascular supply. Paramedian ischemia results from downward displacement of the brainstem when the medial perforating branches of the basilar are stretched, since they are relatively fixed in place. Duret hemorrhages can occur, which are slit-like hemorrhages that are characteristically seen in the brainstem. The vein of Galen can also be compressed as it runs along the dorsal surface of the midbrain; however, venous insufficiency is typically not a major factor [15].

Tonsillar herniation occurs when a sudden increase in pressure in the posterior fossa pushes the cerebellar tonsils against the foramen magnum, compressing the medulla and causing variable degrees of compression of the fourth ventricle. Compression of the medulla may impair spontaneous respiration, and there may be a compensatory increase in blood pressure to improve perfusion. Increased pressure in the posterior fossa can also result in upward herniation through the tentorial notch. The superior cerebellar vermis and midbrain can compress the dorsal mesencephalon and also the cerebral aqueduct causing hydrocephalus [3].

A relatively late sign of increased ICP is the Cushing response (CR), which is characterized by respiratory irregularities, arterial hypertension, and bradycardia [6]. This occurs when pressure is applied to the floor of the medulla and once a mass has reached a particular volume independent of its rate of expansion [16].

Causes of Increased ICP

Several conditions may contribute to elevated ICP. Commonly, a cerebral or extracerebral mass may elevate ICP. This may be due to a brain tumor, stroke with subsequent edema, trauma, hemorrhage (parenchymal, subdural, or epidural), or abscess. The ictus of aneurysmal rupture after SAH results in increased ICP due to the sudden inflow of arterial blood. Global brain edema may occur due to anoxic injury, hepatic failure, hypertensive encephalopathy, hypercarbia, or Reye syndrome [3]. As mentioned above, increases in venous pressure can also increase ICP and can occur from sinus thrombosis, heart failure, or mechanical obstruction of the venous sinuses. CSF flow obstruction or impaired absorption can also increase ICP, with obstruction of CSF flow leading to hydrocephalus. Meningeal disease from infection or malignancy can impair CSF flow and increase ICP. Finally, any process that increases CSF volume will increase ICP. This can occur in the context of meningitis or SAH. Occasionally, ICP may be increased from increased CSF production caused by a choroid plexus tumor [3, 17].

ICP most commonly leads to symptoms by compromising cerebral arterial perfusion. As ICP increases, a larger gradient must be overcome by the systemic arterial circulation to provide adequate perfusion to the brain. As perfusion pressure drops below that necessary to maintain ionic gradients across cell membranes, more edema develops further increasing ICP and decreasing perfusion in a vicious cycle. Two main types of edema exist: cytotoxic and vasogenic. Cytotoxic edema results from energetic failure and the inability to maintain ionic gradients, while vasogenic edema occurs due to extravasation of plasma proteins into the brain interstitial fluid. Different methods for treating increased ICP are effective against particular types of edema. The pathophysiology and natural history of different types of edema have been expertly reviewed elsewhere [18] and will be briefly discussed below.

After ischemia, lack of blood flow limits the availability of ATP and results in energetic failure. Cytotoxic edema occurs due to the cellular influx of osmolites (sodium and chloride). As active transport fails, cells take up sodium primarily through secondary active transport. As ions accumulate intracellularly, a transmembrane gradient forms providing the driving force for water to enter cells, leading to swelling. As mentioned above, swelling can compress nearby tissue, further compromising blood supply and leading to energetic failure and edema. Uptake of calcium can also trigger cellular apoptosis [19].

Vasogenic edema occurs due to permeability of the blood-brain barrier (BBB) allowing extravasation of water and plasma proteins into the brain interstitium. Vasogenic edema occurs as a result of paracellular transport past endothelial cells. Endothelial cells undergo rounding and retraction after ischemia or inflammation leading to increased permeability. Hydrostatic pressure is the main driving force behind vasogenic edema [20], which means that intracranial pressure and blood pressure are still important driving forces. Primary brain tumors and brain metastases produce angiogenic factors promoting the growth of new capillaries with abnormal ultrastructure and abnormal BBB with leaky tight junctions [21–23]. In addition to the abnormalities in the tumor blood vessels themselves, the effects of cytokines, most importantly vascular endothelial growth factor (VEGF), may affect blood vessels near the tumor. VEGF binds to its ligands on the endothelial cell surface called tyrosine kinase receptors flt-1 (VEGFR-1) and Flk-1/KDR (VEGFR2) [24, 25]. VEGF triggers decreased expression of tight junction proteins [26, 27], thereby increasing vascular permeability and promoting the formation of edema [28]. However, VEGF is not only expressed by tumors but also as a result of stroke or TBI [29–31]. Therefore, patients who initially develop cytotoxic edema may progress to developing vasogenic edema.

Algorithm for Management of ICP

Once a patient is suspected to have increased ICP, a series of medical and surgical treatments can be instituted. While the exact sequence may vary from patient to patient, our suggested algorithm is summarized in Fig. 1.1.

Elevated ICP is often first recognized either in the emergency department or by emergency medical services prior to hospital arrival. Initial treatments can include several simple and noninvasive maneuvers. The patient's head should be maintained at 30°. The patient's head and neck should be maintained in a neutral position in order to avoid any obstruction to venous outflow. If central access is emergently

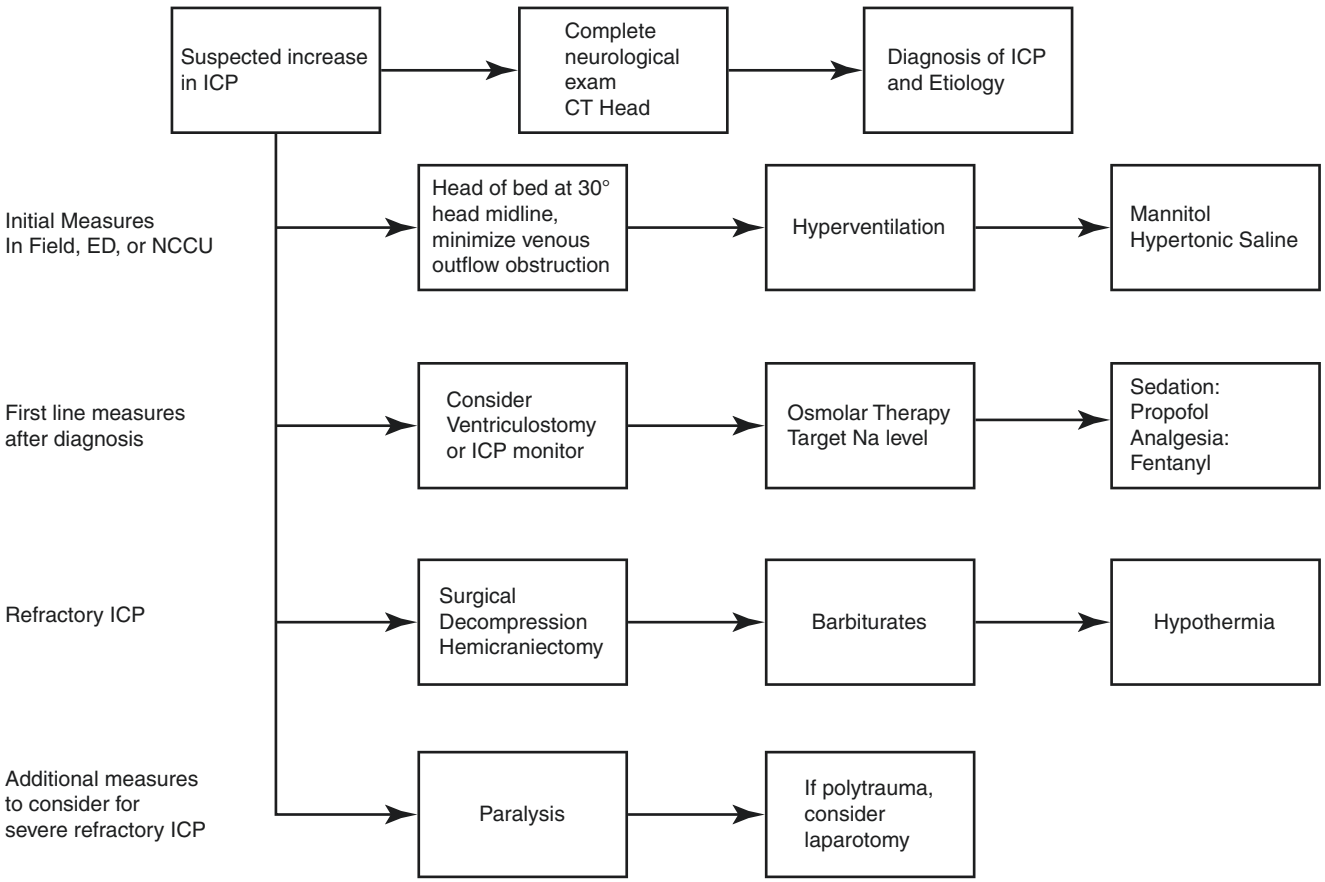

Fig. 1.1 Algorithm for the management of increased ICP. Suggested individual steps are listed after clinical suspicion for increased ICP. Abbreviations: ICP: intracranial pressure, CT: computed tomography

needed, we recommend placement of a femoral central venous catheter (CVC). This prevents any possible obstruction of venous outflow from an internal jugular CVC, and obviates the need to lie the patient flat or in Trendelenburg position, which can lead to herniation [32].

As with any critically ill patient, airway, breathing, and circulation must be addressed initially. Many patients with increased ICP will have depressed levels of consciousness and will require intubation for airway protection [33]. While intubation should not be delayed unnecessarily, it is often helpful to document a neurological examination prior to intubation. Generally, intubation is recommended for patients with Glasgow Coma Scale (GCS) less than eight. This is reflected in the Brain Trauma Foundation guidelines [34]. Rapid sequence intubation (RSI) is commonly recommended when patients have not been fasting, in order to prevent vomiting and aspiration. Succinylcholine is an option for short-term neuromuscular blockade; however, it has been associated with small elevations in ICP along with rhabdomyolysis and hyperkalemia. Rocuronium is likely a safer alternative in patients with elevated ICP, seizures, or following prolonged immobilization [35]. Hypotension is a common problem encountered during intubation and should be dealt with cautiously given that impaired cerebral autoregulation in the neurocritical care population puts patients at risk for decreased cerebral perfusion pressure (CPP) with significant decreases in mean MAP. Use of propofol or fentanyl for induction have been associated with significant hypotension secondary to vasodilation [36]. Etomidate is an alternative and causes less vasodilation and thus less hypotension. However, care must be taken with its use in patients in status epilepticus or at high risk for seizures, since it can lower seizure threshold [37–39].

Once the patient has been stabilized, a computed tomography (CT) scan of the head should be obtained. This is pivotal for diagnosing the etiology of the increased ICP and determining if there is radiographic evidence of herniation. After recognizing the clinical signs of increased ICP and typically around the time the patient is being taken for CT, hyperventilation is often the most readily available treatment modality. Hyperventilation may be utilized after the patient's airway has been secured by intubation as well as in those not yet intubated by utilization of a bag valve mask. Hyperventilation reduces ICP by decreasing PCO_2 in the

blood and CSF, which leads to cerebral vasoconstriction and decreased cerebral blood volume. Hyperventilation results in a rapid decrease in ICP; however, prolonged use of hyperventilation is not recommended given gradual loss of effectiveness and the risk of cerebral ischemia due to vasoconstriction. However, hyperventilation is very useful for patients in the emergency department when increased ICP is suspected as a bridge to initiation of osmolar or surgical treatment. We also use hyperventilation once the patient is in the neurocritical care unit after recognition of an ICP crisis. Jugular bulb oximetry may aid in the detection of cerebral hypoxia [40]; however, in practice it is seldom used. In patients with ICP crisis or showing signs of herniation, $PaCO_2$ can be transiently targeted to 25 mmHg [5, 40].

While the airway is being secured and hyperventilation provided, osmotherapy should be instituted. Mannitol is often the first agent administered and can be given without central venous access. Mannitol is usually made as a 20% solution and administered as a bolus. The dose ranges from 0.25 to 1 gram/kg; however, if there is concern for uncontrolled ICP, we suggest bolusing with 1 gram/kg initially. Given the profound diuresis that can occur after administration of mannitol, the provider should be careful to avoid hypotension from intravascular volume depletion. Hypertonic saline (HTS) may also be used, alone or in conjunction with mannitol. HTS may be given as a bolus of either 2% or 3% solutions, or if central access is available, a 30 mL bolus of 23.4% may be given. While HTS has the advantage of not resulting in diuresis, subsequent volume overload may be an issue in patients with decompensated heart failure or pulmonary edema.

It is around this stage in management that a decision should be made regarding placement of an ICP monitor or external ventricular drain for CSF diversion. Invasive ICP monitoring is generally indicated for patients with GCS<8 and with evidence of mass effect on head CT. While there is significant clinical equipoise, ICP monitoring should also be considered in patients who show signs of posturing on clinical examination or who have a systolic blood pressure less than 90 mmHg, particularly in those patients older than 40 years of age. The specific types of ICP monitors are discussed later. In patients with obstruction to CSF flow from intraventricular hemorrhage or from mass effect, placement of an external ventricular drain (EVD) is preferred. An EVD not only provides the ability to monitor ICP, but also allows ICP to be treated by CSF diversion. In patients with TBI or with slit-like ventricles making placement of an EVD impossible, a parenchymal ICP monitor can be placed [40].

Sedation can be a valuable tool in ICP management. Agitation can increase ICP by increasing the cerebral metabolic rate. ICP can also be affected if agitation results in increased MAP or increased thoracic pressure. Fentanyl can be used to treat agitation, either in boluses or as a continuous infusion. However, providing sedation with propofol is often a more effective way to control ICP. In a patient whose airway has already been secured and who experiences a sustained increase in ICP, a bolus of propofol can be administered with or without initiation of a continuous infusion [41]. More detail regarding other available agents, and the relevant pharmacology and side effects, will be discussed in the next section.

In patients whose ICP remains poorly controlled despite osmotherapy and optimized sedation, consideration should be given to surgical decompression with hemicraniectomy. By removing the rigid constraints of the skull, hemicraniectomy can allow for expansion of brain tissue outside of the cranial vault, thereby eliminating downward pressure on the midbrain and brainstem. In many cases hemicraniectomy can be pursued prior to initiating other therapies such as hypothermia or barbiturate-induced coma. Hemicraniectomy has been found to be particularly effective in patients with mass lesions and in those with malignant MCA stroke [42–44].

If ICP remains poorly controlled, consideration should be given to barbiturate-induced coma. The typical agent used is pentobarbital, and it lowers ICP by causing a marked decrease in the cerebral metabolic rate. Pentobarbital can be administered in 5 mg/kg boluses every 15–30 minutes until ICP is controlled. A continuous infusion at 0.5–5 mg/kg/hour with continuous EEG monitoring can then be instituted [45].

When all of the above methods have failed to adequately control ICP, hypothermia to 32–34°C can be used to lower ICP. Similar to barbiturates, hypothermia decreases ICP by suppressing cerebral metabolism. Hypothermia may be effective in patients who are refractory to barbiturates [46]. While effective at decreasing ICP, hypothermia is associated with numerous complications (discussed later), without clear evidence of improvements in functional outcomes.

If ICP remains poorly controlled despite all of the above interventions, last-ditch efforts have included the use of paralytic agents and laparotomy. Increased intraabdominal pressure can exacerbate ICP by transmission of pressure to the spinal subarachnoid space. Several small studies have demonstrated that laparotomy may be beneficial for decreasing refractory ICP [47, 48]; however, larger studies are needed to define its role in practice.

At every point during ICP management, consideration should also be given to whether a patient is having or at risk for seizures. Given that seizure activity raises ICP [49], seizures should be treated aggressively with benzodiazepines (lorazepam, midazolam, or diazepam) followed by or concomitantly with fosphenytoin, valproic acid, or levetiracetam. For patients at risk for increased ICP, there should be a low threshold for initiating continuous EEG (cEEG) monitoring given the high rate of progression to nonconvulsive status epilepticus (NCSE) [50, 51].

Monitoring ICP

It has long been thought that invasive monitoring of ICP is beneficial given the variable clinical signs of elevated ICP. In general, placement of an invasive ICP monitor is indicated in patients with a depressed level of consciousness (typically GCS<8), imaging revealing a mass lesion with cerebral edema, and a prognosis meriting aggressive care in the ICU [52]. ICP can be monitored using a number of different devices. An EVD is the gold-standard for measuring ICP and also allows for in vivo calibration and recalibration. In addition to being able to transduce ICP, an EVD has the advantage of being able to treat ICP by diverting CSF flow. An EVD should be placed whenever a patient has symptomatic hydrocephalus with GCS<8 [53–55]. In the NCCU, this commonly occurs in the setting of subarachnoid hemorrhage or ICH with intraventricular hemorrhage but can be caused by any obstruction to CSF flow. However, an EVD is associated with risks such as tract hemorrhage (up to 22%) [56] and ventriculitis (5.5–22%) [55, 57–59]. Parenchymal intracranial pressure monitors can also be used. While having a lower risk of infection and bleeding [52, 60], CSF cannot be drained to treat ICP. Furthermore, drift can occur after about 7 days, without the possibility to recalibrate [52, 60]. Intraparenchymal monitors are of most benefit in patients with low GCS and suspected high ICP without hydrocephalus, such as diffuse TBI or hepatic encephalopathy. ICP monitors can also be placed in the epidural or subarachnoid space [55], although this has largely fallen out of favor. While the Brain Trauma Foundation recommends monitoring ICP for patients with severe TBI [40], it remains unclear whether this intervention improves outcomes [61].

Drainage of CSF from an EVD can be performed continuously or intermittently. The question of which method is superior has recently been addressed. One study found that continuous drainage was associated with lower mean ICP values [62]. However, the study was relatively small and was not designed to assess differences in outcomes or mortality. Although there is not very strong evidence, our general practice is to allow for continuous CSF drainage that depends on a specific EVD pressure-based pop-off set by the provider.

Patient Triage and Flow

Management of increased ICP should begin upon a patient's initial presentation, which is often in the field before arriving to a hospital. Important measures can be taken in the prehospital setting and in the emergency department [63]. Signs of increased ICP (described above), including decreased level of consciousness, a unilateral dilated pupil, posturing, or changes in vital signs such as hypertension and bradycardia (Cushing reflex), may occur well before a patient reaches the NCCU. The head of the bed should be elevated to 30°C as soon as possible, while minimizing the time period that the patient is flat. This can be accomplished *en route* to the hospital by placing rolled blankets or towels beneath the patient's head [63]. In addition to the standard ABCs of resuscitation, an end-tidal pCO_2 of 28–32 mmHg can be targeted after intubation as a temporizing measure. Once in the emergency department, a CT of the head should be obtained as soon as possible to characterize whether a mass lesion is present. Mannitol can be given through a peripheral line before central access is established. If there is evidence of obstructive hydrocephalus contributing to increased ICP, neurosurgery should be consulted as soon as possible in order to facilitate ventriculostomy placement. This can occur in the emergency department if needed or on arrival to the NCCU. While a patient requiring ICP management can be managed in a number of different ICUs, data have emerged indicating that treatment in a dedicated NCCU staffed by neuro intensivists results in better outcomes and lower ICU lengths of stay [64–66].

Individual Methods for ICP Control

In the following sections, we will describe in more detail each individual method in the algorithm for ICP control. Current evidence and guideline recommendations are reviewed. Within each section, relevant pharmacology of each medication is discussed. Salient pharmacological features are summarized in Table 1.1.

Head Positioning

It is now common practice to maintain the head of bed at 30° in patients with elevated ICP. It has been recognized for decades that a moderate degree of head elevation is of benefit in decreasing ICP. As the head is raised, the weight of the CSF column is progressively displaced onto the lumbar subarachnoid space, thereby decreasing ICP. Raising the head also likely decreases intrathoracic pressure and improves venous outflow [67]. Concern has been raised in the literature that head elevation results in decreases in CPP, in some cases resulting in the occurrence of CSF pressure waves [68]. However, the preponderance of data currently available suggest that head elevation to 30° is effective in decreasing ICP without comprising CPP, cerebral oxygenation, or systemic hemodynamics [69–71]. On average, this maneuver results in 3–4 mmHg decrease in ICP. For any patient with suspected increases in ICP, we favor placing the head of bed at 30° and assuring minimal head rotation to limit obstruction of jugular venous outflow. We also try to minimize the amount of time any patient is flat. For this reason, when central access is needed emergently for a patient

Table 1.1 Relevant pharmacology. Dosing, monitoring, and side effects are listed for each category of medications used to treat ICP

	Medication	Dosing	Monitoring	Side effects
Osmolar Therapy	Mannitol	0.1–1 g/kg, every 4–6 hours	Osmolar gap, goal <20 mOsm/kg	Dehydration, hypotension, rebound edema, AKI, electrolyte abnormalities
	Hypertonic aline	Bolus of 23.4% Infusion or bolus of 2% or 3%	Target set Na range Na check every 8 hours on 2% Na check every 6 hours on 3%	Pulmonary edema, CHF exacerbation, osmotic demyelination, metabolic acidosis, coagulopathy
Sedation	Propofol	1–2 mg/kg bolus 5–100 μg/kg/minutes	BP, RASS, triglycerides, acid/base status, CK, LFTs, K	Hypotension, PRIS, anaphylaxis, hypertriglyceridemia
	Fentanyl	12.5–100 μg bolus 25–700 μg/hour infusion	Respiratory status, RASS	Respiratory depression, nausea, vomiting, diaphoresis
	Midazolam	0.01–0.05 mg/kg bolus 0.01–0.1 mg/kg infusion	Blood pressure, RASS	Hypotension, respiratory depression, anterograde amnesia
AEDs	Lorazepam	0.1 mg/kg IV push (up to 4 mg per dose)	Respiratory status, BP	Respiratory depression, hypotension
	Fosphenytoin	20 PE/kg loading dose 4–6 mg mg/kg/day maintenance	Target 10–20 μg/mL total or 1–2 μg/mL free level	Hypotension, bradycardia, numerous drug interactions
	Valproic Acid	20–40 mg/kg loading dose 10–15 mg/kg/day	Target 50–150 μg/mL level	Hepatotoxicity, hyperammonemia, thrombocytopenia
Barbiturates	Pentobarbital	5 mg/kg boluses every 15–30 minutes 1–4 mg/kg/hour infusion	Titrate to burst suppression on cEEG Can follow levels	Hypotension, cardiac depression, ileus, immune compromise
Paralytics	Vecuronium Cisatracunium	0.05–0.1 mg/kg bolus 0.05–1.5 μg/kg/minute infusion 0.1–0.2 mg/kg bolus 2–10 μg/mg/kg infusion	Follow TOF while paralyzed Maintain adequate sedation	Pneumonia, neuropathy, myopathy, anaphylaxis, malignant hyperthermia

Na sodium, *AKI* acute kidney injury, *CHF* congestive heart failure, *BP* blood pressure, *RASS* Richmond Agitation-Sedation Scale, *CK* creatine kinase, *LFTs* liver function tests, *PRIS* propofol related infusion syndrome, *K* potassium, *IV* intravenous, *cEEG* continuous electroencephalogram, *TOF* train of four

with ICP crisis, we advocate placing a femoral CVC rather than placing a patient flat or in Trendelenburg for placement of a subclavian or internal jugular CVC [32].

Hyperventilation

As described above, hyperventilation reduces ICP by decreasing $PaCO_2$, which decreases cerebral flow. Given its ability to reduce ICP, hyperventilation was once commonly used prophylactically for patients with increased ICP. However, there is evidence to suggest that prophylactic and long-term hyperventilation can be deleterious. In fact, the Brain Trauma Foundation provides a Level IIB recommendation against the use of hyperventilation for control of ICP [40]. In patients with TBI, outcomes were found to be worse in patients treated with prolonged hyperventilation [72]. Patients were randomized to normal ventilation, hyperventilation, or hyperventilation with tromethamine. Tromethamine treatment was added in order to counter the effects of loss of bicarbonate from the CSF after prolonged hyperventilation. For patients with a motor GCS of 4–5, the GOS scores at 3 and 6 months were significantly worse in patients being hyperventilated. There are a few possible explanations for the lack of benefit of hyperventilation. The effects of hyperventilation on cerebral artery diameter are transient, lasting at most 24 hours [73]. Furthermore, loss of bicarbonate from the CSF during prolonged hyperventilation may result in decreased buffering capacity and subsequent hypersensitivity to small changes in $PaCO_2$ [74]. While there

is concern that prolonged hyperventilation may contribute to ischemia by reduction of CBF [72], a significant reduction in CBF has not been demonstrated after prolonged hyperventilation given the compensatory increase in arterial oxygen extraction [72]. Overall, hyperventilation should not be used prophylactically or for prolonged ICP management. However, we believe that hyperventilation still plays an important role in treatment during ICP crises and will commonly use hyperventilation as a bridge to other treatments.

Osmolar Therapy

The utility of hypertonic solutions has been known since 1919 when Weed and McKibbon demonstrated that various salt and glucose solutions could lower ICP in cats. Cushing and Foley as well as Foley and Putnam obtained similar results. The first reported clinical use of hypertonic agents involved urea solutions in the 1950s [75]. Mannitol started to be used in the 1960s [76] with hypertonic saline (HTS) not being utilized until the 1990s [77].

Hyperosmolar therapy lowers ICP by creating an osmolar gradient, thereby providing a gradient for water egress out of the brain. In order for an osmolar agent to create an effective gradient, it must be impermeable to the BBB. The reflection coefficient describes the BBB permeability of a substance, ranging from 0 (complete permeability) to 1 (complete impermeability) [78]. The effectiveness of hyperosmolar therapy requires an intact BBB. In regions of the brain where the BBB is damaged, there is equilibration of molecules between blood and brain interstitial fluid. Therefore, ICP is mainly reduced via removal of water from portions of the brain with an intact BBB. The majority of the effect of hyperosmolar treatment occurs shortly after maximal osmolarity is reached. With ongoing increased serum osmolarity, the brain begins to accommodate. It has been known for decades that the brain is able to produce "idiogenic osmoles," which are now known to be polyols, amino acids, and methylamines produced by astrocytes as well as small proteins produced by neurons [79, 80]. Consequently, as serum osmolarity is decreased, rebound cerebral edema can occur given the reversal of the osmolar gradient favoring water entry into the brain.

The primary agents used to for hyperosmolar therapy are mannitol and HTS. Mannitol is a carbohydrate that increases serum osmolarity by dehydration as it acts as an osmotic diuretic. It also lowers blood viscosity and causes reactive vasoconstriction of cerebral blood vessels [81]. Mannitol is typically administered as a 20% solution with boluses of 0.25–1.0 gram/kg [82]. It can be dosed at intervals of 2–4 hours or longer, depending on the clinical situation. Mannitol exerts its effects within 10–15 minutes with a maximal effect by 20–60 minutes [83]. The effect of mannitol is typically monitored by following both calculated and measured serum osmolality. Laboratory studies including osmolality and basic metabolic profile should be drawn prior to giving a dose of mannitol. While an osmolality of greater than 320 mOsm/kg has been suggested as a cutoff for mannitol therapy, it is not an accurate measure of excess mannitol and can also be increased due to conditions such as hyperglycemia. The osmolar gap is more useful in the detection of remaining mannitol in the serum with an osmolar gap of >20 mOsm/kg indicating incomplete clearance. With incomplete clearance, mannitol can accumulate in regions of the brain with BBB permeability causing a reverse osmotic shift and rebound ICP elevation. Given its potent osmotic diuretic effect, mannitol can lead to acute kidney injury, dehydration, and hypotension. Electrolytes should also be closely monitored.

In comparison to mannitol, HTS directly increases serum osmolality rather than indirectly via diuresis [82]. It is typically administered as 2%, 3%, or 23.4% solutions. Frequent serum sodium checks should be performed for patients receiving HTS, with the goal of using the lowest dose possible. We typically monitor serum sodium every 8 hours for patients receiving 2% and every 4–6 hours for patients receiving 3% HTS. This agent results in fluid expansion and, unlike mannitol, does not contribute to significant diuresis. Furthermore, HTS has a reflection coefficient of 1.0 compared to 0.9 for mannitol and thus has a theoretically decreased risk of rebound cerebral edema [84, 85]. Given volume expansion secondary to HTS, caution should be used when treating patients with poorly controlled heart failure or pulmonary edema. The patient's baseline sodium should also be taken into consideration due to the risk of osmotic demyelination that may occur in patients with chronic hyponatremia in the context of precipitous increases in sodium concentration.

Studies have shown that hyperosmolar treatments are able to reverse transtentorial herniation [86]. However, controversy remains as to whether HTS or mannitol is more effective. Findings from one study suggested that HTS is more effective than mannitol in lowering ICP and decreasing the total number of ICU days, without having an effect on 2-week mortality [87]. Other studies have shown no difference in the average elevated ICP time or in 6-month outcomes [88].

Sedation

Sedative agents decrease ICP by lowering cerebral metabolic activity. Additionally, reduction in agitation may reduce the amount of Valsalva maneuvering and elevations in jugular venous pressure. Propofol is the most commonly

used sedative agent for ICP control. Propofol is a GABAa receptor agonist with a rapid onset and offset. While able to rapidly and effectively lower ICP, propofol has a number of side effects. Hypotension is often the first side effect encountered, and caution should be taken not to lower CPP. Propofol treatment can also lead to hypertriglyceridemia and pancreatitis, and triglyceride levels should be routinely monitored. The most common serious side effect is propofol-related infusion syndrome (PRIS), in which profound metabolic acidosis, hyperkalemia, hepatomegaly, renal failure, cardiac dysrhythmia, and heart failure occur. Propofol has been compared with morphine, with findings of decreased ICP on day 3 in the propofol group [41]. However, there were no significant differences between the two groups in mortality or GOS. In post hoc analysis, lower dose propofol treatment resulted in no difference in ICP control while being associated with significantly lower mortality [41]. The Brain Trauma Foundation gives a Level IIB recommendation to using propofol to control elevated ICP, although notes the lack of evidence regarding any improvement in mortality or 6-month functional outcomes [40]. Given the adverse side effects associated with high dose and long-term use of propofol, boluses of propofol (1–2 mg/kg IV) can be administered during periods of ICP crises in order to minimize use of continuous propofol infusions. Caution should be used and relevant laboratory values should be closely monitored in patients treated with propofol for longer than 48 hours or receiving doses greater than 5 mg/kg/hour to prevent development of PRIS.

Seizure Control

Seizure activity and especially generalized tonic-clonic seizures are associated with increased ICP [49, 89]. Increases in ICP are believed to be due to the increases in metabolism and blood flow secondary to epileptiform activity [90]. Therefore, in any patient in whom there is a concern for seizure, early treatment should be instituted in combination with continuous EEG monitoring if there is concern for subclinical seizures or status epilepticus. For patients actively seizing, the first line medication is a benzodiazepine. Lorazepam can be administered in doses of 0.1 mg/kg IV every 5–10 minutes. Alternatively, diazepam can be given at doses of 0.15 mg/kg IV every 5 minutes or midazolam can be given at doses of 0.2 mg/kg IV or IM. Patients with frequent seizures or in status epilepticus should also be loaded with fosphenytoin (20 PE/kg IV) or valproic acid (20–40 mg/kg IV). Newer studies have suggested that levetiracetam (20–330 mg/kg) is as effective in treating status epilepticus as phenytoin, and it has the advantage of fewer side effects and drug interactions [91, 92]. Patients with refractory status epilepticus may require a midazolam drip or burst suppression with pentobarbital in the most severe cases. Detailed discussion of the diagnosis and treatment of status epilepticus is provided in Chapter 2.

Hypothermia

Hypothermia is thought to decrease ICP by suppressing brain metabolism. It has been proven to be effective for the treatment of comatose survivors of cardiac arrest, where targeted temperature management has become the standard of care [93–95]. There was significant early enthusiasm for the use of therapeutic hypothermia in the treatment of increased ICP. However, there is no clear evidence regarding the benefit of hypothermia for this purpose. Furthermore, hypothermia is associated with significant side effects, including coagulopathy, immunosuppression, electrolyte imbalances, and cardiac dysrhythmia (Table 1.1).

Nonetheless, hypothermia has been used both prophylactically and for refractory intracranial hypertension. While studies have reported conflicting results regarding the prophylactic use of hypothermia, recent randomized controlled trials (RCTs) have not found a benefit. A large RCT in TBI patients in 2001 showed no difference in mortality or neurological outcomes when comparing normothermia to hypothermia [96]. A follow-up study enrolled patients within 2.5 hours of TBI but again found no difference in mortality or neurological outcomes [97]. It has been suggested that patients who received surgical hematoma evacuation and were cooled quickly benefited more than those with diffuse injury [98]. A large multicenter RCT (POLAR) is currently under way to more rigorously test the use of prophylactic hypothermia in TBI [99]. However, in light of the currently available evidence, the Brain Trauma Foundation gives a Level IIB recommendation against the use of early hypothermia [40].

Use of hypothermia for treatment of increased ICP has been less well tested. Early, small studies suggested that hypothermia was able to reduce ICP and improve outcomes [46]. In the more recent Eurotherm3235 trial, hypothermia did not result in improvement in ICP or better outcomes in patients with TBI and sustained elevations in ICP above 20 mmHg [100]. However, there is ongoing debate as to whether hypothermia may play a role in patients with refractory ICP with sustained elevations above 25 mmHg despite maximal medical therapy when CPP is adequately optimized.

The available evidence suggests that prophylactic use of hypothermia is not beneficial; and while able to lower ICP, it is unclear whether outcomes are improved when hypothermia is used in cases of refractory high ICP. Therefore, hypothermia should still be considered when other options have failed if it is felt that the benefits outweigh the risks.

Decompressive Craniectomy

As discussed above, cerebral edema can lead to increased ICP causing brain tissue to herniate into adjacent compartments. A wide craniectomy with duroplasty aimed at decompressing the frontal, parietal, and temporal lobes has been shown to be beneficial in reducing ICP. While numerous studies have shown that decompressive craniectomy is effective in lowering ICP [101, 102], the optimal timing remains to be established. The DECRA study compared early decompressive craniectomy for patients with standard medical therapy in patients with diffuse TBI [103]. In the craniectomy group, 70% of patients had an unfavorable outcome compared with 51% of patients in the standard medical therapy group. However, criticism of the DECRA study focused on the fact that the threshold for surgery (ICP >20 mmHg for >15 minutes) did not reflect typical clinical practice, where decompressive hemicraniectomy is typically reserved for ICP refractory to all medical interventions. The surgical group also likely had more severe TBI, and the study design allowed for a high rate of crossover from the standard medical therapy arm to the surgical arm [104].

More recently, the RESCUEicp trial evaluated the effectiveness of decompressive hemicraniectomy on clinical outcomes in TBI patients with elevated ICP (>25 mmHg) refractory to aggressive medical therapy [105]. The trial aimed to simulate clinical practice more closely as patients had to fail both stage 1 and 2 treatments before being considered for decompressive hemicraniectomy. Stage 1 treatments included sedation, analgesia, head elevation, and mechanical ventilation, while stage 2 treatments included osmolar therapy, ventriculostomy, and hypothermia. Barbiturates use was not allowed until failing stage 1 and 2 therapies and either being randomized to surgery or continued medical management. While hemicraniectomy improved mortality at 6 months, the proportion of patients with moderate disability and good outcomes were not improved [105]. Therefore, there are Level IIA recommendations from the Brain Trauma Foundation that craniectomy does not improve 6-month outcomes, though the procedure is able to effectively reduce ICP and may reduce the number of days spent in the ICU [40].

Another important issue is the size of decompressive craniectomy. A larger craniectomy is thought to more effectively decompress the intracranial contents and lower ICP. A small bone opening carries with it the potential risk of brain herniating through the opening with a mushroom cap appearance causing constriction and venous ischemia [106]. Studies have shown better outcomes for patients with larger decompressive craniectomies; however, the inclusion criteria and procedures varied [107, 108].

The role of decompressive craniectomy in patients with malignant MCA infarcts is more established. Several large RCTs have demonstrated the benefit of decompressive craniectomy in this population. Over 10 years ago, the DECIMAL and DESTINY trials showed that early decompressive craniectomy reduced mortality and resulted in more patients with moderate disability [43, 109]. The HAMLET trial confirmed the benefit of decompressive craniectomy within 48 hours of stroke onset [110]. The American Heart Association and American Stroke Association therefore recommend that there is Class I evidence for decompressive craniectomy in patients with unilateral MCA infarctions who deteriorate within 48 hours despite medical therapy [111]. DESTINY II showed that early decompressive craniectomy was also beneficial in stroke patients 61 years of age and older [43]. Of note, hemicraniectomy seems to be most beneficial for stroke patients when performed early, when the edema is likely predominantly cytotoxic. Relieving pressure by hemicraniectomy improves tissue perfusion and thus improves the energetic balance, allowing restoration of ionic gradients. If performed late, when patients have already developed vasogenic edema, hemicraniectomy will decrease tissue pressure resulting in a larger hydrostatic pressure gradient driving the efflux of plasma proteins and contributing to more cerebral edema [112, 113].

Barbiturates

Barbiturates have long been known to decrease ICP secondary to decreasing cerebral metabolism [114] in addition to decreasing coughing, movement, and Valsalva maneuvering. It has also been suggested that barbiturates inhibit oxygen radical-mediated lipid peroxidation, which may also contribute to lowering ICP [115–117]. Pentobarbital is the most commonly used barbiturate. Thiopental has also been used for ICP control. Some evidence suggests that treatment with thiopental results in better control of ICP as well as decreased risk of death at 6 months [118]. However, it is currently unavailable for clinical use in the United States. Pentobarbital is typically administered as a bolus of 5–15 mg/kg IV every 15–30 minutes until the ICP has been controlled. Thereafter a continuous infusion of 1–4 m/kg/hour can be initiated. During pentobarbital administration, continuous EEG should be recorded with a goal of achieving burst suppression with 6–8 seconds between bursts [50] Pentobarbital has been used both prophylactically and for refractory ICP. When compared with standard treatment, prophylactic use of pentobarbital resulted in no significant difference in mortality or GOS at 1 year, and 54% of patients in the pentobarbital group vs. 7% of controls developed hypotension [119]. Thus, the Brain Trauma Foundation has given a Level IIB recommendation against the prophylactic use of barbiturates for preventing increased ICP [40]. In 1988, Eisenberg et al. studied the use

of pentobarbital for refractory ICP [120]. The trial demonstrated that pentobarbital was effective in lowering ICP, and that those patients whose ICP responded had improved survival (92% vs, 17%). However, the utility of pentobarbital remains limited by its side effects. While pentobarbital decreases ICP, it lowers blood pressure, thereby lowering CPP. This may account for why treatment with pentobarbital does not result in any improvement in functional outcomes in patients being treated for increased ICP [116]. Additional side effects of pentobarbital treatment include cardiac suppression and ileus. We consider using pentobarbital for ICP control in patients refractory to other interventions provided they can be kept hemodynamically stable, in line with the Level IIB recommendations issued by the Brain Trauma Foundation [40].

Steroids

Glucocorticoids have both genomic and nongenomic effects. After diffusing through plasma membranes, glucocorticoids bind to their cytoplasmic receptor, which results in the exposure of its nuclear localization signals allowing the movement of the glucocorticoid-receptor complex into the nucleus. Glucocorticoids bind to glucocorticoid response elements (GREs) in order to regulate the transcription of nuclear DNA. This results in the transcriptional downregulation of several key inflammatory cytokines such as IL-1β, IL-4, IL-5, and IL-10 [121]. Glucocorticoids also exert anti-inflammatory effects by interfering with NF-κB signaling [122]. As mentioned above, vasogenic edema occurs in the context of increased vascular permeability. Steroids are thought to reduce the permeability of capillaries surrounding tumors [123–125]. Steroids affect the ability of molecules to transfer across the BBB, and have been shown to decrease the amount of peritumoral water without affecting perfusion [126, 127].

Steroids have long been known to be of benefit in the perioperative management of patients with brain tumors [128, 129], and still play an important role in neurocritical care. Steroid treatment remains invaluable in the treatment of increased ICP secondary to tumor-related edema. Dexamethasone is the most commonly used corticosteroid due to its long half-life and low mineralocorticoid activity. Typically, dexamethasone is administered in a 10–20 mg intravenous dose at presentation with tumor-related neurological symptoms in the brain or spinal cord. The dose can be increased up to 100 mg per day with daily maintenance doses usually ranging from 4 to 24 mg in divided doses [130].

Given its success in treating neurological symptoms in patients with brain tumors, steroids have been studied for use in ICP control in other disease processes. The available evidence in TBI suggests that steroids are not beneficial. An RCT consisting of 957 patients with severe TBI conducted in 1998 demonstrated that treatment with tirilazad mesylate (a synthetic 21-amino steroid) had no benefit with respect to death or outcomes [131]. In 2004, the Corticosteroid Randomization After Significant Head Injury Trial (CRASH) studied treatment with either 2 g intravenous methylprednisolone followed by 0.4 mg/hour for 48 hours or placebo. There was an increase in mortality at 2 weeks (21.1% vs. 17.9%, relative risk (RR) 1.18%) and 6 months (25.7% vs 22.3%, RR 1.15) when comparing corticosteroid vs. placebo, respectively [132, 133]. There was also a higher percentage of patients with severe disability at 6 months in the corticosteroid group (38.1% vs 36.3%), although this did not reach statistical significance [132, 133]. The Brain Trauma Foundation has therefore issued a Level I recommendation against the use of steroids in TBI for either improving outcomes or ICP [40].

While not shown to be of benefit in TBI, the use of steroids has become more popular in the treatment of SDH. Localized inflammation occurs after SDH promoting angiogenesis, and perioperative steroid use results in higher survival and lower risk of SDH recurrence [134]. The Steroids in Chronic Subdural Hematomas (SUCRE) trial is a double-blind, randomized trial currently under way that will help to elucidate the role of steroids in the management of SDH [135]. While steroid use remains controversial after aneurysmal SAH, there is some evidence to suggest that dexamethasone treatment may improve outcomes [136], especially in those patients who undergo microsurgical clipping but not endovascular coiling [137].

Care should be taken when using steroids given the large number of potential side effects, which are typically associated with the dose and length of steroid treatment [138]. However, the most common side effects encountered with acute use of steroids in the ICU are insulin resistance leading to hyperglycemia and myopathy [139]. Additional systemic side effects are various and include development of a cushingoid appearance, truncal obesity, hirsutism, acne, impaired wound healing, easy bruising, hypertension, immunosuppression, cataracts, gastrointestinal bleeding, and osteoporosis, among others [139]. Additionally, dexamethasone has several important drug interactions. By inducing CYP3A4, phenytoin increases the clearance of dexamethasone and decreases its plasma half-life by up to 50% [140–142]. Carbamazepine and phenobarbital may also induce metabolism of dexamethasone [143].

Paralysis

Paralysis with neuromuscular blocking agents has been used for ICP control. Paralysis facilitates the lowering of ICP by preventing shivering and coughing and also by decreasing overall energy expenditure [144–148]. It also facilitates mechanical ventilation, allowing for optimization

of pCO_2 and oxygenation [149]. Paralytics may decrease the pro-inflammatory effects of mechanical ventilation [150]. Paralytic agents work by interrupting signal transmission at the neuromuscular junction and can be depolarizing (succinylcholine) or non-depolarizing (all others). Succinylcholine is depolarizing as it mimics the action of acetylcholine, while the other agents are competitive acetylcholine antagonists. Interactions can occur with drugs that inhibit plasma cholinesterase activity. Given that there is no effect on consciousness, adequate sedation and analgesia must always be used in patients receiving paralytics. Suggested dosing is listed in Table 1.1.

Strong evidence does not exist for the use of paralysis in ICP control. Of concern, two studies have shown that use of succinylcholine can lead to increases in ICP [151, 152] Two retrospective studies assessing prolonged used of paralytics found no improvement in outcomes and demonstrated an increased frequency of complications such as pneumonia [153, 154]. In addition to the risk of pneumonia, use of paralysis is also associated with development of critical illness neuropathy and myopathy [155, 156]. Other side effects include anaphylaxis, cardiac arrest and arrhythmias, malignant hyperthermia, hyperkalemia, jaw rigidity, rhabdomyolysis, and myalgias. Given the associated side effects and lack of evidence regarding ICP control and outcomes (summarized in a recent meta-analysis [157]), we generally do not advocate for the use of paralytics. Consideration can be given to a bolus of a paralytic for patients with ongoing ICP crises refractory to all other medical interventions. Paralytics may also play a role in the treatment of refractory shivering in patients being cooled.

Conclusions

Diagnosis and management of ICP crises are cornerstones of neurocritical care. Herein we have summarized key clinical features characterizing increased ICP and outlined our algorithm for ICP management. The relevant literature regarding each step in management is discussed. While several trials have been published in recent years, high-quality data are lacking for most methods of ICP control. We recommend a step-wise treatment approach for the management of ICP and call for additional RCTs to better define the utility and role in management of different methods for ICP treatment.

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Emergent Treatment of Status Epilepticus

2

Sarah E. Nelson and Eva Katharina Ritzl

Definitions and Epidemiology

A single seizure is a significant event during which an electrical discharge in the brain may result in altered awareness often accompanied by motor manifestations. Isolated seizures usually are less than 5 min long and self-limited; however, longer seizures tend not to resolve on their own [1]. Defining status epilepticus (SE) as loss of consciousness or failure to return to baseline as well as other, often tonic-clonic, activity needs to be taken into account. Therefore, the definition of SE as continuous seizure activity or two or more seizures without recovery of consciousness of longer than 30 min in duration seems outdated. Given the non-self-limited nature of seizures longer than 5 min, studies showing that permanent brain injury in SE may occur sooner than 30 min, and recent studies using 5 min as the threshold for SE, SE is now often described as seizure activity lasting 5 min or longer [1, 2].

Subtypes of SE include convulsive SE, epilepsia partialis continua, and nonconvulsive SE (NCSE). Repetitive tonic-clonic movements followed by a post-ictal state occur in convulsive SE. Epilepsia partialis continua is characterized by focal neurologic deficits such as aphasia and motor dysfunction occurring as a result of partial seizures arising from eloquent cortex but in the absence of altered mental status. NCSE is the occurrence of mental status change but without convulsions or outlasting convulsions while electrical seizure activity is ongoing in the brain [2].

SE may also be subdivided based on its response to antiepileptic drugs (AEDs). While refractory SE (RSE) is continuous seizure activity not controlled by first- or second-line AEDs [3], super-refractory SE (SRSE) has been defined in two different ways: SE not controlled by third-line AEDs [4] and SE that continues 24 h or more after anesthesia is given [5].

Annual SE incidence is approximately 12.6/100,000 person-years [6], and 9–43% of patients with SE progress to RSE and 10–20% to SRSE [4, 5]. Seizures or SE may be found in up to 19% of intensive care unit (ICU) patients [7]. This is an important finding as SE in ICU patients is often nonconvulsive. The diagnosis therefore requires a high level of suspicion and a diagnostic electroencephalogram (EEG). Recent studies suggest that SE occurs nearly equally in females and males (11.1/100,000 person-years in females, 11.3/100,000 person-years in males) [6]. Individuals greater than age 50 years (approximately 28.4/100,000 per year) and less than age 10 years (14.3/100,000 per year) seem to be affected most. In addition, more African Americans (13.7/100,000 per year) than whites (6.9/100,000 per year) and other races (7.4/100,000 per year) appear to develop SE [8]. Case fatality rate is approximately 15% though this rate is greater in the elderly (24.9%) and in patients with RSE (33.3%) [6].

SE incidence appears to be increasing over time. In a study evaluating data from US National Hospital Discharge Survey, between 1979 and 2010 the incidence of SE was found to increase from 3.5 to 12.5/100,000 per year but with no significant change in in-hospital mortality [8]. In another recent study that used data from the Centers for Disease Control and Prevention and from the Nationwide Inpatient Sample, SE hospitalizations increased by 56.4% from 1999 (8.9 per 100,000 persons) to 2010 (13.9 per 100,000 persons). Mortality also increased over this same time period, but only by 5.6% (1.8 per 1,000,000 persons to 1.9 per 1,000,000 persons) [9].

Convulsive SE episodes occur 120–180,000 annually in the USA [10], but the incidence of NCSE is not as clear as it cannot be diagnosed without the help of an EEG [11]. The percentage of SE patients progressing to RSE and SRSE is described above. Annual incidence of RSE was found to be 3.4/100,000 in one large study of 395 RSE patients treated in the ICU [12]. As

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expected, prospective studies [13] estimate a lower incidence than ICU retrospective ones [14–16]. However, the exact incidence of SRSE have not yet been delineated, likely due to the low number of patients with this condition and lack of prospective studies [17]. In a recent study that utilized the Finnish Intensive Care Consortium database, 22% of patients with RSE were categorized as having SRSE with an annual incidence estimate of 0.7/100,000 [5].

Etiology

There are a variety of potential causes of SE [1] (see Table 2.1). According to the International League Against Epilepsy, etiology is divided into two groups: (i) known or symptomatic and (ii) unknown or cryptogenic. Subdivisions of the symptomatic group include acute symptomatic, remote symptomatic, and progressive symptomatic [18]. Acute causes may occur more frequently than chronic causes [6]. Importantly, SE mortality can be affected by SE etiology [9].

RSE predictors can include lower level of consciousness, new diagnosis of SE, focal seizures at onset, and NCSE [13, 15]. Low AED levels (or missed doses), metabolic causes, and CNS infections have also been implicated in RSE [19]. RSE was more likely to be associated with encephalitis, and nonrefractory SE with low AED levels in one study [14]. Similarly, another study found that CNS infections were seen in greater frequency in RSE patients compared to patients with nonrefractory SE [20]. The term new-onset RSE (NORSE) has recently emerged to define patients who have prolonged RSE with no readily identifiable cause (though an autoimmune or viral encephalitis etiology may later be found) [21]. Etiology of SRSE may be different from that of SE and RSE [22]. Several studies suggest that encephalitis is a frequent cause of SRSE [23–25].

Table 2.1 Possible causes of SE

Acute Causes
Acute stroke (e.g., ischemic stroke, intracerebral hemorrhage)
Traumatic brain injury
Central nervous system infections
Hypoxic brain injury
Posterior reversible encephalopathy syndrome
Metabolic disorders (e.g., hypoglycemia, abnormal electrolytes)
Drug withdrawal, noncompliance, or toxicity
Autoimmune and paraneoplastic etiologies
Sepsis
Chronic Causes
History of epilepsy
Brain tumor
Preexisting brain pathology (e.g., cortical dysplasia or due to prior trauma or stroke)

Adapted from Brophy et al. [1] with permission

SE Patients: Triage to the Neurointensive Care Unit

Due to the complexities of treatment for SE, RSE, and SRSE, patients in SE benefit from admission to the neurointensive care unit (NCCU) rather than a general ICU. Patients may be triaged to the NCCU in different ways. Most commonly, patients are admitted through the emergency department. In addition, patients are often referred to centers that offer continuous EEG monitoring. Patients may also develop SE after having been admitted for a different reason or for seizures and then subsequently developed symptoms suspicious for SE. There is an absence of literature that discusses the frequency with which these different triage mechanisms occur.

Triage for SE many times begins with dispatch of emergency medical services (EMS), and studies of seizure-related calls to EMS are consistent with seizure patients generally requiring high levels of care [26, 27]. Prehospital management is important – particularly for convulsive SE – until more definitive treatment can occur in the hospital. This includes assessing for and securing the ABCs (airway, breathing, circulation), obtaining history on-scene (e.g., patient's past medical history, physical manifestations, and length of the seizure(s)), preventing injury to the patient, and treating reversible causes of seizures (e.g., hypoglycemia). In addition, EMS may administer first-line therapy (benzodiazepines) [28]. Benzodiazepines have been the most studied medication in the prehospital setting and have been shown to be efficacious. A recent clinical trial showed no benefit to levetiracetam being added to clonazepam in aborting convulsions within 15 min of drug injection in the prehospital setting [29]. Once in the emergency department, patients in SE should have their ABCs reassessed, paying particular attention to the respiratory status of any patients who may have received benzodiazepines prior to arrival. Care should then be guided by the Diagnostic Workup outlined below [28].

One major reason SE patients may require admission to an ICU is airway protection. A few studies have examined predictors of intubation in patients experiencing seizures in the emergency department. One study was a subanalysis of the RAMPART trial, which was a randomized, double-blind clinical trial comparing intravenous lorazepam to intramuscular midazolam for prehospital SE. Of 1023 enrollments in the trial, 218 (21.3%) intubations occurred. Two hundred four (93.6%) of intubations were performed in the hospital (in an inpatient setting or emergency department) and 14 (6.4%) in the prehospital setting. In addition, 133/218 (61.0%) intubations occurred prior to or within 30 min after emergency department arrival. Patients who were intubated were more likely to be men (26 vs. 21%, $p = 0.047$), older (52 vs. 41 years, $p < 0.001$), having ongoing seizures on arrival to the emergency department (32 vs. 16%, $p < 0.001$), and having received rescue AEDs (29 vs 20%, $p = 0.004$)

[30]. In another study, Sato et al. performed a multivariate analysis revealing that age ≥ 50 years, on-scene heart rate ≥ 120 bpm, and meeting definition of convulsive SE were associated with a higher likelihood of intubation whereas a greater on-scene level of consciousness was associated with a reduced likelihood of intubation [31]. In their study, of 822 patients transported to a tertiary care emergency department due to a convulsive seizure, 59 (7.2%) were intubated; of the 270 patients with SE, 43 (15.9%) required intubation [31].

The importance of noting SE early is emphasized in several studies. One group of authors found a median prehospital delay for SE patients of 2 h 4 min, including delays in calling for emergency services, ambulance arrival, and patient transport to the hospital. Time to diagnosis of SE was significantly shorter in cases diagnosed clinically than in those diagnosed by EEG (median 1 h 50 min vs 13 h 20 min, $p < 0.0001$). This is not surprising, as NCSE requires an EEG for the diagnosis. It is therefore important to look for even the subtlest suggestions of ongoing seizure activity. Median delay of administering the first-, second-, and third-line AEDs (if and when each were necessary) were 35 min, 3 h, and 2 h 55 min, respectively [32]. One study examined prehospital delay in managing SE. For example, in multivariate linear regression analysis, the authors found that focal SE (defined by the authors as SE with normal consciousness) was associated with delayed onset-to-initial treatment time (25.8 h, 95% CI 0.4–60.3, $p = 0.049$), delayed time from onset to SE diagnosis (28.5 h, 95% CI 6.2–53.3, $p = 0.002$), and delayed onset to the administration of third-line AEDs (36.0 h, 95% CI 1.5–69.0, $p = 0.002$). Administering an initial treatment before EMS arrival was associated with long duration from SE onset to the first emergency call (4.0 h, 95% CI 0.7–7.3, $p = 0.024$) and with long duration from SE onset to arrival in the emergency department (4.3 h, 95% CI 1.2–8.8, $p = 0.036$). Initial arrival in a healthcare unit other than a tertiary hospital was associated with a delay in SE diagnosis (8.8 h, 95% CI 1.8–15.4, $p = 0.012$) and delay in administering third-line AEDs (9.8 h, 95% CI 2.6–17.8, $p = 0.019$) [33]. In a recent study regarding the ability of EMS to recognize out-of-hospital SE and association with outcome, 150 SE patients were admitted via EMS. Convulsive SE was recognized in 84.6% of cases while nonconvulsive SE (NCSE) was missed in 63.7% of cases by EMS. NCSE was more likely to be missed in patients who were older, had no seizure history, had a greater STESS score (see Clinical Scores below), and had more possibly fatal etiologies. Accordingly, these patients were also less likely to receive benzodiazepines prior to admission. Independent predictors for not receiving benzodiazepines were greater Glasgow Coma Scale and increasing age. In survivors, delayed recognition of NCSE was independently associated with higher likelihood of not returning to functional baseline (OR 3.83, 95% CI 1.22–11.98, $p = 0.021$) [34]. This is an important finding as it suggests that timely diagnosis and treatment of NCSE can result in a tangible improvement in patient outcomes.

Diagnostic Workup

General

The following are generally recommended for all patients with suspected SE [1]:

- Vital sign checks
- Laboratory studies, including complete blood count, basic metabolic panel, calcium, magnesium, glucose
- AED levels
- Computed tomography (CT) of the head
- EEG

In addition, other studies may help in investigating the etiology of SE based on individual presentation [1, 35]:

- MRI of the brain
- Lumbar puncture
- Toxicology screen
- Inborn errors of metabolism panel
- Additional imaging, such as single-photon emission CT (SPECT), MR spectroscopy, and positron emission tomography (PET)
- Studies to evaluate for paraneoplastic and autoimmune encephalitis

EEG

EEG is the mainstay of diagnosing SE and is needed to guide management for all forms of SE, and especially in NCSE, which may only be seen by EEG. One study in a general hospital setting found that 19% of patients with SE had NCSE [36]. In one tertiary care center ICU, NCSE was found in 47% of all SE episodes [37]. In a study of 570 ICU patients who underwent continuous EEG for detection of subclinical seizures or unexplained lower level of consciousness, seizures were found in 19%, and 92% of these patients had only nonconvulsive seizures [38]. NCSE was found in 8% of comatose general ICU patients [39], and within the neurological ICU population, 23 of 170 patients (13.5%) had NCSE detected on EEG [40].

Additionally, electrographic seizures may not be seen in the initial hours after continuous EEG is started. While approximately 97% of patients had their first seizure within 24 h of starting continuous EEG in one study [41], another

study demonstrated that, while seizures were detected on continuous EEG in 88% of patients in the first 24 h, longer than 24 h of monitoring was generally required for seizure detection in comatose patients [38].

Imaging

Various imaging modalities may be especially useful in the diagnosis of the underlying cause of a patient's SE and therefore guide its management. It is well-known that CT and MRI can demonstrate focal lesion(s) that, if addressed, impact the course of SE [42]. SPECT can also detect SE foci [42–44], though PET and PET/CT can provide better resolution and the ability to perform quantitative measurements [35, 45].

Management of SE

Initial SE Management

The efficacy of benzodiazepines as the initial treatment of SE has been demonstrated in multiple studies, and they are therefore standard of care [46–50]. Efficacy of other major antiepileptic drugs (AEDs) in SE has also been evaluated. Lorazepam and levetiracetam were similarly efficacious in stopping clinical seizures in a randomized, open label study of 79 convulsive or subtle convulsive SE patients [51]. An improved seizure termination rate was seen with valproic acid in convulsive SE patients randomly assigned to intravenous valproic acid or phenytoin but seizure freedom at 24 h was similar for both medications [52]. Valproic acid and phenytoin equally terminated seizures in a randomized study of 74 patients with SE or acute repetitive seizures (defined as at least two seizures occurring over 5–6 h different from their usual pattern and not categorized as SE) [53]. Another study suggested that phenobarbital more quickly aborts generalized convulsive SE than diazepam and phenytoin combined [54].

While even successful initial treatment with benzodiazepines should always be followed up with longer-term maintenance therapy using AEDs, approximately 40% of patients with convulsive SE do not immediately respond to benzodiazepines and require second-line AEDs to abort seizure activity. In two randomized studies in which second-line therapy was evaluated, intravenous valproic acid and continuous intravenous diazepam were similarly effective [55], and intravenous valproic acid and phenytoin were also similarly effective [56]. In a meta-analysis of studies of benzodiazepine-resistant SE, seizure cessation with either valproate or phenobarbital was greater than with levetiracetam or phenytoin [57]. Notably, the Established Status Epilepticus Trial (ESETT) is an ongoing (though now closed to enrollment for adults) NIH-supported, multicenter, randomized, blinded, comparative effectiveness study of fosphenytoin, valproic acid, or levetiracetam for patients with benzodiazepine-refractory SE [ClinicalTrials.gov Identifier: NCT01960075] [10].

Each subsequently added AED is usually less effective than those used before it. The effectiveness of the first AED in terminating convulsive SE was 55.5%, the second AED 7.0%, and the third AED 2.3% in a randomized controlled trial that compared four different AED regimens (phenytoin, lorazepam, phenobarbital, and diazepam followed by phenytoin) [2, 46]. This suggests that SE becomes more resistant to treatment the longer it continues. Treatment should therefore progress rapidly along a center's treatment algorithm of 2nd, 3rd, 4th, etc. treatment options.

Refractory SE and Super-refractory SE

RSE management includes controlling seizures, treating seizure etiology, and managing and preventing complications [58]. The degree of background EEG suppression needed to treat RSE is not entirely clear. In a meta-analysis of 193 RSE patients, background EEG suppression was associated with fewer breakthrough seizures versus seizure suppression alone though it was also associated with a greater frequency of hypotension but no difference in mortality [59]. A study including 63 RSE episodes showed that improved functional outcome was associated with seizure suppression versus burst suppression or isoelectric background [58]. In 47 RSE patients, the level of EEG suppression had no effect on outcome [16]. In addition, in 19 patients in RSE and 37 attempts to lift anesthetic coma, it was found that burst suppression ratio (fraction of time spent in burst suppression) and the length of interburst intervals did not predict successful abortion of RSE but that the amount of epileptiform activity within bursts seemed to correlate [60].

RSE is usually treated with continuous anesthetic agents, while progress is assessed with the aid of continuous EEG. These continuous anesthetic agents are typically maintained for 24–48 h before they are weaned to assess for breakthrough seizures, although the optimal duration needed for controlling seizures remains unclear [1]. For 63 episodes of RSE in 54 patients, 11 days was the average duration anesthetic-induced coma was maintained [19].

The four major intravenous anesthetics used for RSE include midazolam, propofol, pentobarbital (thiopental is often used outside the US), and ketamine. Midazolam, propofol, and barbiturates are GABA agonists, and propofol may also act as an NMDA antagonist; ketamine is an NMDA antagonist. All four drugs are primarily metabolized in the liver [4]. It is unclear if the anesthetics with a shorter half-life (midazolam or propofol) should be used before the ones with

a longer half-life (barbiturates). Some algorithms include pentobarbital and ketamine under RSE and others recommend these drugs only for the treatment of SRSE. In one meta-analysis, pentobarbital appeared to be associated with a decreased amount of breakthrough seizures, short-term treatment failure, and changes to another infusion as compared to midazolam and propofol [59]. In RSE cases in which barbiturates were administered, EEG burst or total suppression was achieved more frequently than in RSE cases without the use of this medication [16]. However, barbiturates may be linked to longer hospital stay [16]. In a small randomized trial of propofol versus pentobarbital, time spent being mechanically ventilated was longer in patients treated with pentobarbital, but return to baseline and mortality were similar [61]. One problem with midazolam is that tachyphylaxis can develop, requiring progressively higher doses [58]. On the other hand, propofol infusion syndrome – characterized by bradycardia progressing to asystole, metabolic acidosis, rhabdomyolysis, hyperlipidemia, and enlarged or fatty liver – can be a life-threatening condition typically associated with high doses and long duration of propofol use [62].

Ketamine has recently emerged as an alternative to traditional intravenous anesthetic agents. Unfortunately, knowledge about ketamine and its potential usefulness is limited since it is often added to other continuous infusions [4]. A meta-analysis of 110 adult patients revealed that ketamine may have helped control RSE in about 57% of patients [63]. A review of 95 patients treated with ketamine for RSE or SRSE showed that seizures resolved in 68%, but outcomes were variable: good outcomes were observed in 19 (including discharges to home or rehabilitation), death in 30, and other/unknown deficits in the remaining patients [64]. While the side effects of ketamine for the treatment of SE are not well delineated, concerns include psychiatric symptoms (e.g., hallucinations, delirium, dreams), increased intracranial pressure, increased intraocular pressure, increased secretion of saliva, arrhythmias, respiratory depression, and neurotoxicity [64].

It is important to note that adequate therapy with AEDs must be continued while the patient is being treated with anesthetic agents so that seizure control can be maintained once the patient has been weaned.

Table 2.2 Alternative therapies used in RSE and SRSE

Therapy	Additional information
Neurosurgery	Consider if a seizure focus can be found in a noneloquent brain region [3]. Includes corpus callosotomy; focal, lobar, or multilobar resection; hemispherectomy; and multiple subpial transections with or without focal resection [65]. Of 23 patients undergoing surgery for RSE, 78.3% were seizure-free during a follow-up period of 4 months to 5 years [65].
Repetitive transcranial magnetic stimulation	Intracranial electrical current provided in a noninvasive manner In 21 SE and RSE patients, rTMS was associated with seizure control or reduction in 71.4%, though seizures recurred in 73.3% who had initially responded [66].
Electroconvulsive therapy	In 19 patients who underwent electroconvulsive therapy for RSE, seizure reduction or control occurred in 57.9% [67] Adverse events included 3 patients who had transient amnesia or lethargy [67].
Hypothermia	Several case reports suggested a possible benefit from hypothermia in RSE [68] A recent study in which 270 mechanically ventilated ICU patients in convulsive SE were randomly assigned to standard care alone or standard care plus hypothermia (32–34°C for 24 h) did not find better outcomes in the patients treated with hypothermia [69].
Immunomodulatory agents	Includes plasma exchange, intravenous immunoglobulins, steroids, adrenocorticotropic hormone, rituximab, and cyclophosphamide [3, 70, 71] These could be considered in SE cases suspected to be caused by an immunological process (such as anti-NMDA receptor encephalitis) after infection has been excluded [3, 70, 71].
Ketogenic diet	In 5 SRSE patients who underwent the ketogenic diet after not responding to multiple AEDs, seizure frequency decreased to half at a median of 8 days [72]. After 1 month on the ketogenic diet, seizure reduction for all patients was at least 75%, and 60% of patients were seizure free and the rest suffered nondisabling partial seizures at last follow-up (1–16 months after initiating the diet) [72]. In a prospective multicenter phase I/II study of adult SRSE patients treated with the ketogenic diet, SRSE resolved in 78.6% who completed treatment with the diet at a median of 5 days [73]. Side effects include metabolic acidosis, hyponatremia, hyperlipidemia, hypoglycemia, gastroesophageal reflux, constipation, weight loss, aspiration pneumonia [72, 73].
Allopregnanolone	Neuroactive steroid positive allosteric modulator of $GABA_A$ receptors that has demonstrated success in reducing seizure activity in animal models and in a phase I/II single arm trial [74, 75]. However, there was no difference between the allopregnanolone and placebo arms in treating SRSE in a phase III, randomized, double-blind, placebo-controlled trial [76].
Others	Intravenous magnesium, inhalational anesthetic agents, vagal nerve stimulation, deep brain stimulation, and classical music have been tried [1, 3, 58].

Finally, several other approaches have been used in RSE and SRSE (Table 2.2). The evidence supporting these treatment strategies is often sparse or contradictory.

Table 2.3 Suggested initial SE treatment algorithm

Check vital signs
Evaluate airway, consider intubation
Check finger stick blood glucose
Check laboratories (basic metabolic profile, toxicology screen, AED levels)
Administer 1st AED (usually a benzodiazepine)
Administer 2nd AED if SE continues (see Table 2.2)
Start diagnostic workup concurrently with emergency treatment (e.g., EEG, CT head, lumbar puncture)

Adapted from Brophy et al. [1] with permission

SE Pharmacology

Algorithms have been proposed for managing SE, such as the one described in Table 2.3. Table 2.4 includes second-line AEDs used to treat SE, and Table 2.5 describes continuous infusions used to treat RSE, including dosing and side effects.

Complications of SE

It should be noted that complications may occur in SE. These include cardiac arrhythmias, hypotension, need for intubation, deep vein thrombosis or pulmonary embolus, infections such as pneumonia, critical illness myopathy or neuropathy, and drug rash. Some of these complications may at least in

Table 2.4 Second-line AEDs

Medication	Initial dose	Maintenance dose	Serious adverse effects/notes
Fosphenytoin	20 mg PE/kg IV	Up to 150 mg PE/min	Arrhythmia, hypotension Phenytoin and valproic acid interact [77]
Lacosamide	200–400 mg IV	200 mg IV	PR prolongation, hypotension Minimal drug interactions Has not been used much in SE
Levetiracetam	1000–3000 mg IV	2–5 mg/kg/min IV	Occasional behavioral issues [78] Minimal drug interactions
Phenobarbital	20 mg/kg IV	50–100 mg/min IV	Respiratory depression, hypotension IV form contains propylene glycol
Phenytoin	20 mg/kg IV	Up to 50 mg/min IV	Arrhythmia, hypotension, purple glove syndrome IV form contains propylene glycol Phenytoin and valproic acid interact [77]
Topiramate	200–400 mg PO	300–1600 mg/day PO (divided over 2–4 doses daily)	Metabolic acidosis Not available in IV form
Valproic acid	20–40 mg/kg IV	3–6 mg/kg/min	Gastrointestinal issues (pancreatitis, hepatotoxicity), hyperammonemia, thrombocytopenia Phenytoin and valproic acid interact [77]

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Table 2.5 Continuous infusions for RSE

Medication	Initial dose	Maintenance dose	Serious adverse effects/notes
Isoflurane	Not established	End tidal concentrations 0.8–2% titrated to EEG	Cardiac and respiratory depression Infections
Ketamine	0.5–4.5 mg/kg	Up to 5 mg/kg/h	Hypertension Arrhythmia Pulmonary edema Anaphylaxis
Lidocaine	1.5–2 mg/kg	Up to 3.5 mg/kg/h	Arrhythmia Methemoglobinemia
Midazolam	0.2 mg/kg	0.05–2 mg/kg/h	Respiratory depression Hypotension Tachyphylaxis after long use
Pentobarbital	5–15 mg/kg	0.5–5 mg/kg/h	Cardiac and respiratory depression Hypotension Ileus Loss of neurologic exam at high doses
Propofol	1–2 mg/kg loading dose	30–200 mcg/kg/min	Propofol infusion syndrome Respiratory depression Hypotension
Thiopental	2–7 mg/kg	0.5–5 mg/kg/h	Cardiac and respiratory depression Hypotension

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part be the result of immobility from SE or possibly from induced therapeutic coma. Further, intravenous anesthetic agents and other treatments may cause toxicity and/or immunosuppression [58]. Some complications may result in the death of patients independent of the SE.

In-Hospital Decision-Making

Generally, physicians (including trainees such as residents and fellows) are responsible for making the majority of the decisions regarding SE patients in the NCCU. However, both the epileptologist and pharmacist play important roles as well. The epileptologist provides invaluable information regarding whether SE is ongoing and how SE treatments may or may not have modulated the seizure activity. In the neurocritical care patient population, the analysis of both raw and quantitative EEG data by physicians specialized in interpreting EEG is essential [38, 79]. The pharmacist helps to guide the initiation and continuation of AEDs and also provides information regarding side effects and interactions with other medications patients may be taking (including other AEDs).

Decision-making in the management of SE can be challenging and is definitely a team effort. It is important that physicians and nurses comprehensively and jointly care for the patient with SE [1]. To underscore the importance of this collaborative approach it should be noted that the recent guidelines for the treatment of SE published by the Neurocritical Care Society as well as the American Epilepsy Society both were co-authored by specialists in the fields of epileptology, neurocritical care, and pharmacology [1, 2]. In fact, one of these guidelines specifically indicates that the people who reviewed the studies used in the guideline "consisted of a group of neurologists, neurology nurses, emergency medicine physicians, clinical pharmacists, methodologists, and neurocritical care physicians with experience in status epilepticus and anticonvulsants." [2]

SE Outcomes and Discharge Destinations

Clinical Outcomes

Mortality in patients with SE may be as high as 30% [2]. However, it is not definitively known whether detecting and treating seizures affects outcomes since seizures are often epiphenomena for severe brain injury [7]. Worse discharge outcomes can be seen with the female sex, age > 60 years, smaller hospitals, comorbidities (e.g., hypertension, previous stroke), SE complications (e.g., respiratory failure, sepsis), and etiologies such as post-cardiopulmonary resuscitation [80]. Reduced likelihood of functional deterioration at discharge has been shown to be associated with normal brain imaging and presence of SE on admission [81].

In RSE, mortality rates can reach 16–39% [3]. In a study of 63 RSE episodes, poor outcome at discharge (defined as modified Rankin scale 4–6) was noted in 76.2% and in-hospital mortality in 31.8% of episodes. Mechanical ventilation was required in 90.5% of episodes, and prolonged mechanical ventilation was associated with mortality. Poor functional outcome was associated with greater CSF white blood cell count, days under anesthetic coma, cardiac arrhythmias needing intervention, and pneumonia. Good functional recovery was associated with seizure control without need for deep suppression on EEG (isoelectric or burst-suppression) [19]. Fever was the only independent predictor of outcome after adjusting for acute symptomatic etiology, viral encephalitis etiology, septicemia, and acidosis in another study [20]. In-hospital mortality was 7.4% and mortality at 1 year was 25.4% in 395 RSE patients treated in an ICU. In a multivariate analysis, only Sequential Organ Failure Assessment (SOFA) score was independently associated with in-hospital mortality. Independent predictors of mortality at 1 year were older age, SOFA score, SRSE, and previously not being independent in activities of daily living [12].

Not much is known regarding the outcome of SRSE. Long-term mortality is approximately 30–50% [5, 23, 24]. At 6 months, Glasgow Outcome Scale 4–5 was achieved in 33.3% of SRSE patients, which was significantly worse than in nonrefractory SE patients (79.1%), but similar to RSE patients (57.1%) [24]. In another study, compared to RSE patients, SRSE patients had a longer stay in the neurologic ICU and in the hospital and were also more likely to be functionally dependent at hospital discharge [25].

Prognostic Scores

Scores to predict outcomes in SE are available.

The Status Epilepticus Severity Score (STESS) is based on 4 factors: age, level of consciousness, seizure type, and history of seizures [82]. STESS has been found to be a predictor of survival and ability to achieve baseline clinical condition, and – regardless of whether patients underwent coma induction – patients with favorable STESS scores generally seem to survive [83]. In an external validation study of 171 patients, the score performed better in identifying survivors compared to nonsurvivors [84].

The Epidemiology-Based Mortality Score in Status Epilepticus (EMSE) assigns points based on mortality rates in the literature for factors thought to be predictive for outcome, and includes age, comorbidities, etiology, and EEG findings. This score was found to predict mortality correctly in nearly 90% of cases and to perform superior to STESS [85].

The END-IT score includes the following independent predictors of unfavorable outcome (modified Rankin Scale 3–6) at 3 months after discharge: encephalitis, NCSE (here defined as subtle SE in which myoclonic jerks or nystagmus occur in insufficiently treated convulsive SE), diazepam resistance, imaging abnormalities (unilateral lesions, bilateral lesions, or diffuse cerebral edema), and intubation. Each category is assigned 1 point except for imaging (1 point is given for unilateral lesions, 2 for diffuse cerebral edema or bilateral lesions). A cut-off of 3 or more points provided the best sensitivity and specificity for predicting unfavorable outcomes [86].

Conclusion

SE is a complex condition that requires expert care, preferably provided by a multidisciplinary team in the NCCU. Rapid escalation of treatment with AEDs along an established algorithm should be performed. RSE and SRSE may require treatment with anesthetic agents, which – while they have the potential to abort seizure activity – may introduce significant complications and side effects. Further research is needed to fully evaluate alternative treatments. Prognosis may be tied to the underlying cause and can be estimated with the help of recently developed prognostic scores.

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Acute Airway Management and Ventilation in the Neurocritical Care Unit

3

Matthew F. Sharrock and Kathryn Rosenblatt

Introduction

The history of airway management and mechanical ventilation is intertwined with the development of the modern critical care unit and the treatment of neurological disorders. While neurocritical care has historical roots in the work of neurosurgeon Walter Dandy, who created the first neurosurgical intensive care unit (ICU) at Johns Hopkins Hospital in 1923, the modern ICU traces back to anesthesiologists Anderson, Benidixen, and Pontoppidan providing mechanical ventilation to victims of a global poliomyelitis epidemic at Massachusetts General Hospital in the 1950s [1, 2]. The neurocritical care unit (NCCU) as we know it today is centered on monitoring and management of acute neurological conditions and optimization of patient physiology to reduce the burden of neurological injury and systemic complications. Airway and ventilatory management are central to this mission. Clinicians in the NCCU are called upon to rapidly assess a patient's airway and neurophysiological state to determine: (1) need for intubation, (2) the best method of airway management, (3) indicated pharmacological agents, and (4) the optimal ventilatory mode and settings.

The Decision to Intubate

The primary goal of intubation is to facilitate ventilation and gas exchange because poor oxygenation is known to worsen outcomes after neurological injury [3–7]. Recognizing a patient's need for intubation, determining its urgency, and predicting its difficulty are the critical first steps in airway management. A focused initial assessment will inform these decisions and guide preparation of any subsequent steps. This includes a brief airway and respiratory physical examination to look and listen for signs of inadequate ventilation, respiratory insufficiency, impaired airway protection, and the possibility of a difficult airway. The initial assessment should also include a directed neurological examination, noting level of consciousness, significant cranial nerve or motor deficits, cervical spine injury, or signs of elevated intracranial pressure (ICP). Indeed, a neurological assessment is an essential component of the initial approach to airway management decisions for all critically ill patients both in the NCCU and in other settings. Among a prospective, multicenter study of 1000 consecutive intubations in 42 medical and surgical ICUs, depressed consciousness was the reason for intubation in 25% of cases, and Glasgow Coma Scale (GCS) less than 8 was significantly associated with difficult intubation [8]. Not surprisingly, the decision to intubate in the NCCU is often dictated by a decline in the level of consciousness, suppression of brainstem functions, or disturbances of spinal cord or neuromuscular function that maintain airway protection and patency, control ventilation, and coordinate respiration.

Airway protection requires functional swallow and cough reflexes, two highly coordinated behaviors that involve processing from multiple levels of both the central and peripheral nervous systems. In the setting of traumatic brain injury (TBI) or stroke, patients with GCS less than 9 are at significantly increased risk for aspiration of secretions and gastric contents and development of pneumonia from dysfunctional airway protective reflexes [9, 10]. Clinicians can listen for audible pooling of secretions or a weak cough as indicators of compromised airway protection. If possible, a test of volitional swallowing can be used to gauge how secretions are handled.

Airway patency refers to clear, open tracheobronchial passages for gas exchange. When patients with impaired

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consciousness are laying in the supine position, the tongue may rest against the posterior pharyngeal wall opposite the cervical vertebrae causing upper airway obstruction. Abdominal movements without corresponding chest expansion indicate ineffective respiratory effort and upper airway obstruction, neuromuscular disorder, or spinal cord injury. An increased respiratory effort to overcome upper airway obstruction may generate negative intrathoracic pressure, thereby worsening the obstruction and hastening respiratory failure. Neck hematoma with tracheal deviation causing obstruction of airflow can occur in patients after anterior cervical spine procedures, carotid endarterectomy, TBI, and rarely after intravenous alteplase administration for acute stroke [11]. In fact, up to 30% of TBI patients have associated facial and neck injuries with the potential for disrupting both airway patency and protection [12, 13]. Audible stridor and visible orolingual or oropharyngeal swelling may signal the presence of airway edema from trauma to the face, anterior neck, or spinal cord. Orolingual angioedema, occasionally seen in acute stroke patients, is a well-documented adverse effect of alteplase administration and occurs more frequently among patients taking angiotensin-converting enzyme inhibitors [14–17].

Ventilation may become ineffective in patients with impaired respiratory drive due to metabolic derangements, pharmacologic toxicity or side effects, or infectious processes. Control of ventilation and normal breathing patterns may also be disrupted in patients with elevated intracranial pressure, injury to the lower pons or medulla, seizures, neuromuscular fatigue, or spinal cord injury. Respiratory insufficiency in patients with acute spinal cord injury may be apparent immediately or develop over time depending on the severity and anatomic level of injury and duration of spinal shock [18]. Complete spinal cord injury above the C3 level prompts acute ventilatory failure and apneic respiratory arrest. Lower cervical or thoracic cord injury with phrenic or intercostal nerve paralysis leads to hypoventilation and hypercapnic hypoxemic respiratory insufficiency. Additionally, with paralysis of intercostal muscles, negative intrathoracic pressure during inspiration can lead to a paradoxical inward depression of the ribs. This mechanical imbalance results in increased work of breathing, distal airway collapse, atelectasis, and inefficient ventilation. In these patients, airway secretions accumulate through increased production and decreased clearance secondary to impaired cough [19, 20].

Overall, patients with an evolving neurological injury and signs of airway compromise and respiratory insufficiency are vulnerable to acute deterioration for which intubation is often life-saving. While noninvasive modes of ventilatory support are viable alternatives for certain patients, these modes are relatively contraindicated in unstable patients at risk for aspiration or with significant upper airway obstruction. For example, noninvasive positive pressure ventilation (NIPPV) may be used as an alternative to endotracheal intubation in patients with myasthenia gravis while their condition is being treated. For patients who are adequately ventilating but poorly oxygenating, high-flow nasal cannula or a face mask may be adequate while causes of hypoxemia are being investigated.

Acute Airway Management

Airway assessment is the next step in successful airway management. This requires examining the neurocritical care patient for specific physical and physiological attributes to predict the likelihood of difficulty in performing any of the major procedures in airway management: bag-valve-mask (BVM) ventilation, conventional laryngoscopy, video laryngoscopy, endotracheal intubation, use of a supra-glottic airway, or creation of a surgical airway. All patients admitted to a NCCU, including those arriving from the emergency room or postoperatively with an endotracheal tube in situ, should have an initial airway assessment. The indications for, and details of, an intubation prior to admission should be gathered, and specifics regarding airway difficulty in the past should be noted.

Assessing Difficulty

A difficult airway is defined as a clinical situation where a trained operator experiences difficulty with BVM and/or endotracheal intubation [21]. Difficult BVM had an incidence of about 5% in a prospective observational study of operating room cases [22], whereas difficult intubation, defined as grade 3 or 4 laryngoscopic view on the Cormack-Lehane scale (Table 3.1), may occur in approximately 10% of adult emergency room intubations [23]. Predicting difficult mask ventilation can be as important as predicting tracheal intubation difficulty. When BVM is achieved, intubation can proceed in a measured, orderly fashion without deoxygenation, even after multiple attempts. Recent evidence suggests that the incidence of difficult intubation has declined with the use of video-assisted laryngoscopy [24, 25], and its use

Table 3.1 The Cormack-Lehane and Mallampati Scales

Grade	Cormack-Lehane	Mallampati
1	Full view of the glottis	Soft palate, full uvula & tonsillar pillars visible
2	Partial view of the glottis	Soft palate, partial uvula & tonsillar pillars visible
3	Only epiglottis seen	Soft palate & uvular stalk visible
4	Neither glottis nor epiglottis seen	Only hard palate visible

by inexperienced airway providers may improve the likelihood of success [26–29]. Further, devices capable of displaying the image on a separate video screen allow for distance learning and consultation; during an emergent intubation, the difficulty or success of intubation can be simultaneously viewed by all airway personnel in attendance. When patients are anticipated to have a difficult airway, adjunct equipment (Table 3.2) and skilled providers should be available, and a definitive plan to facilitate gas exchange must be in place prior to administering a neuromuscular blocking medication. If failure of both ventilation and intubation occur, an immediate surgical airway procedure may be necessary. The American Society of Anesthesiologists (ASA) Task Force on Management of the Difficult Airway developed and updated the Difficult Airway Algorithm, which is a widely used reference for airway management both inside and outside of the operating room (Fig. 3.1) [30].

Based on validated studies of difficult airway management and guided by practical experience, researchers and experts have coined mnemonics for expedient evaluation of the airway. The LEMON evaluation, adopted by the American College of Surgeons' Advanced Trauma Life Support (ATLS) course [31], assesses for difficult laryngoscopic intubation and is traditionally performed immediately prior to the assessment for difficult BVM to allow for early identification of the need for advanced airway equipment and for providers with advanced airway techniques, both of which may not be immediately accessible [32, 33].

Look Does the patient convey the general impression of airway difficulty? Is there facial trauma, unusual anatomy, or an abnormal body habitus? [34]

Evaluate (3-3-2 rule) The 3-3-2 fingerbreadths rule estimates if there is a direct line of sight from outside the mouth to the glottis and includes: 3 fingerbreadths of mouth opening (i.e., inter-incisor distance) to allow a view of the glottis and passage of the laryngoscope and endotracheal tube, 3 fingerbreadths from the mentum to the hyoid bone to estimate the submandibular volume in which to displace the tongue, and 2 fingerbreadths in the space between the hyoid bone and the thyroid notch, suggesting the larynx is a sufficient distance from the base of the tongue to allow the creation of a direct line of sight from outside the mouth

Table 3.2 Specialized airway equipment and techniques

Device	Description	Examples	Technique
Specialized stylets			
Endotracheal tube introducer	Specialized stylets over which an ETT can be passed into the glottis and trachea	Bougie (gum-elastic) Frova Cook® Aintree intubation catheter Eschmann stylet	Blind, limited view, flexible fiberoptic, or direct/video technique Rigid or malleable rod of various length/diameter passes through glottis either blindly using palpation of bent tip against tracheal rings or under direct/video visualization ETT then slides over device into trachea and device withdrawn Hollow introducers can be fitted with connectors to breathing circuits, BVMs, or manual jet ventilation or allow internal passage of a flexible bronchoscope
Lighted stylet or light wand		LightWand™[a] Trachlight™[a]	Blind technique with ETT mounted on device inserted in midline of pharynx and manipulated into larynx with transilluminating glow at cricothyroid membrane ETT then slides over device into trachea
Optical stylet		Shikani Optical Stylet BONFILS retromolar intubation endoscope Clarus® Levitan Clarus® Video System C-MAC® Video Stylet	ETT mounted on rigid, semirigid, or directable metal stylet with a fiberoptic or video viewing element at distal end and eyepiece or external monitor for glottic viewing ETT railroads into trachea once tip of stylet passes through vocal cords
Flexible bronchoscope		Ambu® aScope™ C-MAC® Endoskope	ETT mounted on a long flexible and directable endoscope with a fiberoptic or video viewing element at distal end and eyepiece or external monitor for glottic and tracheal viewing ETT slides over device into trachea

(continued)

Table 3.2 (continued)

Device	Description	Examples	Technique
Specialized laryngoscopes			
Optical laryngoscope	Rigid devices of various widths, lengths, and shapes with built-in illumination and optical elements that allow laryngoscopy without a direct line of sight	Truview PCD™ Airtraq™ optical laryngoscope	Angled or L-shaped indirect laryngoscopy uses lenses and an eyepiece or camera to provide view of anterior glottis not possible with direct laryngoscopy ETT passes through vocal cords independent of device
Guide channel laryngoscope		Airtraq™ Avant Pentax-AWS® Ambu® KingVision™	ETT is placed into channel adjacent to optical and illumination elements Rigid device is shaped to match anatomic curve of upper airway and positioned around base of the tongue to obtain glottic exposure Blade tip may be placed in the vallecula (Macintosh blade-like technique) or passed underneath the laryngeal surface of epiglottis (Miller blade-like technique)
Conventionally curved video laryngoscope		C-MAC™ GlideScope® MAC McGRATH™ MAC	Capable of both indirect and direct laryngoscopy with variable-length Macintosh-style or Miller-style blades with or without necessitating a disposable clear plastic sleeve that fits over the adjustable blade and snaps into place A video screen is mounted on the handle or a dedicated portable external monitor displays images ETT passes through the vocal cords independent of the device
Hyperangulated video laryngoscope		GlideScope® C-MAC® D-blade McGRATH™ X-blade	Acute-angle video laryngoscopy not capable of direct visualization Allows better visualization of anterior laryngeal structures With or without necessitating a disposable clear plastic sleeve that fits over the blade and snaps into place A video screen is mounted on the handle or a dedicated portable external monitor displays images ETT is directed independent of the device using a specialized rigid stylet
Specialized extraglottic airway devices			
Intubating supraglottic airway	Laryngeal masks that seal superiorly around the glottic inlet through which an ETT can be passed into the trachea	LMA® Fastrach™ air-Q® i-gel® Ambu® AuraGain™	Flexible fiberoptic or blind ETI through a blindly inserted supraglottic curved airway tube with an oval-shaped inflatable or gel-like cuff that sits in the hypopharynx and forms a low pressure seal around the periglottic tissues at the laryngeal inlet
Surgical airway techniques			
Retrograde intubation	Trans-laryngeal intubation	Cook® Retrograde Intubation Set	ETT passes retrograde from below the vocal cords into the mouth or nose over a guidewire or catheter that is first introduced through a cricothyroid incision
Cricothyrotomy			Tracheal tube is placed through an incision in the cricothyroid membrane

BVM bag-valve-mask, *ETI* endotracheal intubation, *ETT* endotracheal tube
[a]no longer in production

to the glottis. If the first component is less than 3 fingerbreadths, an optical stylet, light wand, or flexible bronchoscope may be required for intubation (see Table 3.2). If the last component is less than 2 fingerbreadths, the angle may not permit direct visualization and a hyperangulated blade should be considered. If the hyoid bone to thyroid notch distance is larger than 2 fingerbreadths, a longer blade may be needed to reach the larynx. Together these three metrics predict the success of direct laryngoscopy [35]. Also, this rule accounts for variations in size by using the patient's own fingers when able.

Mallampati classification This is a simple, validated scoring system to help predict difficult intubation by inspecting the relationship of mouth opening to tongue size and the degree of visibility of the oropharynx [36] (Table 3.1). In general, Mallampati class I predicts easy laryngoscopy: the oropharynx, tonsillar pillars, and entire uvula are visible. Mallampati class II predicts fairly easy intubation: all of the above-mentioned structures are visible except the pillars. Mallampati class III predicts difficulty: only a minimal portion of the oropharyngeal wall is visible. Mallampati class IV predicts extreme difficulty: only the tongue pressed against

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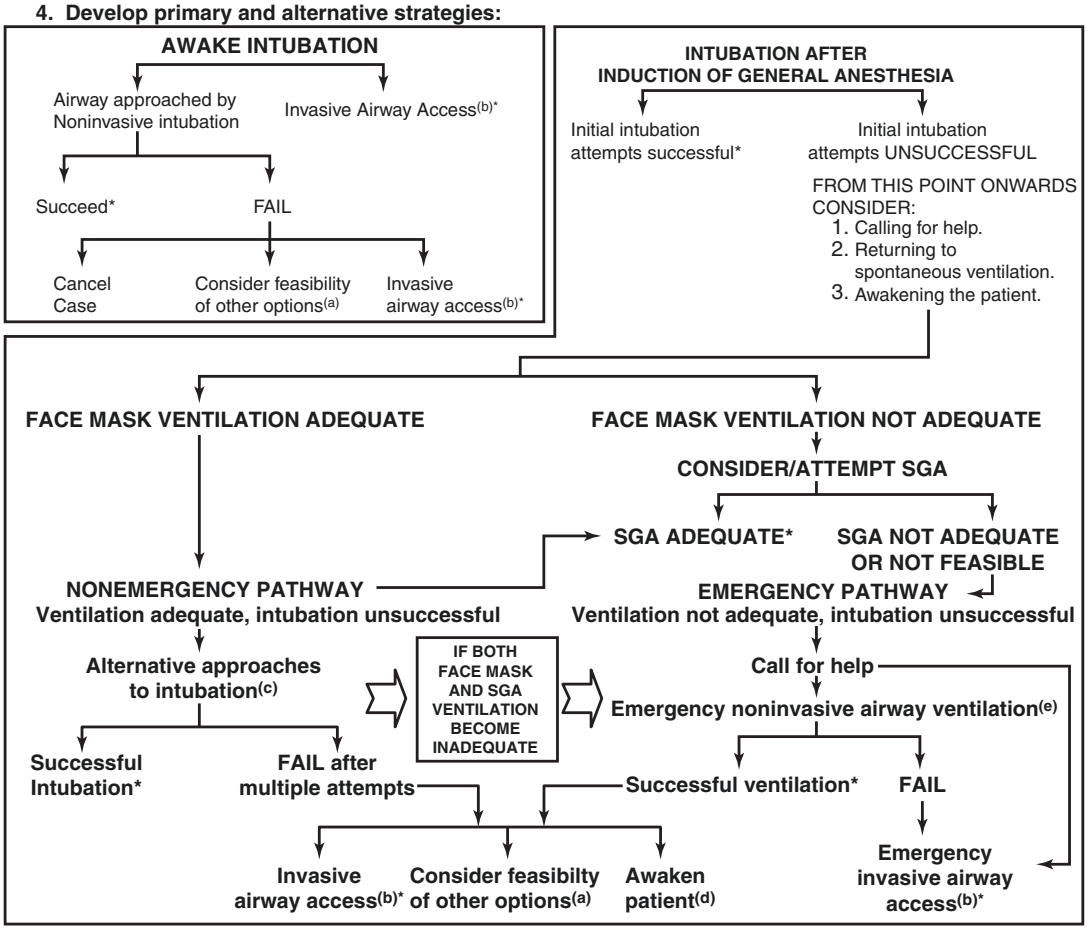
DIFFICULT AIRWAY ALGORITHM

1. **Assess the likelihood and clinical impact of basic management problems:**
   - **Difficulty with patient cooperation or consent**
   - **Difficult mask ventilation**
   - **Difficult supraglottic airway placement**
   - **Difficult laryngoscopy**
   - **Difficult intubation**
   - **Difficult surgical airway access**
2. **Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.**
3. **Consider the relative merits and feasibility of basic management choices:**
   - **Awake intubation *vs.* intubation after induction of general anesthesia**
   - **Non-invasive technique *vs.* invasive techniques for the initial approach to intubation**
   - **Video-assisted laryngoscopy as an initial approach to intubation**
   - **Preservation *vs.* ablation of spontaneous ventilation**
4. **Develop primary and alternative strategies:**



***Confirm ventilation, Tracheal intubation, or SGA placement with exhaled CO_2.**

a. Other options include (but are not limited to): surgery utilizing face mask or supraglottic airway (SGA) anesthesia (e.g., LMA, ILMA, laryngeal tube), local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the Emergency Pathway.

b. Invasive airway access includes surgical or percuteneous airway, jet ventilation, and retrograde intubation.

c. Alternative difficult intubation approches include (but are not limited to): video-assisted laryngoscopy, alternative laryngoscope blades, SGA (e.g., LMP or ILMA) as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, and blind oral or nasal intubation.

d. Consider re-preparation of the patient for awake intubation or canceling surgery.

e. Emergency non-invasive airway ventilation consists of a SGA.

Fig. 3.1 The American Society of Anesthesiologists (ASA) Difficult Airway Algorithm. (Reproduced with permission of Wolters Kluwer Health, Inc. From Apfelbaum et al. [30]. Copyright © 2013 by the American Society of Anesthesiologists, Inc.)

the hard palate is visible. Many neurologically injured patients are unable to cooperate with Mallampati assessment. In such cases, a tongue depressor and penlight may be used to gently open the mouth and assess the size of the tongue and oropharyngeal visibility.

Obstruction/Obesity/Obstructive Sleep Apnea (OSA) Common signs of upper airway obstruction in the neurocritically ill patient include stridor, dyspnea, muffled voice, and inability to swallow secretions. Trauma with subsequent hematoma, injury with upper airway disruption, vocal cord or supraglottic masses, tracheal and supraglottic infections, or airway edema can all obstruct the view of the glottis and/or block access to endotracheal tube insertion. Obese patients often have redundant oropharyngeal tissue, high Mallampati scores, and failure of the 3-3-2 rule.

Neck mobility Decreased cervical spine mobility compromises intubation by restricting movement towards the optimal position for air flow and the best possible view of the larynx by direct laryngoscopy [37]. In uncooperative, *non*-trauma patients, neck mobility can be assessed by passively extending the neck, albeit with caution. Intrinsic cervical spine immobility such as that seen in ankylosing spondylitis, psoriatic or rheumatoid arthritis, or degenerative joint disease can greatly reduce neck mobility and should be considered as seriously as cervical spine immobilization required after spinal cord trauma.

Validated indicators of difficult BVM are summarized by the mnemonic ROMAN as follows [22, 38, 39].

Radiation/Restriction This refers to conditions that cause restriction of forward gas flow and require high-ventilation pressure, such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary edema, acute respiratory distress syndrome (ARDS), multilobar pneumonia, or any other condition that decreases pulmonary compliance. Head and neck radiation are strongly associated with difficult BVM due to reduced pliability of upper airway soft tissue.

Obstruction/Obesity/OSA The 3 "Os" are considered to be linked. Redundant upper airway tissue, chest wall weight, and resistance from abdominal contents all impede airflow. Late third trimester pregnancy is similar to obesity with respect to BVM because of the increased body mass and resistance to diaphragmatic excursion caused by the gravid uterus. Both obese and pregnant patients desaturate more quickly due to decreased functional residual capacity. Placing the bed at an angle with the head higher than the feet (i.e., reverse Trendelenburg) may reduce airflow impedance from abdominal weight. Obstruction caused by soft tissue lesions such as angioedema and abscesses may be more amenable to BVM than that caused by immobile lesions such as tumors, foreign bodies, and hematomas. Increased inspiratory and expiratory pressures will be required to ensure that gas flows past the obstruction in both directions.

Mask Seal/Mallampati/Male sex Adequate mask seal requires absence of facial hair and interfering substances such as bleeding, vomitus, or nasogastric tubes, and the ability to apply appropriate pressure to the face with the mask. Mallampati classes 3 and 4 as well as male sex also appear to be associated with challenging mask ventilation [22].

Age > 55 years Compared to young patients, older patients have decreased elasticity of tissues and increased incidence of restrictive or obstructive pulmonary disease [22].

No teeth Edentulousness creates difficulty with BVM because the face may not adequately support pressure applied by the mask. Gauze rolls may be inserted bilaterally under each cheek to provide mask seal support in the edentulous patient but must be removed before direct laryngoscopy.

It is important to be mindful that the LEMON mnemonic applies to direct laryngoscopy and not to video laryngoscopy because video instruments typically provide Cormack grade 1 or 2 views [40, 41]. In one study of 906 consecutive ICU patients requiring intubation, presence of blood in the airway, airway edema, cervical immobility, and obesity were characteristics associated with higher odds of first-attempt failure using video laryngoscopy [42]. As a general rule, a rigid stylet should be used to guide insertion of an endotracheal tube into the glottis when using video laryngoscopy, particularly with hyperangulated blade designs. Additionally, hyperangulated video laryngoscope blades are preferred to conventional video laryngoscope blade designs when cervical immobility is mandated. However, these hyperangulated blades are not capable of direct glottic viewing if it becomes required. Direct viewing may be necessary in scenarios where a video laryngoscope camera is obscured by fluid; removal of the blade from the mouth to wipe off the tip delays intubation. In such cases, a conventional video laryngoscope blade capable of direct views may be preferred to ensure nearly uninterrupted laryngoscopy.

Initial Management

To increase the chance of successful intubation and to optimize patient safety during extended periods of apnea, proper positioning and pre-oxygenation are paramount [43–46]. Passive pre-oxygenation by spontaneously breathing O_2 at a rate of 15 L/min with a non-rebreather mask or at maximum flush rate with a tightly fitting standard reservoir facemask

for 3 min (or 8 breaths with maximal inhalation and exhalation) can effectively de-nitrogenate the residual capacity of the lungs and is preferred to manual BVM positive pressure ventilation if patients are not hypoxemic and have adequate ventilatory patterns [47, 48]. This is especially true if food may have been ingested within the past 8 hours. In such cases, to reduce the risk of aspiration of gastric contents, preoxygenation can be continued via apneic oxygenation during a rapid sequence intubation technique, which traditionally involves the expeditious sequential delivery of cricoid pressure, induction agent, fast-onset neuromuscular blocking agent, and laryngoscopy. Effective means of providing apneic oxygenation during laryngoscopy include the ubiquitously available nasal cannula, set to 15 L/min, or high flow nasal cannula (HFNC), which delivers heated and humidified gases at a flow rate up to 60 L/min [49, 50]. The smaller functional residual capacity, increased alveolar-arterial O_2 gradients, higher rates of O_2 consumption, decreased cardiac output, and anemia found in many critically ill patients all decrease the likelihood of effective preoxygenation [51]. If patients do not achieve an oxygen saturation greater than 93% after 3 min of tidal-volume breathing at 15 L/min or greater, they are more likely to desaturate during apnea, and augmentation of mean airway pressure is the only effective solution to partially overcome what is likely shunt physiology [52, 53]. In these cases and in all patients with substantial hypoxemia, low inspiratory pressures using a positive end-expiratory pressure (PEEP) valve on a BVM device or continuous positive airway pressure (CPAP) mask should be initiated early and continued until laryngoscopy [52–54].

To facilitate passage of air from the BVM to the lungs, a forward displacement of the mandible known as "chin lift" and a "head tilt" with extension of the neck at the atlanto-occipital joint may be used in any patient in whom cervical spine injury is not a concern. To accomplish the head tilt/chin lift, pressure is applied to the patient's forehead with one hand while the clinician's second hand lifts the mentum, pulling the tongue off the posterior oropharynx wall. In preparation for direct laryngoscopy, the clinician may couple the head tilt/chin lift with slight flexion of the lower cervical spine by placing folded towels, sheets, or blankets in a firm roll under the shoulders, with the goal of aligning the ear canal with the sternal chest. This position aligns the oral, pharyngeal, and laryngeal axes into what is called the "sniffing position." [55] The path from the incisor teeth to the larynx must be a straight line for successful visualization of the vocal cords using direct laryngoscopy. Because the angle of the axis of the mouth to the larynx is 90°, aligning the three axes has been shown to be anatomically impossible without a laryngoscope blade to make the final adjustment [56]. In obese patients, the back-up or head-elevated laryngoscopic position facilitates tracheal intubation, which is typically achieved by creating a ramp under their upper body with blankets or other devices. A jaw thrust maneuver, achieved by moving the condyles of the mandible out of the temporomandibular joint and then pulling the mandible forward, is the safest method to open the airway of a patient with potential cervical spine injury while an assistant provides manual inline stabilization. If properly performed, a jaw thrust can be accomplished without moving the head or neck. Using both hands while positioned at the head of the bed, the closed mandible is grasped with the thumbs on the mentum and the remaining fingers along the body, angle, and ramus of the mandible. The mandible is widely opened and then displaced anteriorly out of the temporomandibular joint.

Once the airway is opened, the mask is positioned on the face in order to optimize a seal. This is accomplished by pulling the patient's face upward into the mask. The mask cuff should sit on the groove between the chin and alveolar ridge of the mandible as well as on the anterior body of the mandible, the malar eminences of the maxillae, and the bridge of the nose. Because the seal between the mask and face is least secure laterally over the cheeks, medial compression of the soft tissue of the face against the outside margins of the cuff can diminish leakage. Pressure on the orbits by the mask should be avoided.

In scenarios when personnel are limited, single-handed BVM ventilation is best achieved using the operator's dominant hand to hold and compress the bag while the nondominant hand is placed on the mask with the thumb and index finger making an "OK" sign and the remaining fingers grasping the mandible upward towards the mask. This grip is also referred to as the "EC sign" because the thumb and index finger form the letter "C" and the third through fifth fingers form the letter "E". If possible, the fifth digit can be placed posterior to the angle of the mandible to augment chin lift with jaw thrust. The mask and face can be rocked from side to side to improve mask seal or the cheek can be gathered with the ulnar aspect of the hand under the "E" fingers and compressed against the mask cuff for a more effective seal.

A two-handed mask hold employing a thenar mask grip is the most effective BVM technique and should be used whenever possible when more than one provider is available because successful one-handed bagging can be extremely fatiguing [57, 58]. Both thenar eminences are positioned on the body of the mask, parallel to one another, with the thumbs pointing caudally (or cephalad if the operator must perform BVM from a position facing the patient).

An oropharyngeal airway (OPA) of appropriate size can improve air flow and prevent the tongue from falling back and occluding the airway; however, inadequately chosen OPAs can make ventilation more difficult. An OPA should extend from the central incisors to just short of the epiglottis and posterior pharyngeal wall. An estimate of this length can be determined by choosing an OPA that extends from the

side crease of the mouth to the angle of the mandible when held alongside the face. Typical adult sizes range from 8 to 11 cm, with a female OPA typically sized at 8 cm and a male at 10 cm. To avoid posteriorly displacing the tongue, the OPA is inserted into the open mouth in an inverted position and is rotated 180° into its final position after insertion is complete. A nasopharyngeal airway can also improve flow but should not be used in patients suspected of having facial trauma nor should it be forced when resistance is encountered.

After obtaining an open airway and appropriate mask seal, ventilation without excessive inspiratory pressure should be initiated. The entire volume of the self-inflating bag should never be delivered. Insufflating gas into the stomach increases risk of regurgitation and aspiration and decreases functional residual capacity as the abdomen distends and compresses the thorax. Notably, upper and lower esophageal sphincters open at approximately 20–25 cm H_2O pressure. Excessive volume delivery can cause pulmonary barotrauma and breath stacking. When delivering tidal volumes (5–7 mL/kg; approximately 500 mL for an average adult), the operator should feel for resistance of the bag to compression and observe the patient's chest for rise and fall. If passive expiration fails to occur, airway closure from inadequate jaw thrust has likely occurred and repositioning of the mask with a re-attempt of jaw thrust is warranted. Maintenance of adequate oxygen saturation and an appropriate waveform on end-tidal carbon dioxide (CO_2) capnography are signs of satisfactory ventilation. Systematic reappraisal of the mechanics of BVM ventilation and the adequacy of airway opening and mask seal can thwart cardiopulmonary decline. Studies have shown that application of the Sellick maneuver (occluding the cervical esophagus against the anterior vertebral bodies by pressing the cricoid cartilage posteriorly) may reduce gastric insufflation during BVM [59]. However, providers should ensure pressure is applied to the cricoid cartilage and not the thyroid cartilage, which could potentially occlude the airway, and avoid excessive pressure, which could distort the airway or cause injury to the esophagus [60]. Cricoid pressure during rapid sequence intubation should be avoided in patients with lower cervical spinal cord injury. Instead, a gentle backward-upward-rightward pressure (BURP) maneuver can be used to facilitate laryngoscopic view if necessary [31].

Before an intubation attempt is made, a freely flowing intravenous line should be secured. The patient should be connected to telemetry, and an audible oxygen saturation monitor and frequent (every 3–5 min) blood pressures (non-invasive or invasive) should be measured. A Yankauer catheter must be easily accessible and connected to continuous suction. A mechanical ventilator and the equipment needed to perform the actual intubation must be at bedside. Either capnography or a carbon dioxide colorimeter detector should be available to verify endotracheal tube placement. An airway supply box or kit should also be at bedside with various endotracheal tube sizes, intubation blades of different styles and sizes, a stylet, a tracheal tube introducer or "bougie," [61] and a supraglottic airway such as a laryngeal mask airway (Table 3.2). In addition, a video laryngoscope with both conventional and hyperangulated blades should be available when a difficult airway is anticipated [62]. As a backup, an emergency cricothyroidotomy kit should be available on the unit where the patient is located. Common emergency airway intubating equipment and adjuncts to facilitate endotracheal intubation are summarized in Table 3.2.

Pharmacotherapy for Airway Management

Hemodynamic stability should be achieved prior to an intubation attempt. Fluids and vasopressors should be available to treat hypotension. Medications that may depress cardiac function or decrease systemic vascular resistance, such as propofol or fentanyl, should be used with caution in patients at risk for hypotension, which can exacerbate ischemia and threaten penumbral perfusion in acute stroke [63], decrease cord perfusion in spinal cord injury patients [64], and diminish cerebral blood flow (CBF) in TBI patients with suspected impaired autoregulation [65, 66]. Conversely, hypertension during intubation in an inadequately sedated patient with intracerebral hemorrhage (ICH) or in postoperative neurosurgical patients can have devastating consequences.

Induction Agents

The choice of induction agent must be closely considered with vasopressors at hand to maintain blood pressure within a narrow range. Medications used during intubation along with their indications and precautions are summarized in Table 3.3. The fast onset, short-acting opioid fentanyl or the sodium channel-blocking antiarrhythmic lidocaine may be useful in blocking the reflex sympathetic response and increase in ICP that occurs during laryngoscopy, with lidocaine having a lower incidence of hypotension at the cost of decreasing the seizure threshold [67].

The gamma-aminobutyric acid (GABA) agonist propofol is an anesthetic and sedative that has neurological properties (antiemetic, anticonvulsant, reduces cerebral metabolism) as well as cardiovascular effects (reduces inotropy, systemic vascular resistance, and venous return and thus consequently lowers CBF and concomitantly ICP). We caution use in patients who are dependent on high cerebral perfusion pressures.

Etomidate, another GABA agonist, has sedative and hypnotic properties with minimal cardiovascular effects and is therefore a preferred agent in patients with hypotension [68]. It is thought to reduce cerebral oxygen demand and ICP while maintaining cerebral perfusion pressure (CPP) [69, 70]. Due to its lowering the seizure threshold, we caution

Table 3.3 Common pharmacologic induction agents used for intubation during acute airway management

Agent	Indications	Limitations	Onset	Duration	Dose[a]
Lidocaine	Pre-induction agent to blunt potential cardiovascular response, cough reflex, dysrhythmias, and elevated ICP from laryngoscopy and intubation	Bradycardia, lidocaine allergy	45 s – 3 min	10–20 min	1.5 mg/kg
Fentanyl	Pre-induction analgesia to blunt potential sympathetic response and elevated ICP from laryngoscopy and intubation	Hypotension, respiratory depression, chest wall rigidity with large bolus dose	2 min	30–60 min	2 mcg/kg in divided doses
Propofol	Induction, sedation, anesthesia, lowers ICP, anticonvulsant	Hypotension, myocardial impairment	10–40 s	3–5 min	1–2 mg/kg
Etomidate	Induction, sedative-hypnotic, minimal BP effects	Adrenal insufficiency, lowers seizure threshold, myoclonus	30–60 s	3–5 min	0.3 mg/kg
Ketamine	Induction, sedation, amnesia, analgesia, minimal BP effects	ICP increase, agitation	1–2 min	5–15 min	2 mg/kg
Succinylcholine	Fastest acting, short-duration paralytic	Severe hyperkalemia if given after acute phase of injury from major burns, upper motor neuron injury, or extensive denervation of skeletal muscle	30–60 s	2–15 min	1–2 mg/kg
Rocuronium	Fast acting, used when succinylcholine is contraindicated	Caution in patients with predicted airway difficulty, use reversal agent if available	2 min	45–120 min	0.6–1.2 mg/kg

BP blood pressure, *ICP* intracranial pressure
[a]intravenous

use in patients with status epilepticus, and its potential to cause adrenal insufficiency precludes its use in patients with sepsis or neuroendocrine disorders [71]. Additionally, etomidate has no analgesic properties, and intubation may require fentanyl to blunt the hemodynamic response to laryngoscopy when hypertension is undesirable [72].

Ketamine, an N-methyl D-aspartate (NMDA) receptor antagonist, is a dissociative anesthetic with sedative, amnestic, and analgesic properties. Additionally, ketamine has sympathomimetic activity resulting in hypertension, tachycardia, increased myocardial and cerebral oxygen consumption, increased CBF, and increased intracranial and intraocular pressure. Its use in neurocritical care has been limited by evidence that its utilization is associated with increases in ICP, but this has more recently come into question with data suggesting that ICP may be unchanged in brain-injured patients receiving ketamine and that CPP may be preserved or improved particularly when it is delivered in conjunction with GABA agonists [73–76].

Neuromuscular Blockade

Neuromuscular blocking agents must be carefully chosen in neurocritical care patients. Depolarizing agents such as succinylcholine initially activate acetylcholine receptors, and the muscle activity created can cause a transient but substantial increase in ICP as well as the release of potassium, particularly in patients with long-term immobility due to neuromuscular weakness and upregulation of acetylcholine receptors (AChRs) at the neuromuscular junction. Succinylcholine should be avoided in patients with spinal cord trauma after 24 hours post-injury due to an exaggerated and potentially life-threatening intracellular potassium efflux [77]. This is because the upregulated AChRs occupy all of the muscle membrane after denervation injury, not only the neuromuscular junction. Additionally, depolarized immature AChRs have a longer open channel time and a greater potential for sustaining a more prolonged potassium leak. In patients with myasthenia gravis, weakness can significantly worsen with succinylcholine, and thus its use is not recommended. Instead we recommend using a nondepolarizing agent, such as rocuronium, in myasthenia patients and reversal with the binding agent sugammadex [78]. In fact, rocuronium can be rapidly reversed with sugammadex, a highly selective modified gamma cyclodextrin that binds and encapsulates (chelates) aminosteroidal neuromuscular blocking agents, resulting in liberation of AChRs, diffusion of the bound complex away from the neuromuscular junction, and prompt excretion by the kidneys [79].

Mechanical Ventilation

Mechanical ventilation of the neurocritical care patient is a concern in both general and specialty ICUs. A significant proportion of patients in non-neurologically focused ICUs are intubated and remain so due to neurological concerns. A prospective observational study in 23 countries of 4968 consecutive patients at 349 participating ICUs found that 20% were mechanically ventilated for neurologic indications, primarily coma or neuromuscular disease, and neurological dysfunction limited weaning from mechanical ventilation in up to 41% of patients in another study [80–82]. The

Table 3.4 Characteristics of common mechanical ventilation modes

Mode	Trigger (type of breath)	Target (breath limit)	Cycle (breath termination)
AC/VC	Mandatory/Assisted	Volume	Volume
AC/PC	Mandatory/Assisted	Pressure	Time
IMV	Mandatory/Assisted/Spontaneous	Volume/Pressure	Volume/Time
APRV	Mandatory/Assisted/Spontaneous	Pressure	Time
PSV	Assisted/Spontaneous	Pressure	Flow/Pressure/Time
VSV	Assisted/Spontaneous	Volume	Flow/Pressure/Time
CPAP	Spontaneous		Flow

AC/VC volume-controlled assist control ventilation, *AC/PC* pressure-controlled assist control ventilation, *IMV* intermittent mandatory ventilation, *APRV* airway pressure release ventilation, *PSV* pressure support ventilation, *VSV* volume support ventilation, *CPAP* continuous positive airway pressure

overall level of respiratory support and choice of ventilator mode and settings should be chosen with both the patient's respiratory physiology and neuropathology in mind. There is a dearth of evidence to suggest the best ventilator modes in neurocritically ill patients. Here we provide some general principles for the use of mechanical ventilation and a description of frequently employed ventilatory modes when treating common neurocritical care pathologies.

Volume Versus Pressure Control

Mechanical ventilation can fully or partially replace spontaneous breathing and decreases ventilation-perfusion mismatch via reduction in physiologic shunting. Volume-controlled ventilation requires clinicians to set the tidal volume, respiratory rate, peak flow rate, flow pattern, fraction of inspired oxygen (FiO_2), and PEEP. The inspiratory time and inspiratory to expiratory (I:E) ratio are determined by the peak inspiratory flow rate. Increasing the peak inspiratory flow rate will decrease the I:E ratio by decreasing inspiratory time and increasing expiratory time. Applied PEEP splints the small airways and alveoli open, preventing collapse and atelectasis. Mean, plateau, and peak airway pressures depend on both the ventilator settings and patient-related variables, such as airway resistance, lung compliance, and chest wall compliance. High airway pressures may be due to large tidal volumes, high peak flows, increased airway resistance, or poor compliance. Pressure-controlled ventilation requires the clinician to set the inspiratory pressure level, respiratory rate, I:E ratio, FiO_2, and applied PEEP. Inspiration ends after delivery of the set inspiratory pressure. The tidal volume is variable during pressure-controlled ventilation and is related to inspiratory pressure level, compliance, and airway resistance. When the set inspiratory pressure level is high and there is good compliance along with little airway or ventilator circuit resistance, the tidal volumes can be high. The peak airway pressure is equal to the sum of the applied PEEP and the set inspiratory pressure level. It is important to note that the use of PEEP in lung-protective ventilation strategies does not produce a significant contribution to ICP and can be applied safely at standard levels to patients with acute brain injury [83].

Ventilatory Modes

Several modes of volume-controlled ventilation can be delivered (see Table 3.4), including controlled mechanical ventilation (CMV), assist control (AC), intermittent mandatory ventilation (IMV), and synchronized intermittent mandatory ventilation (SIMV). It should be noted that pressure-controlled ventilation can be delivered using these same modes.

During *CMV* a ventilator delivers a preset tidal volume at a preset respiratory rate, independent of the patient's respiratory effort. In *AC*, clinicians determine the baseline minute ventilation by setting the respiratory rate and tidal volume (or inspiratory pressure level during pressure-controlled assist control). The patient can increase the minute ventilation by triggering additional breaths. When patients initiate breaths, these breaths trigger the ventilator to deliver a preset volume or pressure. Pressure-regulated volume control is similar to AC, except that the ventilator can regulate the inspiratory time and inspiratory flow to limit the rise in plateau pressure.

In *IMV* a baseline minute ventilation is delivered by a ventilator by setting a respiratory rate and tidal volume (or inspiratory pressure level). However, patients can breathe independently in between set breaths without triggering the ventilator to deliver the preset amount of pressure or volume. When weaning patients from the ventilator, the set rate can be decreased such that patients progressively provide the majority of minute ventilation spontaneously. When the ventilator in IMV mode adaptively coordinates with patient efforts, we call this synchronized IMV or SIMV.

During inspiratory *pressure support (*or *pressure-support ventilation*, *PSV),* the patient's spontaneous breath is augmented with supplementary gas flow. It requires the patient to make an inspiratory effort and generate a negative pressure before augmentation occurs. During inspiratory *volume*

support (or *volume-support ventilation, VSV*) the ventilator monitors the lung properties and modifies the inspiratory pressure support in order to deliver a predetermined tidal volume.

Airway pressure release ventilation (APRV) is a time cycling, pressure-capped mode of mechanical ventilation that allows the patient to breathe spontaneously while maintaining high continuous positive airway pressure, maximizing the recruitment of alveoli. The high pressure setting (P_{High}) continues for a predetermined amount of time (T_{High}), typically around 3–4 s, then reduces to a lower pressure (P_{Low}) for a short duration (T_{Low}), typically less than 1 s. The driving pressure is P_{High} minus P_{Low}. As mentioned previously, the exact size of the tidal volume is determined by the driving pressure and compliance. Spontaneous breathing is possible at any point in the cycle. Theoretical advantages of APRV include improved alveolar ventilation with improved ventilation/perfusion (V/Q) mismatch, the hemodynamic benefits associated with spontaneous breathing, and a reduced requirement for sedation typically needed when using high mean airway pressures in other modes of ventilation. The increase in mean alveolar pressure with sustained alveolar recruitment is certainly an advantage in some patients but may be a concern in neurocritically ill patients with elevated ICPs because high mean airway pressures can reduce venous return and possibly increase ICP. However, several recent reports in patients with aneurysmal subarachnoid hemorrhage (SAH) and TBI have shown that APRV is safe and beneficial, with unchanged or improved ICP and unchanged cerebral perfusion pressure and carotid artery Doppler flow [84, 85]. Furthermore, minute ventilation relies on spontaneous respiration, so hypercapnia may be a concern in certain NCCU patients. Adjustments can be made to increase minute ventilation and thus reduce hypercarbia, such as minimizing sedation to optimize spontaneous breathing efforts and decreasing T_{High} without adjusting T_{Low} for more release breaths per minute.

Adaptive support ventilation (ASV) is a closed-loop controlled ventilatory mode, designed to ensure optimization of the patient's work of breathing. In ASV, pulmonary mechanics dictate adjustments to the respiratory rate and inspiratory pressure necessary to achieve a desired minute ventilation. Patients who are able to trigger the ventilator are given pressure support for the triggered breaths, supplemented with pressure-control breaths as needed to achieve the desired respiratory rate. Patients who are unable to trigger the ventilator are given pressure-control breaths. Adjustments are made based on an equation that determines the respiratory rate that minimizes the work of inspiration at a given minute ventilation. This relies on an expiratory time constant, which is obtained from the expiratory limb of the flow-volume loop during each breath [86, 87]. Patients who have a long expiratory time constant, such as those with COPD, receive a higher tidal volume and a lower respiratory rate than patients with restrictive lungs (such as patients with ARDS) or stiffness of the chest wall (such as patients with neuromuscular disorders, kyphoscoliosis, and morbid obesity) who expire quickly. In one randomized trial, length of time before initiating weaning and duration of weaning were shorter using ASV as compared to pressure assist/control ventilation in a medical ICU; however, studies are needed specifically in the neurocritically ill population to determine its usefulness and safety profile [88]. While the neurointensivist must sometimes take action to improve brain health at the temporary cost of other organs such as the lung, ASV solely works to optimize respiratory function.

Neurally adjusted ventilatory assist ventilation (NAVA) is a proportional ventilatory mode that uses the electrical activity of the diaphragm (EA_{di}) to offer ventilator assistance in proportion to patient effort by triggering a mechanical breath [89]. When a catheter embedded in a gastric tube detects a deflection in the EA_{di} signal greater than the set threshold (typically 0.5 microvolts), a mechanical breath is delivered. The degree of assist varies with the amplitude of the detected EA_{di} and an assist level set by the clinician that allows variation in tidal volume on a breath-to-breath basis. Experimental and clinical data suggest superior patient-ventilator synchrony with NAVA compared to conventional ventilator modes. NAVA depends on the patient having functional respiratory rhythm generation and is most often used in ventilator weaning.

Airway Concerns in Specific Neurologic Conditions

Cervical Spine Injury

Undiagnosed cervical spinal cord injury should be suspected in patients with TBI and loss of consciousness or focal neurological deficit [90]. ATLS guidelines suggest that patients with suspected cervical spine injury have a semi-rigid cervical collar placed, and a properly performed jaw thrust may be used to maintain airway patency [31]. For patients with acute cervical spine injury who require intubation, the standard of care is rapid sequence intubation with in-line spinal immobilization [31]. Care should be taken not to overextend, flex, or rotate the spine. Techniques for mask ventilation and instrumentation of the airway may need to accommodate immobilization devices such as a halo or rigid collar. Manual in-line cervical spine immobilization with an assistant standing at the head of the bed or reaching across the chest can be performed with the anterior portion of a rigid collar removed and is associated with less movement of the spine during intubation than collar immobilization alone. In some patients, direct laryngoscopy can be

used successfully without manipulating the neck. However, video laryngoscopy obtains better views of the glottis in less time than conventional laryngoscopy when intubation is performed in a neutral neck position unless active bleeding or copious secretions compromise image clarity [91]. A hyperangulated video laryngoscope or optical stylet may provide better glottic visualization in cervical spinal cord injury patients with additional risk factors for difficult intubation, such as obesity and restricted mouth opening [92].

Awake fiberoptic bronchoscopy with topicalization (application of local anesthesia) of the airway is commonly used to intubate stable, cooperative patients but is not recommended without extensive experience in its technique [93]. Alternative devices such as the laryngeal mask airway (LMA), optical stylet, or hyperangulated video laryngoscopy with manual in-line stabilization are associated with decreased first attempt failure rate and less cervical spine motion than direct laryngoscopy with manual in-line stabilization and are preferred in emergency scenarios or for patients who cannot tolerate an awake procedure [92, 94, 95].

While reverse Trendelenburg position is best for lung expansion, for reducing aspiration risk, and for TBI patients with elevated ICP, this position may worsen hypotension in patients with high spinal cord injury. Hypotension should be avoided during induction, and guidelines suggest maintenance of mean arterial pressure (MAP) between 85 and 90 mm Hg to avoid secondary ischemic injury to the vulnerable spinal cord [96]. However, this is not supported by class I or II evidence [97–101]. Injury to the cervical and thoracic spinal cord affects respiratory mechanics, ventilatory control, and bronchial reactivity, and respiratory insufficiency and pulmonary dysfunction are common [19, 102]. The degree of respiratory insufficiency is related to the severity of spinal cord injury [18]. Careful respiratory monitoring and aggressive pulmonary hygiene and chest physiotherapy should be undertaken early in intubated patients [103]. A review of respiratory management after cervical spinal cord injury found that early respiratory therapy protocols reduced the duration of mechanical ventilation by 6 days and ICU length of stay by 7 days [104, 105].

Traumatic Brain Injury

The Brain Trauma Foundation guidelines suggest that patients with GCS <9 should be intubated, and in those with GCS >9, intubation should be considered if there is rapid deterioration, concomitant severe body injury, or impending procedures that necessitate airway protection and mechanical ventilation [4]. Patients with TBI often present with elevated ICP, and intubation and mechanical ventilation are part of ICP management. These patients often have depression of consciousness, reflexes, and respiratory drive from the translation of increased ICP through the cortex and into the brainstem. Many patients with elevated ICP on arrival to the NCCU also have hypoxia, hypercarbia, and acidosis that can further exacerbate neurologic injury.

Laryngoscopy and the subsequent reflex sympathetic response can increase ICP during intubation. Pretreatment with a sympatholytic is suggested in patients with intracranial hypertension, as long as the patient is not at risk of hypotension [106]. Etomidate is the preferred choice for induction as it maintains stable hemodynamics. Ketamine is associated with relatively stable hemodynamics but has been associated with increased ICP. Nondepolarizing medications such as rocuronium are preferred over depolarizing agents as they are associated with less rise in ICP [107].

Arterial partial pressure of carbon dioxide ($PaCO_2$) is a modulator of CBF at the arteriolar level, and this relationship is nearly linear in normal physiological ranges ($PaCO_2$ 20–80 mmHg). In patients with reduced intracranial compliance, increased CBF results in increased ICP. On the other hand, arterial partial pressure of oxygen (PaO_2) has little influence on CBF, except in the setting of severe hypoxemia (PaO_2 less than 50 mm Hg), where it can cause a dramatic increase in CBF. Current guidelines state that prolonged prophylactic hyperventilation with $PaCO_2$ of 25 mm Hg or less is not recommended [4]. Although there is limited evidence to support even very short durations (less than 30 min) of therapeutic hyperventilation, a reduction of $PaCO_2$ to 30–35 mm Hg is a reasonable temporizing measure in refractory intracranial hypertension.

Acute Stroke

Patients with acute ischemic stroke (AIS), ICH, and SAH often have respiratory failure due to injury of vital structures responsible for respiration, arousal, and airway protection. The indication for intubation in these patients is often a lack of airway protection, followed by respiratory distress or arrest [108]. A recent US multi-state population study found that approximately 8% of AIS, 30% of ICH, and 39% of SAH patients underwent intubation and mechanical ventilation and that risk factors were concomitant seizures, pneumonia, and hydrocephalus with need for external ventricular drain placement [109]. With the advent of endovascular therapy for stroke, the Sedation vs Intubation for Endovascular Stroke Treatment (SIESTA) trial found no difference in the use of general anesthesia versus conscious sedation. However, intubated patients did have increased rates of hypothermia, delayed extubation, and pneumonia [110]. A single center study showed that pulmonary complications occurred in approximately 70% of stroke patients, with 62% developing pneumonia and 8% developing ARDS [108]. The need for mechanical ventilation after acute stroke has long been

associated with higher mortality [111]; in-hospital mortality is approximately 9 times higher, and the rate of conversion to tracheostomy is 1 in 6 [109]. Further studies are needed to elucidate the mechanical ventilation strategies that optimize long-term outcomes after stroke.

Status Epilepticus

Status epilepticus (SE) is defined in terms of the length of the seizure: either as the time point beyond which the seizure is regarded as continuous (5 min), or as the duration of ongoing seizure activity after which there is a higher risk of long-term consequences (30 min) [112]. Hypoxia can be both a cause and consequence of seizure activity. Patients may initially need suctioning and supplemental oxygen by nasal cannula or face mask. If seizures persist, ventilation is compromised, or administered medications suppress respiratory drive, BVM and endotracheal intubation are considered. Often these actions will happen simultaneously since induction medications such as propofol can have the added benefit of assisting termination of motor seizure activity. Patients who have received a paralytic agent may continue to have deleterious ongoing electrographic seizures. In a secondary analysis of the Rapid Anticonvulsant Medications Prior to Arrival Trial (RAMPART), 21% of patients were intubated with the vast majority (96%) intubated in-hospital [113]. Delayed intubation after 30 min of arrival was associated with increased mortality compared to early intubation. Few guidelines exist regarding the airway and ventilator management of patients with SE [114].

Neuromuscular Disorders

Patients with neuromuscular disorders such as myasthenia gravis, Guillain-Barré syndrome, or myopathy will sometimes be admitted to the NCCU for respiratory monitoring and/or noninvasive ventilation. These patients require a careful airway assessment that includes physical examination for the use of accessory muscles, paradoxical breathing, orthopnea, and management of oral secretions. Bulbar weakness and cranial nerve deficits predict the need for mechanical ventilation [115]. Well-known triggers for considering intubation in patients with neuromuscular weakness include a negative inspiratory force (NIF) of less than negative 20 cm H_2O and a forced vital capacity (FVC) of less than 15 mL/kg ideal body weight. NIPPV can enhance airflow, reduce work of breathing during inspiration, and prevent airway collapse and atelectasis. Retrospective studies have shown that NIPPV is well tolerated, can reduce rates of intubation and reintubation after extubation, and decrease hospital length of stay [116, 117]. Extubation failure in myasthenia patients is often linked to a weak cough and inability to clear the airway [118]. Regardless of choice in management, patients require aggressive scheduled respiratory therapy to avoid developing secondary pulmonary complications. Tracheostomy is generally not needed in myasthenia patients as they are usually intubated less than 2 weeks [119]. In contrast, patients with severe Guillain-Barré syndrome or axonal variants should be considered for early tracheostomy [120].

Extubation and Tracheostomy

Patients who are hemodynamically stable, have stable or improving lung disease, are on low amounts of support (FiO2 < 0.5, PEEP 5-8 mmHg), and initiating spontaneous breaths should undergo a spontaneous breathing trial. Either pressure support ventilatory modes or the application of a T-piece may be used for spontaneous breathing trials [121]. When patients are able to manage oral secretions, protect their airway, and spontaneously ventilate, extubation should be considered without delay. Close monitoring in the post-extubation period is important. As mentioned, in neuromuscular patients, the NIF and FVC have been used to assess the need for ventilatory support. However, there is no specific pulmonary function test that is predictive of successful extubation. The rapid shallow breathing index (RSBI) is the ratio of respiratory rate to tidal volume, and a value of greater than 105 correlates with extubation failure [122]. In patients for whom short-term extubation is deemed unsafe, early tracheostomy reduces long-term mortality, duration of mechanical ventilation, and length of ICU stay [123].

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Cardiac Complications in Neurocritical Care Patients

4

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Introduction

The heart-brain connection has been documented for centuries, and a variety of neurologic emergencies are known causes of disruption of the cardiovascular system [1–3]. While the main focus of this book has been to provide guidance on the triage and management of neurologic disease, it would be remiss to ignore the cardiovascular impact that neurologic disease can have and how management of the cardiovascular system is imperative in preventing further neurologic decline. Here we describe some of the cardiac complications that one might encounter in the emergency department or after admission to the neurocritical care unit (NCCU) that require management in the setting of various neurologic diseases.

Hypertension

Hypertension is the etiology, or at the very least a contributing factor, underlying multiple neurologic conditions, including hypertensive urgency, posterior reversible encephalopathy syndrome (PRES), ischemic stroke, and intracranial hemorrhage. In the NCCU, a provider will be faced with the need to manipulate blood pressure in different ways to reduce secondary injury. Many of these interventions can and *should* be initiated in the emergency department immediately upon identifying the diagnosis.

Hypertensive encephalopathy and the PRES spectrum are the most notable of neurologic diseases directly caused by hypertension. Hypertensive encephalopathy occurs when severe hypertension induces headache, nausea, visual disturbances, confusion, seizures, and ultimately coma. PRES is a manifestation of accelerated hypertension in which encephalopathy can be accompanied by focal symptoms and MRI hyperintensities that are typically posterior and symmetric, though this can vary. In extreme cases, small amounts of subarachnoid hemorrhage can occur. These imaging findings are thought to be due to an alteration in the permeability of blood vessels, leading to edema, *but* these changes most often normalize over the course of several weeks [4]. PRES can also be found in eclampsia, which manifests with seizures in addition to the above findings. Treatment of hypertensive encephalopathy is typically performed using antihypertensive agents. Target blood pressure (BP) is either 20% reduction per day or systolic blood pressure (SBP) <140 mm Hg, generally via intravenous medications (calcium channel or beta-blockers) followed by oral agents once stable. In eclampsia, continuous magnesium sulfate is the mainstay of treatment in addition to BP control.

One of the major causes of intraparenchymal hemorrhage is hypertension. A patient presenting with hypertension and hemorrhage location in deeper brain regions such as the basal ganglia, brainstem, and cerebellum tends to suggest a hypertensive etiology [4]. Regardless of intraparenchymal hemorrhage etiology, BP control post-hemorrhage is vital to reducing the risk of hematoma expansion. This BP control can be difficult to manage, and there has been some controversy regarding the optimal target SBP goal, with the ATACH II and INTERACT-2 trials showing no difference in death or disability with aggressive BP lowering measures. However, SBP goal <140 is generally viewed as safe and is thus an adopted target for many centers, with liberalization of that goal to SBP < 160 after hemorrhage stability is confirmed [5]. Initial BP lowering is recommended via intravenous antihypertensive medications, followed by the addition of oral agents. In some patients, BP can be difficult to manage on an oral regimen, ultimately requiring multiple agents. It is important for these patients to be closely followed as they exit the acute period as there is a risk of developing hypo-

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tension while on these medications as their post-hemorrhage hypertension resolves.

More broadly, intracranial hemorrhage, including epidural hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, and intraventricular hemorrhage of any etiology, is recommended to be treated in the same manner with SBP goal <140 until hemorrhage is confirmed stable after which liberalizing to <160 is often acceptable.

Ischemic stroke can be caused by hypertension as well, though a majority of these strokes tend to be smaller in size compared to their embolic counterparts. Hypertension management becomes more relevant after an ischemic stroke of any etiology occurs. For 24 hours after ischemic stroke, BP should be allowed to autoregulate up to SBP 220 (unless the patient has other active medical problems such as myocardial infarction that often require SBP < 140, or the patient has received thrombolysis, anticoagulation, or thrombectomy in which case SBP < 185 is often used as an upper limit). After this time period, the BP should be brought down by 20% per day to normotension. The exception to this rule is when a patient has evidence of a pressure-dependent exam, meaning that at higher BPs symptoms improve and at lower BPs symptoms worsen, suggesting a relative perfusion deficit with at-risk penumbral tissue. In this instance, close BP monitoring in the intensive care unit (ICU), while maintaining BP in a range that provides the best clinical exam, is crucial. Often IV fluids and vasopressors are considered to maintain this perfusion as needed, though the evidence behind this practice is Class IIb [6].

Traumatic spinal cord injury is another neurologic disease for which blood pressure management is key. Adequate perfusion must be maintained after blunt force injury to the spinal cord. While the data are limited, general practice guidelines suggest maintaining a mean arterial pressure (MAP) goal of 85–90 for 7 days [7]. This often requires vasopressors given the vasoplegia that occurs post-injury. In particular, norepinephrine is often the vasopressor of choice given it is less likely to exacerbate any bradycardia that may already exist. Spinal cord injury itself induces multiple hemodynamic changes both acutely and chronically. Acutely, both spinal shock and neurogenic shock can be observed [8], the latter of which will be discussed in the shock section below.

Autonomic dysfunction is very common after spinal cord injury, usually above T6 and more common in those who suffer American Spinal Injury Association (ASIA) A grade injuries. Hypertension, tachycardia, or bradycardia can be seen along with a host of other manifestations including diaphoresis and spasms. Left untreated, such symptoms can lead to PRES, seizures, intracranial hemorrhage, myocardial infarction, and even death [8]. However, autonomic dysfunction is not limited to spinal cord injury alone. It can be seen in many severe manifestations of brain injury including traumatic brain injury, hypoxic-ischemic injury, infectious or autoimmune encephalitis, and many others. Autonomic dysfunction can be difficult to treat as it manifests as paroxysmal events, which can sometimes be characterized by different autonomic changes. Intravenous management of these episodes often relies upon opiates, benzodiazepines, and antihypertensive medications. Oral treatment options for dysautonomia are extensive and best chosen based upon the predominant symptoms and triggers. For those with mainly BP and heart rate manifestations, beta-blockers, such as propranolol, and alpha-blockers, like clonidine, are commonly used.

Cardiomyopathy

While both electrical and structural abnormalities of the heart have been noted after brain injury, probably none is more famous than Takotsubo cardiomyopathy, the subject of "Voodoo Death" documented in 1942 [1, 2]. Takotsubo cardiomyopathy is also referred to as stress-induced cardiomyopathy or more recently as neurogenic stress cardiomyopathy [9]. The classic abnormality is apical hypo- or akinesis with intact contraction at the base, leading to a ballooning pattern from which its namesake is derived [10]. However, both mid-ventricular and basilar hypokinetic patterns have been described [11–13]. The cardinal rule of neurogenic cardiomyopathy is that there is complete functional recovery in most cases. The exception is very severe cardiomyopathy with such poor ejection fraction as to cause cardiogenic shock and sometimes death.

Neurogenic cardiomyopathy has been reported after nearly all acute brain injuries, including ischemic stroke, seizures, intraparenchymal hemorrhage, infection, traumatic brain injury, and, most commonly, subarachnoid hemorrhage [14–18]. In fact, neurogenic cardiomyopathy has been reported in up to 30% of subarachnoid hemorrhage cases [9, 12]. Patients who develop neurogenic cardiomyopathy as a complication of their acute brain injury have significantly higher mortality than those without [19]. Pathophysiologically, it is thought that there is a catecholamine surge at the time of neurologic injury that leads to contraction band necrosis and early calcifications [2, 12, 19–22].

Early diagnosis of neurogenic cardiomyopathy is important for initiating proactive treatment to prevent complications and speed recovery. It can sometimes be clinically difficult to differentiate from primary ischemic cardiomyopathy, and there have been multiple investigations into the utility of various biomarkers [23, 24]. Troponins are highly sensitive for cardiac dysfunction and should be trended, but alone can mislead a provider into thinking a patient is suffering from a myocardial infarction. Transthoracic echocardiograms are needed to assess bi-ventricular dysfunction and the presence of left ventricular outflow tract (LVOT) obstruction and characterize the pattern of hypokinesis. Concurrent

measurements of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and creatine kinase-muscle/brain (CK-MB) have been found to be more specific in assessing cardiomyopathy and differentiating it from cardiac ischemia. In particular, high ratios of NT-proBNP/ejection fraction and NT-proBNP/CK-MB were found to be most accurate in predicting neurogenic stress cardiomyopathy [23, 24]. This is thought to be related to the high levels of BNP released in the catecholamine surge that induces neurogenic stress cardiomyopathy.

The mainstay of treatment for neurogenic stress cardiomyopathy is supportive care [12, 20]. Because it is a reversible injury in most without hemodynamic instability, diuretics and afterload reduction are important in both optimizing cardiac output and reducing pulmonary edema. If there is no LVOT obstruction, then often beta-blockers and/or angiotensin-converting enzyme (ACE) inhibitors are initiated until functional recovery is documented, though some encourage continuing beta-blockers indefinitely [12, 20, 25]. Short interval repeat transthoracic echocardiogram is recommended, as functional recovery is typically within 1–4 weeks. Approximately 10% of patients develop cardiogenic shock, which may be related to the severity of ventricular dysfunction or the presence of LVOT obstruction [25]. The management of cardiogenic shock is discussed in section entitled "Shock". Of note, in rare cases, LV thrombus formation is a complication of reduced ejection fraction, and anticoagulation should be considered if evidence that the source of hemorrhage, like an aneurysm, is obliterated.

Shock

Cardiogenic Shock

In the majority of patients suffering cardiogenic shock after neurologic injury, neurogenic stress cardiomyopathy is the cause. However, pre-existing cardiac dysfunction can be exacerbated in the setting of acute neurologic injury. Diagnostically, transthoracic echocardiogram is needed to assess bi-ventricular function. Other ancillary tests include pulmonary artery catheterization, the measurement of central venous pressures, and more recently, advanced hemodynamic monitoring using arterial pressure waveform–based cardiac output measurements. Measures of filling pressures and systemic vascular resistance can assist with guiding therapy, though these and the above tests have unclear benefit with regard to patient outcomes.

Treatment of cardiogenic shock depends on whether LVOT obstruction exists. If there is no LVOT obstruction, then cautious fluid resuscitation (if pulmonary congestion is minimal) should be used. This is usually followed by inotropic therapy with dobutamine or dopamine. However, before initiating these therapies, the clinician must first evaluate for LVOT obstruction and heart failure with preserved ejection fraction since these medications can worsen cardiogenic shock if these abnormalities are present [25]. Milrinone and, outside the US, levosimendan have been shown to be promising inotropic therapies as well and can be used as concomitant therapy [12, 14, 20, 26]. Vasopressors may also be necessary in persistently hypotensive patients refractory to the above therapies. Norepinephrine, with both vasopressor and inotropic effects, is often the first-line agent in this scenario. Phenylephrine may be helpful in LVOT obstruction cases by increasing afterload and improving hemodynamics but should be used with close monitoring as the vasoconstrictive properties could be harmful. Vasodilator therapy, such as nitroprusside, is reserved for those with evidence of severe hypertension, acute mitral regurgitation, or acute aortic regurgitation. In most cases, the primary neurologic injury precludes the use of mechanical circulatory support, such as intra-aortic balloon pumps, ventricular assist devices and extra-corporeal membrane oxygenation, due to the risk of hemorrhage. However, if a patient has refractory hypotension and LV dysfunction with a neurologic injury that does not preclude full anticoagulation, then these forms of mechanical support should be considered. More recently, the requirement for anticoagulation in intra-aortic balloon pumps has been called into question, and they have been used successfully without anticoagulation in small case series [27, 28], so this mechanical modality without anticoagulation is also a consideration on a case-by-case basis.

Septic Shock

While septic shock is less common in the NCCU than in the Medical Intensive Care Unit, it can be seen either related to the patient's primary neurologic injury, as is the case in bacterial meningitis or endocarditis, or as a complication of a patient's admission to the ICU (e.g., pneumonia from mechanical ventilation, central line–related infections). In general, sepsis is a leading cause of death in hospitalized patients [29]. There has been a concerted push for early identification and treatment to reduce the mortality and morbidity of this disease, with new international guidelines published in 2016 [30]. For the diagnosis of sepsis, routine cultures (including aerobic and anaerobic blood, urine, sputum, etc.) should be collected without delay, preferably before starting antimicrobial therapy as cultures can sterilize within minutes to hours after treatment administration. Repeat cultures should be completed prior to antimicrobial changes. Establishing urgent vascular access is imperative to care, including the use of intraosseous access if necessary as it is fast and reliable. Intravenous antimicrobials should be started as soon as possible after recognition of sepsis and

septic shock. This is because each hour delay in administration of appropriate antimicrobials is associated with a measurable increase in mortality [29]. Broad-spectrum therapy is recommended to cover all likely pathogens. For many infections, a 7–10-day duration of antimicrobial treatment is sufficient with longer courses reserved for special circumstances. More recently, procalcitonin levels are being used in some institutions both for the diagnosis of bacterial infections and to support shortening the duration of antibiotic therapy [30]. Aggressive fluid resuscitation with crystalloids using an initial infusion of 30 cc/kg is recommended, with volume status reassessment thereafter. If a patient is felt to be euvolemic but remains hypotensive, then vasopressors should be initiated. Norepinephrine is the first-choice vasopressor for septic shock. The addition of vasopressin or epinephrine to either augment MAP goals or decrease norepinephrine dosage is also recommended. Dopamine is only to be used in a select group of patients at low risk for tachyarrhythmias and bradycardia. Dobutamine can be used in patients who show persistent hypoperfusion despite adequate fluid resuscitation and vasopressor agents. Milrinone and levosimendan, where available, can also be considered, though dobutamine is considered the first-line inotrope for septic shock. The use of corticosteroids in sepsis is controversial and generally not recommended, but in refractory cases of septic shock, there is new evidence to suggest that intravenous hydrocortisone plus fludrocortisone confer some benefit [31, 32]. If the source of sepsis is pulmonary with associated evidence of acute respiratory distress syndrome (ARDS), then low-volume ventilation and other maneuvers should be used as needed for proper ARDS management.

Neurogenic Shock

Neurogenic shock is hypotension, and sometimes also bradycardia, due to loss of sympathetic tone leading to vasodilation and increased vagal tone [8]. A majority of cases are related to cervical and high thoracic spinal cord injury, though it can rarely be seen after severe brain injury. This type of shock is different than the above shock types. Normally in shock, the sympathetic nervous system triggers multiple compensatory mechanisms including vasoconstriction, tachycardia, and hyperventilation to shunt blood away from the extremities and toward vital organs. In neurogenic shock, these compensatory mechanisms are impaired. Diagnostically, patients will have clinical evidence of vasodilation, such as warm peripheries and slower heart rates that are unique from other forms of shock. Dopamine is often used as first-line therapy, with the addition of phenylephrine or other vasopressors as needed [8]. Newly available angiotensin II analogs are mechanistically promising in treating hypotension but have yet to be evaluated in neurogenic shock. Atropine can be administered for slowed heart rate. Neurogenic shock usually resolves over the course of 1–6 weeks post-injury [8].

Hemorrhagic Shock

Hemorrhagic shock is never due to primary neurologic injury and is rarely seen in the setting of neurosurgical procedures during which some inadvertent vascular access, such as into the venous sinuses, results in massive blood loss, which without proper transfusions can be fatal. Outside of this infrequent circumstance, hemorrhagic shock after acute brain injury is secondary to either a common preceding event (e.g., a patient on anticoagulation who has an intracranial hemorrhage in addition to other systemic hemorrhage) or a complication of hospitalization (e.g., stress ulcer). Frequent hemoglobin monitoring and assessment of coagulation abnormalities are crucial for diagnosis. Imaging, including endoscopy, is vital to identifying any hemorrhage source. Volume resuscitation is the cornerstone to treating hemorrhagic shock. Crystalloid fluid can be used immediately for volume resuscitation as it is readily available, but ultimately replacement with blood products is preferred as soon as possible. If needed, a massive transfusion protocol should be activated, with the patient being resuscitated with 1:1:1 (red blood cells to platelets to fresh frozen plasma) blood products as suggested by new guidelines [33]. Large bore intravenous catheters (preferably 14 or 16 gauge), intraosseous access, or sheath introducers (e.g., Cordis) are preferred for rapid infusion. The number one priority is to control the source of bleeding whether via surgical or endovascular means. If a coagulopathy is diagnosed, then factor replacement and/or cryoprecipitate should be considered.

Myocardial Infarction

STEMI

ST segment elevations after primary neurologic injury are common, but ST-elevation myocardial infarctions (STEMIs) are not. ST elevations are often due to neurogenic stress cardiomyopathy, demand ischemia, and rarely aortic dissections [15, 23]. ST elevations from coronary artery ischemia that is concurrent with acute brain injury are rare though possible in cases such as hypercoagulable states, cocaine use, and aortic dissection. EKG, troponin, and BNP should be immediately checked [23]. If a bedside echocardiogram is readily available without delaying treatment decisions, it may help to assess

for regional wall motion abnormalities. As with all circumstances in which STEMI is suspected, the hospital procedure for activating the catheterization lab team should be initiated in a time-sensitive manner. However, the concurrent acute neurologic injury may limit treatment options (and perhaps even anticoagulation during the procedure). Primary myocardial infarction treatment often necessitates stent treatment that requires dual antiplatelet therapy, which is often contraindicated in certain acute neurologic injuries such as intracranial hemorrhage or large cerebral infarction. Similarly, coronary artery bypass grafting (CABG) requires significant anticoagulation while on cardiopulmonary bypass during the procedure; risks and benefits should be weighed on a case-by-case basis.

NSTEMI

Non-ST-elevation myocardial infarction (NSTEMI) similarly is an uncommon presentation associated with neurologic disease, but more common than STEMI. NSTEMI evaluation is similar to the STEMI evaluation described above. The classic "MONA" pneumonic (morphine, oxygen, nitrate, aspirin) for initial treatment is recommended for all patients with angina symptoms in which there are no contraindications [34]. Unfortunately, while anticoagulation and antiplatelet therapy are mainstays of NSTEMI treatment they are often contraindicated in acute neurologic injury. Other treatments, such as beta-blockers and statins, are generally recommended if LV function is not acutely compromised and there are no contraindications from a neurologic standpoint [34]. Once antiplatelet agents are considered safe from a neurologic injury perspective, they should be initiated as soon as possible.

EKG Abnormalities and Arrhythmias

EKG Abnormalities

EKG abnormalities are seen in many, if not most, cases of severe acute neurologic injury. Almost all types of abnormalities have been reported [2, 16, 21, 35]. As already discussed, ST changes are quite common, either as elevations, depressions, or T-wave inversions. Heart block is also commonly seen. While first-degree heart block is the most common manifestation, type II Mobitz I and Mobitz II heart blocks can be seen and rarely type III [35]. Asystolic pauses, though rare, can also be seen post injury. "Cerebral T-waves" are a unique EKG abnormality that has been found after brain injury [2]. These are diffuse, inverted T waves that are very large and deep (Fig. 4.1). U waves, which appear after a

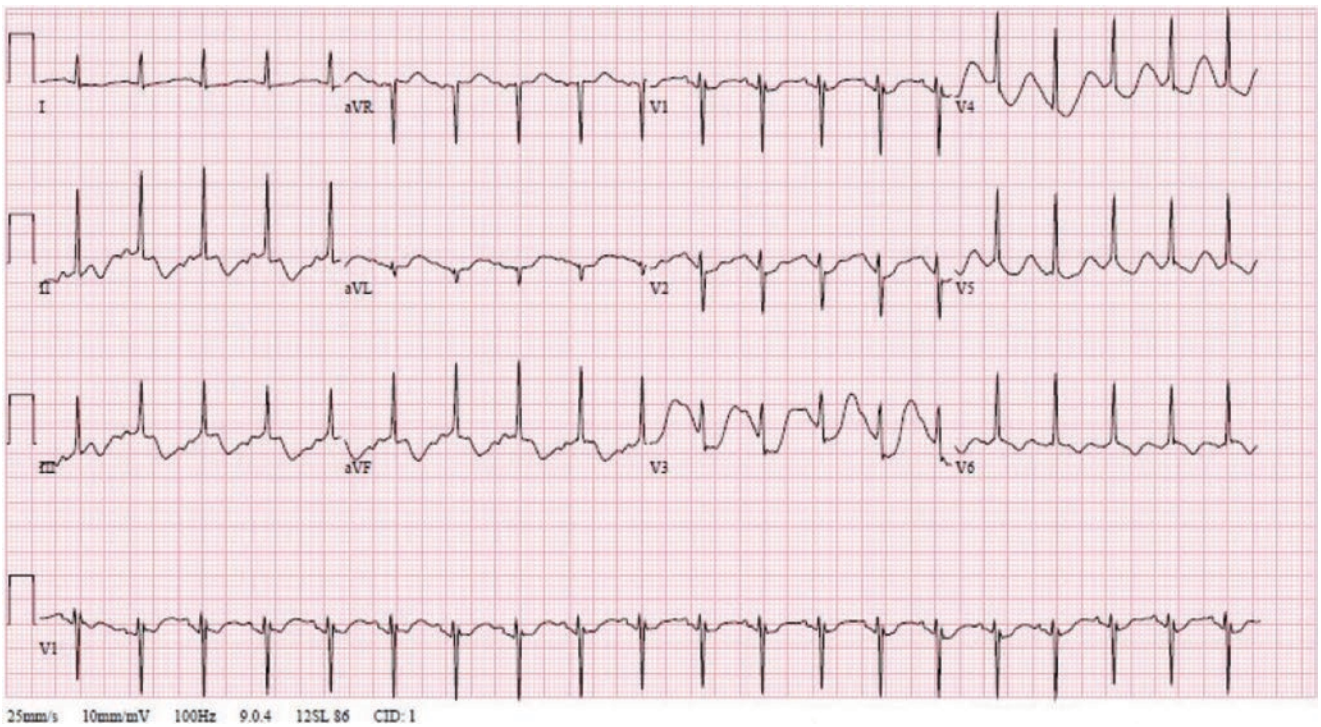

Fig. 4.1 Example of cerebral T-waves on 12-lead EKG. These are diffuse, inverted T waves that show very large, deep morphology. (Image Courtesy of Sarah Nelson, MD)

T wave and typically are too subtle to detect on a normal EKG, have been reported to be prominent after some cases of acute neurologic injury. Finally, QT prolongation is also frequently seen after neurologic injury [2, 16, 21, 35]. Thus, one must be cautious in monitoring the use of QT-prolonging medications and the potential for developing torsades de pointes. EKG monitoring, sometimes daily if abnormalities are found, along with telemetry monitoring is important for diagnosis. Treatment goals include avoiding any medications that could exacerbate the EKG abnormalities observed and maintaining potassium and magnesium levels within high normal range. First-line treatment for torsades is continuous magnesium infusion. If significant abnormalities are found including high-degree heart block or prolonged asystolic pauses, then urgent consultation to cardiology may be warranted with consideration for pacemaker placement.

Arrhythmias

By far, the most common arrhythmia observed after neurologic injury is atrial fibrillation. Often atrial fibrillation is either a previously known diagnosis or a new diagnosis that can sometimes be the etiology of acute neurologic injury, such as ischemic stroke or anticoagulation-related hemorrhage. If atrial fibrillation is a new diagnosis, then it should be documented and addressed, especially in the setting of ischemic stroke; in these cases, this diagnosis will likely dictate ultimate medical management since the presence of atrial fibrillation increases ischemic stroke risk five-fold [36]. Atrial fibrillation can also result from the acute stress of neurologic injury or neurosurgery [36]. Diagnosis of atrial fibrillation is usually made using telemetry monitoring and should be confirmed with a 12-lead EKG. Initiation of anticoagulation is based upon the CHA_2DS_2-VASc score (≥ 2) balanced with bleeding risk (for which there are scores such as HAS-BLED; however, the utility of such scoring systems is controversial). The *timing* of anticoagulation initiation after an acute neurologic injury is based on each individual patient situation. The choice of long-term anticoagulant agent should also be patient-specific, and options include both warfarin and direct oral anticoagulant agents (e.g., apixaban, rivaroxaban, dabigatran, edoxaban). If a patient with atrial fibrillation develops rapid ventricular response, then intravenous beta-blockers or calcium channel blockers can be used as intravenous pushes and/or infusions as needed. In unstable patients, chemical or electrical cardioversion can be considered, but there is a risk that any residual cardiac thrombus may embolize.

Almost all forms of tachy- and brady-arrhythmias have been reported after neurologic injury and can be life-threatening. As already mentioned, torsades de pointes, third-degree heart block, and asystolic pauses can occur [2, 16, 21, 35]. Sustained monomorphic ventricular tachycardia can also be seen, especially in the setting of large intracranial hemorrhage. Cushing response is a classical triad that presents as hypertension, bradycardia, and hypoventilation. This triad is a marker of elevated intracranial pressure and, practically speaking, when all signs are present, is almost exclusively seen during active acute herniation. Immediate hyperosmolar therapy administration and consideration for surgical decompression is warranted in these cases. Direct treatment of the life-threatening arrhythmia should follow Advanced Cardiovascular Life Support (ACLS) guidelines.

The pathophysiology behind EKG abnormalities and arrhythmias is due to multiple anatomic nodes of the "brain-heart connection." The insula and brainstem are the most well-described hubs for such alterations [19, 22, 37]. The insular cortex has been long reported to be associated with arrhythmias, and even the presence of a laterality has been described (although controversial) [19, 38]; classically, the laterality is thought to be a sympathetic drive originating from right insular cortex activation and a parasympathetic drive originating from the left insular cortex. Brainstem compression can lead to any arrhythmia type, though based on Cushing phenomenon, thought to be more commonly presenting with bradycardia [22, 37].

Cardiac Arrest

Cardiac arrest can cause significant neurologic injury; the prognosis, evaluation, and management of neurologic recovery after cardiac arrest will be in part discussed in the "Therapeutic Hypothermia in Neurocritical Care" chapter. Neurologic injury that causes cardiac arrest is much less frequent, though it includes a broad range of pathologies such as intraparenchymal/intraventricular hemorrhage and seizures. Serious arrhythmias or extreme cardiomyopathy are the most likely modes by which cardiac arrest can occur. ACLS algorithms should be followed.

Pharmacology

Table 4.1 summarizes the major continuous infusions mentioned throughout the chapter used to treat patients with cardiac dysfunction induced after neurologic injury. The list provides classes of drugs and common dose ranges used clinically.

Table 4.1 Summary of the major continuous infusions used to treat patients with cardiac dysfunction induced after neurologic injury

Drug name	Dose range
Antihypertensive agents	
Labetalol	0.5–10 mg/min
Nicardipine	5–15 mg/hr
Vasopressors	
Norepinephrine	2–40 mcg/min (though up to 3 mcg/kg/min reported)
Phenylephrine	100–500 mcg/min (though up to 9.1 mcg/kg/min reported)
Vasopressin	0.02–0.04 units/min
Dopamine	0.5–20 mcg/kg/min
Inotropic agents	
Dobutamine	0.1–20 mcg/kg/min (though up to 40 mcg/kg/min reported)
Milrinone	50 mcg/kg × 1 followed by 0.125–0.75 mcg/kg/min
Levosimendan	6–24 mcg/kg × 1 then 0.05–0.2 mcg/kg/min (not available in the USA)

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Therapeutic Hypothermia in Neurocritical Care

5

Vishank Arun Shah and Romergryko G. Geocadin

History of TH

Therapeutic use of hypothermia was first recommended in ancient Egyptian scriptures known as Edwin and Smith Papyrus, written 5000 years ago [1]. Since then, over several centuries, there have been multiple documented applications of TH including reducing wound hemorrhage in war victims, treating tetanus, and others [1]. James Currie in the eighteenth century was the first to study the physiologic effects of hypothermia on the human body. In the nineteenth century, hypothermia was used during amputations by Napoleon's chief surgeon to anesthetize the limbs. In 1892, William Osler improved survival in typhoid patients using TH. In 1938, Temple Fay invented the first cooling blanket, which was used to treat malignancy-related pain [1].

The neuroprotective benefits of TH were first demonstrated in dogs during cardiac surgery by Bigelow et al. in the 1950s [2]. Similarly, Zimmerman and Spencer occluded cerebral circulation in 26 dogs and randomized them such that 14 dogs were subsequently cooled and 12 dogs were not; 57% in the "cooling" group versus only 25% in the "no-cooling" group survived [3]. In an experimental traumatic brain injury (TBI) model, Rosomoff et al. demonstrated that TH reduced cerebral metabolism, cerebral blood flow, and intracranial pressure in dogs [4]. Similarly, TH has been used in neurosurgical procedures such as aneurysm repairs. In 1958, William and Spencer at The Johns Hopkins Hospital published one of the first case series involving 4 cardiac arrest patients treated with TH, with significantly improved neurologic outcomes including functional independence in all patients at 30 days [5]. Subsequently, in 1959, Benson et al. published the first study involving 19 cardiac arrest patients, of which 12 received TH and 7 did not; 50% in the TH group versus only 14% in the no-TH group survived [6]. In 1964, Peter Safar published the first algorithm for cardiac resuscitation and recommended using TH within 30 minutes of resuscitation in comatose patients [7]. However, the benefits of TH were quickly undermined by its associated adverse effects, which were even more prominent at the lower temperature targets (28–32°C) recommended back then [1]. It was not until the 1990s–2000s when TH use for neurologic protection made a resurgence, and after several successful clinical trials (summarized below), it has now become a fairly common practice, although the target temperatures, duration, and indications still remain topics of contention.

Therapeutic Hypothermia: Definitions and Mechanism

Definitions

Hypothermia Hypothermia is defined as body temperature of less than 36°C regardless of cause [8].

Therapeutic Hypothermia (TH) TH is defined as intentional reduction of a patient's core body temperature below 36°C, while suppressing deleterious effects such as shivering, for the purpose of preventing secondary neurologic injury [8].

Degrees of TH [8] *See* Table 5.1

Controlled Prophylactic Normothermia This is defined as maintaining core body temperature between 36 and 37.5°C and preventing fever, while suppressing deleterious effects such as shivering, to prevent secondary neurologic injury [8].

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Table 5.1 Definitions of degrees of TH

Degrees of TH	Temperature range
Mild TH	34–35.9°C
Moderate TH	32–33.9°C
Moderately deep TH	30–31.9°C
Profound TH	<30°C

Targeted Temperature Management (TTM) This involves inducing and maintaining core body temperature at a predetermined target temperature using cooling devices and continuous core temperature monitoring, while controlling and suppressing deleterious effects such as shivering, for the purpose of preventing secondary neurologic injury. As discussed below, this target temperature remains a debated topic with variable targets suggested in the literature. Per the TTM trial methodology [9], the 2017 American Academy of Neurology (AAN) practice parameter [10] for post-cardiac arrest care defines TTM as cooling to 36°C for 24 hours followed by 8 hours of rewarming to 37°C, followed by temperature maintenance below 37.5°C until 72 hours after cardiac arrest.

Mechanism

Understanding the neuroprotective mechanisms of TH requires a review of the pathophysiologic cascades involved in cerebral injury. Cerebral ischemia, i.e., deficient cerebral perfusion, is most often the final common pathway for cell death in any kind of brain injury. Acute ischemic stroke is an example of primary focal cerebral ischemia, and hypoxic-ischemic encephalopathy secondary to cardiac arrest is a classic example of primary global cerebral ischemia. However, other forms of brain injury also eventually lead to brain ischemia. For example, TBI and intracranial hemorrhage not only cause perilesional ischemia, but also lead to secondary global ischemic injury related to cerebral edema and rising intracranial pressure.

Ischemic neuronal injury occurs in two stages: primary or acute and secondary or subacute. In the acute phase (minutes to hours after onset of ischemia), since cerebral perfusion is unable to meet cerebral metabolic demand, there is a deficiency in oxygen, glucose, and adenosine triphosphate (ATP) [1]. Low oxygen and glucose leads to anaerobic metabolism, which causes lactic acidosis leading to tissue necrosis. ATP is essential in maintaining sodium/potassium (Na^+/K^+) pump function, which in turn maintains ionic gradients in neuronal tissue. Deficient ATP leads to Na^+/K^+ pump failure, which leads to cytotoxic edema from ionic imbalance and osmotic flow. In addition, Na^+/K^+ pump failure leads to the opening of calcium channels and calcium influx triggering release of excitatory neurotransmitters such as glutamate [11]. Glutamate and other excitatory neurotransmitters lead to excessive extracellular acidosis, increased production of nitric oxide (NO) and reactive oxygen species (ROS), which lead to excitotoxicity [12]. Moreover, ischemia leads to downregulation of the GluR2 subunits of AMPA receptors, which usually help limit calcium influx, thus perpetuating excitotoxicity [11]. All of the above changes lead to subcellular organelle damage, disruption of cell membranes, mitochondrial dysfunction, cellular swelling, and eventually necrosis. Necrosis is the predominant form of cell death in the acute phase.

In the subacute phase, 1–7 days after the ischemic insult, secondary neuronal injury occurs, predominantly as a consequence of reperfusion, alteration in gene expression, and/or cellular apoptosis. When cerebral blood flow is restored after temporary cessation, there is excessive flow to the ischemic and auto-dysregulated brain, known as hyperemia. Hyperemia leads to the generation of excessive ROS, which would normally be neutralized by mitochondria, but in the absence of functioning mitochondria accumulate and activate cellular apoptotic pathways.

Alterations in gene expression begin to occur hours after the onset of ischemia, but its consequences occur over several days. Micro-RNAs, a subclass of non-coding RNAs, are overexpressed within 2 hours of the onset of ischemia and may have a role in perpetuating cell death, although this remains a subject of active research [13]. It is believed that these changes in gene expression, ROS accumulation, and altered stress signals lead to activation of cellular apoptotic pathways.

There are two apoptotic pathways: extrinsic and intrinsic [11]. The extrinsic pathway is activated by matrix metalloproteinases (MMP), which cleave and activate death ligands. Death ligands bind to cell surface death receptors triggering intracellular caspases that perpetuate apoptosis. The intrinsic pathway occurs in mitochondria and is triggered by increased expression of pro-apoptotic factors such as BCL-2-associated X protein (BAX) and protein kinase C(PKC)δ and reduced expression of anti-apoptotic factors such as BCL-2 and PKCε. This imbalance leads to intracellular caspase activation and cell apoptosis [11].

Cellular necrosis; release of proteins, lipids, and intracellular contents; ROS; and cellular apoptosis trigger an inflammatory response. Neutrophil migration occurs, and microglia are activated, leading to release of pro-inflammatory cytokines, more ROS, and proteases that perpetuate further injury and inflammation, triggering a vicious cycle [14]. This leads to further cell death, vasogenic cerebral edema, raised intracranial pressure, and injury to remote, previously unaltered areas of the brain.

Blood-brain barrier (BBB) disruption also plays a large role in secondary brain injury. All forms of brain injury models – traumatic, ischemic, and hemorrhagic – have evidence of

BBB disruption early in the course. This occurs due to destruction of its various components, particularly tight-junction proteins, vascular endothelial cells, basement membranes, and transport proteins. Activated MMPs often facilitate this process by degrading tight-junction proteins in the BBB. Disruption of the BBB leads to cerebral edema, hemorrhage, and raised intracranial pressure, which leads to further cerebral injury [11]. In addition, aquaporin-4 channels, which help transport water intracellularly, are overexpressed in injured astrocytes, further facilitating cerebral edema.

TH minimizes the extent of primary and secondary neuronal injury by several postulated mechanisms, targeting numerous stages in the injury cascades as demonstrated in animal models (Fig. 5.1). In the acute phase of injury, TH may help limit the extent of primary injury, i.e., cellular necrosis, if initiated early enough. By far, the most commonly endorsed mechanism for this effect is the immediate reduction in cerebral metabolism induced by TH. As previously mentioned, cerebral ischemia is a mismatch between cerebral perfusion and cerebral oxygen demand; thus by reducing cerebral metabolism and consequently oxygen demand, the ischemic deficit is minimized. Cerebral oxygen consumption and glucose metabolism decrease by 6–7% per degree Celsius drop in body temperature [15]. Reduction in cerebral metabolism leads to reduction in local lactic acid production, minimizing acidosis-related necrosis. In addition, preservation of ATP prevents Na^+/K^+ pump failure and reduces the degree of cytotoxic edema. ATP preservation also prevents calcium influx and thus reduces the release of glutamate, abating excitotoxicity [16]. TH may also prevent downregulation of the anti-excitotoxic GluR2 subunits on AMPA receptors, limiting excitotoxicity [11]. All of these effects prevent further cellular necrosis and primary injury. However, these immediate benefits do not explain the improved outcomes that occur even when TH is initiated hours after the initial injury. Moreover, a comprehensive review of the available animal literature minimizes the benefits from the acute mechanisms described above [17]. Instead, TH may play an even more important role in the subacute phase or the phase of secondary injury.

First, by limiting cerebral blood flow, TH prevents reperfusion-related hyperemia, lessening the generation of ROS [12]. Second, TH interferes with the activation of the cellular apoptotic pathways. By deactivating MMPs, TH prevents the activation of death ligands, which are necessary to trigger the extrinsic apoptotic pathway [18]. Moreover, TH restores the balance of anti- and pro-apoptotic factors in the mitochondria. It specifically increases the expression of BCL-2 and decreases BAX, suppressing the intrinsic apoptotic pathway [19]. TH may also directly suppress intracellular caspases and stimulate PKCε, preventing further cellular apoptosis [20, 21].

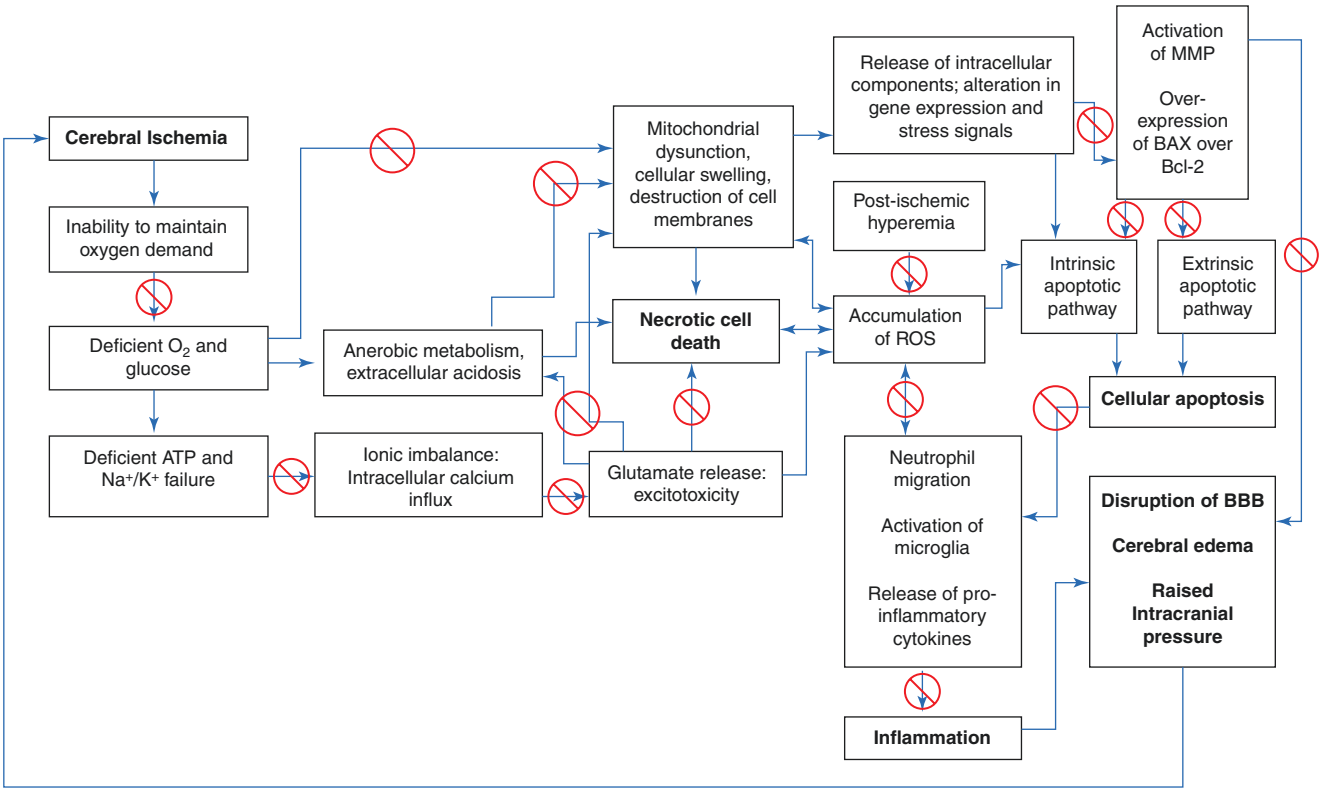

Fig. 5.1 Neuroprotective targets of TH in central nervous system ischemic injury cascades

TH also reduces post-injury inflammation, further reducing secondary brain injury. It decreases neutrophil migration and microglial activation, leading to decreased pro-inflammatory cytokines (specifically IL-6, IL-1β, and TNF-α) and ROS [14, 22, 23]. TH also lowers inflammation by suppressing transcription factors involved in activating inflammatory genes [24]. This leads to reduction in vasogenic edema as well.

Hypothermia also prevents BBB disruption by suppressing MMP activity, which plays a major role in destroying BBB tight-junction proteins [25]. This reduces secondary cerebral edema and elevation in ICP. It also decreases cerebral edema by suppressing the expression of aquaporin-4 channels in reactive astrocytes [26].

Thus, TH may reduce primary cerebral injury by limiting cell necrosis as well as secondary brain injury by blocking apoptotic cascades, reducing central nervous system inflammation, preventing cerebral edema, and reducing ICP. All of these, and many more undefined mechanisms, may be responsible for the clinical benefit seen with hypothermia, specifically after global cerebral ischemia in the setting of cardiac arrest.

Indications for Therapeutic Hypothermia

(a) *Post-cardiac arrest survivors*:
The most robust clinical trial data supporting the use of TH/TTM in clinical practice exists in post-cardiac arrest survivors. The first RCTs supporting TH were published in 2002 and were restricted to out-of-hospital ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT) patients. In a multicenter European trial, Holzer et al. randomized 275 VF or pulseless VT arrest comatose survivors to receive either standard care and normothermia or mild TH (target temperature: 32–34°C, measured with a bladder temperature probe) within 4 hours of return of spontaneous circulation (ROSC) and for a duration of 24 hours, using an external cooling mattress [27]. The predefined primary outcome was functional independence (defined as none, mild, or moderate disability) at 6 months, and the secondary outcome was mortality. Fifty-five percent in the TH group versus only 39% in the control group achieved the primary end-point of functional independence with a number needed to treat of only 6 patients. In addition, mortality at 6 months was 41% in the TH group versus 55% in the control group.

Similarly, Bernard et al. [28] randomly assigned 77 VF arrest patients to receive normothermia (target temperature: 37°C) or mild TH (target temperature: 33°C) using ice packs for 12 hours. The primary end-point was discharge to home or rehabilitation facility, which was achieved by 49% in the TH group versus 26% in the control group. In 2003, the International Liaison Committee on Resuscitation (ILCOR) published an advisory statement supporting the use of TH (32–34°C) in survivors of out-of-hospital arrest with an initial rhythm of VF/pulseless VT [29]. In 2005, the American Heart Association (AHA) updated their guidelines for cardiopulmonary resuscitation supporting the use of TH in out-of-hospital VF/pulseless VT arrest.

Subsequent literature focused on two aspects of TH: the most appropriate target temperature and non-shockable initial cardiac rhythms. In a Korean study [30], 62 out-of-hospital cardiac arrest survivors (pulseless electrical activity (PEA) and asystole were included) were randomly assigned to a target temperature of either 32, 33, or 34°C. No significant differences in mortality or neurologic outcomes were noted, but hypotension was more common while maintaining a target temperature of 32°C. On the other hand, in a single-center study, Lopez-de-Sa et al. [31] randomly assigned 36 patients with ROSC after out-of-hospital cardiac arrest (PEA excluded) to TH with a target temperature of 32°C versus 34°C and found that 44% of patients cooled to 32°C survived with none to moderate disability at 6 months versus only 11% in the 34°C group. Moreover, there was a significantly lower incidence of seizures in the 32°C group.

The largest international multicenter RCT assessing TH in cardiac arrest, known as the TTM trial, was published in 2013. Nielsen et al. [9] randomly assigned 939 cardiac arrest survivors with any initial rhythm to receive TH with a target temperature of 33°C versus 36°C. After ROSC and randomization, TH was initiated as soon as possible using ice packs, ice-cold intravenous fluids, intravenous cooling, and/or external cooling devices. After 28 hours of cooling, rewarming was initiated at 0.5°C per hour. After rewarming was completed at 36 hours, a temperature of 37.5°C was maintained in both groups until 72 hours after cardiac arrest. The primary end-point was all-cause mortality at 180 days and the secondary outcome was poor outcome (modified Rankin score (mRS) 4–6). The study found no significant differences in the primary or secondary outcomes between the two groups.

In a retrospective analysis [32] of a large registry of out-of-hospital cardiac arrest survivors (1145 patients) receiving TH, 62% had VF/pulseless VT and 38% had non-shockable initial rhythms (PEA and asystole). While TH increased odds for good neurological outcome (odds ratio (OR) = 1.9, 95% confidence interval (C.I.) 1.18–3.06) in the VF/VT group, TH had no impact on neurological outcomes in the non-shockable rhythm group (OR = 0.71, 95% C.I. 0.37–1.36). On the contrary,

in a retrospective Austrian study [33] that evaluated 347 cardiac arrest survivors with non-shockable initial rhythms, TH increased odds for a good neurological outcome at 6 months (OR = 1.84, 95% C.I. 1.08–3.13). The FINNRESUSCI study [34], a prospective observational analysis, also found improved odds for good neurological outcome with out-of-hospital VF/VT arrest but no impact on neurological outcomes in patients with non-shockable rhythms after TH.

Notably, all the literature summarized above focuses on out-of-hospital cardiac arrest. Limited data exist for the use of TH in in-hospital cardiac arrest survivors. In fact, there is no RCT data regarding in-hospital arrest patients. The only large study [35] addressing this question is a retrospective analysis of a large multicenter prospective cohort (8316 patients) encompassing in-hospital cardiac arrest survivors. Only 2.6% of the total patient pool received TH, of whom only 40% achieved the target temperature. Although the study had significant limitations, no significant impact of TH/TTM on survival at discharge and neurologically favorable survival was found.

In 2015, the AHA updated its recommendations on post-cardiac arrest care [36]. Current AHA guidelines have replaced TH with the term "targeted temperature management" (TTM). The AHA makes a class 1 recommendation for TTM in all cardiac arrest survivors with no meaningful response to commands after ROSC, including in-hospital and out-of-hospital arrests as well as shockable and non-shockable rhythms. They recommend selecting and maintaining a constant target temperature between 32 and 36°C for a duration of 24 hours. While the use of TTM in patients with non-shockable rhythms or in-hospital cardiac arrest is not strongly supported by the literature, the AHA guidelines continue to support its use due to the extremely low risk of complications at the upper limit of the recommended temperature range.

On the other hand, the 2017 AAN guidelines make slightly different recommendations [10]. The AAN makes a level A recommendation for moderate TH (32–34°C) for a duration of 24 hours in comatose cardiac arrest survivors with an initial cardiac rhythm of VT/VF based on the 2 Class I studies described above. There is insufficient evidence to recommend 32 versus 34°C as a target temperature [10]. In comatose survivors of PEA/asystole arrest, the AAN makes a level B recommendation for TTM (target temperature of 36°C for the first 24 hours followed by rewarming to 37°C over the next 8 hours, followed by fever prevention to <37.5°C for the next 72 hours) to improve neurologic outcomes [10].

Additionally, as described above, the TTM trial [9] showed that comatose cardiac arrest survivors may have similar neurologic outcomes when temperature is maintained at 33 versus 36°C for the first 24 hours. Thus, in high-risk scenarios such as coagulopathy, ongoing hemorrhage, and sepsis, 36°C may be better tolerated and should be considered. The range 32–33°C may be more appropriate in patients with post-anoxic seizures [31].

(b) *Intracranial hypertension*:
Mild-to-moderate TH (32–35°C) is an established treatment option for intracranial hypertension, especially when refractory to standard treatment [37]. In fact, TH has been included in a tiered approach to the management of increased ICP [38]. As described previously, the mechanisms by which TH lowers ICP are multifactorial. What is most commonly described is that lowering body temperature results in decreased cerebral metabolism leading to reduced cerebral blood volume (CBV) and consequently decreased ICP, which is the pressure exerted by the intracranial components (including cerebrospinal fluid (CSF), CBV, and brain parenchyma) on the dura. In addition, TH reduces inflammation and stabilizes the BBB, thus limiting cerebral edema [39].

In a systematic review of the literature [40] that included 11 RCTs and 6 prospective cohort studies of TBI patients receiving TH, average ICP reduction by 10 mmHg was noted, which was higher than the average reduction noted with hyperventilation (6 mmHg), mannitol (8 mmHg), and barbiturates (8.5 mmHg). However, hypertonic saline (15 mmHg), CSF drainage (15 mmHg), and decompressive craniectomy (19 mmHg) were associated with greater ICP reduction than TH. Similarly, Sadaka et al. [41] performed a systematic review and found that moderate hypothermia (32–34°C) was associated with significantly lower ICP when compared to controls. A large meta-analysis of 748 patients with severe TBI receiving TH showed that prolonged hypothermia effectively treated intracranial hypertension that was refractory to standard first-tier therapies [42].

The ideal target temperature for lowering ICP is controversial. Most literature supports a temperature range from 32 to 35°C. Interestingly, Tokutomi et al. [43] evaluated a cohort of 42 patients with severe TBI and elevated ICP who received TH and found that decreasing the temperature from 38 to 35°C was associated with a steady decline in ICP; however, no further effect was noted when the temperature was lowered below 35°C. Moreover, temperatures below 35°C may reduce cardiac output and brain tissue oxygenation [44]. In general, temperatures below 30°C are avoided due to high risk for cardiac arrhythmias, coagulopathy, and infections among other complications. The duration of TH when managing elevated ICP is also controversial and not well studied. Mild hypothermia generally has minimal adverse effects, and thus a prolonged duration of TH (2–5 days) [45] until the ICP is stabilized may be permissible. The European Study of Therapeutic

Hypothermia (32–35°C) for Intracranial Pressure Reduction after Traumatic Brain Injury (the Eurotherm3235 Trial, summarized below) allowed 72 hours of TH [46].

While it is clear that hypothermia decreases ICP, its impact on long-term neurological outcomes remains questionable. The Eurotherm3235 trial [46], a large multinational multicenter RCT that evaluated this question, was published in 2015. The trial randomized 387 TBI patients with ICP > 20 mm Hg despite stage 1 treatments (i.e., mechanical ventilation and sedation) to TH versus standard care. In the TH group, patients were immediately cooled to 32–35°C and stage 2 therapies such as mannitol and hypertonic saline were used only if the ICP could not be controlled with TH. In the control group, patients directly received stage 2 therapy (i.e., osmotic therapy) to control ICP. If ICP was still not controlled, patients in both groups received stage 3 therapies such as barbiturate coma and/or decompressive craniectomy. The study found a significant difference in the use of stage 3 therapies, with a higher use (54%) in the standard care group versus a lower use (44%) in the TH group, indicating that TH seems to help lower ICP. However, long-term functional outcomes were not improved by the use of TH and in fact were slightly worse in the TH group. It is unclear if this effect was related to direct harm from TH or due to differential use of other therapies in the two groups. Regardless, this study has resulted in limited use of TH as an ICP-lowering therapy in routine clinical practice, unless ICP is refractory to standard therapies.

It is imperative to mention that all of the above literature, which shed light on the use of TH in treating intracranial hypertension, involves patients with TBI. While it is clear that persistently elevated ICP in TBI patients is associated with worse outcomes, the causality of this association remains in question, and studies (such as the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial) have shown that utilizing therapies to lower ICP below a specific threshold has no impact on long-term functional outcomes. Notably, there is limited literature that has evaluated TH as an ICP-lowering therapy in other patient populations. Moreover, TH has not been directly compared to other ICP reducing therapies reserved for refractory intracranial hypertension, such as barbiturate coma and decompressive craniectomy.

To summarize, mild to moderate TH (32–35°C) is effective in decreasing ICP although it has not been shown to improve patient outcomes. Further head-to-head comparisons with barbiturate coma, decompressive craniectomy, and paralytic agents as well as evaluation of its use in non-traumatic intracranial hypertension are needed [37].

The 2015 American College of Surgeons Best Practice Guidelines for the Management of Traumatic Brain Injury do not recommend the routine use of TH below 36°C to treat elevated ICP unless other tier 2 and 3 therapies have failed. Based on current literature and guidelines, we recommend that TH use in intracranial hypertension be restricted to patients with elevated ICP refractory to stage 1 and 2 therapies including mechanical ventilation, sedation, and osmotic therapy.

(c) *Traumatic brain injury (TBI)*:
The literature highlighting the use of TH in TBI patients who have developed intracranial hypertension is summarized above and will not be addressed in this section. As described previously, TH has been shown to suppress inflammatory cascades, stabilize the BBB, and prevent secondary injury and cerebral edema in animal models, all of which play important roles in the pathogenesis of TBI and may be responsible for poor long-term functional outcomes. Based on this animal data, studies have sought to assess the early use of prophylactic short-duration hypothermia in patients with TBI in order to prevent secondary brain injury. Clifton et al. [47] randomized 392 patients with severe closed head injury to receive either standard care plus TH to 33°C within 6 hours of injury for 48 hours using surface cooling or standard care alone. There was no significant difference in mortality or functional status at 6 months between groups. Similarly, in a Japanese prospective multicenter RCT [48], 91 severe TBI patients with normal ICP were randomly assigned to receive TH to 34°C for 48 hours with slow rewarming versus normothermia to 37°C for 5 days. No significant difference in functional outcomes were found coupled with significantly higher incidences of infection, leukopenia, and electrolyte imbalances in the TH group. The National Acute Brain Injury Study: Hypothermia II (NABIS: H II) [49], a randomized multicenter trial in USA and Canada, assigned 232 patients to hypothermia (33–35°C) and 113 patients to normothermia within 2.5 hours of injury for a duration of 48 hours. No significant difference in mortality or functional outcomes was noted between the two groups. However, a subgroup analysis demonstrated improved outcomes in patients who had undergone surgical evacuation of hematomas but not in patients with diffuse injury.

In summary, TH may have a role in managing refractory intracranial hypertension in patients with severe TBI. However, the 2017 Brain Trauma Foundation (BTF) guidelines do not recommend the use of early prophylactic TH in patients with TBI [50].

(d) *Intracerebral hemorrhage (ICH)*:
The use of TH in intracerebral hemorrhage remains primarily experimental. Melmed et al. conducted a meta-

analysis of all preclinical animal studies comparing TH to normothermia for ICH models. They found no significant difference in hematoma expansion but showed significant reduction in perihematomal edema and improved behavioral outcomes [51]. Similarly, a systematic review [52] of preclinical and clinical studies involving the use of TTM in spontaneous ICH patients found reduced incidence of perihematomal edema under mild hypothermia and an association with favorable functional outcome. The Targeted Temperature Management after Intracerebral Hemorrhage (TTM-ICH) trial is an ongoing prospective, single-center trial in which ICH patients are randomized within 18 hours of symptom onset to receive 72 hours of TTM (32–34°C) followed by controlled rewarming versus normothermia [53]. Similarly, the Cooling in ICH (CINCH) trial [54] is a German-Austrian multicenter randomized trial in which ICH patients are randomized to receive 8 days of TH to 35°C using endovascular cooling versus conventional management. The results of both of these trials have not yet been published. Currently, the Neurocritical Care Society (NCS) and AHA guidelines on management of spontaneous ICH do not recommend the prophylactic use of TH in ICH patients.

(e) *Aneurysmal subarachnoid hemorrhage (aSAH)*:
In experimental aSAH models, TH has been shown to have beneficial effects early in the course of the disease. TH has been demonstrated to improve post-hemorrhagic cerebral blood flow (CBF) in the first hours after aSAH likely due to hypothermia-induced vasodilation and prevention of autoregulatory impairment [55]. Regional analysis of apparent diffusion coefficient sequences of magnetic resonance imaging has shown that TH at 32°C reduces cortical edema formation after aSAH. This might be related to decreased lactate production, which has been shown to occur after aSAH [55]. TH has also been shown to reduce the stress response after aSAH in experimental models [55].

In the clinical setting, only few retrospective non-randomized studies have reported the effects of TH in aSAH with variable success and no significant impact on functional outcomes or mortality. Nagao et al. applied mild TH to 9 poor-grade aSAH patients with no improvement in mortality [56]. With multimodality monitoring, improvement in cerebral oxygen metabolism was found but no impact on outcomes [55]. Kuramatsu et al. [57] performed an observational matched controlled study on 36 poor-grade aSAH patients: 12 patients received mild TH (35°C) within 48 hours of aSAH onset for a duration of 7 days and were matched to 24 control aSAH patients. All patients received angiography and transcranial Dopplers to detect vasospasm. They found significant reductions in the degree of macrovascular vasospasm, peak spastic velocities, and the occurrence of delayed cerebral ischemia (DCI). Gasser et al. [58] evaluated the feasibility and safety of long-term mild TH (>72 hours) in 21 poor-grade aSAH patients with severe brain edema and found no difference in functional outcomes. Intraoperative TH during aneurysm clipping surgery [59] also failed to show any impact on outcomes. Choi et al. [60] randomized poor-grade aSAH patients after successful aneurysm securement to receive TH for 48 hours in addition to standard care or standard care alone. While it was a feasibility and safety study, there was some reduction in mortality and DCI in the TH group.

Currently, the AHA and the NCS make no specific recommendations on the use of TH or prophylactic hypothermia in the management or prevention of DCI in patients with aSAH. The 2012 AHA guidelines do not recommend the routine use of intraoperative hypothermia during aneurysm clipping, except in select cases [61].

(f) *Acute ischemic stroke (AIS)*:
TH has been evaluated in the management of malignant cerebral edema following acute hemispheric ischemic strokes. Schwab et al. [62] evaluated 25 patients with severe middle cerebral artery (MCA) strokes who were treated with TH to 33°C within 14 hours of symptom onset, for a total duration of 48–72 hours, along with ICP monitoring. While ICP and cerebral edema were well controlled during the TH phase, there was no impact on mortality due to worsening in cerebral edema and ICP during the rewarming phase. In a follow-up trial, Schwab et al. induced moderate TH in 50 patients with MCA stroke and demonstrated that worsening cerebral edema and intracranial hypertension occurred during the rewarming phase [63]. Controlled warming at less than 0.1°C per hour resulted in improved control of ICP [64]. In a prospective single-center study, Els et al. randomly assigned 25 consecutive hemispheric ischemic stroke patients to receive hemicraniectomy with TH to 35°C versus hemicraniectomy alone. TH was noted to be safe and feasible with a tendency toward better outcomes in the TH group although this difference was not statistically significant [65]. In addition, induction of TH in AIS patients has been associated with a higher risk of infections such as pneumonia [66]. Late TH as a replacement for hemicraniectomy has failed in several trials and is not recommended [43]. The 2018 AHA guidelines for the management of AIS patients do not recommend the routine use of TH, and it should be offered only in the context of clinical trials (Class IIb) [66].

(g) *Status epilepticus (SE)*:
As previously described, TH has neuroprotective properties, especially in animal models. In animal seizure mod-

els, TH has been shown to have antiepileptic effects. In fact, TH has been used as an adjunct to antiepileptic medications in super-refractory status epilepticus [67]. Zeiler et al. performed a systematic review on the use of TH for refractory SE and its impact on seizure control. They found 13 studies with a total of 40 patients who were cooled to a median temperature of 33°C for a median duration of 48 hours. Seizure cessation rate was noted to be 62.5% [68]. However, in a multicenter trial involving 270 patients with convulsive SE randomized to receive TH (32–34°C) for 24 hours along with standard care versus standard care alone, no significant difference in functional outcomes or seizure duration was noted. To summarize, while anecdotal evidence suggests reduction in seizure control with TH, the impact on functional outcomes remains questionable. However, there may be a role for TH in super-refractory status epilepticus not responding to multiple antiepileptic medications and infusions.

The 2012 NCS guidelines on the management of convulsive SE do not make a specific recommendation on the use of TH, but do mention TH as an alternative therapy that may be reserved for patients not responding to standard management recommendations for refractory SE [69]. The 2016 American Epilepsy Society guidelines on the management of SE do not make any recommendations on the use of TH in SE [70].

Induced Normothermia for Fever Prevention in Neurocritical Care

Fever occurs very commonly in neurologic illnesses and has been shown to be associated with increased morbidity in various acute neurologic conditions. Fever is associated with increased cerebral metabolic oxygen demand, elevated ICP, and worsening cerebral ischemia, and it propagates inflammatory cascades, promoting secondary neurologic injury. TTM to prevent fever has been evaluated in several neurocritical care illnesses, and the evidence is summarized below.

(i). *Intracerebral hemorrhage (ICH)*:
Schwarz et al. showed that there is a high incidence of fever post-ICH especially in patients with intraventricular hemorrhage. The duration of fever correlated with poor neurologic outcomes [71]. Rincon et al. [72] analyzed 300 patients from the Virtual International Stroke Archive (VISTA) database and found that fever after ICH was independently associated with hematoma expansion, which is a predictor of poor outcomes. Lord et al. [73] performed a retrospective case-control study where they compared spontaneous ICH patients before and after initiation of an institutional TTM protocol to a target temperature of 37°C. TTM was started within a median of 3 days after ICH for a median duration of 7 days. They did not find any improvement in functional outcomes, and the patients in the TTM group had a longer length of stay, more ventilator days, and higher incidence of tracheostomy. Similarly, other studies have failed to consistently show an improvement in outcomes with prophylactic TTM to prevent fever in ICH patients. The 2015 AHA guidelines on the management of spontaneous ICH recommend treatment of fever but do not recommend controlled prophylactic normothermia for fever prevention, except in experimental conditions [74].

(ii). *Aneurysmal subarachnoid hemorrhage (aSAH)*:
Fever occurs in 70% of patients following aSAH and is often part of a systemic inflammatory response rather than infectious in origin. Predictors of fever in aSAH patients include higher Hunt-Hess grade, presence of intraventricular hemorrhage, and higher Fisher grade (i.e., greater amount of subarachnoid blood) [75, 76]. Retrospective studies in patients with aSAH have shown that fever is an independent predictor of poor outcome and is associated with a higher incidence of vasospasm [75]. DCI and cerebral infarcts are more common and larger in size in aSAH patients with fever [77]. Fever has also been associated with worse cognitive outcomes in survivors of aSAH [75]. In a case-controlled study, Badjatia et al. demonstrated improved functional outcomes with induced normothermia in SAH patients [78]. However, prophylactic prevention of fever with induced normothermia has not been prospectively studied in aSAH patients.

Despite low-quality evidence, the 2011 NCS guidelines on the management of SAH patients recommend aggressive fever control during the period of DCI risk [77]. Although non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen have low efficacy, the NCS recommends a trial of these first and, if not effective, recommends using surface cooling devices and/or intravascular cooling. Similarly, the 2012 AHA guidelines make a Class IIa recommendation (level B evidence) to aggressively control fever to target normothermia in the acute phase of aSAH [61].

(iii). *Traumatic brain injury (TBI)*:
Fever after TBI is common and occurs more frequently in patients with lower GCS, cerebral edema, and diffuse axonal injury [79]. Although most commonly fever is related to underlying infections, TBI patients may also have central fever related to hypothalamic dysfunction. Fever in the first week after TBI is associated with intracranial hypertension, worse neurologic function, and prolonged duration in the intensive care unit [80, 81]. Jiang et al. demonstrated that TBI patients with fever

during the early period after injury had worse neurologic outcomes [82]. Similarly, Bao et al. also demonstrated that TBI patients with higher fever burden had worse neurologic outcomes at 6 months [83]. Thus it may be prudent to treat fever aggressively early in the illness [84]. Despite the above, the 2017 BTF guidelines make no recommendations regarding fever management. Additionally, as described above, the BTF guidelines do not recommend prophylactic normothermia or hypothermia for fever prevention [50].

(iv). *Acute ischemic stroke (AIS)*:
Fever is associated with negative consequences in patients with cerebral ischemia [84]. It has been linked to the release of excitotoxic neurotransmitters, destabilization of the BBB, increased cerebral metabolism, free radical release, ischemic cortical depolarizations, and worsening cerebral edema [85]. Sixty percent of patients with AIS are reported to have a temperature > 37.5°C in the first 72 hours after stroke onset [86]. Fever within the first 24 hours is independently associated with larger infarct volume and higher odds (OR = 3.41) of functional dependence at 3 months [86]. Similarly, an admission temperature > 37.5°C is independently associated with increased 12-month mortality in AIS patients [87]. In a large retrospective cohort study involving 9366 AIS patients, peak temperatures >39°C within the first 24 hours were independently associated with in-hospital mortality [88]. Impact of fever or hyperthermia beyond the first 24 hours after stroke onset is questionable and poorly studied; however, due to the high risk for cerebral edema in the first 3–5 days, it may be prudent to aggressively control and treat fever during this period. The 2018 AHA guidelines on the management of AIS recommend that sources of hyperthermia (defined as >38°C) be identified and treated and that antipyretic medications be administered to reduce temperature in hyperthermic patients with stroke [66].

(v). *Status epilepticus (SE)*:
Eighty percent of patients with generalized convulsive SE have fever within the first few hours after onset [89]. Fever is typically related to excessive muscle activity rather than an underlying infection [90]. In SE animal models, fever is associated with cerebellar and hippocampal neuronal loss [90, 91]. Conversely, relative hypothermia leads to shorter seizure duration and prevents neuronal damage in SE animal models [90]. There are no retrospective or prospective studies evaluating induced normothermia for fever prevention in SE patients. The American Epilepsy Society and NCS do not make any recommendations regarding the prophylactic use of induced normothermia for fever prevention in SE patients.

Critical Care Management During Therapeutic Hypothermia

As described above, the main utility for TTM/TH remains in preventing secondary brain injury in post-cardiac arrest survivors, with some sporadic use in other extreme situations such as refractory intracranial hypertension and super-refractory status epilepticus. In this section, we will review the induction of TH, critical care management during TH, and rewarming.

Monitoring Temperature

Brain temperature Ideally TTM would be most effective when guided by brain temperature measurements, since the brain tissue is the primary site of action. Several studies have evaluated different intracranial temperature monitoring methods including epidural, subdural, intraventricular, and brain parenchymal temperature probes. Intracranial temperature measurements also vary depending on the site of measurement. Mellergard and Nordstrom demonstrated that temperature measured in the epidural space is always lower than in the lateral ventricle by a gradient of 0.4–1.0°C [92]. Moreover, Hirashima et al. measured brain temperatures at multiple depths in 20 patients with hydrocephalus and found that the temperature increased closer to the ventricle and found a strong correlation between the depth and brain temperature [93]. Given that the primary site of action of TH is the brain parenchymal tissue, in general, brain parenchymal temperature measurements (e.g., by using brain tissue oxygen (Licox) probes) are considered the gold standard. However, intraparenchymal temperature measurement is invasive, carrying the risk of intraparenchymal hemorrhage and infection, and thus surrogate measurements using core temperature are generally used in clinical practice.

Core body temperature In general, peripheral temperature measurements (e.g., axillary temperature) are inaccurate, often underestimate body temperature in the setting of TH given peripheral vasoconstriction, and are not recommended for TH purposes. Core body temperature measurement is considered more accurate and is recommended. The gold standard for measuring core body temperature is the pulmonary arterial (PA) catheter temperature probe [94]. However, this is invasive, associated with great risk, and not common clinical practice. Esophageal, deep rectal, and bladder temperature measurements using a thermistor probe are less invasive methods of monitoring core body temperature [95]. Of these, bladder and esophageal temperature probes are the most accurate, with strong correlations with PA temperatures [94], and are preferred for continuous temperature measurement during TH. Although deep rectal

Table 5.2 Difference between core body and brain temperature measurements

Core body temperature measurement	Difference from brain temperature (BT) measurements
Pulmonary artery temperature	BT is 0.3 ± 0.3°C higher
Bladder temperature	BT 0.5–2.5°C higher
Rectal temperature	BT 0.3–2.0°C higher
Esophageal temperature	Not studied

thermistor probes also measure the core temperature, these measurements are less consistent, have poor correlation with PA temperatures [94], and are not recommended for the purpose of TH. In fact, the NCS recommends using the esophageal probe preferentially and, if unavailable, using a bladder temperature probe [96].

The difference between core body temperature and brain temperature measurements also needs to be considered. In general, albeit limited, observational studies have demonstrated that brain temperatures are higher than core body temperatures. When studied in cardiac arrest patients, the mean brain temperature was noted to be 0.34°C higher than core body temperature and in 7% patients was >1°C higher [97]. The median differences between these measurements are summarized in Table 5.2 [98].

Induction of TH

This phase involves rapid cooling to a set target temperature using temperature modulation devices. As described above, peripheral temperature monitoring devices are considered inaccurate, and it is recommended to use core temperature monitoring while inducing and maintaining TH [96, 97]. In post-cardiac arrest comatose survivors, while the AHA recommends a fixed target temperature anywhere between 32 and 36°C, the 2017 AAN guidelines recommend 32–34°C in patients with initial VF/VT rhythm [10] and 36°C in patients with initial asystole/PEA arrest [10].

Once the target temperature is established, the next phase of care involves deciding the method of cooling. Several advanced temperature modulation devices with the ability to regulate temperature tightly within ±0.2°C have made TH/TTM more convenient [99]. However, many centers may not possess advanced devices, and TH should not be delayed due to this. Conventional cooling with the application of ice packs and/or infusion of 30–40 ml/kg of cold intravenous fluids (normal saline or lactated ringer's solution cooled to 4°C) over an hour are the most ubiquitous, simplest, and most cost-effective methods of inducing TH [45]. In fact, cold intravenous fluids, when used in conjunction with advanced devices, can drop the core temperature by 4°C/hour [45]. However, this effect can be mitigated by shivering, and thus shivering control techniques must be instituted prior to infusing cold fluids. Caution must be practiced in patients with congestive heart failure due to risk of acute pulmonary edema [99].

All advanced devices decrease core body temperature by promoting conductive heat loss [99] using surface (non-invasive or external) or endovascular (invasive or internal) cooling techniques. Surface cooling devices (e.g., the Arctic Sun temperature management system) include pads that are applied to the skin and contain circulating cold air or fluid [100]. Internal cooling devices include endovascular heat exchange catheters that are placed in a central vein and cool the blood as it flows around the catheter [99]. Intranasal and esophageal cooling devices are also available but with limited literature to support their use. All the advanced systems modulate temperature using feedback from continuously monitored esophageal, bladder, or rectal core temperatures, and strictly maintain the core temperature within ±0.2–0.5°C of the set target temperature. Hoedemaekers et al. [101] randomized 50 intensive care unit patients with indications for mild to moderate TH to receive TH with either conventional methods (such as ice packs, cold intravenous fluid infusions, fans, cooling blankets) or advanced cooling techniques (such as air- or water-circulating blankets, endovascular cooling devices). Patients in the advanced techniques group achieved the target temperature more rapidly and the temperature was maintained for a much longer duration than with conventional methods. In another randomized trial [102], 45 cardiac arrest survivors were randomized to receive TH either using internal cooling methods or external cooling methods. While patients who received internal cooling had tighter temperature control, there was no significant difference in mortality and functional outcomes. Regardless, the NCS recommends using surface or endovascular cooling devices and/or cold intravenous fluid infusions over conventional methods such as cooling blankets, fans, and ice packs [96].

Maintenance of TH

The next phase of care involves maintaining TH and management of the critical care issues and complications associated with ongoing hypothermia. With the advent of new technologies, maintaining the set target temperature is straightforward. External and internal cooling devices can maintain the target temperature to within ±0.2–0.5°C. The NCS recommends continuous monitoring of core temperature, preferably with an esophageal probe, during the maintenance period [96]. The use of the Bedside Shivering Assessment Scale (BSAS) and aggressively controlling shivering is also recommended by the NCS. And the NCS mandates continuous cardiac monitoring in all TH patients [96]. Overall, the primary

focus of care during this phase is to detect and manage adverse effects associated with induced hypothermia. This will be addressed in the subsequent sections.

Rewarming

Rewarming is the most critical phase of induced hypothermia. Uncontrolled rapid rewarming can reverse all the beneficial impacts of TH and lead to worsening of cerebral edema, mass effect, and intracranial hypertension. Rapid rewarming leads to systemic vasodilation, arterial hypotension, and consequently a reduction in CBF. This triggers autoregulatory cerebral vasodilation, resulting in elevated ICP and cerebral edema. Thus, active controlled rewarming is preferred over passive rewarming. In patients with intracranial hypertension or cerebral edema, rewarming should be performed at a rate of no more than 0.1°C per hour [99]. In patients with no concern for raised ICP or cerebral edema, rewarming may be pursued at a faster rate, up to 0.5°C per hour [99]. In most cases, however, controlled rewarming at 0.25°C per hour and avoidance of hyperthermia is considered appropriate [103].

Adverse Effects of TH

The most important aspect in the critical care management of TH patients is the detection, prevention, and management of adverse effects and complications associated with induced hypothermia.

1. *Shivering*:
   Shivering is the most common adverse effect associated with TH and leads to slower rates of achieving target temperatures and increased oxygen and metabolic demand leading to cerebral hypoxia and worsening of secondary brain injury. In physiologic situations, shivering, a thermoregulatory response to maintain core temperature at the hypothalamic setpoint, sets in at temperatures below 35.5°C [104]. This threshold shifts to a higher temperature in patients with brain injury [84]. The first step in controlling shivering is a quantitative method to detect shivering. The NCS recommends the use of the BSAS, a 4-point, easy-to-use, validated scale with good inter-rater reliability [96].

   In general, therapy for shivering should focus on suppressing the central thermoregulatory reflex, as the use of paralytics alone to halt shivering does not minimize the systemic and central stress response. The first step involves the use of non-sedating techniques such as acetaminophen, buspirone, and magnesium infusions. Counter skin-rewarming does not affect the core body temperature and increases the sense of warmth, thus reducing shivering. Intravascular cooling techniques, in general, are associated with lower incidence of shivering. If shivering persists despite the above measures, dexmedetomidine, a central alpha 2 agonist, may be infused as it lowers the shivering threshold. Opioids such as meperidine and fentanyl and sedatives such as propofol can control shivering but are associated with prolonged duration of mechanical ventilation and should be used only after other therapies have failed. Finally, if antipyretics, sedation, and skin counter-warming do not control shivering, then paralytic infusions such as vecuronium may be used [45].
2. *Electrolyte and acid-base derangements*:
   Hypothermia leads to fluid and electrolyte shifts. Lowering the core temperature causes intracellular and extravascular migration of potassium, magnesium, and phosphate ions. This leads to hypokalemia, hypomagnesemia, and hypophosphatemia. Mirzoyev et al. [105] showed that inducing TH to 33°C was associated with a potassium nadir of 3.2 +/− 0.7 mmol/L at 10 hours after induction. Levels below 3.0 mmol/L are associated with premature ventricular contractions and arrhythmias [105]. However, during rewarming, electrolytes (particularly potassium) migrate back into the extracellular space. Over-correction of potassium during hypothermia may lead to hyperkalemia and arrhythmias in the rewarming phase. Thus, the NCS recommends monitoring electrolytes and maintaining potassium between 3.0 and 3.5 mmol/L during the TH phase [96].

   With the induction of hypothermia, carbon dioxide becomes more soluble and PCO_2 levels decrease, leading to a rise in pH. Managing acid-base status during TH is controversial with limited data to guide management. In general, two methods are available and include alpha-stat management versus pH-stat management [96]. In alpha-stat, the arterial blood gas (ABG) results are interpreted at 37°C regardless of the actual core temperature. In the pH-stat method, ABG results are corrected for the patient's body temperature. Theoretically, normalizing pH using the pH-stat method may require hypoventilation and consequent hypercarbia, which may lead to elevation in the ICP; however, this has not been studied extensively. The NCS recommends using any one of the above methods consistently to interpret ABG results during TH.
3. *Infections and impaired immunity*:
   Theoretically, induced hypothermia results in the impairment of leukocyte phagocytic function and leads to an immunosuppressed state. In addition, TH reduces the production of cytokines and inflammatory mediators, thus further suppressing immunity and increasing the occurrence of bacterial infections such as pneumonia [99].

   Retrospective studies have found a higher incidence of pneumonia in patients receiving TH versus normothermia (19% versus 6%) [106]. The duration of TH may also

influence the occurrence of infections as shown by a study that found that 50% of patients who received TH longer than 7 days developed nosocomial pneumonia [106]. Larger prospective studies, although not powered to detect the incidence of infections, found no difference in the incidence of pneumonia or other infections between normothermia and hypothermia groups [96]. In addition, detection of infections may be difficult in patients receiving TH due to lack of a fever. Some suggest that the water temperature in the cooling device may help detect an ongoing febrile response to an underlying infection. It is thought that the patient may be mounting a fever if the water temperature is lower by >10°C compared to the patient's core temperature [99]. However, there are no studies to support this practice. Moreover, the standard serum markers of infections such as C-reactive protein and procalcitonin among others are unaffected by TH and will rise in the setting of infection. The NCS recommends using standard practices while looking for infections in patients receiving TH and does not recommend hypervigilance or prophylactic antibiotics [96].

4. *Cardiac dysfunction*:
Induced hypothermia to temperatures below 35°C leads to sinus bradycardia and reduced myocardial contractility. Cardiac output may decrease by 25% [106] and arterial hypotension may ensue. However, temperatures as low as 33°C are well tolerated. Below 32°C severe cardiac arrhythmias may occur including atrial and ventricular tachycardia and fibrillation [107]. An increase in the need for vasopressors and inotropes as well as elevated lactate levels has been noted even with mild TH but does not appear to impact outcomes [107]. Usually, 33°C is considered a safe lower limit. The NCS recommends continuous cardiac monitoring while patients are receiving TH.
5. *Coagulation abnormalities*:
Theoretically, induced hypothermia may lead to platelet dysfunction, increased fibrinolysis, and decreased activity of the coagulation cascade, leading to increased risk of bleeding during hypothermia. Mild laboratory derangements in coagulation and platelet function have been noted with mild TH; however, trials have not shown an increased risk of intracranial or systemic hemorrhage with TH [108]. The NCS does not recommend routine monitoring of the coagulation profile and platelet function or any measures, beyond standard care, to prevent hemorrhage or thrombosis in patients receiving TH [96].
6. *Insulin resistance*:
TH reduces the release of insulin from the pancreas and also increases insulin resistance, leading to hyperglycemia [106]. Poor glycemic control in patients with brain injury and intracranial hemorrhage is associated with worsening cerebral edema, and, in general, critically ill patients with hyperglycemia have increased morbidity and mortality. Thus, monitoring blood glucose and maintaining blood sugars between 140 and 180 mg/dl is recommended. Short-acting insulin or insulin infusions may be preferable as during the rewarming phase insulin resistance may resolve, reducing the insulin requirement and leading to hypoglycemia if the patient is receiving high doses of long-acting insulin [109].
7. *Kidney function, pharmacodynamics/kinetics*:
Induced hypothermia leads to peripheral vasoconstriction diverting blood flow to the kidneys (and other organs). This leads to tubular dysfunction and impaired reabsorption of solutes from the ascending loop of Henle. Moreover, increased central venous pressure leads to the release of atrial natriuretic peptide and a decrease in antidiuretic hormone levels. All these changes lead to a phenomenon known as "cold diuresis," resulting in excessive urine output, dehydration, arterial hypotension, and loss of electrolytes, making fluid and electrolyte management challenging in patients receiving TH. In addition, arterial hypotension may lead to cerebral hypoperfusion, consequent cerebral vasodilation, and elevation in ICP. Thus, hemodynamic monitoring and appropriate correction of hypovolemia are necessary [106].

   TH also has an unmeasurable influence on pharmacokinetics of several commonly used medications. TH decreases the activity of cytochrome P450 enzymes, thus resulting in decreased clearance of sedatives such as benzodiazepines, propofol, opioids (including fentanyl), calcium channel blockers, and paralytics among others. This may lead to a sustained effect of sedatives and prolonged iatrogenic impairment in the neurologic examination. The NCS recommends that this effect be kept in mind while interpreting the neurologic examination and prognosticating after cardiac arrest [96].
8. *Skin changes*:
Erythema, mottling of the skin, severe desquamation, and ischemic injury may occur in patients being cooled with surface cooling devices. This effect is particularly more prominent in patients with shock, those receiving vasopressors, and patients with left ventricular failure due to significant peripheral vasoconstriction and low perfusion [110]. The NCS recommends increased vigilance for skin changes and breakdown especially in patients receiving surface cooling and on vasopressors or with left ventricular heart failure [96].

Conclusion

Induction of hypothermia to prevent brain injury has been used in clinical practice for several decades. TH/TTM predominantly prevents secondary brain injury by multiple

mechanisms including reducing cerebral metabolism, blocking inflammatory cascades, stabilizing the BBB, decreasing cerebral edema, and controlling ICP. Despite significant theoretical benefits noted in experimental models, multiple attempts at reproducing those benefits in brain-injured humans have failed. Currently, TH is primarily indicated in comatose post-cardiac arrest survivors. Both the AHA and AAN recommend early and prompt initiation of TH/TTM after cardiac arrest. The 2015 AHA guidelines make a class 1 recommendation to cool to a fixed target temperature anywhere between 32 and 36°C for a duration of 24 hours regardless of the initial rhythm. On the other hand, the 2017 AAN guidelines continue to make a class A recommendation to cool to 32–34°C in patients with initial VF/VT arrest given two Class 1 studies, while they recommend TTM to 36°C for 24 hours followed by controlled rewarming and fever prevention for 72 hours in patients who presented with asystole/PEA arrest [10].

The use of TH in other neurologic diseases remains controversial. There is some retrospective contradicting evidence supporting the use of TH in patients with refractory intracranial hypertension and super-refractory status epilepticus. Better clinical trials are needed in patients with TBI, SAH, ICH, and AIS before TH may be applied in these populations. Regardless, aggressive fever treatment during the early stages of all of the above critical neurologic illnesses may be associated with reduction in secondary neurologic injury and better functional outcomes and should be practiced. However, prophylactic controlled normothermia for fever prevention in neurocritical care illnesses needs further prospective validation.

Induction of TH after cardiac arrest should be prompt and may be performed using conventional methods such as ice packs and cold saline infusions en route to advanced centers. Maintenance of TH is rather simplified with modern cooling devices, which can perform strict temperature control within ±0.2–0.5°C. Critical care management of patients receiving TH includes detection, prevention, and management of common complications such as shivering, cardiac depression, infections, cold diuresis, electrolyte derangements, acid-base abnormalities, hyperglycemia, coagulopathies, and skin changes. Rewarming is as critical as induction of TH and should be performed in an active controlled manner rather than rapidly or passively, keeping in mind the risk for worsening cerebral edema and elevated ICP.

Finally, TH impairs clearance of analgesics and sedatives in an unmeasurable manner and may prolong their effect on the neurological status of the patient. Moreover, there is limited data on appropriate timing for neurologic prognostication in patients who have received TH. These factors must be accounted for when providing important prognostic information to distressed family members in order to avoid a self-fulfilling prophecy. Current practice is to defer attempting neurologic prognostication until >72 hours after rewarming is completed.

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Pharmacological Challenges in Neurocritical Care

6

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Introduction

Pharmacokinetics (PK), the process by which medications are absorbed, distributed, metabolized, and eliminated by the body, dictates appropriate drug selection and dosing as well as subsequent monitoring [1]. Critically ill patients including neurocritical care patients often have altered absorption, metabolism, distribution, and elimination of drugs for a variety of reasons that will be described in this chapter. In addition, interventions such as renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO), and plasma exchange (PLEX) can further complicate the medical management of these patients. Finally, the incidence of obesity is increasing in the United States; PK changes with increased body mass presents challenges with respect to the optimal dose of pharmacological agents to use in critical illness. This chapter will provide guidance on PK changes observed in such cases and dosing principles as well as specific examples when applicable.

Principles of Pharmacokinetic Changes in Adult Critically Ill Patients

Absorption, Distribution, Metabolism, Elimination (ADME)

Alterations in normal physiological processes (such as pH, blood flow, surface area, and gastrointestinal motility) and the physical properties of medications (such as size, solubility, and lipophilicity) can affect the rate and extent of absorption of medications in the intensive care unit [2]. Gastrointestinal absorption is often decreased by reduced blood flow and tissue perfusion in shock states, intestinal atrophy due to interrupted enteral nutrition, dysmotility induced by opiates and barbiturates, and medication-enteral nutrition interactions [3]. Intravenous (IV) administration of medications, when possible, is therefore preferred in patients with unreliable absorption.

Changes in serum pH, frequently seen in shock states as well as respiratory and renal failure, affect the ionized state of many drugs. This in turn impacts their penetration across lipophilic-based membranes such as the blood-brain barrier and overall distribution [2]. Fluid shifts and third-spacing induced by increased vascular permeability and low oncotic pressure can lead to increased volume of distribution of hydrophilic medications [4]. In addition, hypoalbuminemia in critically ill patients increases the unbound (free) fraction of highly albumin-bound medications such as phenytoin and diazepam, which can result in drug toxicity and adverse reactions [5].

Although drugs are commonly metabolized to more water-soluble and less active compounds, some drug metabolites are equally or more active than the parent drug. Prodrugs such as fosphenytoin and clopidogrel are metabolized into their pharmacologically active forms. Metabolism for most drugs occurs primarily in the liver. This hepatic metabolism depends on hepatic blood flow, enzyme activity, and protein binding [2]. Alterations in hepatic blood flow, as seen in shock states, can affect drug metabolism particularly for medications with a high hepatic extraction ratio such as midazolam [6]. Hepatic extraction ratio refers to the fraction of the drug entering the liver and irreversibly removed. Hepatic enzymes can be induced or inhibited by a variety of pathophysiological processes. For instance, Cytochrome P 450 (CYP450) isoenzymes are inhibited during the acute phase of critical illness [7]. On the other hand, drug metabolism is enhanced in other critically conditions

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such as traumatic brain injury (TBI). Specifically, pentobarbital and phenytoin metabolism increases over a period of several days early after TBI, resulting in sub-therapeutic concentrations [8–10].

Regardless of the route of administration, renal elimination of parent drugs or metabolites is the primary excretory pathway for most drugs. This is particularly important in critically ill patients with renal dysfunction and for drugs whose active metabolites are cleared renally. Dosing recommendations for patients with renal dysfunction are available from different resources. For patients on renal replacement therapy, the type (intermittent versus continuous) and the frequency and duration of dialysis should also be considered [11].

Renal Replacement Therapy (RRT)

The removal of drugs by various modes of RRT is dependent on a combination of drug-related and RRT-related factors. The renal route of elimination, low protein binding, and low volume of distribution are important drug-related factors that impact the degree of drug removal by dialysis [12]. In addition, medications with a narrow therapeutic index such as aminoglycosides require more rigorous adjustments and therapeutic drug monitoring compared to medications with a wide therapeutic index [13]. RRT-related factors to consider include blood flow, dialysate flow and ultrafiltration rates, replacement solution flow rate, and the type of RRT membrane [12, 14]. For example, membranes used in high-flux hemodialysis have large pore sizes that allow removal of large molecules such as vancomycin that otherwise cannot be removed by conventional hemodialysis [15]. Given many factors impact drug removal in RRT, one must consider the severity of the disease, drug levels if applicable, and other patient-related individual factors to provide optimal dose adjustments. This chapter provides guidance on appropriate dosing in RRT for selected medications.

Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) can alter the PK and pharmacodynamics (PD) of drugs in a number of ways [16]. ECMO circuits can sequester drugs given the large surface area of the tubing and membranes, which can increase the volume of distribution of selected drugs [17]. In addition, the circuit may become saturated over time, which can result in increased serum drug levels as no more drug can become sequestered. Importantly, after the discontinuation of drug therapy the ECMO circuit may continue to release the drug into the circulation, resulting in unpredictable effects [16]. Lipophilic and highly protein-bound drugs such as propofol and midazolam are particularly susceptible to such alterations, but other factors such as molecular weight and ionization may also play a role in this process [18, 19]. In addition, ECMO is usually associated with reduced drug clearance as a result of alterations of end-organ perfusion and is often combined with some form of RRT, which complicates estimation of drug elimination even further. This chapter includes important drug-specific PK changes in ECMO in each section.

Plasmapheresis

In the neurocritical care unit, plasmapheresis is often utilized to manage neuro-autoimmune disorders such as Guillain-Barré syndrome and myasthenia gravis. Currently drug dosing guidance in plasmapheresis, or plasma exchange (PLEX), is limited to case reports. Unlike RRT, PLEX removes whole plasma, which includes both the free fraction and the protein-bound portion of a drug. The volume of distribution is therefore the most important drug factor to consider when estimating drug removal by PLEX. In general, drugs with low volumes of distribution such as valproic acid are removed to a greater extent than those with a large volume of distribution such as phenytoin [20, 21]. Other factors that affect drug dosing in PLEX include the duration and frequency of PLEX, exchange volume, and rate of intercompartmental equilibration.

Obesity

Significant variations in PD and PK responses can occur in obesity (body mass index (BMI) > 30 kg/m^2). Without clear evidence to guide medication dosing in obesity, understanding how body composition influences PK and PD can be helpful in estimating the optimal dose [22, 23]. In general, absorption is not affected by obesity [23]. For lipophilic drugs such as phenytoin, the volume of distribution can be significantly increased in obesity leading to delayed onset and prolonged half-life [24]. Liver metabolism is variably affected in these patients; for example, CYP 2C9 is induced but CYP 3A4 is inhibited. These changes are not reported to be significant enough to warrant dose adjustments [25]. It appears that clearance correlates to lean rather than adipose weight as adipose

tissue has little metabolic activity [26]. In obese patients, the excess adipose weight is often accompanied by about 20–40% increase in lean body mass [22]. When lean body mass rises, an increase in drug clearance occurs and a dose increase may be required [26]. Some evidence suggests correlation of fentanyl and propofol clearance with lean body weight [27]. In addition, renally cleared drugs may have lower plasma concentrations in obese patients due to increased glomerular filtration and kidney mass in these patients [28].

Therapeutic Classes

Anti-seizure Drugs

Many anticonvulsants are used in the neurocritical care unit for emergent and urgent treatment of status epilepticus (SE) [29]. Most institutions have specific SE algorithms that guide clinicians in selecting the optimal drugs and the order in which each agent should be given. Benzodiazepines are first-line therapy for emergent treatment of SE. Fosphenytoin/phenytoin, valproate, and continuous infusion midazolam can be given next for urgent treatment of SE [29]. Individual patient factors should always be taken into account when treating critically ill patients. Table 6.1 reviews usual doses as well as dosing in obesity and RRT of commonly used anticonvulsants in SE.

Limited data exist regarding anti-seizure medication dosing in ECMO. As a general rule, therapeutic drug monitoring (TDM) should be performed when possible. If TDM is not an option, titrating medications to seizure suppression should be done. If this is not achieved despite higher doses, alternative agents should be considered. Increasing maintenance doses of highly lipophilic or highly protein-bound medications such as propofol and midazolam is particularly important due to sequestration in the ECMO circuit [16, 18]. One study showed that only 13% of baseline midazolam was detectable after 24 h [40]. One case report suggested ECMO has little impact on the removal of levetiracetam, which has a low volume of distribution and low protein binding [41]. In cases where dose escalations are done, clinicians should anticipate the need for significant dose reductions at the time of ECMO discontinuation given the likely rapid decrease in the volume of distribution [42].

Anti-seizure medications with low volumes of distribution (<0.2 L/kg) such as valproic acid reside in the vascular compartment, and PLEX would be expected to remove a significant portion of the total body stores of the drug. On the other hand, for drugs with higher volumes of distribution such as propofol and phenytoin, PLEX therapy would not be expected to have as large of an impact. For example, multiple reports that describe PLEX in the setting of phenytoin overdose suggest that only about 2.5–10% of total body phenytoin is removed [20, 21].

Table 6.1 Dosing of commonly used anticonvulsants in neurocritical care [22, 30–39]

Agent	Adult usual dose	Recommended weight for dosing calculations	Maximum per dose	Dose in CRRT	Dose in iHD
Clobazam	LD: 10–30 gm PO MD: 5–30 gm PO q12 hr	NA	30 gm[a]	Not affected by CRRT	Not affected by iHD
Diazepam	LD: 0.15–0.2 gm/kg IV MD: NA	Actual or in obesity use IBW	10 gm	Not affected by CRRT	Not affected by iHD
Fosphenytoin	LD: 15–20 gm/kg IV MD: 4–6 gm/kg/day IV	Actual or in obesity (>125% IBW) use: Adjusted BW: [IBW + 1.33 (Actual BW – IBW)]	1500 gm	Variable[b]; should be done in conjunction with TDM	Variable; should be done in conjunction with TDM
Ketamine	LD: 1.5 gm/kg IV (may repeat up to *total* load of 4.5 gm/kg). MD: 0.3–7.5 gm/kg/hr; titrate to seizure suppression	LBW	150 gm	Not affected by CRRT	Not affected by iHD
Lacosamide	LD: 200–400 gm IV MD: Up to 600 gm/day IV or PO in two divided doses	NA	400 gm	200–600 gm/day	Up to 50% replacement dose after HD

(continued)

Table 6.1 (continued)

Agent	Adult usual dose	Recommended weight for dosing calculations	Maximum per dose	Dose in CRRT	Dose in iHD
Levetiracetam	LD: 20–60 gm/kg IV MD: Up to 4000 gm/day in two divided doses IV or PO	Actual No data in obesity	4500 gm	1000 gm IV q12h	50% removed; add 50% of AM dose to PM dose post iHD.
Lorazepam	LD: 4 gm IV; may repeat to three doses or 12 gm. MD: NA	Actual or in obesity use IBW	4 gm	Not affected by CRRT	Not affected by iHD
Midazolam	LD: 0.2 gm/kg IV up to 2 gm/kg MD: 0.05–2 gm/kg/hr IV	Actual or in obesity use IBW	20 gm	Active metabolite (1-hydroxy-midazolam glucuronide) not removed effectively by CRRT; consider dose reduction	Not affected by iHD
Phenobarbital	LD: 20 gm/kg IV, may repeat with an additional 5–10 gm/kg MD: 1–3 gm/kg day IV or PO (often divided in two doses)	Actual	1500 gm	Initial dosing regimen of 2–3 gm/kg/day may be considered (TDM is advised)	20–50% removed, may give full daily dose post HD (TDM is advised)
Pentobarbital	LD: 5–15 gm/kg IV MD: 0.5–10 gm/kg/hr IV	No data available in obesity	500 gm	Not effectively removed (case reports of pentobarbital removal in massive pentobarbital toxicity by CRRT)	Not effectively removed
Phenytoin	LD: 15–20 gm/kg IV MD: 4–6 gm/kg/day IV or PO	Actual or in obesity (>125% IBW) use: Adjusted BW: [IBW + 1.33 (Actual BW – IBW)]	1500 gm	Variable[b]; should be done in conjunction with TDM	Variable[b]; should be done in conjunction with TDM
Propofol	LD: 1–2 gm/kg (Max 10 gm/kg) IV MD: 20–250 mcg/kg/min IV	Actual or in obesity use: LBW for load and actual body weight for maintenance	200 gm	Not affected by CRRT	Not affected by iHD
Valproate	LD: 20–40 gm/kg IV MD: 5–15 gm/kg/day IV or PO	Actual or in obesity use IBW	3000 gm	Variable[c]; should be done in conjunction with TDM	Variable[c]; should be done in conjunction with TDM

IBW ideal body weight, *LBW* lean body weight, *CRRT* continuous renal replacement therapy, *iHD* intermittent hemodialysis, *TDM* therapeutic drug monitoring, *LD* loading dose, *MD* maintenance dose

[a]In case reports, single doses of up to 60–70 gm are given in refractory status epilepticus

[b]In critically ill patients with hypoalbuminemia receiving RRT, monitoring of free phenytoin (1–2 μg/mL) levels should guide future dosing

[c]Existing case reports have described the possibility of valproic acid removal in patients on RRT even when concentrations are not supratherapeutic

Oral Antiplatelets

Antiplatelet agents are commonly used in neurocritical care, and their use has continued to increase over the preceding decade [43]. For example, oral antiplatelets are commonly used in primary and secondary ischemic stroke prevention. More recently, with the growing use of neuro-endovascular stents, coil embolization, and flow diverters, oral antiplatelets are used for the prevention of intra- and post-procedural thrombosis. Specific dosing recommendations for these agents are listed in Table 6.2.

PD data suggests a higher platelet reactivity (HPR) and suboptimal platelet response to antiplatelet drug therapy in obese patients [45]. In fact, increased body weight has been reported to be an independent predictor of impaired clopidogrel response due to HPR [46, 47]. Prasugrel, despite more potent PD effects, has not been shown to have sustained antiplatelet activity during maintenance dosing when compared to high-dose clopidogrel in obese patients (BMI $\geq$ 30 kg/m^2) [48]. Ticagrelor appears to have less variable effects in obese patients [45]. Studies assessing the clinical impact of antiplatelet therapies in obese patients are needed. Aspirin may be prone to elimination effects of PLEX due to its high affinity for plasma proteins. As such, replacement doses or divided doses may be preferred when used in the setting of PLEX [20].

Systemic and Oral Anticoagulation

Anticoagulants may be used in the neurocritical care setting for a variety of reasons. Given the risk of bleeding, particularly intracranial bleeding, with these agents, PK/PD changes in each patient should be considered, and dose adjustment and TDM are necessary when applicable.

Similar to antiplatelet drug therapies, dose modifications of anticoagulant drug therapies may be necessary in the setting of renal impairment or obesity. For example, while patients with a high body mass index (BMI ≥ 40 kg/gm^2) may require higher than standard dosing of enoxaparin for venous thromboembolism (VTE) prophylaxis (40 gm every 12 h), a dose reduction of enoxaparin from 1 or 1.5 gm/kg to 0.7–0.8 gm/kg total body weight (TBW) every 12 h may be considered for VTE treatment in patients with BMI ≥ 40 kg/gm^2 [49]. Safety assessments of target-specific oral anticoagulants (TSOACs) in obese patients in the setting of VTE treatment or stroke prevention in atrial fibrillation are limited as the majority of data did not include a safety analysis with weight considerations [50]. As such, recommendations for the dosing of TSOACs in obese patients and patients with renal impairment are based on small studies and expert opinion.

The International Society on Thrombosis and Haemostasis (ISTH) and other reviews have aimed to provide general guidance for dosing considerations of TSOACs in the setting of obesity and renal impairment [50, 51]. Rivaroxaban should generally be avoided in patients with BMI > 40 kg/m^2 or weight > 120 kg due to lack of clinical data in this population [50]. In a phase 1 study, patients with body weight ≥ 120 kg on apixaban had a 30% lower maximum concentration (Cmax) and 20% lower area under the curve (AUC) [52]. However, since variation in weights led to slight changes in plasma concentrations, a fixed dosing approach was recommended. Guidelines suggest that the use of edoxaban should be avoided in patients with a BMI > 40 kg/m^2 or weight > 120 kg [50]. Measuring peak and trough anti-Xa levels are highly recommended when dosing edoxaban in obese patients; and in the event that anti-Xa levels are outside of recommended ranges, guidelines suggest transitioning to a vitamin K antagonist in lieu of edoxaban dose adjustment [50]. Similarly, the current body of literature evaluating the use of dabigatran has only included a few patients with the body weight of >100 kg or a BMI of >30 kg/m^2, and there are no clinical outcome data of dabigatran in this setting [53].

Patients undergoing ECMO are exposed to coagulopathies due to activation of the coagulation and immune systems by the extracorporeal circuit, and thus therapeutic anticoagulation is commonly performed [54]. Unfractionated heparin remains a preferred anticoagulant in this setting due to its desirable PK profile with ease of monitoring. If an alternate continuous infusion anticoagulant such as argatroban is warranted (in the setting of heparin-induced thrombocytopenia, for example), dose modification is recommended with appropriate therapeutic drug monitoring (e.g., activated partial thromboplastin time (aPTT)) (Table 6.3) [54].

Antimicrobials

Bacterial meningitis is a devastating inflammatory disease of the meninges with 1.2 million cases identified worldwide annually [55]. Recommended empiric therapy for bacterial meningitis consists of a third-generation cephalosporin (ceftriaxone or ceftazidime) or cefepime in combination with vancomycin [56]. Ampicillin is often used in the treatment of meningitis secondary to Listeria infection [56]. High-dose IV

Table 6.2 Dosing of commonly used oral antiplatelets in neurocritical care [30, 44]

Agent	Usual dose	Recommended weight for dosing calculations	Maximum per dose	Dose in CRRT	Dose in iHD
Aspirin (PO/PR)	LD: 325 gm MD: 81–325 gm daily	Actual body weight	325 gm	No dose adjustments recommended	Not affected by iHD
Aspirin/ Dipyridamole (PO)	25/200 gm q12 hr	Actual body weight	25/200 gm	No dose adjustments recommended; avoid use if eGFR < 10 mL/min	Not affected by iHD
Clopidogrel (PO)	LD: 600 gm MD: 75 gm daily	Actual body weight	600 gm	[a]No dose adjustments recommended	Not affected by iHD
Prasugrel (PO)	LD: 60 gm MD: 5–10 gm daily	Actual body weight	60 gm	No dose adjustments recommended	Not affected by iHD
Ticagrelor (PO)	LD: 180 gm MD: 90 gm BID	Actual body weight	180 gm	No dose adjustments recommended	Not affected by iHD

LD loading dose, *MD* maintenance dose, *PO* oral, *PR* rectally

[a]End stage renal disease or an eGFR <15 mL/min is associated with higher residual platelet reactivity with maintenance dosing

acyclovir is the drug of choice for the treatment of viral (e.g., herpes simplex virus) encephalitis. Fungal meningitis treatment options are also discussed in this section, and these infections can occur in immunocompromised hosts. Finally, many antimicrobials may be used in neurocritical care for surgical prophylaxis indications.

Due to the lack of extensive data regarding ampicillin dosing in obese patients, providers should consider using the upper limit of normal dosing in the treatment of Listeria meningitis. Cephalosporins are highly protein-bound and hydrophilic drugs. These characteristics hinder penetration of these agents into adipose tissues, which may in turn affect these agents' efficacy in the treatment of skin and soft tissue infections and surgical prophylaxis. Increased drug exposure can be achieved by using higher doses, increasing dosing frequency, or using extended/continuous infusions. Vancomycin doses do not show linear correlation with body weight. Obese patients with BMI $\geq$ 40 kg/m^2 typically require lower weight–based daily dosing to attain targeted trough levels [57–60]. To achieve more accurate dosing, the use of software capable of performing Bayesian analysis might be beneficial. This will require two point measurements, peak and trough levels, for accurate AUC estimates [57].

There is limited data regarding antimicrobial dosing in patients on ECMO. Most beta-lactams, such as ampicillin, ceftriaxone, and ceftazidime, are hydrophilic and have variable protein binding with potential for sequestration [61]. For these agents, it is crucial to ensure optimal duration of adequate concentration above the minimum inhibitory concentrations. An ex vivo study demonstrated a 20% loss of ceftriaxone dose due to in-circuit sequestration and similarly a 15–71% loss of ampicillin dose due to this sequestration [62]. This primarily depends on the type of circuit priming fluids [63]. Current data does not show that ECMO affects vancomycin PK properties, and altering vancomycin dosing is most likely not necessary [64] but TDM is highly recommended. A larger loading dose might be required to achieve adequate levels for azole antifungals such fluconazole and voriconazole. Voriconazole is highly lipophilic and has shown 71% loss of dose in ex vivo studies of ECMO circuits [61]. Voriconazole levels should be monitored, and dose reduction is warranted once circuit saturation occurs [65].

Ceftriaxone and ceftazidime have low volumes of distribution and therefore can be cleared by PLEX. It is recommended to administer ceftriaxone either immediately post-PLEX or 15 h before PLEX and ceftazidime 2 h before plasmapheresis [66, 67]. Vancomycin is minimally removed

Table 6.3 Dosing of commonly used anticoagulants in neurocritical care [30]

Agent	Usual dose	Recommended weight for dosing calculations	Maximum per dose	Dose in CRRT	Dose in iHD
Apixaban (PO)	VTE: 10 gm BID × 7 days, then 5 gm BID nVAF: 5 gm BID	Actual body weight	10 gm	Limited data; not recommended	Limited data; 2.5 gm BID may be considered. Warfarin is the preferred agent
Argatroban (IV)	Titrated to aPTT	Actual body weight	None	Titrated to aPTT	Titrated to aPTT
Bivalirudin (IV)	Titrated to aPTT	Actual body weight	None	Titrated to aPTT	Titrated to aPTT
Dabigatran (PO)	150 gm BID	Actual body weight	150 gm	Not recommended	Not recommended. Warfarin is the preferred agent
Edoxaban (PO)	60 gm daily	Actual body weight	60 gm	Not recommended	Not recommended. Warfarin is the preferred agent
Enoxaparin (SQ)	1 gm/kg q12 hr or 1.5 gm/kg daily	Actual body weight Dose reduction (0.7–0.8 gm/kg) may be considered in obese patients	Fixed upper dose limit not recommended; anti-Xa monitoring recommended	Not recommended	Not recommended
Fondaparinux (SQ)	5–10 gm once daily (dependent on weight)	Actual body weight	10 gm	Not recommended	A reduced dose and increased dosing interval may be considered (anti-Xa monitoring recommended)
Rivaroxaban (PO)	VTE: 15 gm BID × 21 days, then 20 gm daily nVAF: 20 gm daily	Actual body weight	20 gm	Not recommended	Not recommended. Warfarin is the preferred agent
Unfractionated Heparin (IV/SQ)	Titrated to aPTT or anti-Xa	Actual body weight	None	Titrated to aPTT or anti-Xa	Titrated to aPTT or anti-Xa
Warfarin	2.5–5 gm daily, titrated per INR	Actual body weight	Variable	No dose adjustments	Not dialyzable

VTE venous thromboembolism, *nVAF* nonvalvular atrial fibrillation, *aPTT* Activated partial thromboplastin time, *BID* twice daily, *INR* international normalization ratio, *PO* by mouth, *IV* intravenous

during plasmapheresis; hence dose adjustment is unnecessary [68–70]. Table 6.4 summarizes specific antimicrobial dose recommendations in this setting.

Sedation and Analgesia

Similar to other critically ill patients, pain should be addressed first in neurocritical care since untreated or undertreated pain often manifests as agitation. Opioids, which are the mainstay of acute pain management, may pose risks to patients with neurological disease particularly by masking the neurological exam [75]. It is therefore important to utilize opioids only after the objective assessment of pain is completed [76]. Non-benzodiazepine sedatives such as dexmedetomidine and propofol are recommended by the Society of Critical Care Medicine as first-line pharmacological treatments when continuous IV sedation is needed [76]. Although propofol's short half-life makes it an ideal sedative in neurocritical care patients because it permits frequent neurological assessments, its prolonged use can be associated with propofol-related infusion syndrome and is therefore not recommended [77]. Dexmedetomidine, a selective α_2-adrenergic agonist sedative, is not associated with respiratory depression and therefore can be used in non-intubated patients. Another advantage is its short duration of action. Its use may be limited by hypotension and bradycardia especially in patients who require augmentation of mean arterial pressure and cerebral blood flow [78]. Table 6.5 summarizes agents used for pain and sedation in the neurocritical care unit and considerations in obesity and RRT.

Achieving desired levels of sedation in critically ill patients including neurocritical care patients receiving ECMO is a challenge. At this point, limited data exist on the use of the most appropriate opioid or sedative in adult patients on ECMO. One study showed that only 3% of an initial fentanyl dose was detected at 24 h [40]. On the contrary, the ECMO circuit did not substantially alter concentrations of morphine with almost 103% recovery at 24 h.

Table 6.4 Summary of commonly used antimicrobials in neurocritical care [30, 71–74]

Agent	Usual dose	Recommended weight for dosing calculations	Maximum per dose	Dose in CRRT				Dose in iHD
				Loading dose for CRRT	CVVH	CVVHD	CVVHDF	
Ampicillin (IV)	2 g q4 hr	No data available	2 g	2 g	2 g q8 hr	2 g q8 hr	2 g q6 hr	2 g q12 hr
Ceftriaxone (IV)	2 g q12 hr	NA	2 g	2 g	2 g q12 hr	2 g q12 hr	2 g q12 hr	2 g q24 hr
Ceftazidime (IV)	2 g q8 hr	NA	2 g	2 g	2 g q12 hr	2 g q12 hr	2 g q12 hr	1 g q24 hr
Cefepime (IV)	2 g q8 hr	NA	2 g	2 g	2 g q12 hr	2 g q12 hr	2 g q12 hr	1 g q24 hr
Vancomycin (IV)	LD: 20–25 gm/kg TBW (maximum 2.5 g) MD[a]: 15 gm/kg q12 hr[b]	ABW	2.5 gm	15–25 gm/kg	15 gm/kg q24 hr	15 gm/kg q24 hr	10 gm/kg q12 hr	Load 15–25 gm/kg then 5–10 gm/kg after HD
Acyclovir (IV)	10 gm/kg every 8 hr	IBW or Adj BW	1250 gm	None	10 gm/kg q24 hr	10 gm/kg q12–24 hr	10 gm/kg q12–24 hr	5 gm/kg q24 hr
Amphotericin B liposomal (IV)	6 gm/kg	ABW or Adj BW	Not well defined	None	5 gm/kg q24 hr	5 gm/kg q24 hr	5 gm/kg q24 hr	5 gm/kg q24 hr
Fluconazole (IV, PO)	400 gm daily	ABW	12 gm/kg to maximum 1200 gm/day	800 gm q24 hr	400 gm q24 hr	800 gm q24 hr	800 gm q24 hr	200 gm q24 hr
Voriconazole[c]	Oral: 200 gm q12 hr IV: LD 6 gm/kg q12 hr for two doses followed by MD 4 gm/kg q12 hr	Oral: No dose adjustment IV: ABW or IBW	Adjust based on TDM	400 gm PO q12 hr for two doses	200 gm PO q12 hr	200 gm PO q12 hr	200 gm PO q12 hr	200 gm PO q12 hr

ABW actual body weight, *Adj BW* adjusted body weight, *CRRT* continuous renal replacement therapy, *CVVH* continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *CVVHDF* continuous venovenous hemodiafiltration, *IBW* ideal body weight, *iHD* intermittent hemodialysis, *TBW* total body weight, *IV* intravenous, *TDM* therapeutic drug monitoring

[a]Adjust maintenance dose based on TDM

[b]Consider q8h regimen based on renal function (e.g., CrCl > 100 mL/min) and age

[c]Oral therapy recommended over intravenous to prevent accumulation of cyclodextrin vehicle

It may be therefore more reasonable to use morphine if an opioid is needed for analgesia or sedation [40]. Although there is no data available on plasma concentrations of ketamine in ECMO patients, there is some evidence that when used as an adjunctive sedative, it may decrease concurrent sedative and/or opioid infusions without altering Richmond Agitation Sedation Scale (RASS) scores [88]. In cases where a benzodiazepine is used for sedation, lorazepam may be an optimal initial agent as sequestration of midazolam in the ECMO circuit leads to increased volume of distribution and lower plasma levels [89]. Propofol is not an ideal agent in such cases due to its high lipophilicity; in fact, about 98% of propofol was lost only after 40–120 min of infusion initiation in ECMO [90, 91]. Interestingly, one study reported that almost 93% of dexmedetomidine was lost at 24 h [92]. There is no data on the

Table 6.5 Opioids and sedative agents in neurocritical care [27, 30, 76–87]

Agent	Usual dose	Recommended weight for dosing calculations[a]	Maximum per dose	Dose in CRRT	Dose in iHD
Fentanyl	Bolus: 0.35–0.5 mcg/kg IV Infusion: 0.7–10 mcg/kg/hr	Actual or in obesity use IBW or LBM	Variable per patient/formulation	Not affected by CRRT	Not affected by iHD
Hydromorphone	Bolus: 0.2–1 gm IV Infusion: 0.5–3 gm/hr IV	Actual or in obesity use IBW or LBM	Variable per patient/formulation	No data available	Plasma levels reduced to 40% of pre-dialysis levels (metabolites are not removed and risk for metabolite accumulation)
Ketamine	LD: 0.5–1 gm/kg IV Infusion: 0.1–0.5 IV gm/kg/hr	IBW	50 gm	Not affected by CRRT	Not affected by iHD
Morphine	Bolus: 2.5–5 gm IV infusion: 2–30 IV gm/hr	Actual or in obesity use IBW or LBW	Variable per patient/formulation	Morphine and metabolites can be removed ∗Drug and/or metabolites re-equilibrate between CNS and plasma∗ Use an alternative opioid	Morphine and metabolites can be removed ∗Drug and/or metabolites re-equilibrate between CNS and plasma∗ Use an alternative opioid
Methadone	Dose: 2.5–10 gm IV every 8–12 hr	Methadone displays high interpatient variability, unrelated to body weight	Variable per patient	Inactive metabolites, and not dialyzed. No dose adjustments necessary	Inactive metabolites, and not dialyzed. No dose adjustments necessary
Dexmedetomidine	LD: 1 mcg/kg IV (optional) MD: 0.2–1.5 IV mcg/kg/hr	Actual or in obesity use LBW	Variable per patient (no single dose reported in the literature)	Dose adjustment unlikely but no data exists	Dose adjustment unlikely but no data exists
Lorazepam	LD: 0.02–0.06 gm/kg IV MD: 0.01–0.1 gm/kg/hr IV	Actual or in obesity use IBW	Variable per patient	Not affected by CRRT	Not affected by iHD
Midazolam	LD: 0.01–0.05 IV gm/kg MD: 0.02–0.1 IV gm/kg/hr	Actual or in obesity use IBW	Variable per patient	Active metabolite (1-hydroxy-midazolam glucuronide) not removed effectively by CRRT, consider dose reduction	Not affected by iHD
Propofol	LD: 2.5–1 gm/kg IV MD: 5–50 mcg/kg/min IV	Actual or in obesity use lean body mass for load and actual body weight for maintenance	Variable per patient ∗titrate to effects∗ Use caution with doses over 80 mcg/kg/min for >48 hr	Not affected by CRRT	Not affected by iHD

IBW ideal body weight, *LBW* lean body weight, *CRRT* continuous renal replacement therapy, *iHD* intermittent hemodialysis, *CNS* central nervous system

[a]In all cases, titrate dose to effect

extent of opioid or sedative removal in PLEX. Given the high volumes of distribution of most agents in these therapeutic classes, it is expected that PLEX will not impact the clearance of these agents significantly.

Hyperosmolar Therapy

Hyperosmolar agents are commonly used in the neurocritical care unit for the treatment of intracranial hypertension and cerebral edema. Unlike mannitol, 23.4% saline must be administered via a central line due to its high osmolality and risk of extravasation and phlebitis if administered peripherally. Other concentrations of hypertonic saline may be used based on individual patient factors, and many can be administered peripherally. See the chapter entitled "Management of Elevated Intracranial Pressure" for more details. Medication-specific information is summarized in Table 6.6.

The extent of hypertonic saline removal by ECMO or PLEX is not described in the literature. Perhaps the extent of removal is dependent on how long the hypertonic saline has been infusing (if a continuous infusion is used) in relation to the initiation of PLEX or ECMO. Given that mannitol has a volume of distribution of ~34 L and is mostly confined to the extracellular space [30], its removal by PLEX generally is not significant. Currently there is no clinical data on how ECMO may impact mannitol removal.

Neuromuscular Blocking Agents

Neuromuscular blocking agents are most commonly used in neurocritical care for rapid sequence intubation and airway management; however, patients may receive these agents for other indications such as shivering prevention while on hypothermia protocols or management of intracranial hypertension [1]. Table 6.7 summarizes commonly used agents in this class and drug-specific dosing and PK parameters.

Table 6.6 Hyperosmolar agents utilized in neurocritical care [30, 93, 94]

Agent	Usual dose	Recommended weight for dosing calculations	Maximum per dose	Dose in CRRT[a]	Dose in iHD[a,b]
Hypertonic saline 23.4%	23.4% NaCl: 0.3 mL/kg (30–60 mL)	Actual (no data available in obesity[c])	23.4% NaCl (60 mL)	Dialyzed	Dialyzed
Mannitol 25%	0.25–1 g/kg/dose	Actual In obesity consider lower dose (0.25–0.5 g/kg)[d]	150 g	Dialyzed	Dialyzed

[a]The dialysate sodium concentration will determine how fast sodium is removed from the blood. If the blood sodium concentration > dialysate sodium concentration, then sodium goes from blood to dialysate. If the dialysate sodium concentration > blood sodium concentration, then sodium goes from dialysate to blood
[b]Intermittent HD should be minimized due to acute shift in osmolality and hypotension
[c]Fixed volumes listed may be repeated to titrate to effect (ICP reduction)
[d]Higher plasma mannitol concentrations were observed in patients with obesity than in those without when 1 g/kg dose was given

Table 6.7 Summary of commonly used neuromuscular blocking agents in neurocritical care [30, 86, 95–109]

Agent	Usual dose	Recommended weight for dosing calculations	Maximum per dose	Dose in CRRT	Dose in iHD
Succinylcholine	Intubation: 0.3–1.1 gm/kg Rapid sequence intubation: 1–1.5 gm/kg	TBW[a]	IVP 150 gm	Not affected by CRRT	Supplemental dose not necessary. Increased risk of serious hyperkalemia; caution use in iHD
Rocuronium	Bolus 0.6–1 gm/kg followed by 10–12 mcg/kg/min	Actual or in obesity use IBW[b]	Variable per patient	Not affected by CRRT Titrate to effect	No change
Vecuronium	Bolus 0.08–0.1 followed by 0.8–1.2 mcg/kg/min	Actual or in obesity use IBW	Variable per patient	Not affected by CRRT Titrate to effect	No change[c]

(continued)

Table 6.7 (continued)

Agent	Usual dose	Recommended weight for dosing calculations	Maximum per dose	Dose in CRRT	Dose in iHD
Atracurium	Bolus 0.4–0.5 gm/kg followed by 4–20 mcg/kg/min	Actual or in obesity use IBW	Variable per patient	Not affected by CRRT Titrate to effect	No change[d]
Cisatracurium	0.1–0.2 gm/kg followed by 2.5–3 mcg/kg/min	Actual or in obesity use IBW	Variable per patient	Not affected by CRRT Titrate to effect	No change[d]

CRRT continuous renal replacement therapy, *IBW* ideal body weight, *iHD* intermittent hemodialysis, *TBW* total body weight, *IVP* intravenous push
[a]In morbidly obese patients, the enzyme that metabolizes succinylcholine, pseudocholinesterase, is increased. Therefore, when administering succinylcholine, the use of total body weight rather than lean body weight or ideal body weight is recommended
[b]In general, using patients' total body weight will result in a prolonged duration of action in morbidly obese patients
[c]Decreased renal clearance of active metabolite, 3-desacetylvecuronium
[d]Laudanosine, a metabolite of both atracurium and cisatracurium with neurotoxic side effects, can potentially accumulate in patients with renal dysfunction

The extent of removal of neuromuscular blocking agents by ECMO or PLEX is not well established at this point. In a worldwide survey of ECMO centers, the average hourly rate of vecuronium and cisatracurium was reported to be 2.5–5 gm/hr and 6–15 gm/hr, respectively, in patients on ECMO [110].

Conclusion

Safe and effective use of pharmacological agents in neurocritical care is challenging due to PK changes and altered physiology commonly seen in this population. In addition, adequate data on optimal pharmacotherapy in critically ill patients receiving interventions such as ECMO and PLEX or in those with obesity often is not available outside of case reports and case series that may not be applicable to the individual patient being treated. Familiarity of clinicians with PK and PD changes in critical illness and in interventions such as PLEX and ECMO is invaluable in providing care for these patients.

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Coma and Brain Death

7

Anna M. Cervantes-Arslanian, Melissa Mercado, and David M. Greer

Coma

Definition

Consciousness has been defined as "a state of awareness of self and environment and responsiveness to external stimulation and inner need" [1]. In this manner, coma can be described as the "loss" of consciousness. Comatose patients are not aware of external or internal stimuli in that they are unable to perceive it via neuronal transmission to their cerebral cortex. They are also not alert and cannot respond to external stimuli even with minimal activities such as eye opening. Other disorders of consciousness aside from coma exist along a continuum of "alertness" and "awareness." The vegetative state or unresponsive wakefulness syndrome refers to the presence of alertness without awareness: patients are alert in that they may be able to open their eyes and may have reflexive movements such as grimacing or grasping of objects, but they lack awareness of their external environment [2–4]. Although many patients have been given the clinical diagnosis of vegetative state for decades, recent findings suggest that these patients may be erroneously classified, as some may have evidence of residual awareness only detected via functional magnetic resonance imaging (fMRI) [5–7]. The minimally conscious state (MCS) was defined in 2002 as a disorder of consciousness "in which minimal but definitive behavioral evidence of self or environmental awareness" exists [8]. These patients may show limited but reproducible evidence of environmental perception, such as reaching for objects, sustained visual fixation of moving objects, simple command following, gesturing or verbalizing yes/no in response to questions. Brain-injured patients who have shown any of these behaviors and are thus classified as MCS have less unfavorable long-term outcomes than those who remain vegetative [9, 10]. Although the locked-in state may render patients unable to respond to most external stimuli, it is not a true disorder of consciousness, as there is no disturbance of either awareness or alertness. These patients have preserved brainstem nuclei capable of relaying external stimuli, but they cannot respond to them since descending motor pathways have been lost. It is more of a state of "de-efferentation." Upper brainstem nuclei controlling vertical eye movements are usually preserved, and patients may still respond to questions or commands via up- or down-gaze.

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Neuroanatomical Structures Involved in Maintaining Consciousness

Multiple subcortical and cortical brain structures are required for the maintenance of an awake and alert state. The brainstem reticular activating system (RAS) is a network of neurons in the paramedian tegmentum of the brainstem that is responsible for inducing and maintaining alertness and modulating sleep–wake cycles. RAS fibers extend from the superior pons through the midbrain to the posterior hypothalamus and thalamic reticular formation to the cerebral cortex. Prior experiments in cats demonstrated

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reproduction of arousal patterns on electroencephalography (EEG) via direct stimulation of the RAS [11]. Any injury to the RAS will result in a comatose state, whereas injuries below the level of the pons do not tend to result in loss of consciousness. The thalami are a pair of bilateral midline subcortical nuclei that function as the main "relay" center between the brainstem and cortical structures. Whereas unilateral injury may result in varying focal neurological deficits such as hemiplegia or hemi-sensory loss, only bilateral injury will result in a comatose state. Bilateral thalamic infarcts can be caused by an artery of Percheron occlusion, or by a vein of Galen thrombosis. Cortical perception is required for the awareness of external stimuli, and thus the bilateral cerebral hemispheres play a role in consciousness. Although a unilateral injury (such as a middle cerebral artery stroke) would not be associated with a depressed level of consciousness unless it exerts mass effect on brainstem structures, bilateral injury such as that seen in anoxia results in a comatose state. Bihemispheric cortical dysfunction is also seen in toxic-metabolic syndromes causing encephalopathy.

Differential Diagnoses

In a study of 500 patients who presented to the emergency room with coma, Plum and Posner ascertained that the majority (57%) of the final diagnoses were secondary to toxic-metabolic disorders such as hypoglycemia, anoxia, uremia, or hepatic encephalopathy [12]. A psychiatric diagnosis was established in only 2% of the patients. The remainder had experienced primary neurological events leading to coma, including supratentorial lesions (20%), infratentorial lesions (13%), and diffuse brain injury (8%). A summary of etiologies for coma may be found in Table 7.1.

Primary Neurological Diagnoses

Cerebrovascular Injuries

As previously mentioned, acute ischemic strokes (AIS) affecting only one cerebral hemisphere do not in and of themselves lead to a depressed level of consciousness unless significant cerebral edema is present causing downward herniation and brainstem compression. Rarely, cardioemboli

Table 7.1 Summary of differential diagnoses for coma

Primary neurological diagnoses	History and findings	Studies
Cerebrovascular		
Acute ischemic stroke Intracerebral hemorrhage Intraventricular hemorrhage Subarachnoid hemorrhage	Focal neurologic deficits, cranial nerve deficits if brainstem involvement or herniation Thunderclap headache	CT angiogram Head CT, coagulation profile Lumbar puncture if head CT negative
Electrographic		
Subclinical/nonconvulsive seizures	Convulsions, facial twitching, prior history of seizure disorder or brain injury	Continuous EEG, ASM levels
Hypoxic-ischemic	Cardiac arrest, cranial nerve deficits, myoclonus	Head CT, EEG, brain MRI
Infectious		
Bacterial meningitis Viral encephalitis	Fevers, chills, rigors Subacute mental status changes	Head CT if comatose, lumbar puncture
Inflammatory		
ALE SREAT	Subacute mental status changes, refractory seizures, history of other autoimmune syndrome	MRI brain, lumbar puncture
Space-occupying lesions		
Neoplasm Abscess	Focal neurologic deficits, history of malignancy Recent neurosurgical intervention, mastoiditis or bacteremia	Head CT, MRI brain with contrast
Trauma	Other bodily trauma, battle sign	Head CT
Toxic-metabolic derangements		
Hypo−/hyperglycemia	History of diabetes, focal seizures	Fingerstick glucose
Uremia	Acute kidney injury, myoclonus, asterixis	Basic metabolic panel
Acute hepatic failure	Jaundice, asterixis	Liver function panel, ammonia level
Substance ingestion	Pinpoint pupils, history of drug use	Urine and serum toxicology screen
Hypercapnia	History of respiratory disease	ABG, chest X-ray
Hypothyroidism	History of thyroid disorder, hypotension, bradycardia, hypothermia, myxedema, depressed DTRs	Thyroid function panel
Hypoadrenalism	Hypotension, hypothermia, hypoglycemia	Cortisol
Vitamin deficiencies	Malnutrition, alcoholism, gastric bypass	Thiamine level, vitamin B12 level

ABG arterial blood gas, *ALE* autoimmune limbic encephalitis, *ASM* anti-seizure medication, *CT* computed tomography, *EEG* electroencephalogram, *MRI* magnetic resonance imaging, *SREAT* steroid-responsive encephalopathy with autoimmune thyroiditis

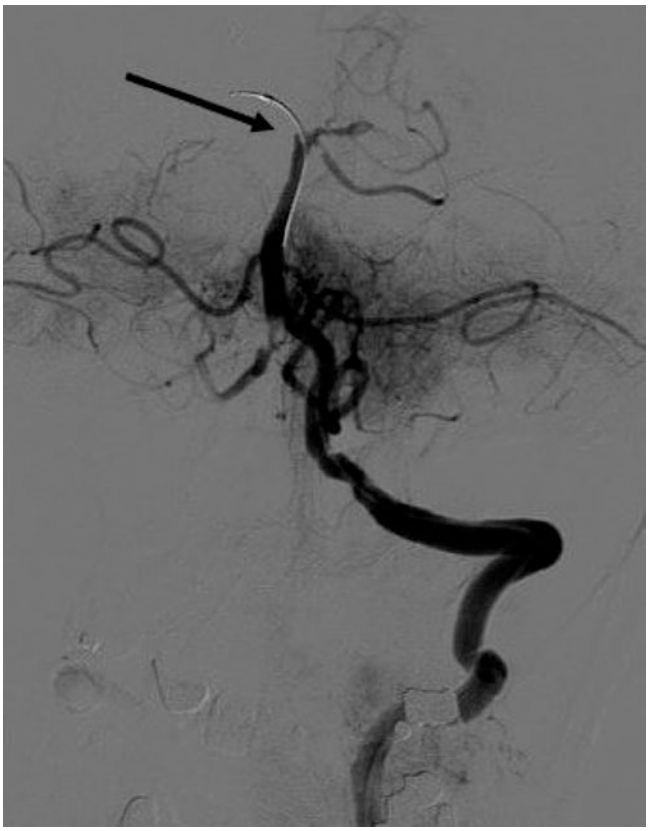

Fig. 7.1 Conventional angiogram demonstrating distal basilar artery occlusion

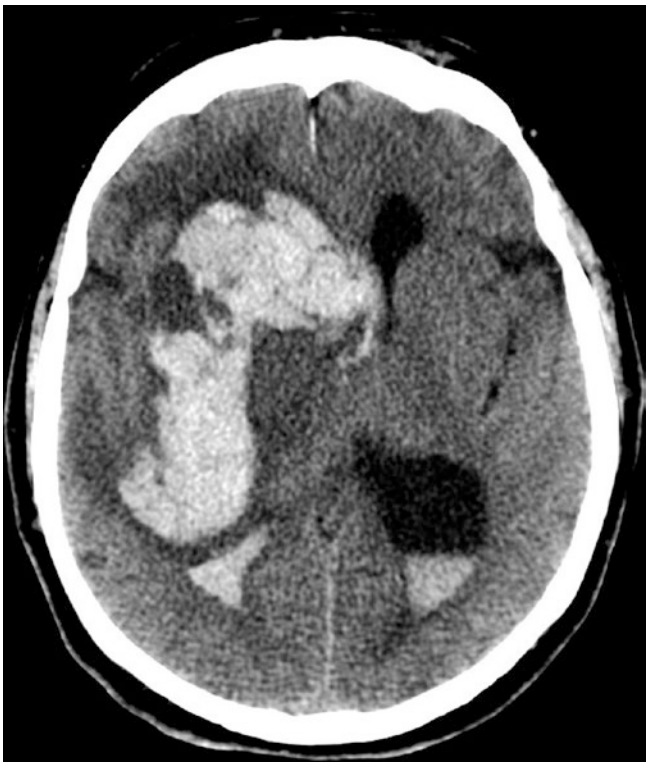

Fig. 7.2 Head CT showing large right-sided ICH with mass effect and midline shift

can cause occlusions to the bilateral middle cerebral arteries, which will present as loss of consciousness. Most acute strokes presenting with sudden coma involve occlusion of the basilar artery (Fig. 7.1). Patients with a "top of the basilar" syndrome can also experience vivid hallucinations ("peduncular hallucinosis"), and ocular abnormalities can often be elucidated on detailed neurologic examination [13]. As previously mentioned, bi-thalamic infarcts caused by artery of Percheron occlusion or vein of Galen thrombosis will also result in coma [14, 15].

Treatment of AIS relies on an early diagnosis. Intravenous alteplase (IV tPA) is the only available pharmacological treatment for AIS within a 4.5 hour window of symptom onset (Food and Drug Administration approval is only for within a 3-hour window). Administration of IV tPA is associated with improved neurologic outcomes at 3 months [16, 17]. For patients presenting outside of the 4.5 hour window, endovascular thrombectomy for large vessel occlusions can improve functional outcomes [18, 19]. For patients who have suffered from large territorial infarcts, close monitoring for the development of "malignant" cerebral edema is recommended, since medical and surgical treatments can lead to improved outcomes [20].

Spontaneous intracerebral hemorrhages (ICH) that are limited to one hemisphere and do not cause significant mass effect do not tend to result in coma. Most unilateral cerebral ICHs present with sudden headache and focal motor or sensory deficits (Fig. 7.2). In contrast, brainstem ICHs frequently present with sudden loss of consciousness, and as with basilar artery occlusions, close neurologic examination may reveal cranial nerve deficits. Causes of spontaneous ICH include: hypertension, coagulopathy, cerebral amyloid angiopathy, metastatic brain lesions, septic cerebral emboli, and hemorrhagic conversion of ischemic strokes. Metastatic tumors such as renal cell carcinoma, thyroid cancer, and melanoma have hemorrhagic tendencies, and a contrast-enhanced MRI of the brain should be obtained to evaluate for an underlying mass lesion in patients with any concern for malignancy. Treatment of ICH is guided toward management of the underlying etiology, but reversal of coagulopathy, blood pressure control, and administration of hyperosmolar therapies in the acute setting are of utmost importance in preventing hemorrhage expansion and edema [21]. Although evidence for surgical interventions in ICH is limited, neurosurgical procedures such as decompressive hemicraniectomy or hematoma evacuation can be considered in certain patients if medical therapies have failed in preventing neurologic deterioration [22].

Intraventricular hemorrhage (IVH) can result from either extension from a primary parenchymal ICH or from a vascular abnormality such as an aneurysm or arterio-venous malformation. Acute IVH may present with sudden onset headache, but depressed mentation may occur with the development of hydrocephalus causing brainstem compression. In this setting, external ventricular drain (EVD) placement is warranted, as it is associated with improved outcomes and lower mortality [23].

Coma or stupor is seen in up to 30% of patients presenting with aneurysmal subarachnoid hemorrhage (aSAH) and is associated with higher mortality [24]. As with IVH, patients may become comatose due to hydrocephalus (Fig. 7.3), and EVD placement is associated with improved outcomes in certain patients [25]. Treatment of aSAH involves both acute interventions to prevent aneurysmal re-bleeding, such as blood pressure control and aneurysm securement, as well as close intensive care monitoring to prevent further complications including delayed cerebral ischemia [26].

Electrographic

Subclinical/nonconvulsive status epilepticus (NCSE) should be suspected in patients who had any convulsive-like activity and remain comatose. A high index of suspicion should exist in patients with a prior seizure disorder or prior stroke. In one prospective study, the most frequent causes of seizures in adults included: low anti-seizure medication (ASM) levels (34%), remote brain injury including trauma or cerebrovascular events (24%), acute stroke (22%), hypoxia (13%), metabolic derangement (15%), and alcohol-related (13%) [27]. NCSE can only be excluded with continuous electroencephalography (cEEG). Electrographic seizures may be discovered on EEG in up to 22% of medical intensive care unit (ICU) patients (30% if sepsis is present) and 16% of surgical ICU patients [28–30]. Current guidelines recommend cEEG in patients who are persistently comatose without a known underlying cause, as earlier discovery and treatment of seizures leads to improved outcomes [31, 32].

The first-line therapy for seizures lasting more than 5 minutes is administration of a benzodiazepine. Either intravenous (IV) lorazepam or intramuscular midazolam are equally effective [33, 34]. Following benzodiazepine administration, second-line therapies include long-acting ASM such as phenytoin, valproate, phenobarbital, or levetiracetam. Although there are no studies to date that suggest a benefit of one ASM over another, the ongoing Established Status Epilepticus Treatment Trial (ESETT) seeks to determine the most efficacious ASM among phenytoin, levetiracetam, and valproate [35]. Once seizures become refractory to first- and second-line agents, third-line therapy should include initiation of a continuous sedative/anesthetic medication [36]. Third-line agents available include midazolam, pentobarbital, or propofol.

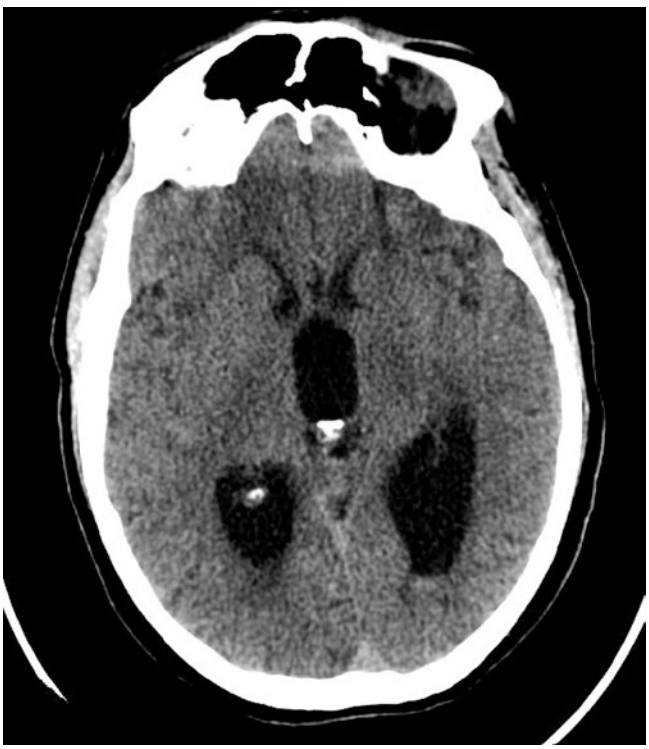

Fig. 7.3 Head CT showing ventricular enlargement consistent with hydrocephalus in the setting of IVH

Hypoxic-Ischemic

Patients who have sustained cardiopulmonary arrest may develop differing severities of hypoxic-ischemic/anoxic brain injury. The majority of patients will remain comatose after the return of spontaneous circulation (ROSC), and some may even lack brainstem reflexes. Initial brain imaging with computed tomography (CT) may show varying degrees of anoxic cerebral edema, ranging from a normal exam to subtle loss of gray-white differentiation to diffuse sulcal effacement and tonsillar herniation (Fig. 7.4). It is important to note that up to 30% of patients may recover brainstem reflexes after 24 hours, and brain death examination should be postponed in certain clinical settings [37]. There is no treatment for irreversible anoxic brain injury, but targeted temperature management (TTM) has become standard of care to prevent it [38, 39]. Electrographic seizures may be captured in up to 30–40% of cardiac arrest patients, so early cEEG is warranted in the setting of coma [40, 41]. Prior to the establishment of TTM as standard of care, most prognostication evaluations were routinely performed at 72 hours post-arrest. However, in the post-therapeutic hypothermia era, half of the patients may not regain consciousness until more than 3 days post-arrest, and delaying prognostication is recommended when early assessments remain indeterminate [42].

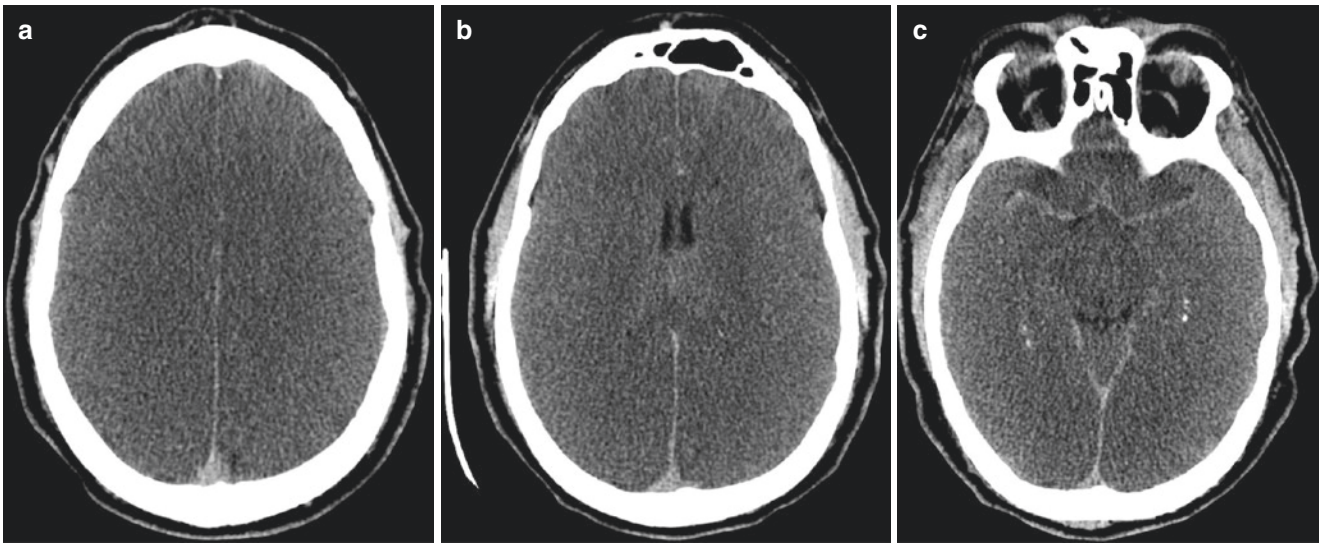

Fig. 7.4 Head CT showing diffuse cerebral edema with sulcal effacement (**a**, **b**) as well as pseudo-subarachnoid sign (venous engorgement appearing as hyperdensities near the subarachnoid spaces) (**c**) as a result of anoxic brain injury

Infectious

Meningoencephalitis should be suspected in any patient presenting with an altered level of consciousness and infectious symptoms such as fever, chills, nausea, vomiting, rigors, or an immunocompromised state. Clinical examination may show encephalopathy, meningismus, or papilledema. Bacterial meningitis is a neurological emergency, and prompt administration of antimicrobials is necessary in any encephalopathic patient with a fever. Blood cultures should be obtained as soon as possible. Although patients with no focal deficit and no history of immunosuppression are at low risk for lumbar puncture–induced herniation, any obtunded patient should have a non-contrast head CT performed prior to lumbar puncture to ensure no space-occupying intracranial lesions are present [43]. Broad spectrum antibiotics, including a third-generation cephalosporin and vancomycin, should be initiated for coverage of the two most common pathogens, *Streptococcus pneumoniae* and *Neisseria meningitides* [44]. For elderly patients, immunocompromised hosts, or those with a history of alcohol abuse, addition of ampicillin for *Listeria monocytogenes* coverage is also necessary. Concurrent administration of steroids along with antibiotics is recommended since it has been shown to decrease neurologic sequelae in patients with streptococcal meningitis [45, 46]. Cerebrospinal fluid (CSF) should be analyzed as soon as possible, ideally within 4 hours of antibiotic administration to avoid sterilization of the sample [47]. CSF findings in bacterial meningitis include an elevated white blood cell count in the hundreds to thousands with a polymorphonuclear predominance, a glucose level that is less than two thirds of the serum glucose, and markedly elevated protein (Table 7.2). In bacterial central nervous system (CNS) infections, MRI may show leptomeningeal contrast enhancement or parenchymal edema suggestive of encephalitis. Antibiotic therapy length should be titrated according to the causative organism, and a full course should be considered in patients who have CSF findings suspicious for meningitis but negative cultures [48]. Viral encephalitis may present as a more subacute decline in the level of consciousness and confusion. The most frequent pathogen encountered in the Western hemisphere is herpes simplex virus (HSV), but other infections such as varicella zoster virus (VZV), West Nile virus (WNV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), enterovirus, or human herpes virus (HHV) may also be encountered, especially in immunocompromised patients [49]. CSF in HSV encephalitis may show a white blood cell count in the tens to hundreds with a lymphocytic predominance, mildly elevated protein, normal glucose, and frequently a red blood

Table 7.2 CSF findings in meningoencephalitis

	WBC (cells/mm^3)	Protein (mg/dL)	Glucose (mg/dL)	RBC
Normal	<5	<45	50–80	Normal
Bacterial	>1000 (PMNs)	>100	<40 or < 2/3 of serum concentration	Normal
HSV	100–1000 (lymphocytes)	40–100	>45	Elevated
Fungal	100–500 (lymphocytes)	>50	<40 or <2/3 of serum concentration	Normal
TB	100–500 (lymphocytes)	>50	<40 or < 2/3 of serum concentration	Normal

PMN polymorphonuclear leukocytes

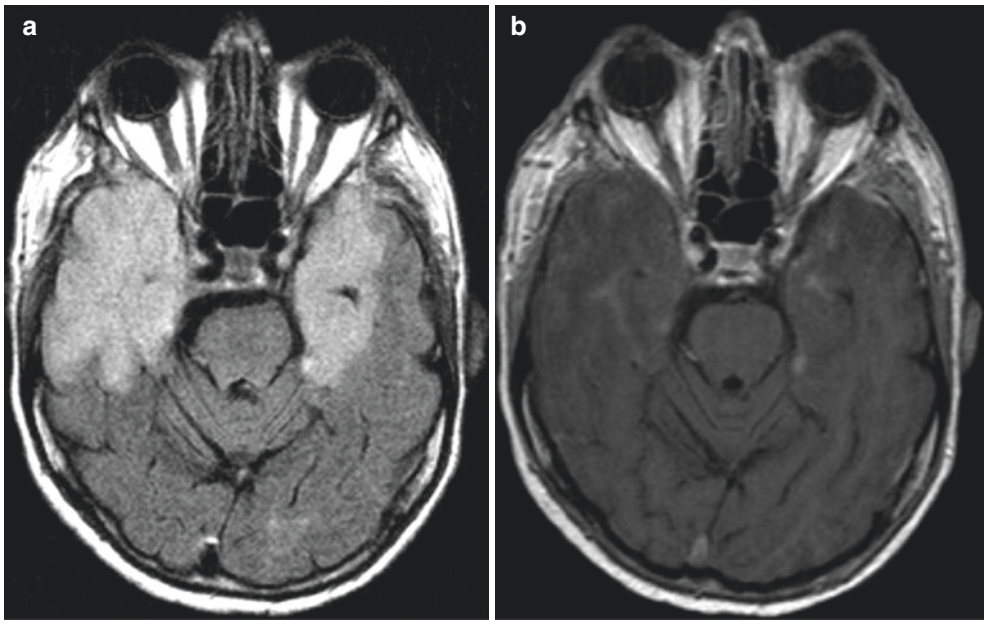

Fig. 7.5 MRI brain showing FLAIR hyperintensity (**a**) and contrast enhancement (**b**) of the bilateral temporal lobes secondary to HSV encephalitis

cell count in the hundreds due to its hemorrhagic nature [50]. MRI in HSV encephalitis may show cerebral edema with a predilection for the medial temporal lobes and occasionally hemorrhagic changes (Fig. 7.5). Antimicrobial therapy with acyclovir should be initiated as soon as a viral encephalitis is suspected, pending CSF HSV polymerase chain reaction (PCR) results, since delays in treatment are associated with worse outcomes [51]. In patients with severe immunodeficiency, tuberculous (TB), parasitic (e.g., toxoplasmosis) and fungal (e.g., cryptococcus) meningitis should be considered. Fungal meningitis may present in a more indolent fashion, with patients experiencing symptoms such as headache, fevers, and malaise over 2–4 weeks [52]. The CSF may show a mononuclear pleocytosis, significantly elevated protein, and low glucose. Diagnostic confirmation requires microscopic analysis, but direct antifungal antigen detection assays may also be useful in both CSF and serum [53]. Ventricular involvement may be encountered in cryptococcus and neurocysticercosis infections, and evaluation for these diagnoses in a patient with new-onset hydrocephalus should be carried out. Certain CNS infections such as VZV, TB, aspergillus, and syphilis may also be associated with an inflammatory or invasive vasculitis, and resultant cerebral infarctions can be seen on brain imaging.

Inflammatory

Over the past decade, physicians have become more aware of the diagnosis of autoimmune limbic encephalitis (ALE), leading to its increased detection and incidence [54]. ALE is mediated by antibodies against either extracellular synaptic or intracellular neuronal cell membrane proteins. Paraneoplastic ALE is associated with an underlying malignancy and tends to be mediated by antibodies directed to intracellular antigens [55]. ALE symptoms may include psychiatric disturbances, seizures, dyskinesias (orofacial, choreoathetosis, dystonia), language disturbances (mutism, diminished output, echolalia), and autonomic instability [56]. It may be seen in conjunction with other disorders of immunity, and high titers of other auto-antibodies have been demonstrated in these patients [57]. EEG may show focal or generalized slowing or epileptiform activity; CSF may be abnormal and show lymphocytosis, elevated protein, elevated IgG index, or oligoclonal bands. MRI most commonly shows fluid-attenuated inversion recovery (FLAIR) hyperintensities in the limbic system, especially in the medial temporal lobes, with extralimbic involvement seen in up to 55% of patients [58]. However, both CSF and MRI findings vary depending on which antibody is the culprit, with some syndromes more frequently having normal findings [57]. Treatments include immunosuppressive therapies such as steroids, IV immunoglobulin (IVIg), or plasma exchange. However, there are no randomized studies to indicate which may be of more benefit. In cases where a tumor is found, resection is recommended [56].

Steroid responsive encephalopathy with autoimmune thyroiditis (SREAT) refers to a heterogeneous group of neurological symptoms that manifest in patients with thyroiditis, but that is also seen in other autoimmune diseases. Neurological symptoms can include seizures, aphasia, psychosis, movement disorders, and coma [59]. Previously termed "Hashimoto's encephalopathy," this disorder likely represents the activation of anti-neuronal antibodies in patients with an established autoimmune disease. In these patients, there should be consideration of other diagnoses such as a paraneoplastic or non-paraneoplastic ALE. Other autoimmune disorders associated with CNS involvement

include systemic lupus erythematosus (SLE), Sjögren's syndrome, sarcoidosis, and Behçet's disease.

Space-Occupying Lesions

Intracranial neoplasms include primary CNS neoplasms as well as metastatic lesions, which are more common in adults. Slow-growing tumors may occupy a substantial amount of intracranial space prior to the development of symptoms, as the brain parenchyma acclimatizes to the mass effect. Once the tumor is sufficiently large or causes seizures, patients may present with a depressed level of consciousness. The diagnosis will often be confirmed by a non-contrast head CT if the tumor is large enough and exerting significant mass effect, but MRI with and without contrast may be required to elucidate any smaller metastatic foci. In patients who present with intracranial mass lesions, a search for a primary malignancy should be carried out, including CT of the chest, abdomen, and pelvis with and without contrast, or full body positron emission tomography scan (PET). If there are any clinical signs of herniation, administration of hyperosmolar therapy may be indicated as well as initiation of steroid treatment for vasogenic cerebral edema. Neurosurgical consultation is always warranted, as patients may benefit from either tumor resection or biopsy. Once pathological data is acquired, oncological and radiation oncological services should also be consulted for further treatment.

Intracranial bacterial abscess may also cause coma in cases of herniation or seizures. Prompt administration of broad-spectrum antibiotics including vancomycin, ceftriaxone, and metronidazole is indicated once the diagnosis is suspected. Lumbar puncture is frequently contraindicated in the setting of mass effect, and neurosurgical evacuation is usually the treatment of choice. A search for a primary source of infection should be carried out. Sources of cerebral abscesses may include direct spread from cranio-facial infections such as mastoiditis or hematogenous spread such as that seen in bacterial endocarditis.

Trauma

Traumatic brain injury (TBI) may be severe enough to be associated with coma. There are several mechanisms by which TBI may cause coma, most of which will be revealed on initial head CT. A unilateral mass lesion may present with herniation and brainstem compression and should be suspected if the patient has any lateralizing signs on their examination. Diffuse TBI refers to injury that may lead to global cerebral edema and intracranial hypertension, which decreases cerebral perfusion. Published guidelines specify the indications for surgical intervention in different types of brain injury [60]. In patients who have sustained cranial trauma but do not have any apparent imaging abnormalities to explain their clinical state, cEEG monitoring to rule out NCSE is warranted. If unexplained coma remains, a brain MRI may be indicated to evaluate for diffuse axonal injury, which may be associated with irreversible coma if found in the dorsal brainstem [61]. Intracranial lesions with mass effect, clinical or radiographic herniation, or intracranial hypertension (found via direct intracranial pressure monitoring) require aggressive hyperosmolar therapies to avoid permanent brainstem injury [62].

Toxic-Metabolic Derangements

Hypoglycemic coma should be treated promptly, as blood glucose levels below 50 mg/dL may lead to irreversible neuronal injury [63]. Hyperglycemia can also be associated with a depressed level of consciousness, especially if there is a coexisting hyperosmostic state or ketosis. In both instances, close evaluation for improvement in the level of consciousness should commence, and other underlying etiologies suspected if patients do not improve once normoglycemia is achieved. MRI findings in severe hypoglycemia may include T1 or T2 hyperintensities in subcortical structures such as the basal ganglia or hippocampi, or white matter diffusion restriction similar to an acute toxic leukoencephalopathy [64, 65]. Although seizures are rare in hypoglycemia, hyperglycemia may present with seizures up to 25% of the time, most frequently focal tonic activity with or without generalization [66–68]. Treatment of hypoglycemia should include administration of thiamine prior to IV dextrose so as not to induce Wernicke's encephalopathy. Correction of hyperglycemia with or without ketosis should include aggressive hydration, insulin administration, as well as frequent monitoring and repletion of electrolyte derangements [69].

There are several mechanisms by which acute or chronic renal failure may lead to alterations in consciousness. Uremic encephalopathy may present in either acute or chronic renal dysfunction, but symptoms tend to be more pronounced in acute kidney injury. No single toxin accumulation is responsible for the neurological effects of uremia, but elevated CSF levels of multiple organic molecules have been discovered including uric acid, phenols, and guanidine compounds [70, 71]. Elevations in these molecules are associated with increased cerebral excitatory glutamate activity and depressed inhibitory gamma-aminobutyric acid (GABA) activity, leading to overall enhanced cortical excitability. Patients may have a depressed level of consciousness, asterixis or myoclonus, and potentially seizures, but focal motor or cranial nerve deficits should be absent. Uremic encephalopathy is a diagnosis of exclusion, as CSF studies, brain imaging, and EEG may show a range of abnormalities but no pathognomonic findings. The encephalopathy should improve with renal replacement therapy if there is appropriate lowering of the blood urea nitrogen (BUN). Other mechanisms by which renal dysfunction may cause altered sensorium include drug toxicity due to poor renal clearance (particularly agents with sedative effects); dialysis

disequilibrium due to osmolar shifts causing transient cerebral edema; hypotensive syncope due to decreased global cerebral perfusion; thiamine deficiency due to accelerated loss via hemodialysis; and intracranial hemorrhage due to platelet dysfunction.

Hepatic encephalopathy may be encountered in patients with acute hepatic failure. Severity ranges from grade 1, consisting of mild confusion and some asterixis, to grade 4, with coma and possible raised intracranial pressure (ICP) with signs of herniation. Neurologic injury in the setting of fulminant hepatic failure is caused by the accumulation of certain toxins normally cleared by the liver and is most often seen in acute rather than subacute liver injury [72]. Although serum ammonia levels are useful in detecting hepatic encephalopathy, it is the conversion of ammonia into glutamine that leads to cerebral edema [73, 74]. Therapies aimed at decreasing ammonia burden include lactulose and rifaximin. If there is clinical or radiographic evidence of raised ICP, hyperosmolar therapies directed at reducing cerebral edema should be instituted [75, 76].

There are several toxic substance ingestions that may depress the level of consciousness. According to the Center for Disease Control (CDC), opiate overdoses in the United States have increased by 30% on average over the last year. As such, the suspicion for drug overdose in young patients presenting with acute coma should be high, and early naloxone administration should be considered to evaluate for reversal of symptoms. Certain drugs such as opiates, ethanol, barbiturates, benzodiazepines, tricyclics, and acetaminophen can be discovered in serum or urine toxicology results, but newer synthetic agents may not. Carbon monoxide poisoning should be suspected during winter months and can be detected via the measurement of serum carboxyhemoglobin levels [77]. Treatment may include high-flow oxygen but hyperbaric oxygen therapy is recommended in the setting of coma. Most other therapies for drug intoxication are supportive, such as mechanical ventilation in the setting of respiratory failure, but assistance from local Poison Control centers is recommended [78]. Activated charcoal may be useful for certain toxins if administered within 2 hours of ingestion, but may not be useful in the comatose patient unless intubated [79]. Drugs such as tricyclic and dopaminergic agents may cause cardiac arrhythmias, and patients should be monitored closely on telemetry. Hemodialysis or urine alkalinization with IV sodium bicarbonate may be required for life-threatening poisonings such as lithium, phenobarbital, salicylates, and theophylline [80].

Hypothyroidism may be so severe that patients present in myxedema coma. Myxedema refers to the edematous appearance patients may show due to the accumulation of glycosaminoglycans. Other signs include bradycardia, hypotension, hypothermia, nonpitting edema, hyponatremia, coarse hair, and dry skin [81]. It should be suspected in patients with a prior history of thyroid dysfunction. The presence of exophthalmos may be an aid to diagnosis. Multiorgan failure including acute renal failure and cardiomyopathy may also be encountered. There may be concomitant adrenal insufficiency, which may be suggested if hyperpigmented skin is also present. Diagnosis is made via laboratory thyroid function tests, with low free thyroxine (T4) levels. Thyroid-stimulating hormone (TSH) levels are usually high but may be normal in patients with primary/central hypothyroidism. Treatment consists of thyroid replacement, supportive care, and early steroid replacement if adrenal insufficiency is suspected.

Wernicke's encephalopathy (WE) is caused by thiamine (vitamin B1) deficiency. The classic triad of ataxia, nystagmus/ophthalmoplegia, and encephalopathy is rarely encountered, and physicians should instead suspect the disorder in anyone with coma and a clinical condition that may lead to thiamine deficiency [82]. Although the majority of patients presenting with WE are alcoholics, it may also be encountered in patients with hyperemesis gravidarum, bariatric surgery, cancer, and hemodialysis use. MRI of the brain may show T2 hyperintensities in the bilateral thalami, hypothalamus, or mammillary bodies [83]. Treatment consists of high-dose thiamine (500 mg every 8 hours) administered IV for 3 days [84].

Triage

Emergency Room

Patients who present to the emergency room will require the initial diagnostic workup detailed below. Circulation, airway, and breathing will need to be assessed urgently, and the decision whether to secure the airway should be performed prior to transport to any imaging studies. If no diagnosis is found in the initial assessment, if patients require intubation, or if they do not improve with emergent interventions, they should be admitted to a high level of monitoring in an ICU. If brain imaging reveals any abnormalities that require neurosurgical intervention, patients may need to go directly to the operating room prior to admission to the ICU.

Outside Hospital

The workup for comatose patients who are transferred from outside hospitals is sometimes complete, but many still require interventions or studies not available at that medical center. Patients should always be hemodynamically stable prior to any transfer between hospitals.

From Within the Hospital

Patients admitted for any medical or surgical disease are at risk for developing coma due to many of the above-mentioned etiologies. In the event of sudden onset of coma, an emergent neurological consultation should always be requested prior to triage.

Diagnostic Workup and Decision-Making

Circulation, Airway, Breathing

The initial evaluation of a comatose patient is focused on his/her hemodynamic and respiratory stability. Cardiopulmonary resuscitative efforts should be initiated on any comatose patient who lacks palpable pulses. In the event that a patient is hemodynamically stable and oxygenating appropriately, airway protection capacity in the setting of profound coma should be assessed, and endotracheal intubation performed if there is any risk for impending respiratory failure.

History

The history of presenting illness should be obtained from any available resources at the time of evaluation. Available family members and/or emergency medical services personnel should be interviewed for details regarding the patient's presenting symptoms. Acute onset of coma is indicative of either a cerebrovascular or electrographic event. A more subacute or chronic onset as well as preceding encephalopathy is more suggestive of an infectious, inflammatory, or toxic-metabolic etiology. Focal neurological deficits preceding the loss of consciousness are indicative of cerebrovascular events. Any recent history of trauma should be elucidated, as certain types of intracranial hemorrhages may gradually enlarge over days to weeks. Infectious symptoms such as fevers, rigors, muscle aches, upper respiratory symptoms, or gastrointestinal distress should also be reviewed. A detailed medication list should always be obtained, as certain drugs (e.g., psychiatric, anticonvulsant, diabetic, and anticoagulant) may provide clues as to the underlying diagnosis.

Physical Examination

Vital Signs

Vital sign abnormalities should be corrected promptly, but may serve a diagnostic purpose. Severe hypertension can suggest a cerebrovascular event or can be evidence of underlying intracranial hypertension, especially when coupled with bradycardia ("Cushing response").

Level of Consciousness

A detailed neurologic assessment should be performed once hemodynamic stability has been achieved. The patient's level of consciousness should be assessed by administering differing levels of external stimulation and evaluating the patient's response to each. Evaluation of eye-opening is frequently performed first, although spontaneous eye opening is not indicative of consciousness and lack of it is also not strictly indicative of coma. The physician should next determine whether the patient can track or attend to a visual stimulus. If the patient's eyes remain closed to any verbal or painful stimulus, as can occur in the setting of an eye-opening apraxia, the physician should open the eyes for the patient and evaluate for tracking in this manner. Patients should always be asked to perform both appendicular and midline commands even if they appear comatose, and these should include the instruction to "look up" or "look down" in order to discern a locked-in patient. Command-following should be strictly defined as the ability to give a "thumbs-up," show two fingers, or close and open the fist. Hand-gripping alone should not be interpreted as command following, as this is a reflexive motion often seen in brain-injured patients. Several scales have been evaluated for measuring the level of consciousness. The Glasgow Coma Score (GCS) and the Full Outline of Unresponsiveness (FOUR) score have been used to supplement the neurological assessment (Table 7.3) [85, 86].

Brainstem Examination

The pupillary light response is measured by shining a light into each pupil and assessing for size, reactivity, and asymmetry. Afferent and efferent fibers are provided by cranial nerves II and III, respectively, which course through the midbrain. Disruption of the pupillary light reflex can occur in different brain injury types. In the setting of uncal herniation from a supratentorial lesion, stretching of cranial nerve III can cause a unilateral dilated pupil that does not react to either direct or consensual stimulation. Injuries to the midbrain can cause mid-position (4–6 mm) fixed pupils. Pontine lesions can present with "pin-point" (1 mm or less) pupils that are also sluggishly reactive. This finding may be

Table 7.3 Full Outline of Unresponsiveness (FOUR) score

	0	1	2	3	4
Eye	None	Open to pain	Open to voice	Open spontaneously but not tracking	Open spontaneously, tracking, or blinking to command
Motor	None	Extension/ decerebrate posturing to pain	Flexion/ decorticate posturing	Localizes pain	Thumbs-up, fist or peace sign to command
Brainstem reflexes	Pupil, corneal and cough reflexes absent	Pupil and corneal reflexes absent	Pupil or corneal reflex absent	One pupil wide and fixed	Pupil and corneal reflexes present
Respiration	Breathes at ventilator rate or apnea	Breathes above ventilator rate	Not intubated, irregular breathing	Not intubated, Cheyne-stokes breathing pattern	Not intubated, regular breathing pattern

Each category is added together to determine the total FOUR score

mistaken for opiate overdose, and a diagnosis of brainstem stroke may be delayed if brain imaging is deferred. Although other brainstem reflexes may be affected by paralytic agents, pupillary responses should remain intact in the presence of neuromuscular blockade [87].

The pathway for the corneal reflex consists of cranial nerve V afferent and cranial nerve VII efferent fibers and is evaluated via direct corneal stimulation with sterile cotton. Unilateral pontine injuries can cause a depressed blink response on one side. Facial asymmetry with grimacing may also represent a cranial nerve VII injury.

Extraocular movements can be evaluated via either the oculo-cephalic or vestibulo-ocular maneuvers. The oculo-cephalic maneuver should be deferred in the setting of cervical spine instability and is tested by rapidly turning the head to either side. The vestibulo-ocular reflex is performed after confirming intact tympanic membranes. After the instillation of 50 mL of cold water into each auditory canal, contralateral horizontal nystagmus and ipsilateral gaze deviation should be observed in the setting of an intact pons. Several ocular abnormalities may be noted in the setting of brainstem injury. Ocular bobbing may be seen in pontine strokes, and a forced downgaze may be observed in patients with hydrocephalus compressing the superior colliculi of the midbrain.

Cranial nerves IX and X may be assessed via endotracheal suctioning to elicit a cough reflex as well as oropharyngeal stimulation with a tongue depressor to elicit a gag reflex.

Breathing Pattern

Several derangements in respiratory patterns can be seen in the setting of brain injury [88]. Cheyne-Stokes respiration is characterized as an incremental-decremental tachypnea followed by short apneic periods. It may be encountered in patients with global bi-hemispheric injury as well as bithalamic dysfunction, or other lesions above the diencephalon. It may also be seen in non-neurologic disorders such as heart failure, uremia, and high altitudes. Central hyperventilation consists of prolonged periods of rapid tachypnea and is usually not mitigated by sedatives. It is seen with lesions of the midbrain and rostral pons. Other underlying metabolic derangements that may result in tachypnea should be excluded prior to considering a neurogenic source. Apneustic breathing presents as a prolonged inspiratory phase, a pause at full inhalation, followed by expiration. Caudal pons lesions can cause this type of breathing pattern. The irregular pattern observed in clustered breathing may be seen with low pontine or high medullary lesions. Ataxic/Biot's breathing consists of periods of inspiration with varying degrees of amplitude and length interspersed with apneic periods and indicates a lesion of the dorso-medial medulla.

Motor Findings

Evaluation of motor deficits in the comatose patient may be difficult due to the inability to cooperate with isometric testing. The examiner should focus on the presence of any abnormal reflexive movements as well as any asymmetry. Purposeful movements such as withdrawing to a painful stimulus or localizing pain stimuli applied to other locations suggest an intact cerebral cortex. Flexor posturing consists of adduction of the shoulder and arm, flexion at the elbow and wrist, and lower extremity extension. It occurs when there is a brain injury above the level of the red nucleus in the midbrain. Extensor posturing involves adduction of the shoulder and arm, extension of the elbow, pronation of the forearm, and lower extremity extension with plantar flexion. It suggests a lesion below the midbrain red nucleus and the pons. With lesions below the pons, all motor pathways may be severed and the patient will not exhibit any limb withdrawal or reflexive brainstem response. Spinal reflexes such as triple flexion of the lower limbs at the hips, knees, and ankles are not considered cortical or brainstem responses. Other abnormal movements should also be noted, including tremors, dyskinesias, and asterixis. When present diffusely, these should raise suspicion for a toxic-metabolic etiology of coma.

Deep Tendon Reflexes and Pathological Reflexes

Deep tendon reflexes (DTRs) are examined by tapping the biceps, triceps, brachioradialis, patellar, and Achilles tendons with a reflex hammer. A normal reflex will elicit contraction of the muscle stimulated, and hyperactivity is noted if there is any "spread" with other muscles in close proximity also contracting. The presence of a pectoralis or jaw jerk reflex should be regarded as abnormal DTR hyperactivity. Pathologically hyperactive reflexes refer to those in which sustained clonus is seen, where the muscle continues to contract repeatedly even after discontinuation of the stimulus. This may be seen in the setting of upper motor neuron CNS injury or in the setting of metabolic derangements such as hyperthyroidism, hypomagnesemia, serotonin syndrome, or neuroleptic malignant syndrome. Hypoactive reflexes may be encountered in patients with chronic illnesses such as diabetes, due to their susceptibility to peripheral neuropathies. Decreased reflexes may also be seen in metabolic disorders such as hypothyroidism or hypermagnesemia. Reflex asymmetry should be considered a lateralizing sign of either acute or chronic CNS injury.

Pathological reflexes refer to primitive reflexes that were present at birth but are normally inhibited by intact cortical structures. These include the Babinski, Hoffman, snout, glabellar, and palmomental reflexes.

Skin Evaluation

A thorough skin examination should be performed on the undraped patient, including visualization of the thorax/back and extremities as well as close inspection of the palms and soles and nailbeds. Certain findings can assist with diagnosis, especially in the setting of toxic-metabolic derangements. A petechial rash in the extremities should raise suspicion for a thrombocytopenic source such as Neisseria/meningococcal septicemia, in which case prompt administration of broad-spectrum antibiotics may be life-saving, or thrombotic thrombocytopenic purpura (TTP), which may respond to plasmapheresis or immunosuppressant medications. Patients with high-grade hepatic encephalopathy often exhibit jaundice and scleral icterus, and laboratory evaluation of serum ammonia levels should be obtained. In patients with septic cerebral emboli, stigmata of endocarditis such as Janeway lesions and splinter hemorrhages are often detected. In patients who have been found unresponsive, post-auricular ecchymosis or a "Battle sign" could be evidence of underlying basilar skull fracture and traumatic brain injury.

Laboratory Findings

The initial laboratory evaluation performed on all comatose patients should be a finger-stick blood glucose. Hypo- or hyperglycemia should be corrected as detailed above. Other serum chemistries should also always include a basic metabolic panel, a liver function panel, and a complete blood count. A serum and urine toxicology screen should be sent if drug ingestion is suspected. If there is a history of pulmonary disease, an arterial blood gas (ABG) should assist in determining whether hypercarbia could be contributing to coma as well as to decide whether endotracheal intubation is warranted. In patients suspected of having a cerebrovascular event or on known anticoagulation, a coagulation panel is indicated. If these initial laboratory (or imaging) studies do not assist with diagnosis, other studies such as thyroid-stimulating hormone, ammonia, vitamin B12, and thiamine levels should be considered in the appropriate context.

Indications for Neuroimaging

A non-contrast CT of the head should be performed in all comatose patients. Although its sensitivity for detecting acute ischemic strokes is low, it can help exclude intracranial hemorrhage as the cause for coma. In patients who present with acute onset of coma, CT angiography of the head and neck should be obtained to evaluate for basilar artery occlusion, especially if they have any cranial nerve deficits or posturing on their examination. CT angiography and venography should also be obtained on any patient who reported thunderclap headache in order to evaluate for an aneurysm or venous sinus thrombosis. Although brain MRI is useful in the diagnosis of ischemic stroke in patients with localizing findings, the physician should note that acute care may be delayed while obtaining the study and that its sensitivity for vertebrobasilar infarcts within the first 24 hours may not be reliable [89].

Indications for Electroencephalography

Published guidelines exist for the selection of patients who benefit from cEEG monitoring [31]. Patients who have met criteria for convulsive status epilepticus and have not regained baseline mentation should be expeditiously evaluated for NCSE with cEEG. In any patient who has sustained a primary neurologic injury (e.g., traumatic, cerebrovascular, infectious, inflammatory, hypoxic) and remains with unexplained coma or encephalopathy, cEEG should be obtained. Critically ill patients without any primary neurologic disorders who meet any of the following criteria should also undergo cEEG evaluation: fluctuating mental status, periodic discharges on routine EEG, requirement for pharmacologic paralysis, and risk for seizures and clinical paroxysmal events suspected to be seizures [90]. EEG should also be considered in patients with ongoing encephalopathy even after sepsis or other metabolic derangements have already been corrected.

Indications for Lumbar Puncture

Comatose patients who present with any infectious symptoms such as fever, leukocytosis, rigors, or subacute malaise should be suspected to have meningoencephalitis. Although metabolic derangements such as acute kidney injury due to hypovolemia and sepsis may coexist, infectious workup with lumbar puncture and CSF examination is still warranted in these patients. Initial CSF studies should include cell counts, protein, glucose, Gram stain, culture, and herpes simplex virus (HSV) PCR. Empiric antibiotics should be initiated without delay for anyone suspected of having meningoencephalitis, even while awaiting a lumbar puncture. Other instances in which lumbar puncture should be pursued include patients with refractory seizures in whom an underlying infectious or inflammatory etiology may be contributing.

Indications for Multimodal Neuromonitoring

Direct continuous monitoring of ICP, cerebral perfusion pressure (CPP), or brain tissue oxygenation (pbO2) may be required in comatose patients with brain lesions in whom close monitoring of their neurologic exam is difficult or unachievable. TBI patients with GCS 3–8 should undergo continuous ICP monitoring, either via an intraparenchymal

or an intraventricular catheter. Other comatose patients who may benefit from close ICP monitoring include those with global cerebral edema from non-traumatic etiologies such as infection or inflammation. If hydrocephalus is found on imaging, comatose patients should have an EVD placed, as this intervention is both diagnostic and therapeutic. Although there is no evidence for improved outcomes, and some evidence showing worse outcomes, ICP monitoring may be included in the management of grade 3 and 4 hepatic encephalopathy [91, 92].

Discharge Destinations

The duration of coma in patients with disorders of consciousness varies depending on the underlying etiology and its reversibility. As such, some patients may recover to their baseline level of functioning during the hospital stay, while others may require months to years. One of the most important determinations to make when discussing goals of care with families is whether the cause of coma is irreversible or not and how long the physician suspects it may take for the patient to regain independence, if at all possible. Patients who remain comatose at the completion of their hospital stay will likely require long-term acute care services (especially if they remain dependent on life-supportive measures such as mechanical ventilation or artificial nutrition) or subacute nursing facilities. Patients who recover adequate neurologic function prior to discharge may benefit from acute rehabilitation therapies prior to returning home.

Brain Death

Introduction

Though it has been known for many years that a victim of a devastating brain injury may stop breathing prior to circulatory arrest, the concept of brain death was not formally described until the late 1950s [93, 94]. With the advent of mechanical ventilation, an increasing number of patients with devastating neurologic injuries could be sustained for periods long enough to observe the consequences of cardiopulmonary support in patients without CNS function.

Mollaret and Goulon first described a cohort of such patients, existing in "*coma dépassé*," literally the state beyond coma [95]. The cardinal features of this cohort were loss of all brainstem reflexes, apnea, polyuria, hemodynamic instability, and thermoregulatory impairment. A flat EEG was also noted.

A formal definition of brain death did not exist until 1968 when an ad hoc committee at Harvard set out to "define irreversible coma as a new criteria for death" using essentially the same features described by Mollaret and Goulon [96]. Brain death, or death by neurologic criteria, was legally recognized in the United States in 1981 by the Uniform Determination of Death Act as equivalent to death by cardiopulmonary criteria, though no specific criteria for diagnosis were mandated [97].

Due to the need for clarity and direction, the American Academy of Neurology (AAN) produced guidelines for the determination of brain death in adults in 1995 [98] and updated them in 2010 with multi-society support (the Neurocritical Care Society, the Child Neurology Society, the Radiological Society of North America, and the American College of Radiology) [99]. Though the key components of declaration of death by neurologic criteria are the same in pediatrics, the process is not identical. Guidelines were published by the American Academy of Pediatrics (AAP) in 1987 [100] and updated in 2011 by the AAP with multi-society support (the Child Neurology Society and the Society of Critical Care Medicine) [101].

All 50 states [102] and most countries [103] accept that death can be determined by cardiopulmonary or neurologic criteria, but there is no specific mandate as to the required protocol [104]. This has led to a wide variety in practices amongst institutions [105–107]. Notably, there is no mandate as to the number of examiners needed (1 or 2) or their qualifications (neurologist or non-neurologist, attending level physician or house staff). Though there have been no reports of any persons who have recovered from brain death when it is properly declared [99], there continue to be challenges to the validity of brain death. Undoubtedly the inconsistencies in declaration between states and institutions may contribute to this [108]. Some have advocated for a national regulatory agency to mandate consistency or global consensus diagnostic criteria [103]. In an effort to promote standardization of the declaration process, the Neurocritical Care Society has produced a set of useful online resources regarding brain death for both healthcare professionals and for the public called The Brain Death Toolkit [109].

Diagnosis

Preparing for Brain Death Examination

A variety of clinical conditions result in brain death, the most common of which is severe traumatic brain injury, followed by hemorrhagic stroke and hypoxic-ischemic encephalopathy post-cardiac arrest [110]. The first step in considering a diagnosis of brain death is to know, with certainty, the proximate cause. There are many reversible conditions that can mimic brain death, mostly due to intoxications [111]. Neuroimaging should be reviewed and should demonstrate findings consistent with the cause for brain death. Normal imaging should raise suspicion for a condition that might mimic brain death.

If there is any question as to whether a cervical spine injury could lead to quadriparesis, an MRI of the cervical spine can be performed.

The key features of declaring brain death are based upon a reliable clinical examination demonstrating coma and irreversible cessation of all functions of the brainstem, including respiratory drive [99]. Ancillary testing may be necessary to support the clinical diagnosis in some situations, specifically when aspects of the examination cannot be adequately or safely performed, but is not required in the majority of cases. Proper care must be taken to determine that a patient is suitable for brain death determination. Laboratory analysis should be reviewed to show that no complications exist that might confound the bedside examination (such as acute hepatic or renal failure, severe electrolyte or acid-base disorders, or endocrine disorders). Toxicology must be performed in addition to a thorough review of the medical record to ensure previously administered sedatives or paralytics are not influencing the clinical exam. Keep in mind that the metabolism of these drugs may be decreased in the setting of renal or hepatic impairment or hypothermia [112]. If a positive toxicology test was present on admission, it should be checked again prior to the examination. Careful attention should be paid to any IV infusions running at the time of the examination. The patient needs to be normothermic (>36°C) with a stable blood pressure (>100 mmHg systolic; the use of vasopressors is acceptable). We recommend using a checklist (Table 7.4, modified from the Brain Death Toolkit, Neurocritical Care Society [109]).

Table 7.4 Brain death checklist

Preparing for brain death testing	**Yes**	**No**
Proximate cause for brain death is known?		
Clinical history and/or imaging compatible with a cause for brain death?		
Absence of severe metabolic or endocrine conditions that may confound the bedside neurologic exam?		
Absence of sedating drugs or paralytics?		
Normothermia (96.8°F/36°C)		
Physical examination	**Yes**	**No**
Absence of any cerebrally mediated response to auditory and tactile noxious stimulation, peripherally and in the cranium (supra orbital or TMJ pressure). Spinally mediated reflexes are permissible.		
Pupils ≥4 mm and non-reactive to light?		
Absent OCR and OVR?		
Absent corneal response?		
Absent gag?		
Absent cough to deep suction?		
Apnea testing	**Yes**	**No**
Normothermia (≥96.8°F/36°C)		
SBP ≥100 mmHg (vasopressors ok)		
$pO_2 \geq 90$ mmHg		
pCO_2 35–45 mmHg (in non-CO_2 retainer)		
Well oxygenated with PEEP of 5 cm H_2O		
No spontaneous ventilation after $PaCO_2 > 60$ mmHg (or $PaCO_2 > 20$ mmHg over baseline in patients with history of CO_2 retention)?		
Ancillary testing Only one required if reliable bedside examination or apnea test cannot be performed		
Cerebral angiogram		
Nuclear cerebral blood flow study		
EEG		
TCD		

Modified with permission from the Neurocritical Care Society
TMJ temporomandibular joint, *OCR* oculocephalic reflex, *OVR* oculovestibular reflex.

Examination

There are no evidence-based guidelines to determine the appropriate timing of brain death testing after neurologic injury. We advise waiting until 24 hours after cardiac arrest as it is known that pupillary and corneal reflexes sometimes return after initially being abolished. For other disease states, the observation period should be dictated on a case-by-case basis according to the nature and extent of injury. Therapeutic hypothermia has been shown to delay neurologic recovery and also decrease the metabolism of drugs, including psychoactive medications [112].

Assess for Coma

The patient should be deeply comatose without any evidence of responsiveness. The examination should show no response to verbal requests that the patient follow commands, including to look up to exclude the possibility of a locked-in syndrome. Noxious stimulation should be given in the extremities by nail-bed pressure and proximally by axillary pinch or sternal rub. Noxious stimulation should also be applied in the face at the temporomandibular joint or supraorbital notch to exclude the possibility of absent motor response due to high cervical spinal cord injury. If there is any doubt as to the effect of residual paralytics, a peripheral nerve stimulator can be used. Spinal cord reflexes may be present and are sometimes difficult to distinguish from posturing or seizure [113, 114].

Pupil Response

The pupils should be mid-position or dilated. Miotic pupils should raise suspicion for drug intoxication. A bright light should be shown on the pupils directly, and a magnifying glass or pupilometer can be used to ensure no reactivity.

Eye Movements

There should be no spontaneous movements of the eyes or in response to noxious stimulation. The oculocephalic reflexes should be absent and can only be tested in patients without suspicion for cervical spine injury. This reflex is performed by turning the head from mid-position to 90 degrees to test horizontal eyes movements. The movement of the eyes should normally proceed in the opposite direction but is absent in

brain death. Vertical eye movements can be excluded in a similar fashion by passively flexing and extending the neck. The eyes should not open or move. Care must be taken to avoid extubating the patient during the procedure.

Oculovestibular testing should be performed ("cold calorics") in all patients including those with cervical spine injury, as long as it has been determined that the tympanic membrane is intact. To perform this test, the head of the bed should be raised to 30 degrees. 50 mL of ice cold water should be instilled into the external auditory canal for 60 seconds to stimulate the tympanic membrane while the eyelids are kept open. The normal response is for the eyes to tonically deviate to the side of the cold water stimulus. In brain death, no movement of the eyes should be seen with instillation of ice water into either ear.

Facial Responses

The corneal reflex must be absent. This should be tested by direct physical stimulation of the cornea itself with pressure applied by a cotton swab at the border of the iris (testing a "lash reflex" or using saline drop instillation is not sufficient stimulation to confirm the absence of the corneal reflex).

There should be no facial grimace to noxious stimulation. Facial myokimias are acceptable [113, 114], but only if they occur spontaneously and not in response to any stimulation of the patient.

Pharyngeal and Tracheal Responses

There should be no gag with the stimulation of the posterior pharynx with a tongue blade or suction device. A suction catheter should be advanced through the endotracheal tube to the level of the carina and should not elicit a cough response.

Apnea Testing

Apnea may be demonstrated by the absence of spontaneous respirations when given a carbon dioxide challenge [98, 99].

In order to perform the test, the patient must be normothermic (>36°C), normotensive (>100 mmHg; vasopressor use is acceptable), normovolemic, eucapnic (PCO_2 35–45 mmHg), and without hypoxia. If the patient cannot maintain an oxygen saturation of >95% without needing >5 cm H_2O PEEP, they will likely not tolerate the testing [115].

To begin, pre-oxygenate the patient for at least 10 minutes with 100% oxygen (to a $PaO_2 > 200$ mmHg). Obtain an ABG for baseline PCO_2.

The patient should be disconnected from the ventilator. Oxygenation is provided through an insufflation catheter placed into the endotracheal tube at the level of the carina. Oxygen should be given at 4–6 L/min. Higher rates may displace CO_2 which may lengthen the duration of observation needed to ensure appropriate hypercarbia has been reached.

Observe the patient closely with an undraped thorax and abdomen for any signs of attempted respirations. Observation should be performed for 8–10 minutes, as it is expected for the PCO_2 to rise at a rate of 2.5–3 mmHg per minute. At this time an ABG should be drawn again. If the $PaCO_2$ is >60 mmHg (or 20 mmHg higher than the baseline PCO_2 in chronic CO_2 retainers), the patient is apneic.

The test needs to be aborted if the systolic blood pressure drops below 90 mmHg or if the oxygen saturation drops below 85% for >30 seconds.

At the conclusion of the apnea test (or after aborting the test due to instability), give the patient 10 hyperinflating breaths with the resuscitation bag and reconnect the patient to the ventilator at his/her previous settings.

It should be noted that several reports have been made of ultra-sensitive flow detection triggering ventilator autocycling or a hyperdynamic precordium triggering the ventilator to provide breaths. It is for these reasons that the ventilator must be discontinued during apnea testing [116, 117].

Ancillary Testing

For the majority of patients, brain death can be determined by the clinical findings of irreversible coma, loss of brainstem reflexes, and apnea. An ancillary test is required if a patient cannot tolerate an apnea test or if the reliability of the clinical examination is compromised (e.g., severe facial trauma, cervical spine injury, or presence of sedating drugs).

The tests currently accepted for this use include cerebral angiography, nuclear scan, transcranial Doppler (TCD), and EEG [99]. The authors favor the use of the nuclear scan, angiography, or TCD as they all demonstrate lack of cerebral blood flow (Figs. 7.6 and 7.7).

Though there are many reports about the use of computed tomography angiography (CTA), magnetic resonance angiography (MRA), or perfusion imaging in brain death, these technologies have not been proven to have sufficient reliability for use in brain death determination [118–120].

Communication with Loved Ones

The time of death is documented as the time the PCO_2 reached the target value during the apnea test. If an ancillary test was required, the time of death is the time that the study was officially reported by an attending physician [99].

It should be noted that permission is not needed to perform brain death testing, but good practice dictates that families be kept informed as to the testing and its implications. Time should be taken to explain the meaning of brain death and for questions to be answered. The family should be notified upon the determination of death by neurologic criteria. This is the legal time of death, and a death certificate should

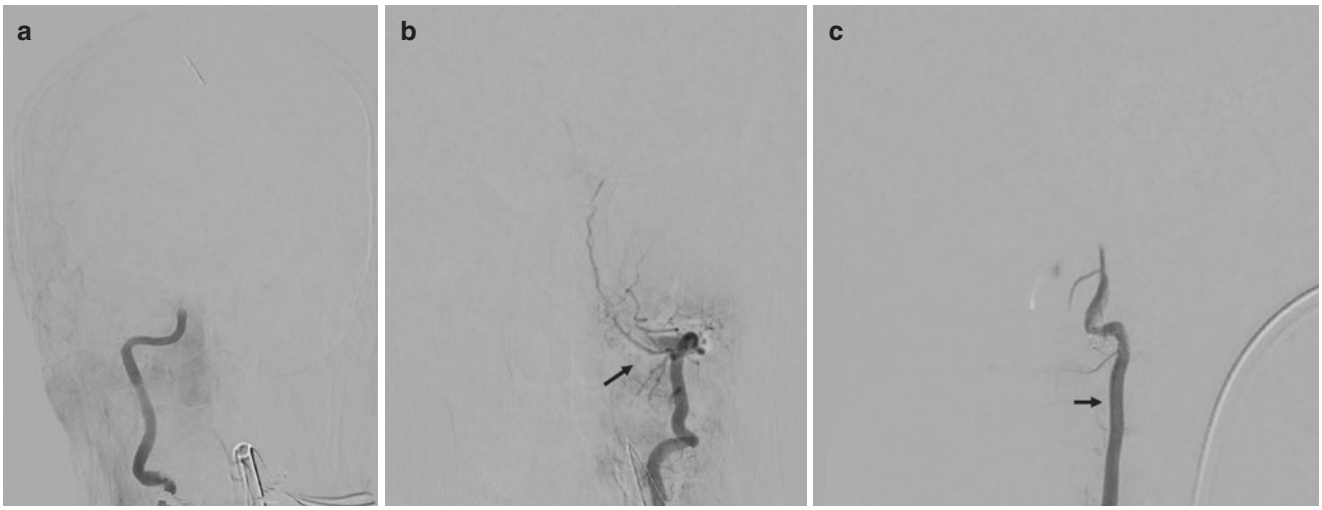

Fig. 7.6 (**a**) Right internal carotid artery: The diagnostic catheter is seen in the right internal carotid artery. There is vasospasm and stagnation of contrast of the cervical, petrous and proximal cavernous aspect of the right internal carotid artery without intracranial filling. There is reflux seen into the right external carotid artery circulation. (**b**, **c**) Left vertebral artery (AP view and lateral view, respectively): Opacification is seen in the cervical aspect of the left vertebral artery (with opacification of the muscular cervical branches). There is no intracranial filling. (*Angiograms provided courtesy of Mohamad Abdalkader, MD*)

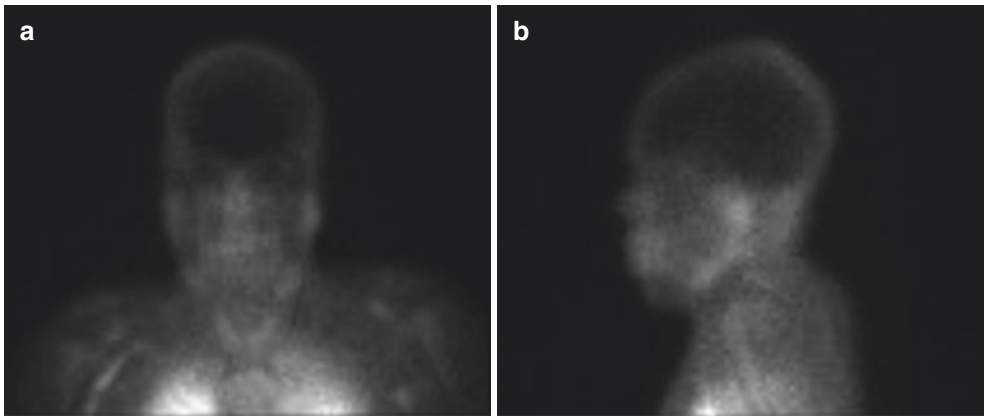

Fig. 7.7 Radionuclide angiogram: There is good blood flow through the bilateral extracranial common carotid arteries indicating a good tracer bolus. A "hot nose" sign is seen. There is no blood flow to the brain

be produced. Families do not need to consent to the removal of medical support, including removal of an endotracheal tube and ventilator, as the patient is deceased. Moreover, the term "removing life support" should be avoided since it sends mixed messages to the families. A reasonable period of time may be given to the family to grieve and come to terms prior to removal of medical support. In some cases a family member refuses to accept the medical and legal validity of death by neurologic criteria [121]. This has led to several prominent cases in the media, and rarely attempts are made to transfer patients to other facilities to avoid brain death declaration and discontinuation of organ support [122, 123]. In our experience, reasonable agreements can be made with initially objecting families with the assistance of an ethics committee, spiritual leaders, patient advocacy, and time.

Organ Donation

While the concept of brain death was certainly necessary to herald the increase in organ transplantation, declaration of brain death is important for reasons beyond organ donation. Declaration of brain death is crucial in conveying prognosis, both to families in order to understand finality and to the health care institution to allow distribution of finite resources.

The role of the neurointensivist continues beyond declaration of brain death. Though the organ procurement agency will screen the potential donor for suitability and direct care as needed for this determination, the intensivist will work collaboratively to ensure adequate viability of the organs and tissues. Careful support needs to be provided to the potential donor who may have significant physiologic derange-

ments that ensue as brain death occurs. In particular, it is common for the patient to develop diabetes insipidus and hemodynamic instability. Diabetes insipidus is suspected in the patient with polyuria (>300 mL/hour for 2 or more hours) and can be treated with IV desmopressin or the use of a continuous vasopressin drip. Hemodynamic instability may be multifactorial and treatment should be aimed at the presumed cause (hypovolemia, loss of autonomic coupling, altered thyroid function, decreased left ventricular function, arrhythmia, acid-base disturbance, thermoregulation failure) [111, 124]. Cardiac arrest often follows but is not inevitable following the diagnosis of brain death. In practice there are reports of many patients who have been sustained for prolonged periods of time with medical support [125].

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Part II

Cerebrovascular Emergencies

Ischemic Stroke in the Neurocritical Care Unit

8

Steven K. Feske

Introduction

Ischemic stroke is the most common severe neurologic disorder, the most common neurologic diagnosis leading to hospital admission, and the most common diagnosis prompting admission to the NCCU. Intravenous (IV) tPA (alteplase), the first successful therapy for acute ischemic stroke, was introduced in 1996. This therapy and advances since then, including strong evidence for the benefit of endovascular thrombectomy for rapid recanalization of occluded large intracranial arteries, have increased the demand for effective utilization of the NCCU to manage acute stroke. In this chapter, we discuss the current care of acute ischemic stroke, reviewing the clinical trials that support aggressive efforts to achieve early recanalization, the use of the NCCU to support optimal outcomes in this new treatment paradigm, and other issues pertaining to critical care for patients with unstable acute strokes.

Need for NCCU Care for Patients with Ischemic Stroke

Urgent treatments for acute ischemic stroke are time-sensitive and are most commonly initiated before admission to the NCCU. Their successful application requires the collaboration of acute stroke teams, including stroke neurologists, neurointensivists, emergency room physicians, interventional neurologists or neurosurgeons or neuroradiologists, and the technical and nursing teams that support these urgent efforts. Neurointensivists frequently play a role in the early decision-making for such patients. Many patients treated with IV thrombolysis and endovascular thrombectomy for stroke will be best served by the close monitoring provided by the NCCU for aftercare that includes monitoring for hemorrhage, recurrent stroke, and malignant cerebral edema, when large strokes occur despite the treating team's best efforts. In addition, cerebellar infarcts present a particular concern with regard to deterioration due to the potential for edema and mass effect in the posterior fossa. Many patients with unstable symptoms due to vascular stenoses will benefit from close monitoring and interventions to optimize collateral blood flow. Finally, medically ill patients, such as those with infectious endocarditis, may present with acute strokes and require NCCU care. In all of these conditions, the expertise of NCCU nurses skilled in the early recognition of neurologic deterioration is a critical component of effective care. Some medications commonly used in the acute setting for ischemic stroke are summarized in Table 8.1.

Intravenous Thrombolysis for Acute Ischemic Stroke

The National Institute of Neurological Disorders and Stroke (NINDS) trial of IV tPA established the benefit of this therapy for the first time in a large-scale clinical trial [4]. Therapy in this trial was limited to administration within 3 hours of symptom onset, setting the early standard for clinical implementation. Meta-analysis of data from the NINDS trial and other large trials suggested that clinical benefit might extend beyond this 3-hour window, and the European Cooperative Acute Stroke Study (ECASS) III trial provided evidence of benefit within a treatment window of 4.5 hours for selected patients [5–11]. Phase 4 post-marketing studies have demonstrated the successful implementation of protocols similar to those used in the NINDS and other trials in the community [12–15]. These clinical studies have established the standard of care for medical treatment of acute ischemic stroke [1–3]. Although the studies confirmed benefit for selected

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Table 8.1 Medications commonly used for acute ischemic stroke

Medication	Route	Dose	Indications	Major side effects
Alteplase	IV	0.9 mg/kg; max 90 mg	Acute ischemic stroke within 4.5 hours	Systemic and intracranial hemorrhage, angioedema
		10% bolus over 1 minute	(see Table 8.2 for details)	
		90% infuse over 1 hour	(off label for 3–4.5 hours use)	
Tenecteplase	IV	Dose for stroke not established	Acute ischemic stroke (off label for stroke)	Systemic and intracranial hemorrhage, angioedema
Heparin	IV	Targeting aPTT 60–80 s: 80 U/kg bolus, start infusion at 18 U/kg/hour; targeting aPTT 50–70 s: 60 U/kg bolus, start infusion at 12 U/kg/hour; check aPTT in 6 hours and adjust target	Mechanical heart valve, hypercoagulable state, venous sinus thrombosis, DIC, etc.	Systemic and intracranial hemorrhage, heparin-induced thrombocytopenia (HIT)
	SC	5000 U q 8–12 hours	DVT prophylaxis	Systemic and intracranial Hemorrhage, HIT
Enoxaparin (LMWH)	SC	40 mg daily lower dose for renal insufficiency and low body weight	DVT prophylaxis	Systemic and intracranial hemorrhage, HIT
Enoxaparin (LMWH)	SC	1 mg/kg q 12 hours; or 1.5 mg/kg daily	Treatment of DVT, PE, etc.	Systemic and intracranial hemorrhage, HIT
Fondaparinux	SC	2.5 mg q 24 hours	DVT prophylaxis (e.g., with history of HIT)	Systemic and intracranial hemorrhage
Fondaparinux	SC	<50 kg: 5 mg q 24 hours	Treatment of DVT, PE, etc.	Systemic and intracranial hemorrhage
		50–100 kg: 7.5 mg q 24 hours		
		>100 kg: 10 mg q 24 hours		
Argatroban	IV	Start: 1 mcg/kg/minutes; adjust to aPTT 1.5–3× initial value (with normal liver function)	IV anticoagulation in setting of HIT	Systemic and intracranial hemorrhage
Bivalirudin	IV	Start: 0.15 mg/kg/hour	IV anticoagulation in setting of HIT	Systemic and intracranial hemorrhage
		Adjust to aPTT 1.5–3× initial value (with normal renal function)		
Lepirudin	IV	Bolus: 0.4 mg/kg	IV anticoagulation in setting of HIT	Systemic and intracranial hemorrhage
		max 110 mg		
		Infusion: 0.15 mg/kg/hour		
		Adjust to aPTT 1.5–2.5× initial value (with normal renal function)		
Warfarin	PO	Targeting INR	Stroke prevention in AF, mechanical heart valve, hypercoagulable state, venous sinus thrombosis, etc.	Systemic and intracranial hemorrhage, acute hypercoagulability, skin necrosis, teratogenicity
Dabigatran	PO	150 mg bid (adjust for CRI)	Stroke prevention in AF, DVT, PE	Systemic and intracranial hemorrhage, dyspepsia
Apixaban	PO	5 mg bid (2.5 mg bid, if ≥2 of these: ≥80 y/o, ≤60 kg; SCr ≥ 1.5)	Stroke prevention in AF, DVT, PE	Systemic and intracranial hemorrhage
Rivaroxaban	PO	20 mg daily (adjust for CRI)	Stroke prevention in AF, DVT, PE	Systemic and intracranial hemorrhage
Edoxaban	PO	60 mg daily (adjust for CRI)	Stroke prevention in AF, DVT, PE	Systemic and intracranial hemorrhage
Cryoprecipitate	IV	Based on fibrinogen	Alteplase-related hemorrhage; low fibrinogen	Transfusion reaction
RiaSTAP	IV	Based on fibrinogen and weight	Alteplase-related hemorrhage; low fibrinogen	Thrombosis, allergic reaction
FFP	IV	Based on INR and weight	Reversal of INR elevation	Volume overload, transfusion reaction
PCC	IV	Based on INR and weight	Rapid reversal of INR elevation	Thrombosis, allergic reaction
ε-aminocaproic acid	IV	1–5 g q 4–8 hours (rate 1 g/hour)	Alteplase-related hemorrhage	Thrombosis
Tranexamic acid	IV	Load: 1 g over 10 minutes	Alteplase-related hemorrhage	Systemic thrombosis
		Infusion: 1 g q 8 hours given over 8 hours		

Table 8.1 (continued)

Medication	Route	Dose	Indications	Major side effects
23% saline	IV	30 cc and repeat adjusting to effect on serum Na and Osm	Cerebral edema	Volume overload, hypernatremia
Mannitol	IV	0.25–2 g/kg; repeat adjusting to effect on serum Na and Osm	Cerebral edema	Dehydration, volume contraction hyponatremia, hypernatremia, renal failure

IV intravenous, *AF* atrial fibrillation, *aPTT* activated partial thromboplastin time, *DIC* disseminated intravascular coagulation, *SC* subcutaneous, *DVT* deep vein thrombosis, *HIT* heparin-induced thrombocytopenia, *LMWH* low-molecular-weight heparin, *PE* pulmonary embolism, *PO* oral, *INR* international normalized ratio, *CRI* chronic renal insufficiency, *SCr* serum creatinine, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate, *Osm* osmolality

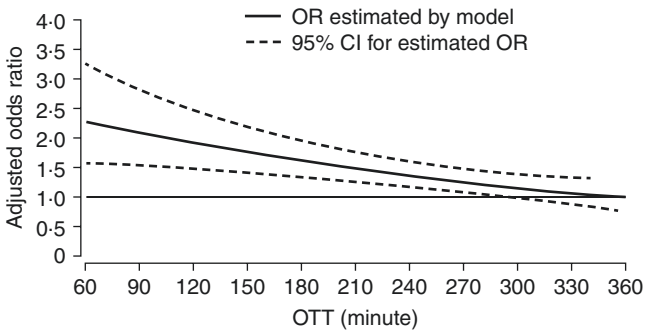

Fig. 8.1 Estimated odds ratio for favorable outcome at 3 months in IV t-PA-treated patients compared to controls by time of onset to start of treatment (OTT). OTT onset to start of treatment, OR odds ratio. (Reprinted with permission from Hacke et al. [7])

patients treated within the 3- and 4.5-hour windows, it is important to emphasize that, in all cases, the chance of improved outcome is maximized by the most rapid treatment possible within these times windows (Fig. 8.1) [4, 7]. Standard inclusion and exclusion criteria for treatment with IV tPA are shown in Table 8.2. Tenecteplase offers some theoretical advantages over alteplase, and some studies suggest enhanced benefit and better safety in patients with coronary occlusion and stroke [16–20]. Further study of this agent will determine its possible future entry into clinical practice for acute stroke. Reteplase and abciximab, alternative thrombolytic and antiplatelet agents, respectively, are under investigation.

Based on the protocol used for the NINDS trial, recommendations for the first 24 hours after treatment with IV tPA include maintenance of systolic blood pressure (BP) below 180 mm Hg and diastolic BP below 105 mm Hg and avoidance of antiplatelet and anticoagulant agents and of interventions that present a risk of hemorrhage (see Tables 8.3 and 8.4).

The degree of systemic fibrinolysis conferred by IV tPA varies among patients [21]. Because the fibrinolytic state is transient, and we do not intervene unless the patient develops clinically significant hemorrhagic transformation, testing of international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen are not recommended except to address clinical needs. If patients are stable without significant hemorrhage after 24 hours, then antithrombotic or anticoagulant therapy and chronic antihypertensive therapy should be implemented as indicated by the clinical circumstances.

The ECASS study provided a classification system for hemorrhagic transformation after IV thrombolysis, vary-

Table 8.2 Inclusion and exclusion criteria for intravenous thrombolysis [1–3]

Major inclusion criteria[a]
Age ≥18 years (for 3-hour window)
Severe or mild but disabling stroke
Blood pressure can be lowered to <185/110 mm Hg
Glucose >50 mg/dl (may consider therapy if focal deficit persists after correction of low glucose)
Major exclusion criteria[a]
Non-contrast head CT with extensive frank hypodensity of early infarction or with hemorrhage
Ischemic stroke within 3 months
Severe head trauma within 3 months
Intracranial or spinal surgery within 3 months
History of intracranial hemorrhage
Signs and symptoms of subarachnoid hemorrhage
Gastrointestinal malignancy or recent GI bleeding within 21 days
The following coagulation abnormalities: platelets <100,000, INR >1.7, aPTT >40 s, PT >15 s
Low-molecular-weight heparin given within 24 hours
Dose of direct thrombin inhibitor or direct factor Xa inhibitor with 48 hours, unless aPTT, INR, thrombin time, ecarin clotting time, or appropriate direct factor Xa activity are normal
Infective endocarditis
Aortic dissection
Intra-axial intracranial neoplasm

CT computed tomography, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *PT* prothrombin time

[a]The following additional exclusions are recommended for use in the 3–4.5 hours window: (1) Age >80 years, (2) history of both diabetes mellitus and prior stroke, (3) National Institutes of Health Stroke Scale (NIHSS) >25, (4) use of oral anticoagulant regardless of INR or other laboratory tests, and (5) CT evidence of ischemic injury involving >1/3 of the MCA territory

Table 8.3 Protocol for post-tPA management [1, 3]

Monitor closely and if severe headache, acute hypertension, nausea, vomiting, or worsening neurological examination occur, discontinue IV tPA, if still running; and obtain emergency head CT
Avoid nasogastric tube, urinary catheter, and arterial lines for 24 hours, if the patient can be managed without these
Maintain BP below SBP 180 and DBP 105 (see Table 8.4)
Obtain follow-up head CT or MRI 24 hours after treatment before starting antiplatelet or anticoagulant therapies

IV intravenous, *CT* computed tomogram, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MRI* magnetic resonance imaging

Table 8.4 Recommended management of high blood pressure before and after initiation of IV tPA [1, 3]

Pretreatment: If SBP >185 or DBP >110
Labetalol 10–20 mg IV over 1–2 minutes, may repeat 1 time
Nicardipine 5 mg/hour, titrate up by 2.5 mg/hour every 5–15 minutes; maximum 15 mg/hour
Clevidipine 1–2 mg/hour, titrate up by doubling the dose every 2–5 minutes; maximum 21 mg/hour
Or other agents, such as hydralazine, enalaprilat, etc.
Posttreatment: If SBP >180 or DBP >105
Labetalol 10 mg IV followed by IV infusion 2–8 mg/minutes
Nicardipine, clevidipine, or other agents, as above
For DBP >140, consider sodium nitroprusside

SBP systolic blood pressure, *DBP* diastolic blood pressure

Table 8.5 Classification of hemorrhagic transformation [5]

Hemorrhagic infarction
HI1 – small petechiae along the margins of the infarct
HI2 – confluent petechiae within the infarcted area
Parenchymal hemorrhage
PH1 – hematoma not exceeding 30% of the infarcted volume with mild mass effect
PH2 – dense hematoma exceeding 30% of the infarcted volume with significant mass effect

ing from scattered petechial hemorrhage with no mass effect to hematoma causing significant mass effect [5]. This nomenclature has come into common use (Table 8.5). Approximately 3–6% of patients treated with IV tPA will develop clinically significant hemorrhage [4–6, 8, 9, 11–15, 22]. Patients should be examined carefully to document neurologic function, including the National Institutes of Health Stroke Scale (NIHSS) before treatment and periodically for 24 hours (Table 8.3). Any deterioration in the examination (i.e., any increase in the NIHSS) should prompt discontinuation of IV tPA if it is still infusing and urgent imaging with non-contrast head computed tomography (CT) to look for cerebral hemorrhage. The serum half-life of tPA is very brief (<5 minutes), but tPA binds to thrombus and exerts its biological effects over many hours, hence the recommendation to avoid antiplatelet agents and anticoagulants for 24 hours. The risk of tPA-related hemorrhage correlates with depletion of plasma fibrinogen [21]. Patients with symptomatic

Table 8.6 Protocol for treatment of symptomatic IV tPA-related hemorrhage [3]

1. Discontinue IV tPA infusion
2. Obtain STAT CBC, PT (INR), aPTT, fibrinogen, type, and cross-match
3. Obtain urgent non-contrast head CT
4. Give cryoprecipitate (includes factor VIII) 10 U IV over 10–30 minutes; repeat if fibrinogen <200 mg/dl
5. Give tranexamic acid 1000 mg IV over 10 minutes or ε-aminocaproic acid 4–5 g over 1 hour, and then 1 g IV q 4–8 hours until bleeding is controlled
6. Consult neurosurgery
7. Support BP, ICP, CPP, and MAP, and control temperature and glucose

CBC complete blood count, *PT* prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *CT* computed tomography, *IV* intravenous, *BP* blood pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *MAP* mean arterial pressure

hemorrhage should undergo STAT laboratory testing, including fibrinogen, complete blood count (CBC) (which includes platelets), INR, and aPTT, and they should be treated with either cryoprecipitate or fibrinogen concentrate (RiaSTAP^{T}) until fibrinogen has been normalized. Elevated INR should be treated with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP), and thrombocytopenia should be treated with platelet transfusions. In the case of severe or uncontrolled bleeding, ε-aminocaproic acid or tranexamic acid, both agents that inhibit the conversion of plasminogen to plasmin, may be given to arrest hemorrhage. Once bleeding has been stopped, the patient should be managed by prioritizing efforts to avoid further hemorrhage and limit mass effect. Neurosurgical decompression may be offered in some cases after correction of measurable disorders of coagulation and, ideally, after a delay of at least 24 hours. The American Heart Association (AHA)/American Stroke Association (ASA) guidelines for the treatment of tPA-related hemorrhage are summarized in Table 8.6.

Endovascular Thrombectomy for Acute Ischemic Stroke

Although the introduction of IV thrombolysis represented a breakthrough in the treatment of acute ischemic stroke, many patients, especially those with occlusion of large proximal arteries (e.g., internal carotid artery (ICA), middle cerebral artery (MCA) stem (M1), basilar artery), will not benefit from this therapy.

Aims of treatment with intra-arterial tPA are thus to optimize the state of cerebral blood flow (CBF) and to minimize the risk of recurrent thrombosis and hemorrhagic transformation. In patients who have a large stroke despite thrombolytic therapy, goals include minimizing the detrimental

effects of cerebral edema and mass effect. The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial showed clinical benefit from endovascular administration of a thrombolytic agent, pro-urokinase, in patients with M1 occlusions [23]. However, the procedure studied in the PROACT II trial did not include mechanical disruption of the occluding thrombus, and, as technology advanced to include clot disruption and extraction with wires, snares, and suction devices, the intra-arterial administration of thrombolytics was never replicated in a large-scale trial. Along with the development of improved techniques for clot extraction, it has remained a goal of early stroke therapy to define patient eligibility not by time from stroke onset alone but based more directly on the state of the brain as defined by imaging of the infarct core and the penumbral territory at risk. The first large-scale trials to test the hypothesis that patients with large strokes will benefit from endovascular clot extraction with or without adjunctive intra-arterial thrombolysis were disappointingly negative. On March 7, 2013, three studies were published in *The New England Journal of Medicine*, all having failed to prove benefit [24–26]. With the perspective of the successful endovascular thrombectomy trials published in 2015, these failures likely had many explanations, including lack of angiographic proof of the target occlusive lesion leading to the enrollment of many patients without it, selective enrollment by many sites, and the lack of the availability of stent retriever devices, which later proved to be most efficacious, until the very end of enrollment in these 2013 trials. Subsequent trials addressed these shortcomings of design and technology, and in early 2015 and 2016, seven trials were published showing a large and consistent clinical benefit for endovascular clot retraction [27–33]. (Fig. 8.2). In particular, these studies established a clear benefit of endovascular thrombectomy with stent retriever devices in patients with proximal anterior circulation arterial occlusions (ICA, M1, M2) when treated within approximately 6 hours of symptom onset. The AHA/ASA updated their guidelines for the treatment of ischemic stroke incorporating this new evidence [3] (Table 8.7).

The 2015 studies left several open questions. These investigations did not include patients with distal MCA, anterior cerebral artery (ACA), or posterior circulation occlusions. Most practitioners and guidelines agree that it is most reasonable to extrapolate these results to include selected patients with occlusions of the M2 segment, ACA, basilar artery, vertebral arteries, and proximal posterior cerebral arteries (PCA), and that thrombectomy might be extended to some patients with pretreatment disability, large pretreatment infarcts, and milder but disabling strokes [3] (Table 8.7). In 2018, two studies were published extending the window of opportunity for treatment to 16–24 hours for patients with a small infarct core by imaging and evidence of significant tissue at risk, either by mismatch of a large clinical deficit to a small core or by mismatch of a perfusion imaging deficit to a small core [34, 35] (Fig. 8.2). The revised 2018 AHA/ASA guidelines for the management of acute ischemic stroke incorporate these new data (Table 8.7). Practitioners will surely also extend these indications to some patients who do not fall strictly within the studied populations.

Careful management of patients after intravenous thrombolysis or endovascular thrombectomy is essential to maintain the benefits of successful recanalization and to identify and treat complications of both the therapies and infarctions. Almost all patients will have some cerebral infarction after these therapies. Some patients will not achieve recanalization. Those who do may have small or large infarcts,

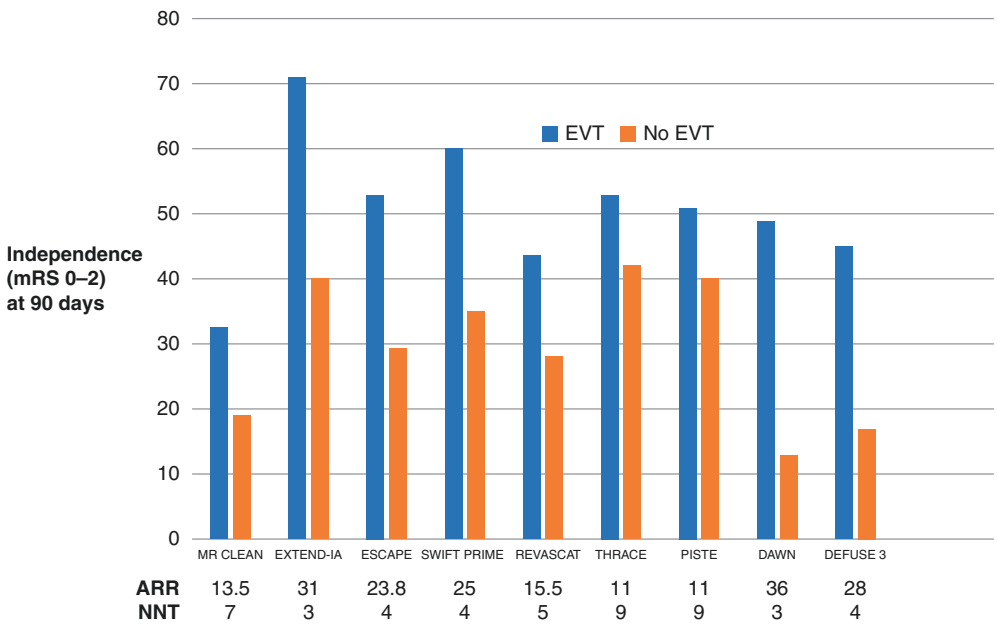

Fig. 8.2 Independence at 90 days after endovascular thrombectomy for acute ischemic stroke. Notes: mRS modified Rankin Scale, ARR absolute risk reduction, NNT number needed to treat to achieve one additional good outcome

Table 8.7 Guidelines for the treatment of acute ischemic stroke with endovascular thrombectomy [3]

Patients should receive mechanical thrombectomy with a stent retriever device if:
Strong recommendation (I, A)[a]
1. Pre-stroke mRS is 0–1
2. Causative occlusion is demonstrated in the internal carotid or MCA stem (M1)
3. Age ≥18 years
4. NIHSS ≥6
5. ASPECTS ≥6
6. Treatment can be initiated (groin puncture) within 6 hours of symptom onset
Less certain recommendations
7. M2 and M3 occlusions (IIb, B-R)
8. ACA, VA, BA, and PCA occlusions (IIb, C-EO)
9. Pre-stroke mRS >1 (IIb, B-R)
10. ASPECTS <6 (IIb, B-R)
11. NIHSS <6 (IIb-B-R)
16- to 24-hour window
12. Selected patients with onset within 6–16 hours with LVO in the anterior circulation who meet DAWN and DEFUSE 3 eligibility criteria (I, A)
13. Selected patients with onset within 6–24 hours with LVO in the anterior circulation who meet DAWN eligibility criteria (IIa, B-R)

MCA middle cerebral artery, *M1, M2, M3* first, second, and third segments of MCA, respectively, *ACA* anterior cerebral artery, *VA* vertebral artery, *BA* basilar artery, *PCA* posterior cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *ASPECTS* Alberta Stroke Program Early CT Score, *mRS* modified Rankin Scale, *LVO* large vessel occlusion, *DAWN* DWI or CTP assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with trevo trial, *DEFUSE 3* endovascular therapy following imaging evaluation for ischemic stroke trial

[a]I, IIa, and IIb refer to strength of recommendations: strong, moderate, and weak, respectively; A, B-R, C-EO refer to level of evidence: A = high-quality (more than 1 randomized controlled trial), B-R (randomized) = moderate-quality (1 randomized controlled trial), C-EO = expert opinion in the absence of strong evidence

depending on the site of vascular occlusion, the duration of occlusion before recanalization, and the status of collateral vessels. Initial concerns are to maintain vascular patency and to minimize the risk of hemorrhagic transformation. For post-thrombectomy patients who have received IV tPA, we generally follow guidelines for post-thrombolysis management (Tables 8.3 and 8.4). For those who have not received IV tPA, we typically begin antiplatelet agents immediately to lower the risk of local reocclusion at the site of procedure-related endothelial trauma and retained thrombus. We allow moderate systolic BP elevation to the 160–180 range to promote perfusion but limit risk of reperfusion hemorrhage. Patients should be monitored closely with serial neurologic examinations for the first 24 hours after treatment. Those who deteriorate should undergo urgent head CT to look for hemorrhage or extension of infarction. Other potential complications after thrombectomy include reocclusion of a recanalized artery, arterial dissection, and groin site complications, including groin site hematoma and femoral artery dissection and pseudoaneurysm formation.

After angiography for acute stroke, it is common to see some extravasation of radiopaque contrast material into the irrigation field of the treated vessels. Such extravasation creates hyperdense areas of contrast staining on non-contrast CT that may be difficult to distinguish from acute hemorrhage, or such extravasation may be mixed with hemorrhage. Hounsfield unit (HU) measurements do not reliably clarify the cause of the hyperdensities, since low values consistent with blood (<90 HU) may be due to contrast that is not densely distributed in tissue, and high values (>90 HU) do indicate the presence of contrast but do not eliminate the possibility that contrast is mixed with blood. Susceptibility or gradient-echo magnetic resonance imaging (MRI) sequences might be expected to make the distinction, but the blooming artifact of small amounts of blood makes interpretation problematic in practice. Such extravasation does not seem to indicate increased risk of hemorrhage, although it does correlate with prior hemorrhage and infarct [36, 37]. Yet, not all areas of post-thrombectomy contrast staining are destined to progress to infarction (Fig. 8.3). If post-procedural hyperdensities are seen on CT without severe mass effect, a repeat CT in 6–12 hours will usually clarify the cause. The groin puncture site should be inspected for evidence of hemorrhage and palpated for evidence of a pseudoaneurysm, and distal pulses and capillary filling should be documented. A pseudoaneurysm may be found as a pulsatile mass near the puncture site or may be demonstrated by ultrasound. If found, consultation with a vascular surgeon should be obtained for arterial repair.

Cerebral and Cerebellar Edema and Swelling After Infarction

Some patients will develop malignant edema during the first hours and days after large, usually MCA territory, infarcts. Cytotoxic edema resulting from infarction and the resultant brain swelling is the main cause of early death from ischemic strokes, and it threatens to extend the volume of stroke in those who survive. Such edema results from lysis of necrotic cells and the breakdown of the blood-brain barrier in areas of ischemic injury, although the reasons that one patient develops severe edema and another does not are not clear. A non-selective cation channel, the $NC_{Ca\text{-}ATP}$ channel, in neurons, astrocytes, and capillaries is opened by the adenosine triphosphate (ATP) depletion caused by stroke and trauma and promotes the development of cytotoxic edema. This channel is regulated by the sulfonylurea receptor 1 (SUR1) providing a possible therapeutic target [38].

Current therapy for edema depends on hyperosmolar agents and surgical decompression. Mannitol and/or

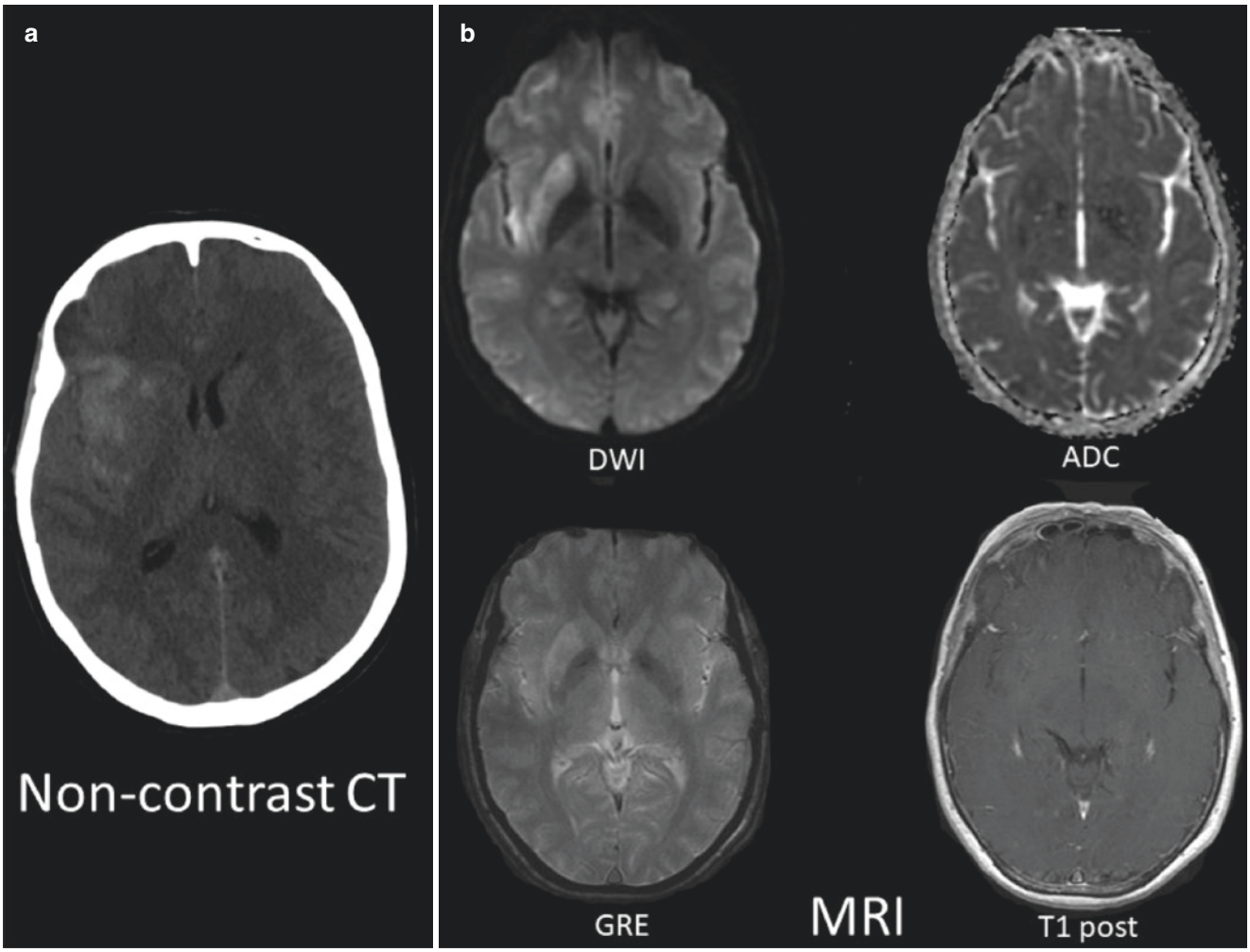

Fig. 8.3 A 58-year-old woman presented with left hemiparesis and neglect and was found to have right M1 occlusion that was treated with endovascular thrombectomy 14 hours after she had been last seen well. Two stent-retriever passes achieved TICI 2b reperfusion. (**a**) Non-contrast head CT completed approximately 1 hour after recanalization shows contrast staining in the right frontal, temporal, and insular cortices. (**b**) MRI performed 3 ½ hours later demonstrates evidence of acute infarct in the right putamen on DWI and ADC sequences but no infarct in the areas of cortical contrast staining. GRE sequence shows no evidence of hemorrhage. T1 sequence after gadolinium administration reveals no enhancement in the same area. She had a near-full functional recovery with only minimal left facial weakness and subtle left pronator drift at discharge. TICI thrombolysis in cerebral infarction scale, DWI diffusion-weighted image, ADC apparent diffusion coefficient, GRE gradient echo

hypertonic saline may be given to reduce edema. We prefer the use of 23% saline to rapidly achieve a high osmotic gradient between the intravascular and intracranial space for best effect. Slow infusion of 3% saline does not clearly achieve an adequate gradient given that the injured blood-brain barrier does not effectively exclude the passage of sodium, and, even in the presence of an intact blood-brain barrier, the exclusion of mannitol and sodium from crossing the blood-brain barrier is time-limited. Clinical trials are now underway to test the effect of the SUR1-inhibitor glibenclamide on cerebral edema after large strokes [39, 40].

The permanent harm due to cerebral edema results from the swelling of the brain in the enclosed cranial space causing elevated intracranial pressure (ICP) with compromise of cerebral perfusion and herniation of brain tissue. These consequences are most effectively countered by decompressive hemicraniectomy. Several studies have convincingly shown that early hemicraniectomy decreases mortality and improves outcomes in patients 60 years of age or younger [41–44]. In older patients, hemicraniectomy reduces mortality without benefit in functional recovery in survivors [45].

Because most patients who survive after hemicraniectomy will have major neurologic deficits, and because the benefits are lost if surgery is delayed until after severe swelling and herniation have developed, it is important that those caring for such patients develop protocols for the proper consideration and application of this life-saving surgery. The goal is to define clinical features that will allow the prediction of

malignant edema within the first 24–48 hours and to precede any decision to act with a frank and open conversation with the patient's caretakers so that they can make an informed decision on the desirability of survival given the expected neurological deficits and disability. For this purpose, the STATE criteria, though not definitive, offer some direction, taking into consideration the degree of neurologic dysfunction on presentation (NIHSS) including level of consciousness, size of the infarct by CT or MRI, the patient's age, time since stroke onset, and, very importantly, expectations of the patient's health care proxy [46] (Table 8.8).

The issue of infarction-related cytotoxic edema in a closed space presents itself most urgently in the setting of large cerebellar strokes. The posterior fossa offers less space than the supratentorial compartment for swelling. Swelling after a cerebellar stroke can block the IVth ventricle and cerebral aqueduct causing acute hydrocephalus, and it can cause a rapid increase in pressure and compression of the vasculature and brainstem parenchyma, leading ultimately to secondary infarction of the brainstem. Progression of such edema will often lead to irreversible coma and death. The potential for such life-threatening complications must be considered in all patients with acute cerebellar infarcts. The larger the infarct, the more likely it is that threatening swelling will develop. Because the posterior inferior cerebellar arteries (PICA) supply the largest portion of the cerebellar hemispheres, most ominous lesions include infarctions in these territories. There is evidence that patients with cerebellar infarcts affecting 1/4 to 1/3 of the cerebellar volume with Glasgow Coma Scale (GCS) ≥9 and without deterioration of GCS before surgery benefit from suboccipital decompressive craniectomy (SDC), including achieving better functional outcomes and decreased mortality [47–50]. All patients with moderate-sized or large acute infarcts in the cerebellum should be closely monitored for such complications so that corrective interventions can be applied rapidly when needed and before progression to clinical deterioration. We monitor all such patients in the NCCU during the first several days after cerebellar infarction, and we engage our neurosurgical colleagues in anticipation of a potentially needed surgical decompression. All such patients should receive central venous access. Early use of hyperosmolar therapy with 23% saline and/or mannitol may prevent progression and forestall the need for surgery in some patients. Patients will often be fully alert on presentation and then deteriorate rapidly with the progression of edema and the development of obstructive hydrocephalus or brainstem compression. The first clinical signs of such deterioration are impaired upgaze and depression in level of consciousness. In patients with infarction of >1/4 of the cerebellar volume, or those with early compression of the IVth ventricle, SDC with or without external ventricular drain (EVD) should be performed before such clinical deterioration. If an EVD without SDC is placed in a patient with cerebellar infarction, continued close surveillance is critical, since many such patients will continue to progress due to direct brainstem compression or upward transtentorial herniation into the decompressed supratentorial compartment, and these patients will need urgent SDC. After surgery, patients are managed with hyperosmolar therapies as needed until swelling has subsided and catheters and EVDs can be safely removed.

Table 8.8 STATE criteria for hemicraniectomy for malignant edema in patients with MCA stroke [46]

Score	NIHSS item 1a ≥ 1 and NIHSS >15
Time	Within 45 hours of onset
Age	18–60 years old
Territory	MRI: DWI infarct volume >145 cm^3; CT: Infarct ≥50% of MCA territory
Expectations	Understanding that surgery improves survival, but the patient will probably still have major disability

MCA middle cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *MRI* magnetic resonance imaging, *DWI* diffusion-weighted imaging, *CT* computed tomography

Symptomatic Cervical and Intracranial Arterial Stenosis and Occlusion

Patients with severe vascular stenoses or occlusions, either intracranially or in the cervical internal or common carotid artery, may present with acute ischemic symptoms that prove to be reversible, either spontaneously or with augmentation of the BP to increase CBF.

The normal cerebral circulation has parallel channels that, if occlusions or stenoses are proximal to them, can provide immediate pathways of collateral flow. With occlusion or stenosis of the carotid artery below the origin of the ophthalmic artery, these channels include (1) the ophthalmic artery, which can reverse to provide flow from the external carotid to the distal ICA; (2) the posterior communicating artery, which can provide flow from the PCA to the distal ICA; and (3) the anterior communicating artery, which can provide crossing flow from the opposite carotid and ACA. Contrariwise, if basilar flow is blocked, an open posterior communicating artery can supply the distal basilar artery and its branches with flow from the anterior circulation. When such proximal channels are developmentally small or occluded by disease, or when blockage of flow is distal to these collateral connections, then collateral flow may be supplied by leptomeningeal branches filling from adjacent open vessels. For example, after occlusion of the MCA stem, leptomeningeal branches of the open anterior and posterior cerebral arteries may provide enough flow to penetrate deeply into the distal MCA branches. The effectiveness of such collateral flow to avert acute infarction depends on the size of the native collateral arteries and the CBF within them. CBF depends on

the equation for flow dynamics: CBF = CPP/CVR = MAP – CVP/CVR (where CPP = cerebral perfusion pressure, MAP = mean arterial pressure, CVP = cerebral venous pressure, and CVR = cerebral vascular resistance) (CVP, though not directly measured, should be nearly the same as the ICP when ICP is normal.). As this relationship shows, CBF varies directly with MAP. Hence, by driving up the MAP, we might augment flow from collateral channels allowing it to reach penumbral tissue at risk of infarction.

In addition to these standing collateral vessels, extended periods of oligemia will induce the growth of new vessels. This process is most important with longstanding stenoses, such as in moyamoya syndrome; however, some new vessel formation begins within days of oligemia onset [51, 52].

Although controlled studies have not shown the benefit of induced hypertension in large populations, clinical observations confirm its safety and benefit in many cases [53, 54]. Serving as his or her own control, a patient may demonstrate resolution of deficits with higher MAP and return of these deficits with lower MAP. When this relationship is reproducible in a patient with an appropriate vascular lesion, then the effect of augmenting collateral flow by induced hypertension is convincing. Such collateral flow can be demonstrated with various forms of flow and perfusion imaging. For example, transcranial Doppler (TCD) can show the directional change in the ophthalmic artery that accompanies ICA occlusion with external carotid artery/ophthalmic collateralization or in the ipsilateral ACA A1 segment that accompanies cross-filling from the anterior communicating artery. Also, vasoreactivity TCD studies can show the degree of compensatory vasodilation in potentially stressed tissues by showing a loss of capacity to dilate further with hypercarbia, and single photon emission computed tomography (SPECT) scans can similarly show lack of flow augmentation from acetazolamide (a vasodilatory stimulus) in vessels that have already reached their maximal caliber. CT and MR perfusion imaging can also be employed to show the extent of areas of delayed and poor blood flow. All of these modalities can be employed to show collateralization and flow augmentation that may be dependent on BP.

To capitalize on potential collateral flow in the setting of acute ischemic stroke, we hold antihypertensive agents (except beta-blockers in patients with coronary artery disease and sometimes in those with atrial fibrillation) to allow the systolic (and mean) BP to run high during the acute phase of stroke. Typically, the BP spontaneously rises acutely and remains high for several days after stroke onset before it begins to fall toward its baseline. We allow this autoregulatory rise to go untreated, unless hypertensive complications occur (heart failure, coronary ischemia, hypertensive encephalopathy, acute renal failure, or in cases of aortic dissection) or unless the protocol for post-IV tPA care demands the compromise of lowering to systolic BP <180. Acute ischemic stroke management guidelines typically recommend no treatment of BP unless it rises to 200–220/110–120, assuming that higher pressures will be no more effective above that high level and given concern for excessive elevations [1].

When a patient presents with stenosis or occlusion and a functional deficit larger than would be expected based on the volume and location of demonstrable infarction, then we proceed to a trial of induced hypertension. We place the head of bed flat; if tolerated, give IV fluids to optimize volume and BP and perfusion; and then using phenylephrine (or norepinephrine), we push the BP up in stages to a maximum of approximately systolic BP 200 or MAP 130 to see if function recovers at the higher BP. If it does not after a sustained interval of induced hypertension, then we consider that a failed trial and allow BP to autoregulate. However, if induced hypertension successfully improves function, then we will allow the BP to fall under close observation. If the symptoms re-emerge, then we will consider that a successful trial, and we will maintain BP augmentation at the lowest level needed for sustained maximal function.

In the best of situations, the endpoint of such induced hypertension will be spontaneous recanalization, which will allow the patient to tolerate normal BP. However, early recanalization is uncommon when acute recanalization has not been achieved by thrombolytic agents or endovascular thrombectomy. Commonly, patients who improve with induced hypertension will adapt to the occlusion over a period of days allowing withdrawal of vasopressors without functional deterioration. In patients whose deficits re-emerge when BP is allowed to autoregulate after a prolonged period of induced hypertension, we are left to consider surgical revascularization. Although we do recommend surgical revascularization in highly selected cases without satisfactory alternatives, the literature has not shown benefits of such procedures in controlled trials. So, before we discuss our approach, let us review the major trials.

Surgical bypass for symptomatic atherosclerotic disease has been studied in two large clinical trials. In 1985, the Extracranial-to-Intracranial (EC-IC) Bypass Study failed to show a benefit of EC-IC bypass [55]. This procedure was done infrequently after this study's publication. However, the techniques were improved, and an updated trial, the Carotid Occlusion Surgery Study (COSS), was completed in 2011 [56]. This trial, too, failed to show benefit from EC-IC bypass, arguing against its use in the manner built into the trial design. Endovascular angioplasty and stenting has also been studied in two clinical trials. Stenting of symptomatic intracranial stenoses was studied in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial; this trial was stopped early due to poorer outcomes in the stented patients [57]. In fact, the patients in the medically treated group fared better than had been anticipated based on preliminary work.

A second similar trial, the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT), also found poorer outcomes in stented patients [58].

Following these results, we also recommend optimal medical management for patients like those in the trials. However, in all of these trials, the enrolled subjects included mostly those who were stable ambulatory patients off vasopressors without induced hypertension. That is, patients who had proven themselves possessed of adequate collateral circulation to achieve that outcome. Left with a small subset of patients who are in the early phase of stroke or transient ischemic attack (TIA) and who cannot be weaned from induced hypertension without deterioration, we feel that favorable experience justifies surgical revascularization where proper neurovascular surgical expertise is available. This is usually done by grafting the superficial temporal artery to an M2 (insular) or M3 (opercular) branch of the MCA. Though not tested, by extension, other grafting procedures to the proximal PCA or by using venous grafts, can also be done based on surgical need. With this highly selective approach, we have had good outcomes with surgical revascularization of patients with unstable intracranial and cervical artery occlusions. We do not recommend stenting of intracranial stenoses, but rather treating such patients with dual antiplatelet therapy and intensive risk factor management as recommended by the relatively good outcome in the medical arm of the SAMMPRIS trial.

Other Critical Care Issues

Any patient with acute stroke or high risk for acute stroke due to hemodynamic lability will need close monitoring in the NCCU during this period of instability. Patients with acute lacunar stroke syndromes may be unstable initially, sometimes with dramatically fluctuating symptoms alternating between sudden severe syndromes, such as hemiplegia and dysarthria, and then abrupt recovery of function. There is no established treatment for such small vessel strokes. However, rather than allowing such "stuttering lacunes" to recur and ultimately progress with only antiplatelet therapy given lack of proven treatments, we recommend optimization of BP and flattening the head of the bed, then a trial of induced hypertension, and, when these measures fail, heparinization. Anecdotal experience suggests that these measures may terminate fluctuations in some patients. Having stabilized the situation, we then move to validated therapies for long-term secondary prevention.

Patients with infectious endocarditis do not typically require NCCU care; however, monitoring in either a neurology or cardiac care intensive care unit is advised when patients present with neurologic complications, including hemorrhagic infarction, subarachnoid hemorrhage, recurrent cardio-embolism, or cardiac complications, such as valvular decompensation, heart failure, or conduction block, or systemic complications such as sepsis. Because neurologic complications are often the initial and most critical early signs of endocarditis, neurointensivists must be prepared to care for these patients in consultation with their cardiology, cardiac surgery, and infectious disease colleagues.

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9 Treatment of Subarachnoid Hemorrhage in the Neurocritical Care Unit

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Epidemiology and Risk Factors

The annual incidence of aneurysmal subarachnoid hemorrhage (aSAH) worldwide is approximately 9 per 100,000 and varies by region [1], ranging from 2 per 100,000 in China (Beijing) to 22 per 100,000 in Finland and Japan [2]. The annual incidence in the United States is between 7 and 10 per 100,000, affecting up to 30,000 Americans annually [3, 4]. These estimates, however, are likely conservative as nontraumatic SAH comprises a higher-than-predicted percentage of hospital discharges based on these estimates [5], and death prior to hospital admission occurs in approximately 12% of aSAH cases [6].

Non-modifiable risk factors for aSAH include gender, race/ethnicity, socioeconomic status, age, and genetic predisposition. aSAH is more common in women [5, 7, 8] with a pooled risk that is 1.24 times higher than men [9]. Some female subpopulations may have an even more exaggerated risk compared with their male counterparts. A prospective study of aSAH in a southeast Texas population enriched for Hispanic race found an age-adjusted risk that was 1.74 times greater for women than men [10]. Female gender has been shown to confer even greater risk in cases of nulliparity (OR 3.24) or early menarche (OR 4.23) in Japanese women [11]. Age amplifies the gender risk discrepancy starting at age 50, with this difference increasing thereafter [1]. Furthermore, the effects of modifiable risk factors, such as smoking, may be magnified in women compared with their male counterparts [12, 13].

aSAH is infrequent in the pediatric population [14] and most frequently presents in the fifth and sixth decades of life, with a slight decline in frequency thereafter [2]. Lower socioeconomic status is also associated with a higher risk of aSAH, a finding that has been independently reported across diverse geographic populations [15–17]. Risk is further stratified by race and ethnicity as higher rates of aSAH have been reported in blacks and Hispanics compared with whites [4].

Individuals with a family history of aSAH have a higher incidence of aneurysmal rupture as compared with individuals harboring similarly sized aneurysms but without a family history [18]. Autosomal dominant syndromes such as polycystic kidney disease and perhaps type IV Ehlers-Danlos demonstrate the heritability of cerebral aneurysms but account for a minority of aSAH. Individuals without a defined genetic syndrome who have more than one first- through third-degree relative with an intracranial aneurysm have an 8% risk of harboring an intracranial aneurysm, and these aneurysms are more likely to rupture at a young age [19]. With the exception of haptoglobin (Hp) 2–2 (see below), no genetic basis for aneurysm formation and rupture has been definitively identified; however, recent genome-wide association studies have found at least six single nucleotide polymorphisms correlating with aSAH risk, confirming that these clinical patterns have genetic underpinnings [20, 21].

Modifiable risk factors include hypertension, smoking, alcohol abuse, sympathomimetic drugs, and body mass index (BMI). Chronic hypertension has been consistently linked to an increased risk of aSAH. The HUNT study, which prospectively followed 74,997 participants in Norway, reported hazard ratios (HR) of 2.3 and 3.3 for SBP 130–140 and >170 mmHg, respectively [22]. In addition to hemodynamic stress, chronic hypertension is thought to induce ischemic vessel wall damage secondary to compression of the

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vasa vasorum [23]. Transient hypertensive episodes have also been shown to precipitate aneurysm rupture. A study by Vlak et al. identified eight trigger factors for aneurysm rupture, including physical exercise, coffee consumption, anger, nose blowing, and sexual intercourse [24]. The authors hypothesized that the common mechanism among these activities was an acute spike in blood pressure.

Smoking contributes to the risk of aneurysm formation and rupture via multiple mechanisms, including induced hypertension, vessel wall inflammation, increased protease activity, and increased blood viscosity [23]. In the HUNT study, prior smoking history was associated with an increased risk of SAH (HR 2.7), and current smoking status increased the HR to 6.1 [25]. Smoking synergistically increases the risk imparted by other risk factors as well, including female gender, race, hypertension, and family history [26, 27]. Duration and intensity of smoking exposure is associated with an increased risk of aSAH; however, smoking cessation does not appreciably reduce this risk beyond the effect predicted from decreasing cumulative exposure [28]. Interestingly, a Swedish study showed that smokeless tobacco does not increase the risk of aSAH, suggesting that nicotine exposure is unlikely to be responsible for the aSAH risk associated with smoking [29].

Low BMI is associated with an increased risk of aSAH, and overweight BMI confers a protective effect independent of HDL, cholesterol, or triglyceride levels [30]. Cocaine use has been associated with rupture of smaller aneurysms at a younger age [31]. Heavy alcohol use has also been associated with an increased risk of aneurysm rupture. A recent retrospective study including 6411 intracranial aneurysms found that current alcohol use (OR 1.36) and current number of alcohol beverages per day (OR 1.23) were associated with aneurysm rupture. Unlike smoking, however, neither prior alcohol use nor frequency of prior alcohol use was associated with an increased risk of aneurysm rupture [32].

Recent data have confirmed that Hp 2–2 genotype strongly predisposes to vasospasm following aSAH and contributes to worse outcomes [33]. There are two Hp alleles in humans (Hp 1 and Hp 2) giving rise to three Hp genotypes (Hp 1–1, Hp 2–2, and Hp 2–1). The Hp 2–2 genotype impairs binding of free hemoglobin and predisposes to worse outcomes in several disease states, including diabetes, sickle cell, and cardiovascular disease [34]. In aSAH, Hp 2–2 drives a pro-inflammatory phenotype mediated by myeloid cells [35, 36]. In a landmark study, Leclerc and colleagues reported that Hp 2–2 phenotype was significantly associated with a higher risk of moderate ($p = 0.014$) and severe ($p = 0.008$) vasospasm as well as a trend toward increased mortality ($p = 0.079$) and lower functional status 1 year after discharge ($p = 0.055$) [37]. This association is becoming widely accepted as a growing body of evidence suggests that the Hp 2–2 phenotype is associated with larger aneurysms and more severe vasospasm in patients and preclinical models of aSAH [36, 38–40]. Ongoing research is probing the underlying pro-inflammatory mechanisms of the Hp 2–2 phenotype in an effort to identify molecular targets that will mitigate vasospasm and DCI in these patients.

Triage and Admission (Initial 12 Hours)

The initial presentation of aSAH is variably dramatic, ranging from nonspecific headache to coma or death. Sudden death occurs in 10–15% of patients, and coma from acute brain injury and/or cardiopulmonary complications is common [41]. Loss of consciousness (LOC) is the presenting symptom in approximately 40% of patients and is associated with higher clinical and radiographic severity scores [42]. Even transient LOC is a negative prognostic indicator, presumably due to severe early brain injury as no association has been identified between LOC and rebleeding risk or delayed cerebral ischemia [42, 43].

In patients able to provide a history, headache is the most frequent presenting symptom and is described in more than 95% of patients presenting with aSAH [44]. The classic description of "worst headache of life" or "thunderclap headache" is recounted by approximately 80% of patients; however, the specificity of severe, sudden onset headache or "worst headache of life" is low [45]. Mild sentinel headache is reported by 10% of patients, typically 2–8 weeks before presentation [46]. More severe headaches precede the precipitating event that leads to a diagnosis of aSAH in approximately 20% of patients. Warning leaks prior to aneurysm rupture are associated with overall worse outcomes; therefore, a high degree of suspicion is warranted in patients presenting with new-onset headaches and no prior history or a patient with a history of headaches presenting with atypical headache symptomatology [47].

Misdiagnosis of aSAH is unfortunately common. A study by Kowalski and colleagues that followed patients from 1996 to 2001 at a single tertiary center reported a misdiagnosis rate of 12% [48]. Migraine and tension headache were the most common incorrect diagnoses. Thirty-nine percent of these patients developed neurologic complications, and rebleeding occurred in 21%. Among patients with a normal mental status on initial presentation, misdiagnosis was associated with lower quality of life scores at 3 months and an increased risk of death or severe disability at 12 months. Although aSAH is diagnosed in only 1% of patients presenting with a chief complaint of headache [49], the consequences of misdiagnosis are dire; therefore, a noncontrast head computed tomography (CT) should be obtained in any patient presenting with severe, sudden headache and no history of similar episodes. Other symptoms commonly associated with aSAH are nausea/vomiting (77%), nuchal rigidity (25%), fixed or transient neurologic deficits (10%), and seizures (6%)

[50–52]. These symptoms may be present alone or in combination. Headache accompanied by nuchal rigidity, focal neurologic deficits, or seizures should invariably trigger an aSAH workup.

Noncontrast head CT is the initial diagnostic test of choice and has a sensitivity of nearly 100% in the initial 5 days following aneurysm rupture [53]. After 5 days the sensitivity of head CT declines sharply, and additional studies are warranted in the appropriate clinical context. Lumbar puncture to assess for red blood cell count or xanthochromia has relatively low sensitivity and specificity but may be beneficial in select patients with a high pretest probability of aSAH based on history and clinical presentation and a negative head CT [54]. Magnetic resonance imaging (MRI) has demonstrated utility in detecting aSAH in patients with a negative head CT and may be used in select cases as an adjunct to or in lieu of lumbar puncture; however, logistic considerations including resource utilization and the challenges of obtaining MRIs in critically ill patients make routine use of MRI in aSAH patients impractical at most centers [46]. Patients with CT and/or lumbar puncture evidence of aSAH next undergo vascular imaging. Catheter-based cerebral angiography is the gold standard for imaging cerebral aneurysms as this modality provides detailed information about aneurysm morphology, spatial relationships to critical vessels, and collateral circulation. Computed tomography angiography (CTA) is useful for triage and planning when angiography is not immediately available. We do not typically use magnetic resonance angiography (MRA) in aSAH patients due to its high false-positive rate (60%) [55] as well as the aforementioned logistic challenges.

Early transfer of aSAH patients from low-volume to high-volume centers improves patient outcomes and decreases overall healthcare costs [56, 57]. Accordingly, the American Stroke Association (ASA)/American Heart Association (AHA) guidelines recommend early transfer from hospitals that admit <10 aSAH annually to high-volume centers (>35 aSAH annually). Furthermore, these centers should have experienced cerebrovascular neurosurgeons as well as endovascular specialists and neuro-intensive care services [46]. Aneurysm rerupture prior to or during hospital transfer is a potentially devastating event that has been reported in 13% of patients in some series [58], and some authors have reported that the highest risk of rebleeding is within 6 hours of presentation [59]. These findings underscore the necessity of expeditious transfer to centers that can provide definitive treatment.

Once the patient has been medically stabilized, the focus shifts to management of acute hydrocephalus and early intervention to mitigate the risk of aneurysm rerupture. It is important for triaging physicians to be familiar with the diagnosis of acute hydrocephalus as well as measures to minimize the risk of early aneurysm rebleeding since these life-threatening emergencies may require intervention prior to transfer from the emergency department to the neurocritical care unit (NCCU) or to another facility.

Hydrocephalus

Hydrocephalus in aSAH can result from communicating, obstructive, or mixed physiology and occurs acutely as well as in a delayed manner. Obstructive hydrocephalus is typically due to intraventricular hemorrhage or a parenchymal hematoma blocking cerebral spinal fluid (CSF) flow through the ventricular system. Communicating hydrocephalus results from impaired CSF resorption at the level of the arachnoid granulations. In addition, some evidence suggests that a systemic inflammatory response may increase the risk of delayed hydrocephalus [60, 61]; however, the mechanism underlying this observation has not yet been elucidated.

Rates of hydrocephalus and shunt dependency vary widely in the literature due to inconsistent parameters for defining hydrocephalus and a lack of standardized, objective thresholds for shunt placement. Acute hydrocephalus has been reported in 15–87% of aSAH patients, chronic hydrocephalus develops in 9–64%, and 2–36% require permanent CSF diversion [62–65]. Failure to recognize acute hydrocephalus and emergently place an external ventricular drain (EVD) or lumbar drain can result in irreversible neurologic injury and death. Conversely, timely placement of an EVD has been shown to improve neurologic outcomes in patients presenting with poor grade aSAH [66]. Untreated chronic hydrocephalus can severely hinder a patient's neurologic recovery and may result in permanent neurologic injury or death. It is paramount, therefore, that all members of the care team from presentation until discharge are familiar with the diagnosis and treatment of hydrocephalus.

There is no consensus regarding the best method for EVD weaning in aSAH patients. A single prospective randomized trial including 81 patients was conducted from December 2001 to December 2002 [67]. Forty-one patients were randomized to rapid weaning, which was defined as closure of the EVD within 24 hours. Forty patients were randomized to gradual weaning, which involved weaning over a 96-hour period with daily, sequential height elevations of the EVD system followed by EVD closure for 24 hours. The authors reported no significant difference in rates of shunt placement between the two groups, but they did report longer intensive care unit and hospital stays for the gradual weaning group. Other studies, however, support the strategy of monitoring CSF output to determine the necessity of permanent CSF diversion [65, 68]. Our practice incorporates this strategy as we incrementally increase pop-off settings and perform serial clamping trials. Patients who fail a clamping trial but demonstrate a trend toward decreased CSF output undergo subsequent clamping trials. We proceed with shunt placement only in patients who demonstrate persistently high CSF drainage. While this may increase length of stay, we have found this strategy to be effective in decreasing the rate of shunt placement. Our practice is consistent with a recent

multi-institutional survey, which found that a majority of institutions use a strategy that incorporates gradual EVD weaning based on CSF output [69]. Additional randomized trials are needed to reconcile the prevailing clinical practice of gradual weaning with the available evidence from the only randomized trial to date.

In theory, aggressive CSF drainage in the setting of an unsecured aneurysm could precipitate aneurysm rerupture by increasing the transmural pressure gradient across the wall of the aneurysm. This concern underlies the common practice of maintaining a relatively high pop-off for patients with unsecured aneurysms and decreasing the pop-off to facilitate CSF drainage once the aneurysm is secured [69]. Available evidence, however, suggests that this theoretical risk may be minimal or nonexistent in practice. Hellingman et al. retrospectively reviewed 34 patients who underwent EVD drainage matched with 34 controls with untreated hydrocephalus as well as 34 controls without hydrocephalus and found no difference in rebleeding rate among the groups [70]. In a retrospective review of 304 consecutive patients with aSAH, McIver et al. reported a 4.4% rate of rebleeding for patients who underwent EVD placement vs. a 5.4% rate of rebleeding in patients without an EVD [71]. Small retrospective studies have demonstrated that lumbar drainage similarly does not increase the risk of aneurysm rerupture and may be a viable alternative to EVD placement in some cases [72–74]. Of note, patients with obstructive hydrocephalus, parenchymal hematomas, significant intraventricular hemorrhage, or otherwise high suspicion for elevated intracranial pressure should have an EVD placed rather than a lumbar drain due to the risk of herniation conferred by induced pressure gradients between the intracranial compartment and the lumbar cistern.

Fenestration of the lamina terminals at the time of surgery has been suggested to decrease the rate of shunt-dependent hydrocephalus following aSAH. A nonrandomized prospective study including 95 patients concluded that fenestration of the lamina terminalis decreased the rate of shunt-dependent hydrocephalus [75]. The utility of this technique, however, is a subject of ongoing debate. A meta-analysis of 11 nonrandomized studies including 1973 patients reported that 10% of patients in the fenestrated cohort vs. 14% in the nonfenestrated cohort ($p = 0.089$) required ventriculoperitoneal shunt placement [76]. Based on these data, the current ASA/AHA guidelines do not recommend routine fenestration of the lamina terminalis [46]. In our experience, fenestration of the lamina terminalis decreases the incidence of shunt-dependent hydrocephalus by 80% [77]. Other authors have reported that fenestration of the lamina terminalis combined with fenestration of the membrane of Liliequist decreases rates of shunt dependency [78]. A randomized controlled trial is needed to determine the effectiveness of lamina terminalis fenestration. Such a trial would also have to include strict, objective metrics for EVD weaning and shunt placement. Based on the current available evidence, we routinely fenestrate lamina terminalis whenever this structure is safely accessible.

Measures to Prevent Aneurysm Rebleeding

Aneurysm rebleeding and acute hydrocephalus are the most immediate risks in the initial hours following aneurysm rupture. Several factors have been associated with an increased risk of aneurysm rebleeding, including prolonged time to treatment, LOC, sentinel headache, large aneurysm size, and poor neurologic status [58, 79]. A review of the literature from 2011 by Starke and colleagues found that while early studies estimated the rebleeding risk to be approximately 4% in the first 24 hours and between 1% and 2% per day for the next 14 days, these studies often failed to capture very early rebleeding [80]. Subsequent series designed to capture early rebleeding have estimated the risk in the first 24 hours to be between 9% and 17%. The International Cooperative Study on the Timing of Aneurysm Surgery, a prospective observational study involving 3521 patients, reported rebleeding in 6% of patients planned for surgery in the first 3 days and 22% for patients planned for surgery days 15 through 32 [81]. Rebleeding is unequivocally associated with poor outcomes, including increased morbidity and a decreased chance of regaining functional independence [79]. Accordingly, securing the aneurysm promptly by endovascular coiling or surgical clipping is now widely accepted as standard of care. This is reflected in the ASA guidelines, which recommend that aneurysms be secured as early as possible in the majority of patients (Class I, Level of Evidence B) [46]. A detailed discussion of the indications for microsurgical clipping vs. coil embolization is beyond the scope of this chapter; however, centers caring for aSAH patients should have both experienced neurosurgeons and neurointerventionalists available. It is our practice to secure the aneurysm by the appropriate method within 24 hours of presentation.

The most extensively studied medical interventions to reduce the risk of aneurysm rebleeding are antifibrinolytic therapy and blood pressure control. Enthusiasm for the use of antifibinolytics to prevent rebleeding was curbed by data from randomized trials, which indicated that the potential benefit was outweighed by an increased incidence of delayed ischemic complications [82]. These trials, however, were conducted before there was a widespread emphasis on securing aneurysms promptly, and, as a result, antifibrinolytics were administered during the vasospasm period. A randomized controlled trial published in 2002 randomized 254 patients to receive tranexamic acid (TXA) 1 g every 6 hours until the aneurysm was occluded, but not longer than 72 hours, and 251 patients

to controls who did not receive TXA [83]. This trial found that 6 patients in the TXA group experienced early rebleeding compared with 27 patients in the control group. Furthermore, the authors did not find an increased risk of vasospasm or delayed cerebral ischemia in the TXA group. Starke and colleagues instituted a protocol for administration of epsilon-aminocaproic acid (EACA) for a maximum of 72 hours and found a significant reduction in rebleeding in the EACA group (2.7% vs. 11.4%) without an increase in ischemic complications [84]. The authors did report an eightfold increase in deep vein thrombosis, although there was no increase in pulmonary embolism in the EACA group. Neither TXA nor EACA is FDA approved for the prevention of aneurysm rebleeding. Nevertheless, both the ASA/AHA and the Neurocritical Care Society's Multidisciplinary Consensus Conference guidelines state that it is reasonable to administer antifibrinolytic therapy for 72 hours or less when there is an unavoidable delay in securing the aneurysm [46, 85].

It is common practice to control hypertension until the aneurysm is secured; however, there is a paucity of data regarding the benefit of this practice, and no definitive blood pressure guidelines have been established. Premorbid hypertension has been weakly associated with worse outcomes and higher rebleeding rates, [86] and acute hypertension has been observed at the time of rebleeding; however, these studies were unable to address the temporal relationship between hypertension and aneurysm rupture [82]. The ASA/AHA guidelines recommend blood pressure control with a titratable agent and encourage a blood pressure goal that balances the risk of rebleeding with cerebral perfusion (Class I, Level of Evidence B). In patients who are normotensive or mildly hypertensive at baseline, it is reasonable to target a systolic blood pressure <160 mm Hg according to the ASA/AHA guidelines (Class IIa, Level of Evidence C).

Aneurysm occlusion by endovascular coil embolization or microsurgical clipping is the only definitive measure proven to prevent aneurysm rebleeding. The Cerebral Aneurysm Rerupture After Treatment (CARAT) study evaluated aneurysm rebleeding after treatment in 1001 patients treated with coil embolization or surgical clipping across nine centers from 1996 to 1998 with follow-up until 2005 [87]. Nineteen patients rebled following treatment. Degree of aneurysm occlusion was significantly associated with rebleeding risk: 1.1% for complete occlusion, 2.9% for 91–99% occlusion, 5.9% for 70–90% occlusion, and 17.6% for <70% occlusion. There was no significant difference between the coil embolization and surgical clipping groups. Rebleeding was associated with a 58% mortality rate in this study. These data illustrate the benefits of upfront definitive aneurysm occlusion and reinforce the necessity of early transfer to centers with expertise in both microsurgical and endovascular treatment of cerebral aneurysms.

Summary of Pharmacology in the Triage Setting

- Antifibrinolytic therapy with intravenous (IV) TXA (1 g every 6 hours) or EACA (4 g loading dose followed by 1 g/hours) up to 72 hours is reasonable if there is an unavoidable delay in securing the aneurysm but is not a substitute for early transfer and definitive management.
- Blood pressure should be closely regulated with short-acting, titratable antihypertensives such as intravenous (IV) nicardipine. Uniform blood pressure goals have not been established but should balance cerebral perfusion with the risk of rebleeding. For patients who are normotensive or mildly hypertensive at baseline, a systolic blood pressure goal of <160 mmHg is reasonable.

NCCU Care (Days 1–14)

Patients transferred to tertiary centers should be admitted to a dedicated NCCU, and a complete neurologic exam should be performed as rapidly as practicable, including calculation of common aSAH severity scores: Hunt and Hess, World Federation of Neurosurgical Societies (WFNS) scale, and modified Fisher scales (Table 9.1). Sedation should be minimized during transfer. If sedation is deemed necessary for patient safety, the definitive admission exam should be com-

Table 9.1 Common scales for grading aneurysmal subarachnoid hemorrhage and predicted outcomes

Grade	Criteria	Outcome
Hunt and Hess		**Survival**
1	Asymptomatic or minimal headache/ nuchal rigidity	70%
2	Moderate to severe headache/nuchal rigidity, no focal deficit	60%
3	Drowsy, minor, or no neurologic deficit	50%
4	Stuporous, hemiparesis (moderate to severe), possible early decerebrate rigidity, vegetative disturbances	20%
5	Deep coma, decerebrate rigidity, moribund	10%
World Federation of Neurosurgical Societies (WFNS)		**Survival**
1	GCS 15, no focal deficit	70%
2	GCS 13–14, no focal deficit	60%
3	GCS 13–14, with focal deficit	50%
4	GCS 7–12 with or without focal deficit	20%
5	GCS <7, with or without focal deficit	10%
Modified Fisher scale		**Symptomatic vasospasm**
0	No SAH or IVH	0%
1	SAH <1 mm thick without IVH	24%
2	SAH <1 mm thick with IVH	33%
3	SAH >1 mm thick without IVH	33%
4	SAH >1 mm thick with IVH	40%

pleted after sedating agents have been held and the patient has recovered from their effects. Sedation thereafter should be kept to an absolute minimum in order to maximize sensitivity of the clinical exam.

Once the patient is medically stabilized, hydrocephalus is treated, and the aneurysm is secured, the focus shifts to monitoring and interventions that will optimize that patient's functional recovery. Mitigating the effects of vasospasm/delayed cerebral ischemia (DCI), seizures, and systemic complications take precedence in the days and weeks following aSAH. These measures are discussed in the sections below. General medical care for aSAH patients during the transition from the acute to subacute phases of care is not covered extensively in this chapter but includes antiemetic medications, analgesia, proton pump inhibitors for gastrointestinal ulcer prophylaxis, and subcutaneous heparin and intermittent pneumatic compression devices to reduce the risk of deep vein thrombosis.

Seizures

Controversy exists regarding the frequency with which seizures occur in aSAH patients as well as the long-term consequences of seizure activity. Seizure rates reported in the literature range from 2% to 26%, with higher rates in older series that employed less stringent criteria for defining seizures [46, 88–90]. A retrospective review of 547 aSAH patients reported a cumulative seizure rate of 15.2% with 7.9% having seizures at the time of symptom onset, 6.2% having perioperative seizures, and 3.1% developing late epilepsy [91]. The risk of seizures also varies across subgroups of aSAH patients. Patients with focal brain injury, including extensive hemorrhage, subdural hematoma, and cerebral infarction [91, 92], as well as patients with hypertension [93], are more likely to develop seizures. Treatment modality also affects a patient's seizure risk. Extended follow-up from the International Subarachnoid Aneurysm Trial (ISAT) showed an increased incidence of seizures in patients who underwent microsurgical clipping (13.6%) compared with endovascular coiling (8.3%) [94], which is consistent with seizure rates for patients undergoing craniotomies. This difference in seizure risk may be particularly relevant in good-grade aSAH patients [95], reflecting the relatively low baseline rate of seizures in aSAH patients who are neurologically intact.

One single-center, randomized controlled trial of short course (3 days) vs. extended (until discharge) levetiracetam in 84 aSAH patients detected a trend toward lower seizure rates in the extended treatment group (9% vs. 2%) [96]; however, the study was stopped early due to slow enrollment, and the trend toward improved seizure control with prolonged levetiracetam did not reach statistical significance. Otherwise, there are no randomized controlled trials to guide seizure management and prophylaxis in this patient population. A propensity-matched score analysis of 353 patients found that antiepileptic drugs (AEDs) did not significantly reduce the risk of clinical or electrographic seizures [97]. A Cochrane Review published in 2013 concluded that the available evidence to support or refute the use of AEDs for primary or secondary prevention of seizures in aSAH is inadequate and that well-designed randomized trials are urgently needed [98]. The long-term consequences of seizures in the acute aSAH period are also unclear. Some authors have reported that early seizures are not associated with long-term epilepsy [91, 99], while other authors have identified nonconvulsive status epilepticus as an independent predictor of poor outcomes [100, 101].

Potential benefits of seizure prophylaxis must be weighed against the risk profile of AEDs in aSAH patients. Adverse events associated with routine AED administration were reported in 23.4% of patients in a retrospective series of 547 patients [91]. On the one hand, another retrospective study found that the use of prophylactic phenytoin was an independent predictor of worse cognitive outcomes at 3 months [102]. These results should be interpreted with caution, however, as extended AED prophylaxis in these studies was disproportionately administered to patients with other well-established negative prognostic factors, including vasospasm, cerebral infarction, and fever [103]. On the other hand, the trial by Human and colleagues found that brief administration of levetiracetam was associated with better functional outcomes (modified Rankin Scale 0–2) compared with extended seizure prophylaxis [96]. Despite the previously mentioned limitations to this study, this finding does support the notion that there is some benefit to minimizing exposure to AEDs in aSAH patients who are at a low risk for seizures.

Balancing the evidence that nonconvulsive status epilepticus is correlated with poor outcomes, but prolonged seizure prophylaxis has not been shown to be beneficial and may be associated with worse outcomes, we opt for an individualized approach. All aSAH patients are initially placed on prophylactic levetiracetam (500–1000 mg every 12 hours). The duration of therapy is tailored to a patient's risk of seizures based on neurologic status and radiographic and/or clinical evidence of focal injury. Levetiracetam is discontinued within the first few days in patients who have no evidence of seizure activity and are at a low risk for developing seizures. Conversely, patients who have a change in clinical exam or a persistently poor exam routinely undergo an electroencephalogram (EEG), and electrographic and/or clinical seizures are treated aggressively, including additional AEDs as necessary.

Vasospasm and Delayed Cerebral Ischemia

Cerebral artery narrowing (vasospasm) is detectable by angiography in 67% of aSAH patients 3–14 days after aneurysm rupture, typically peaks at 7–10 days, and resolves spontaneously after 21 days [104]. Twenty percent of aSAH patients with radiographic vasospasm experience clinically significant cerebral ischemia [105]. The distinction between vasospasm and DCI is important, as the degree of vasospasm correlates with, but does not reliably predict, the severity of DCI in all patients. This variability is partially due to intrinsic patient characteristics, including collateral circulation, integrity of the microvasculature, vessel reactivity, and autoregulation. Non-modifiable risk factors for vasospasm include younger age, poor neurologic status, thick subarachnoid and/or intraventricular hemorrhage, and a history of smoking [106, 107]. Other processes, including inflammation, microvascular thrombus formation, cortical spreading ischemia, and blood-brain barrier breakdown, are potentially modifiable [108–110]. For the clinical team, vasospasm, DCI, and resultant cerebral infarction are major sources of morbidity and mortality for aSAH patients; therefore, vigilant monitoring during the vasospasm period and aggressive interventions are prudent.

Detailed serial neurologic examinations are the most sensitive screening test for DCI [111]. DCI most frequently presents as headache, neck stiffness, confusion, or drowsiness with or without focal neurologic deficits. Transcranial Doppler ultrasound (TCD) is an adjuvant to the clinical exam; however, TCD data alone have limited utility for detecting vasospasm and even less accuracy for predicting DCI due to altered local and systemic blood flow dynamics in aSAH patients. The Lindegaard ratio attempts to correct for hyperemia by normalizing velocities in the intracranial circulation to the mean velocity in the extracranial circulation [112]. A ratio of 3:1 in the middle cerebral artery compared with the external carotid artery loosely correlates with radiographic vasospasm [113]. TCD is not as sensitive for detecting vasospasm in other intracranial vessels, and different criteria have been proposed, including lower thresholds in the posterior circulation [112]. A retrospective study of 1877 TCD examinations in 441 aSAH patients found that nearly 40% of patients with DCI never had TCD velocities >120 cm/s [114], which is typically the middle cerebral artery TCD threshold for vasospasm. Despite these limitations, a meta-analysis concluded that frequent TCDs remain a valuable screening tool for vasospasm [115]. We agree that—given the paucity of alternative frequent screening methods—TCD remains a useful screen for vasospasm provided the data are interpreted in the appropriate clinical context.

Patients with a change in clinical exam who have been ruled out for other etiologies, including acute hemorrhage, cerebral salt wasting (CSW), infection/fever, and hydrocephalus, are presumed to have vasospasm by exclusion. If the clinical scenario and TCD values strongly support a diagnosis of vasospasm, our practice is to take the patient directly to catheter angiography as this is the most sensitive test for vasospasm, and treatment can be administered immediately. For patients in whom a diagnosis of vasospasm is equivocal, noninvasive imaging may be useful. CTA has been shown to correlate closely with cerebral angiography for detecting vasospasm in the proximal circulation [116–118]. CTA and cerebral angiography, however, provide no direct data on cerebral ischemia. CT perfusion (CTP) provides such information and is increasingly being used in aSAH patients [119]. A retrospective study comparing CTA/CTP to angiography found that a mean transit time (MTT) threshold of 6.4 seconds was 93% accurate for predicting angiographic vasospasm while decreased regional cerebral blood flow was the most sensitive predictor of patients going on to endovascular therapy [120]. While CTA/CTP is superior to TCD, the utility of these tests for frequent screening is limited due to contrast administration and radiation exposure.

The historical cornerstone of treatment for vasospasm/DCI is triple-H therapy, which classically included hypertension, hemodilution, and hypervolemia [121–123]. These interventions can be associated with severe complications, however, including pulmonary edema, hyponatremia, and cardiac dysfunction. Therefore, more recent studies have evaluated the relative contributions of each component in an effort to maximize benefit and minimize risks. A retrospective study of 45 patients found that moderate hypertension to achieve a cerebral perfusion pressure of 80–120 mmHg increased brain tissue oxygenation in 90% of cases and was associated with a complication rate of 8%. Conversely, hypervolemia had minimal effect on brain tissue oxygenation, and the combination of hypervolemia and hypertension did not improve oxygenation over hypertension alone but conferred a complication rate of 50% [124]. A randomized trial of hypervolemia vs. euvolemia in 82 patients found no difference in the rate of symptomatic vasospasm between these groups [125]. A systematic review of the literature by Dankbaar and colleagues evaluated the evidence for each component of triple-H therapy and concluded that only hypertension has a demonstrable effect on cerebral blood flow [126]. The ASA/AHA guidelines recommend inducing hypertension (Class I, Level of Evidence B) while maintaining euvolemia and normal circulating blood volume (Class I, Level of Evidence B). We routinely use a transpulmonary thermal dilution system (Pulse Contour Cardiac Output; PiCCO) system to monitor hemodynamic parameters in

aSAH patients and generally set a mean arterial pressure goal 20% above baseline. We increase this goal by another 10% if the initial goal does not produce a clinical response up to a maximum systolic blood pressure of 220 mmHg or a diastolic blood pressure of 120 mmHg.

A multi-institution, double-blind, placebo-controlled, randomized trial by Allen and colleagues published in 1983 found that administration of nimodipine during the initial 21 days following aneurysm rupture significantly reduced persistent ischemic neurologic deficits [127]. In this trial 1/56 patients treated with nimodipine and 8/60 patients treated with placebo developed persistent deficits referable to cerebral ischemia. A 2007 Cochrane Review synthesized data from 16 trials of calcium antagonists and found a relative risk of 0.67 (CI 0.55–0.81) for poor outcomes [128]. The authors concluded that oral nimodipine reduces the risk of DCI in aSAH patients while evidence for the use of IV nimodipine or other calcium antagonists is inconclusive. It is our practice to administer oral nimodipine 60 mg every 4 hours for 21 days. If the patient's blood pressure goals cannot be maintained on this regimen, we implement a schedule of 30 mg every 2 hours.

Magnesium sulfate has been studied as a neuroprotective agent for preventing vasospasm and DCI in aSAH. Additionally, there is some evidence indicating that magnesium sulfate may increase cerebral blood flow in aSAH patients [129]. The Intravenous Magnesium Sulfate for Aneurysmal Subarachnoid Hemorrhage (IMASH) trial enrolled 327 patients and randomized 169 patients to IV magnesium sulfate infusion vs. 158 patients randomized to placebo and found that favorable outcomes according to the Extended Glasgow Outcome Scale were not different between the two groups at 6 months [130]. The Magnesium for Aneurysmal Subarachnoid Hemorrhage (MASH-2) trial was a multi-institutional, randomized, placebo-controlled trial of IV magnesium sulfate initiated within 4 days of symptom onset [131]. A total of 1204 patients were enrolled, and 606 were assigned to the magnesium group. Among them, 158 patients (26.2%) had a poor outcome (modified Rankin Scale 4–5) at 3 months in the magnesium group compared with 151 (25.3%) in the placebo group. Subsequent studies have evaluated whether earlier administration of magnesium sulfate is beneficial. A meta-analysis of magnesium administration within the first 24 hours, however, similarly concluded that there was no benefit [132]. Based on the current clinical evidence, we do not administer magnesium sulfate to aSAH patients.

Milrinone administered intravenously, intra-arterially, or intrathecally has garnered recent attention for the treatment of refractory vasospasm. Arakawa et al. first reported that milrinone reliably produced vasodilation in a small series of 7 aSAH patients [133]. In 2008 Fraticelli and colleagues reported their experience with intra-arterial milrinone followed by IV infusion in 22 patients with vasospasm [134]. The authors reported that intra-arterial milrinone produced a 53% increase in arterial diameter (p <0.0001). Subsequent studies in aSAH patients with medically refractory vasospasm have similarly reported a significant increase in vessel diameter following intra-arterial milrinone [135, 136]. The mechanism of action of milrinone in this context is not entirely clear. Some authors have proposed that milrinone works via an anti-inflammatory mechanism in addition to its ionotropic and vasodilator effects [137]. Randomized trials are needed to evaluate the efficacy of milrinone for vasospasm and DCI. At present, Level III evidence indicates that it is reasonable to consider intra-arterial milrinone with or without subsequent IV milrinone infusion in patients with vasospasm refractory to other therapies.

Inflammation is by now a well-established contributor to vasospasm and DCI [38, 138–140]. Endothelin receptor antagonists and statins have been proposed to mitigate vasospasm and DCI by targeting underlying inflammatory processes. Endothelin is a potent vasoconstrictor produced by activated leukocytes and has been isolated from the CSF of aSAH patients [141]. The Clazosentan to Overcome Neurologic Ischemia and Infarction Occurring after Subarachnoid Hemorrhage (CONSCIOUS-1) trial was a randomized, placebo-controlled, double-blind phase 2b trial that found that clazosentan mitigated angiographic vasospasm in a dose-dependent manner [142]. The CONSCIOUS-2 trial was a double-blind, placebo-controlled, phase 3 study with endpoints of all-cause mortality, cerebral infarction, DCI, and neurologic deficits attributable to vasospasm/DCI in patients undergoing surgical clipping [143]. Both this trial and the subsequent CONSCIOUS-3 trial [144], which evaluated this therapy in patients who underwent endovascular coiling, failed to demonstrate that clazosentan reduced mortality or improved neurologic outcomes.

The Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) trial was a multicenter randomized phase 3 trial that enrolled 803 aSAH patients presenting within 96 hours of symptom onset [145]. Patients were randomized to either simvastatin 40 mg daily (391 patients) or placebo (412 patients). The primary outcome was modified Rankin score at 6 months, and all patients were included in an intention-to-treat analysis. The authors reported that 271 patients had a favorable outcome (modified Rankin Scale 0–2) in the simvastatin group compared with 289 patients in the placebo group and concluded that aSAH patients did not benefit from simvastatin therapy. A more recent trial compared 54 aSAH patients randomized to a long-acting statin (pitavastatin 4 mg daily) with 54 patients randomized to placebo and found a statistically significant improvement in angiographic vessel narrowing in the pitavastatin group, but no difference in DCI or clinical outcomes [146].

Patients with clinically symptomatic vasospasm despite euvolemia, induced hypertension, and oral nimodipine are candidates for intra-arterial chemical spasmolysis or and/or mechanical angioplasty. Several vasodilatory medications have been used for selective spasmolysis, and there is limited evidence to support efficacy and safety of one medication over another. In the United States, the most commonly used vasodilator is verapamil while nimodipine is more commonly used worldwide [147]. Hoh and colleagues reviewed the literature on mechanical angioplasty and reported clinical improvement in 62% of cases with a 5% major complication rate and a 1.1% rate of vessel rupture [148]. Given the risks associated with this procedure, it is typically reserved for patients who have failed intra-arterial spasmolysis but remains a valuable part of the armamentarium for select patients with recalcitrant vasospasm.

Cardiomyopathy

Cardiac dysfunction is common in aSAH patients and is the second leading cause of death after neurologic compromise [149]. Neurogenic stress cardiomyopathy (NSC) occurs in the acute period following aSAH and typically resolves over a period of weeks [150]. NSC manifests as multi-territorial regional ventricular wall-motion abnormalities, reduced left ventricular ejection fraction, and elevated cardiac enzymes with a normal coronary angiogram. Takotsubo cardiomyopathy is clinically similar to NSC but is due to psychological stress rather than direct neurologic damage and is more common in women [149, 151]. Electrocardiographic abnormalities are observed in a majority of aSAH patients, and 4% develop clinically significant arrhythmias that are independently associated with an increased risk of mortality and severe morbidity [152]. Clinical severity of aSAH is the most important risk factor for cardiomyopathy as several authors have reported a positive correlation between Hunt and Hess grade and cardiac dysfunction [153–155]. Severity of aSAH has also been associated with elevated levels of serum brain natriuretic peptide [156] and early heart failure-like afterload mismatch [157].

The mechanisms of NSC in aSAH are incompletely understood, and treatment remains primarily supportive; however, a growing body of evidence indicates that catecholamines may be important mediators of NSC [158, 159]. A study by Neil-Dwyer et al. randomized 90 aSAH patients to propranolol 80 mg every 8 hours vs. placebo and reported a decrease in myocardial necrosis on postmortem examination in the propranolol group [160]. More recently, Liang and colleagues retrospectively reviewed the effects of preadmission beta-blockade in aSAH patients and found that beta-blockade reduced the incidence of NSC [161]. Enthusiasm for beta-blockade in aSAH patients has been appropriately tempered, however, by the concern that these agents induce hypotension that may exacerbate vasospasm/DCI [162]. Importantly, even transient cardiac dysfunction can hinder efforts to administer other neuroprotective therapies, particularly regulation of fluid/sodium balance and blood pressure augmentation. In extreme cases of NSC and refractory vasospasm, an intra-aortic balloon pump has been successfully used for hemodynamic support [163, 164].

Fluid Balance and Hyponatremia

Derangements in fluid balance and sodium levels are frequent in aSAH patients and are associated with worse outcomes [165, 166]. Furthermore, standard calculations of volume status typically misrepresent circulating blood volumes in aSAH patients. Hoff et al. randomized 102 aSAH patients to fluid management based on blood volume measurements in the intervention group (54 patients) vs. that based on fluid balance in the control group (48 patients) during the first 10 days following aneurysm rupture [167]. The authors reported significantly fewer episodes of severe hypovolemia (<50 mL/kg) in the intervention group (6.7%) vs. the control group (17.1%). Volume measurements have become safer and easier in the NCCU as Swan-Ganz catheters have largely been replaced by other methods of volume status monitoring [168]. We preferentially use a PiCCO to manage volume status in aSAH patients [169, 170]. A retrospective study of 47 patients found that global end-diastolic volume index (GEDI) was the parameter that correlated most consistently with DCI with mean values of 783 +/− 25 mL/m vs. 870 +/− 14 mL/m in the vasospasm and no vasospasm groups, respectively [171]. The authors concluded that GEDI should be maintained in the high normal or slightly above the normal range (680–800 mL/m), and this is also our practice. A subsequent randomized trial demonstrated that implementing early goal-directed therapy (within the first 24 hours) based on hemodynamic monitoring decreased the rate of DCI in patients with high-grade aSAH [172].

Hyponatremia in aSAH patients is commonly due to CSW or syndrome of inappropriate antidiuretic hormone secretion (SIADH). The etiology of CSW is renal loss of sodium, which manifests as hypovolemic hyponatremia, while SIADH is characterized by inappropriate retention of free water resulting in euvolemic or hypervolemic hyponatremia. SIADH is classically treated with fluid restriction; however, this can be problematic given the harmful effects of hypovolemia and hypotension in aSAH patients. Hypertonic saline can be safely used to correct hyponatremia in aSAH patients while maintaining volume status and blood pressure parameters [173]. CSW is more common than SIADH in aSAH patients and can be treated with corticosteroids. A randomized, placebo-controlled trial of hydrocortisone for

hyponatremia in aSAH found that the treatment group maintained sodium goals more frequently than the placebo group [174]. Fludrocortisone has also been shown to improve sodium retention in aSAH patients in randomized controlled trials [175, 176] and reduced vasospasm in a nonrandomized, prospective study [177].

Pulmonary Dysfunction

Pulmonary dysfunction occurs in over 20% of aSAH patients with infection and pulmonary edema being the most frequent etiologies [178]. The latter process has been termed neurogenic pulmonary edema (NPE) and is due to a combination of iatrogenic fluid administration and cardiac dysfunction [179]. aSAH patients are also susceptible to other pulmonary disorders associated with critical illness, including acute lung injury, atelectasis, and acute respiratory distress syndrome (ARDS) [180, 181]. It is notable that in a retrospective study of 305 patients, Friedman et al. reported a higher incidence of vasospasm in aSAH patients with pulmonary complications [178]. Although causality cannot be inferred from this study, it is reasonable to deduce that pulmonary dysfunction precluded maintenance of fluid balance and blood pressure goals. These findings reinforce how systemic complications can severely impact neurologic outcomes for these patients.

Fever

Fever occurs in approximately 50% of aSAH patients and is independently associated with increased morbidity and mortality [182–184]. A retrospective study of 584 consecutive patients with aSAH reported an infectious source in 44.8% of febrile patients [182]. Furthermore, the authors reported that the number of febrile days was independently associated with poor outcomes on multivariate analysis. Prompt workup is paramount as fever may be a harbinger of treatable, underlying processes, including infection and vasospasm [185]. Risk factors for central (noninfectious) fever in aSAH patients include greater extent of hemorrhage, intraventricular hemorrhage, and increased severity of neurologic injury [186, 187]. It is our practice to send an infectious workup including blood, sputum, urine, and CSF cultures in all febrile aSAH patients with an EVD in place. For patients without an EVD, consideration is given to lumbar puncture based on the clinical scenario. Regardless of etiology, we initially treat febrile patients with acetaminophen followed by cooling as necessary. The ASA/AHA guidelines recommend aggressive fever control to target normothermia in the acute phase of aSAH (Class IIa, Level of Evidence B).

Anemia

Anemia is common in aSAH and has been associated with worse outcomes [188]. A retrospective study of 575 patients by Giller and colleagues reported that 18% of patients had a hematocrit value <26% at some point, and 57% recorded a value of <30% [189]. Although red blood cell transfusions have been associated with worse outcomes in critically ill patients, the overriding risk of cerebral ischemia in aSAH patients differentiates these patients from the general critical care population and warrants additional consideration [190]. Early retrospective studies initially appeared to support the predominantly negative effects of red blood cell transfusions in aSAH patients; however, there was no dose-dependent response observed, and this association was no longer found to be significant when confounding variables were considered [191]. Naidech and colleagues performed a randomized trial of hemoglobin level goals in 44 aSAH patients with a high risk for vasospasm [192]. Patients were randomized to a hemoglobin goal of 10 g/dL or 11.5 g/dL. The National Institutes of Health Stroke Scale and modified Rankin Scale values were recorded at 14 days, 28 days, and 3 months. The higher hemoglobin group received more blood transfusions, but outcomes were similar between the two groups. The authors concluded that blood transfusion was safe and feasible in this patient population.

The ideal hemoglobin goal for aSAH patients has not been established although animal studies have indicated that a hematocrit near 30% is optimal for cerebral blood flow [193]. A secondary analysis of patients in the CONSCIOUS-1 study reinforced the negative impact of anemia and the safety of red blood cell transfusion in aSAH patients with a hemoglobin goal of 10 g/dL [194]. A recent study demonstrated that maintaining hemoglobin goals in this range has a significant impact on oxygen delivery as raising the hemoglobin from an average of 9.6 to 10.8 g/dL increased cerebral oxygen delivery, particularly to ischemic regions [195]. It is our practice to strictly maintain a hemoglobin goal >10 g/dL and transfuse as necessary.

Summary of Pharmacology in the NCCU Setting

- Oral nimodipine 60 mg every 4 hours should be administered to all aSAH patients. If a patient's blood pressure cannot be maintained on this regimen, the dosing can be adjusted to 30 mg every 2 hours.
- Selective intra-arterial administration of a vasodilator such as verapamil, nicardipine, or milrinone with or without mechanical angioplasty has been demonstrated to treat refractory vasospasm. IV or intrathecal milrinone is being evaluated for refractory vasospasm, but the evidence is insufficient to make a recommendation regarding these regimens at this time.

- Given the frequency of seizures in aSAH patients, we believe that a short course of levetiracetam (500 mg–1 g every 12 hours) is prudent. Patients in whom clinical and/or electrographic seizures are observed should be aggressively treated with additional AEDs as necessary.
- Hypertonic saline IV infusion can be safely used to correct hyponatremia and maintain volume status. Fludrocortisone 0.1–0.4 mg oral daily is beneficial for correcting hyponatremia due to CSW.
- Acetaminophen (every 4–6 hours up to a maximum of 4 g per day) can be used as a first-line antipyretic so as to avoid the antiplatelet actions of NSAIDs.

Transfer from NCCU and Preparation for Discharge (Day 14 and Beyond)

It is our general practice to monitor patients in the NCCU for 14 days following aneurysm rupture. At that time patients who are neurologically stable are transferred to the general neurosurgery floor, daily TCDs are discontinued, and preparations for discharge commence. There is a great degree of variability in the deficits patients experience following aSAH and even greater diversity in the challenges they encounter in resuming their premorbid physical, social, and professional lives. Even patients without residual focal neurologic deficits frequently suffer from some degree of cognitive dysfunction [196]. All aSAH patients at our institution undergo thorough neuropsychological testing in addition to evaluation by physical and occupational therapists in order to determine therapy needs and appropriate placement after discharge. We then work closely with the patients, and their families, and social workers to determine the discharge setting most conducive to their ongoing recovery.

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Emergency Management of Acute Intracerebral Hemorrhage

10

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Levels of Evidence [LOE]

- Level A: data obtained from multiple randomized controlled trials or meta-analyses.
- Level B: data obtained from a single randomized controlled trial or nonrandomized studies.
- Level C: expert opinion, case studies.

Introduction

Definition

Intracerebral hemorrhage (ICH) refers to acute, spontaneous, nontraumatic bleeding in the brain parenchyma [1]. By definition, "primary" ICH is the acute manifestation of a progressive cerebral small vessel disease leading to vessel rupture, typically hypertensive arteriopathy or cerebral amyloid angiopathy (CAA) [2]. ICH can also be secondary to other intracranial pathologies such as vascular malformations, neoplastic lesions, and hemorrhagic conversion of ischemic strokes.

Epidemiology and Risk Factors

ICH accounts for up to 20% of all cerebrovascular events, with an incidence ranging from 10 to 30 cases per 100,000 persons/year in Western populations [3]. Hypertension is the most important modifiable risk factor for ICH, whereas age is the main non-modifiable factor [4]. Antithrombotics and in particular dual antiplatelet treatment and anticoagulant therapy have been consistently associated with greater odds of developing an ICH, especially in elderly subjects with chronic small vessel disease [5–7]. Diabetes, alcohol intake, and current smoking may also lead to increased risk [3]. Among genetic risk factors, the gene most strongly associated with ICH is the apolipoprotein E (APOE) gene and its ε2 and ε4 alleles [8].

Clinical Presentation and Pathophysiology

As with ischemic stroke, the typical ICH presentation includes the acute onset of a focal neurologic deficit [1, 9]. Decreased level of consciousness, vomiting, and headache can be presenting symptoms, especially in large or infratentorial hemorrhage. None of the symptoms/signs of ICH are specific enough to reliably distinguish it from ischemic stroke, and therefore the diagnosis of ICH always requires neuroimaging. Brain damage in acute ICH is mainly mediated by the mass effect of the hemorrhage and extension of the bleeding to the ventricular system (intraventricular hemorrhage (IVH)), leading to clinical deterioration secondary to increased intracranial pressure (ICP) [10, 11]. ICH is a dynamic disease and up to one-third of patients experience active bleeding with secondary hematoma enlargement in the first hours after stroke onset [12, 13]. In anticoagulant-associated ICH, the rate of hematoma expansion is even higher and more delayed, happening up to 48 h from onset [14]. Hematoma expansion is a major determinant of early clinical deterioration and unfavorable prognosis and represents an appealing target for acute ICH care.

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Prehospital Care

Treatment specific to ICH cannot be performed before the diagnosis of ICH. Therefore, prehospital care of suspected ICH is focused on airway, breathing, and circulation (ABC). Multiple studies show that ischemic stroke treatment in mobile stroke units equipped with CT scanners is feasible and reduces the time from onset to treatment [15]. It is therefore possible that in the near future ICH diagnosis and treatment may start in the prehospital phase [16].

Diagnostic Workup in the ED

Clinical Assessment

Vital signs should be measured and monitored [17]. The examiner should determine if intubation is required for the patient's safety during imaging. Neurological examination should be performed using validated tools such as the National Institutes of Health Stroke Scale and Glasgow Coma Scale (GCS) to establish a baseline severity score [17, 18] *[LOE:B]*. If intubation is required, rapid sequence intubation is typically preferred. The use of lidocaine, etomidate, and fentanyl may mitigate a transient increase in ICP associated with intubation [9].

Blood Tests

Complete blood cell count, electrolytes, glucose, liver, renal function tests, and routine coagulation studies should be obtained for all ICH patients [17, 18]. In cases of ongoing treatment with direct oral anticoagulants (DOACs), routinely available coagulation tests cannot accurately measure the degree of anticoagulant activity. Specific blood tests are required, and their results should always be interpreted taking into account renal function and timing of last dose. DOAC coagulation tests are summarized in Table 10.1 [19–22].

Imaging

Non-contrast Computed Tomography

Non-contrast computed tomography (NCCT) is the gold standard technique for the diagnosis of acute ICH in the emergency setting [23] *[LOE:A]*. NCCT allows rapid estimation of ICH volume, the strongest predictor of ICH prognosis, with the ABC/2 method [24]. Other useful elements that clinicians can obtain from a baseline NCCT are hemorrhage location, intraventricular extension of the bleeding, mass effect of the hematoma, and presence of hydrocephalus [17]. Figure 10.1 shows different ICH cases diagnosed with

Table 10.1 Direct oral anticoagulant coagulation tests

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
aPTT	Abnormal only at moderate/high levels of drug Provides only a qualitative indication	Low sensitivity Possible paradoxical response	Low sensitivity Possible paradoxical response	Low sensitivity
PT/INR	High interindividual variability Mild effect (INR ranging from 0.9 to 1.2)	Provides qualitative indication only with specific reagents	Unaffected	Linear dose-dependent association but low sensitivity at lower therapeutic drug levels
dTT	Already prolonged at low drug concentrations Normal dTT can rule out anticoagulant activity Needs calibration			
ECT	Sensitive indicator Not widely available			
Anti-Xa activity		Sensitive indicator Normal value rules out anticoagulant activity Not widely available Needs calibration	Sensitive indicator Normal value rules out anticoagulant activity Not widely available Needs calibration	Sensitive indicator Normal value rules out anticoagulant activity Not widely available Needs calibration
Specific test system	Hemoclot ®: dabigatran-calibrated dTT	Rivaroxaban-calibrated anti-Xa activity	Apixaban-calibrated anti-Xa activity	Edoxaban-calibrated anti-Xa activity
Non-hemostatic treatment	Discontinue the drug Activated charcoal if last dose within 3 h Hemodialysis	Discontinue the drug Activated charcoal if last dose within 3 h	Discontinue the drug Activated charcoal if last dose within 3 h	Discontinue the drug Activated charcoal if last dose within 3 h

aPTT indicates activated partial thromboplastin time, *PT* prothrombin time, *INR* international normalized ratio, *dTT* diluted thrombin time, *ECT* ecarin clotting time

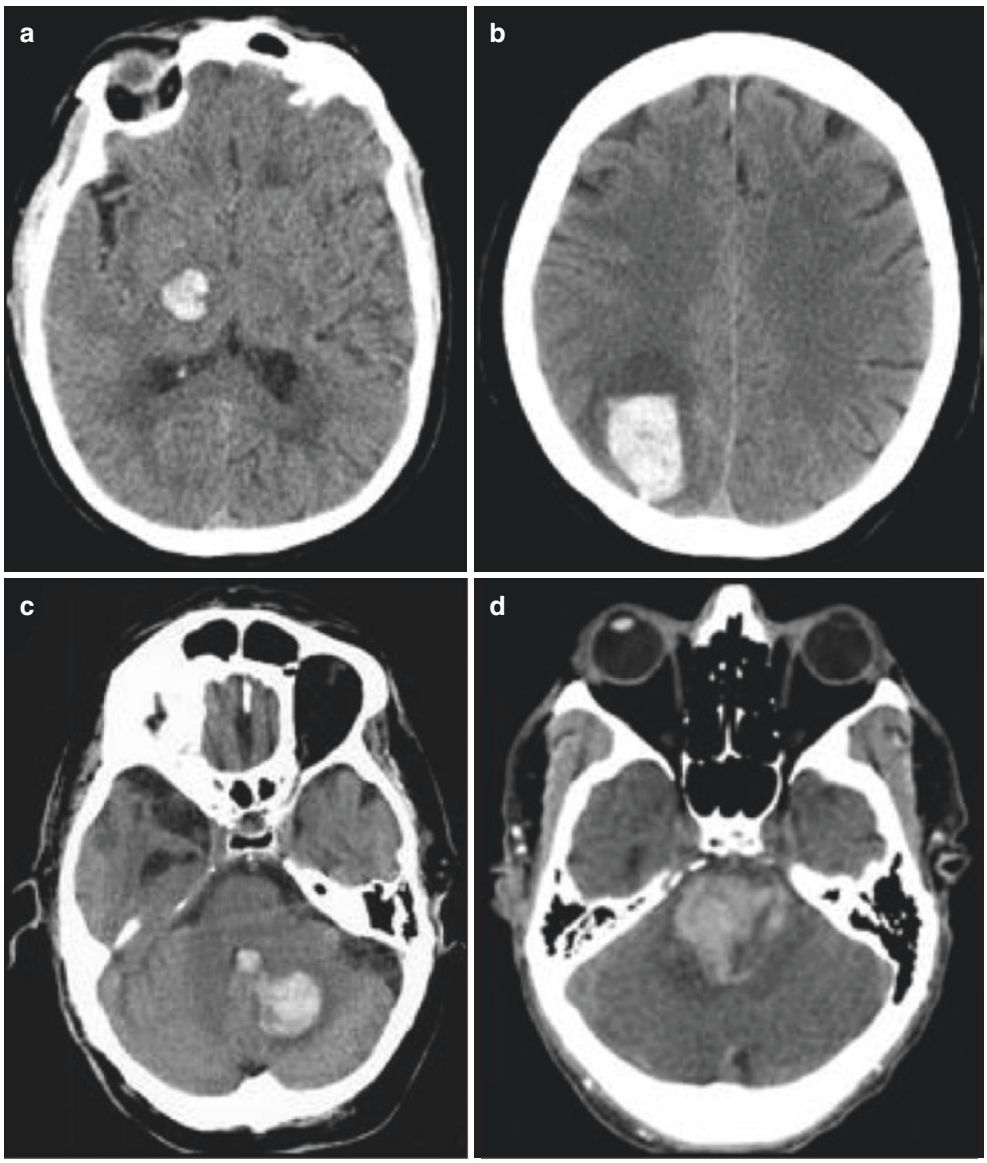

Fig. 10.1 Intracerebral hemorrhage on non-contrast CT. ICH with deep (**a**), lobar (**b**), cerebellar (**c**), and brainstem (**d**) locations

NCCT. In addition, several NCCT markers of hematoma expansion have recently been described, including intrahematoma hypodensities, blend sign, black hole sign, swirl sign, hematoma density and shape, and presence of fluid level [25]. These radiological signs may improve the stratification of ICH risk, identifying those patients requiring closer neurological monitoring. An illustrative example of an intrahematoma hypodensity is provided in Fig. 10.2.

Computed Tomography Angiography

Computed tomography angiography (CTA) is the fastest noninvasive method to detect vascular abnormalities as secondary causes of intracranial bleeding [26] *[LOE:B]*. The following red flags should trigger suspicion of ICH secondary to vascular intracranial pathology: lobar location of the hemorrhage, primary IVH, young age, female sex, and lack of traditional vascular risk factors, in particular absence of medical history of hypertension [26–28]. Rapid detection of vascular malformations is crucial because these lesions have a high rate of recurrent bleeding and may be susceptible to intervention. CTA is a useful tool in the emergency setting but digital subtraction angiography (DSA) has superior accuracy for the diagnosis of cerebral vascular malformations. Patients for whom an intracranial vascular lesion is highly suspected but have a negative CTA should undergo DSA [29]. CTA also allows rapid detection of a spot sign (iodine contrast extravasation within the hemorrhage) *[LOE:B]* (Fig. 10.3). This radiological marker is a robust validated predictor of hematoma expansion [30]. CTA appears to be safe in ICH patients with impaired renal function [31], and its main disadvantage compared with magnetic resonance angiography (MRA) is radiation exposure.

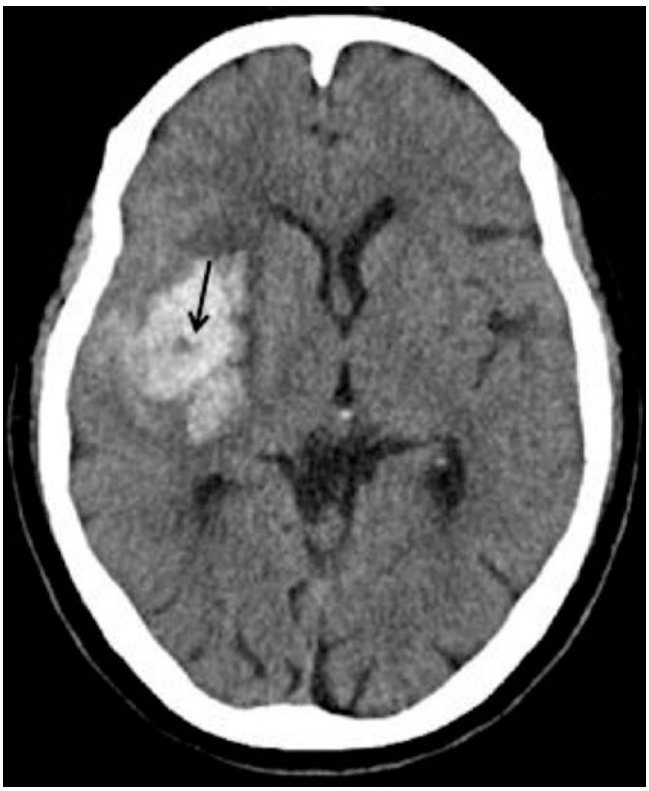

Fig. 10.2 Intrahematoma hypodensity. Non-contrast CT showing an intrahematoma hypodensity (arrow)

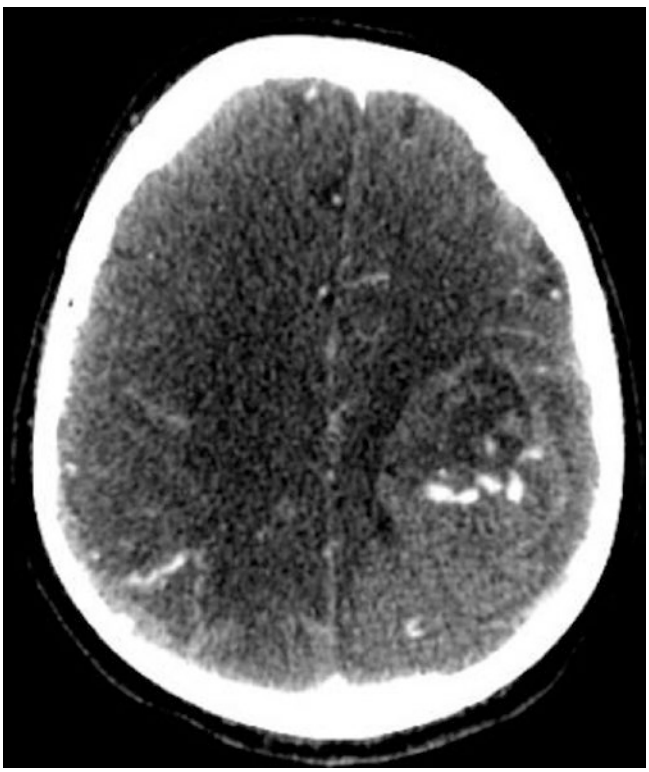

Fig. 10.3 Spot sign. CT angiography showing a large left lobar intracerebral hemorrhage with multiple foci of contrast extravasation (spot signs)

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is superior to NCCT and CTA for the detection of hemorrhagic conversion of ischemic strokes and neoplastic lesions as causes of intracranial bleeding [29]. MRI is also the best technique to detect radiological signs of cerebral small vessel disease, such as leukoaraiosis, microbleeds, and superficial siderosis [32]. MRA is an option for obtaining high-quality images of the intracranial vessels and can be performed without contrast *[LOE:B]*. The main drawback of MRI/A is its limited availability in many centers and its long duration, making it less suitable for unstable patients.

Digital Subtraction Angiography

While CTA is an excellent screening tool, all cases of intracranial bleeding suspected to arise from vascular malformations should be considered for DSA *[LOE:B]*. DSA has superior sensitivity compared with CTA and MRA for the diagnosis of vascular lesions and allows dynamic characterization and endovascular treatment of these malformations. This imaging modality is associated with radiation exposure, use of high volumes of iodinated contrast material, and a rate of severe complications around 0.4–1.3% [33]. Its availability is often limited, and ICH patients carrying a high suspicion of an underlying vascular malformation should be transferred to medical centers with around-the-clock DSA capability and presence of neurosurgery and neurointensive care teams.

Treatment

Blood Pressure

The majority of ICH patients have high blood pressure in the acute phase. Previous studies have shown that elevated systolic blood pressure (SBP) is associated with greater odds of hematoma expansion; therefore, multiple randomized trials have evaluated whether intensive blood pressure reduction can limit hematoma growth [34, 35]. First, the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) randomized ICH patients to intensive vs. standard SBP control (SBP <140 mm Hg vs. SBP <180 mm Hg, respectively) for the first 7 days after ICH onset [36]. The study did not meet its primary endpoint of major disability or death at 90 days, but secondary analysis showed that intensive SBP reduction may increase the proportion of patients with favorable functional outcome. Second, the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial randomized patients to intensive vs. standard SBP treatment (SBP <140 mm Hg vs. SBP <180 mm Hg, respectively) within 4.5 h from onset for the subsequent 24 h. Again the primary endpoint (disability or death at 3 months) was not met [37], and intensive blood

pressure treatment was associated with an increased risk of renal injury. In two secondary analyses of the ATACH-2 trial, intensive blood pressure lowering did not improve outcomes in patients with a CTA spot sign or NCCT markers of hematoma expansion, who theoretically might be more likely to benefit from anti-expansion treatment [38, 39]. To summarize, intensive SBP lowering to 140 mm Hg (not below) appears safe *[LOE:A]* and may improve functional outcome *[LOE:B]* (in ICH patients similar to those included in clinical trials) compared with a less restrictive BP management strategy. Blood pressure fluctuations should be avoided as these are consistently associated with unfavorable prognosis [40, 41]. The current American Heart Association/American Stroke Association (AHA/ASA) guidelines indicate that SBP lowering to 140 mm Hg seems safe and might be associated with better outcome in patients presenting with admission SBP ranging from 150 to 220 mm Hg [18]. The American College of Cardiology/AHA guidelines for the management of hypertension indicate that intensive SBP lowering below 140 mm Hg within 6 h from ICH onset is potentially harmful [42]. Intravenous (IV) antihypertensive agents with short half-lives should be used, and hydralazine and nitroprusside should not be the first choices because these medications may lead to increased ICP [9].

Hemostatic Treatment

Platelet Transfusion

The concern that ICH in the setting of antiplatelet agent use may lead to worse outcomes led many to treat with platelet transfusion [43, 44]. However, a randomized controlled trial evaluating platelet transfusions in ICH patients on antiplatelet therapy found an increased risk of death or poor outcome in those who received platelet transfusions [45] *[LOE:B]*. Platelet transfusions should therefore be reserved for ICH associated with severe thrombocytopenia *[LOE:C]*, although the optimal platelet count threshold that should trigger platelet transfusion remains controversial (between 50,000 and 100,000 platelets per microliter) [18]. The Neurocritical Care Society (NCS) guidelines state that platelet transfusions may be considered in ICH patients on antiplatelet medications who require surgery [17]. However, there is little evidence to routinely support preoperative platelet transfusion in ICH patients undergoing hematoma evacuation and/or external ventricular drain (EVD) placement.

Reversal of Coagulopathy from Vitamin K Antagonists

Anticoagulation with vitamin K antagonists (VKA) leads to increased extent of bleeding and poor outcome in ICH [6]. Coagulopathy reversal is thought to reduce the risk of hematoma expansion. For all patients, VKA use should be discontinued, and they should receive 10 mg of IV vitamin K (slow infusion over 10 minutes to minimize the risk of anaphylaxis) and coagulation factor repletion with either fresh frozen plasma (FFP) or 4-factor prothrombin complex concentrates (PCCs) [46]. The latter is the preferred option in many cases because of its more rapid international normalized ratio (INR) normalization and relatively small infusion volumes compared with FFP [9, 46, 47] *[LOE:B]*. FFP may be preferred if volume replacement is needed. The optimal INR that should be achieved remains debated, with thresholds ranging from 1.3 to 1.5 according to different international guidelines [17, 18, 48].

Reversal of Coagulopathy from Heparin

The best currently available option for heparinoid reversal is protamine sulfate *[LOE:C]*, although it is not yet clear whether this intervention improves outcomes [46, 49]. More details on dose and mode of administration of protamine are provided in the Pharmacology section below.

Reversal of Coagulopathy from Direct Oral Anticoagulants

The direct thrombin inhibitor dabigatran is the only DOAC with a specific reversal agent available *[LOE:C]*: idarucizumab, a monoclonal antibody that binds dabigatran with high affinity [19, 50, 51]. In an effort to reverse the other DOACs (apixaban, edoxaban, rivaroxaban), some guidelines suggest the administration of PCC (dose: 25–50 U/kg), although there is little evidence that PCC administration reduces the extent of bleeding in DOAC-associated ICH [17, 18, 46] *[LOE:C]*. To minimize the gastrointestinal absorption of DOACs, activated charcoal can be considered within 2–3 h from presumed last drug dose [52]. Of all the DOACs, dabigatran has the lowest protein binding and therefore can be removed from plasma with hemodialysis, especially in cases of drug overdose or acute renal failure [53].

Management of Elevated Intracranial Pressure

Large hematoma volume with edema, intraventricular hemorrhage, infratentorial location, and hydrocephalus are the main factors that contribute to increased ICP. ICP monitoring is recommended in patients with a GCS <8, clinical or imaging evidence of transtentorial herniation, and extensive IVH [17]. The suggested cerebral perfusion pressure target ranges from 50 to 70 mm Hg. Elevation of the head to 30 degrees, sedation, and hyperosmolar therapy *[LOE:C]* (either with mannitol or hypertonic saline) are the mainstays of medical management of increased ICP [54, 55], although recent data suggests that routine head elevation after ICH does not improve outcomes [56]. When ICP cannot be controlled with medical therapy, decompressive surgery may be considered.

Surgery

External Ventricular Drain Placement

An EVD should be placed in patients with hydrocephalus, coma, and extensive intraventricular bleeding to allow continuous drainage of ventricular blood [57] *[LOE:B]*. Preliminary studies suggested that intraventricular thrombolytic drugs may accelerate blood clearance and improve outcome. However, a randomized controlled trial specifically addressing this question, the CLEAR III (Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage III) trial, failed to meet this primary endpoint and showed that patients treated with an EVD in conjunction with thrombolytic treatment did not have improved outcomes [58] *[LOE:B]*. In patients with anticoagulant-associated ICH, coagulopathy reversal should be performed before EVD placement.

Surgical Hematoma Evacuation

Surgical evacuation of supratentorial ICH has been evaluated in two large randomized controlled trials [59, 60]. The main result of these trials was that surgery has not been proven superior to best medical management in terms of mortality and functional outcome. However, many patients in the medical arm of those trials crossed over to the surgical arm following neurologic deterioration, suggesting that while initial surgical management is not superior, it may be that hematoma evacuation upon deterioration might still improve outcomes. Surgery for supratentorial ICH should therefore be considered mainly as a life-saving measure in patients with rapid clinical deterioration and impending cerebral herniation *[LOE:C]* [18]. Decompressive craniectomy without hematoma evacuation is also a valuable option and may improve outcomes in patients with elevated ICP not responsive to medical therapy [61, 62]. There is more evidence to support surgery for cerebellar ICH, especially when associated with hydrocephalus and clinical or imaging evidence of significant mass effect leading to brainstem compression *[LOE:B]*. The benefits of traditional hemicraniectomy and hematoma evacuation in supratentorial ICH may have been offset by the very high rate of secondary complications of this approach [63]. Minimally invasive surgery (MIS) techniques are under development and may allow rapid hematoma evacuation with less damage to healthy brain tissue and lower rate of complications [64–66]. These promising techniques are currently under investigation.

Pharmacology

Reduction of elevated blood pressure and reversal of coagulopathy to limit hematoma expansion are the two mainstays of ICH acute medical management. Blood pressure reduction should be achieved using IV drugs with short half-lives such as labetalol, urapidil, and nicardipine. The pharmacological properties, side effects, and mode of administration of these agents are summarized in Table 10.2.

Table 10.2 Antihypertensive drugs

Drug	Dose and route of administration	Side effects/drawbacks
Urapidil	12.5–25 mg IV bolus 5–40 mg/h IV infusion	Hypotension, nausea and vomiting, headache, dizziness
Labetalol	10–40 mg IV bolus or 5–100 mg/h IV continuous infusion	Bronchospasm, bradycardia, heart failure, hypotension
Nicardipine	IV infusion, start at 2.5 mg/h and then 2.5 mg/h increase every 15–20 min Max infusion rate: 15 mg/h	Rebound tachycardia, emesis, headache, flushing, hypotension. Avoid in severe aortic stenosis

IV indicates intravenous

Vitamin K administration followed by PCC or FFP treatment is the main therapeutic option for reversal of coagulopathy in VKA-associated ICH. Protamine sulfate should be used to neutralize the anticoagulant activity of heparin in cases of ICH. Dabigatran is the only DOAC with a specific antidote available (idarucizumab), whereas PCC may be considered in cases of acute ICH associated with direct factor X inhibitors. Table 10.3 provides a summary of the agents used for coagulopathy reversal.

Secondary Complications

Fever and Infections

Fever and infections are major determinants of morbidity and mortality in ICH patients and frequent causes of clinical deterioration [10, 11, 67–69]. Targeted temperature reduction and prophylactic antibiotic treatment failed to improve ICH outcome in randomized controlled trials [70–72]. However, a care bundle including the use of acetaminophen for fever did improve outcome in a cluster randomized trial [73] *[LOE:B]*. Therefore, fever should be treated, although the optimal target temperature in ICH patients remains unclear [74]. Some factors such as age, dysphagia, stroke severity, lymphopenia, and hypoalbuminemia identify patients at high risk of infectious complications [75, 76]. In these patients, closer monitoring and intensive preventive measures may be warranted.

Seizures

Seizures are common after ICH, especially in patients with large cortical ICHs and patients experiencing infections

Table 10.3 Coagulopathy reversal agents [18, 46, 88]

Hemostatic therapies		
Drug	Dose and route of administration	Side effects/drawbacks
Vitamin K	10 mg IV, slow infusion (at least 10 minutes)	Anaphylaxis
4-factor PCC	*VKA-associated ICH* INR 1.5–1.9 → 10 U/kg (max 1000 U) INR 2.0–3.9 → 25 U/kg (max 2500 U) INR 4.0–5.9 → 35 U/kg (max 3500 U) INR >6.0 → 50 U/kg (max 5000 U) (PCC IV infusion rate: max 100 U/min) *DOAC-associated ICH* 25–50 U/kg	Prothrombotic Small risk of allergic reaction
FFP	15–20 mL/kg IV infusion	Large-volume, long infusion time Requires compatibility testing and thawing Allergic reaction, infections, transfusion-related lung injury
Protamine sulfate	*Unfractionated heparin* 1 mg for each 100 U of heparin if heparin infusion is still ongoing (max 50 mg) 0.5 mg for each 100 U of heparin if last heparin administration 30 min before 0.25 mg for each 100 U of heparin if last heparin administration 2 h before *Low-molecular-weight heparin* 1 mg for each 100 U of LMWH administered in the last 8 h (max 50 mg) 0.5 mg for each 100 U of LMWH administered in the last 8–12 h (max 25 mg) Max infusion rate: 5 mg/min	Hypotension
Idarucizumab	5 g divided in two IV infusions (2.5 g + 2.5 g), each with a duration of 5–10 minutes	Skin rash, hematoma at site of infusion, epistaxis

IV intravenous, *PCC* prothrombin complex concentrate, *VKA* vitamin K antagonist, *LMWH* low-molecular-weight heparin, *FFP* fresh frozen plasma

and other medical complications [77–79]. However, prophylactic antiepileptic therapy does not clearly improve outcomes and may be associated with worse outcomes *[LOE:B]*; therefore, only patients with clinical and/or electroencephalographic evidence of seizures should receive treatment *[LOE:A]* [17].

Glycemia Management

Both hyperglycemia and hypoglycemia are independently associated with poor outcome after ICH [80, 81]. There is no evidence in favor of intensive blood glucose reduction with IV insulin infusion. The AHA/ASA and NCS guidelines recommend avoiding hypo- and hyperglycemia, but clear thresholds for blood glucose control remain unclear [17, 18]. The best data in favor of normoglycemia comes from a cluster randomized trial that found that a bundle of therapies (normothermia, normoglycemia, and dysphagia screening) improves outcomes *[LOE:B]* [73]. Therefore, we suggest treating blood glucose over 140 mg/dl with subcutaneous insulin sliding scale in the first 24–48 h after ICH.

Deep Venous Thrombosis Prevention

ICH patients are at high risk of deep venous thrombosis and at the least should receive prophylactic treatment with intermittent pneumatic compression devices *[LOE:A]* [82]. A follow-up NCCT scan at 24–48 h from onset should be obtained to exclude the presence of ongoing bleeding before the initiation of prophylactic treatment with unfractionated or low-molecular-weight heparin (LMWH), which can be considered as early as 24–72 h after ICH *[LOE:B]* [18] .

Patient Flow and Discharge Destination

A stroke team (ideally including a stroke neurologist or other clinician specifically trained in stroke) should be activated for every patient with a clinical presentation suggestive of an acute cerebrovascular event. After diagnosis of ICH, neurosurgical consultation should be obtained for all patients who may benefit from surgical intervention.

The following criteria can be used to select patients for intensive care unit (ICU) admission:

- Frequent neurologic and vital sign monitoring
- Need for invasive monitoring
- Need for invasive ventilation
- Organ failure
- Hemodynamic instability
- GCS <8
- Requiring surgical treatment

After ICU-level care, patients can be transferred to a lower level of care (stroke unit or general neurology ward) if all the following conditions are met:

- Stable vital signs
- Invasive monitoring and ventilation are no longer required
- Secure airway
- Absence of major medical complications

ICH care in a stroke unit or neurological intensive care unit is associated with favorable functional outcome and lower mortality compared with admission to a general neurology ward [83]. All ICH patients should therefore be admitted to a unit with a dedicated stroke or neurointensive care team. If the stroke unit/neurointensive care unit has limited availability, patients at low risk for early neurological deterioration (small supratentorial hemorrhages without IVH or hydrocephalus, lack of coagulopathy, optimal control of airway and vital signs) may well be appropriate for the general neurology wards.

Prognosis

ICH remains the deadliest type of stroke, and accurate prognostication is an important aspect of ICH care. ICH size, infratentorial location, age, admission GCS, and presence of IVH are the strongest predictors of unfavorable outcome [84]. Several scores have been developed to predict functional outcome and mortality, but the accuracy of these tools is suboptimal, and recent studies suggest that clinicians' judgment may be superior [85]. In addition, withdrawal of care is an independent predictor of death, and therefore full medical support is recommended for at least 48 h in all patients with acute ICH *[LOE:C]* [86, 87].

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Management of Cerebral Venous Thrombosis

11

Xiaomeng Xu and Magdy Selim

Definition and Epidemiology

Definition

Cerebral venous thrombosis (CVT) refers to clot formation within the dural venous sinuses or the cerebral venous drainage system. The most commonly affected sinuses are the superior sagittal sinus, transverse sinuses, straight sinus, cortical veins, internal jugular veins, and deep veins.

Incidence

Cerebral venous thrombosis is a rare but important cause of stroke, especially among young individuals. The reported incidence of CVT in different studies varies greatly. It was traditionally estimated to be 2–4 cases per million per year, but recent studies reported a much higher incidence of 13 cases [1] to 15 cases [2] per million each year as a result of improved diagnosis by advanced imaging techniques [2, 3].

Age and Sex

CVT occurs predominantly in young and middle-aged patients, of whom >90% are less than 65 years old [4]. The male to female ratio is 1:3, and the greater prevalence in women is likely due to sex-specific risk factors such as the use of oral contraceptives, pregnancy, and postpartum [5, 6]. However, despite previous CVT, pregnancy causes a low absolute risk for recurrent CVT. Therefore, prior CVT should not be a contraindication for pregnancy [7].

Risk Factors

There are several risk factors that predispose to CVT. In women, oral contraceptives, pregnancy, and postpartum are predominant risk factors. In addition, hereditary and acquired prothrombotic conditions can increase the risk for CVT. Table 11.1 lists many of these risk factors. Thorough history and examination will often identify acquired factors.

Diagnosis

The diagnosis of CVT requires the following: (1) clinical suspicion based on the presenting symptoms and signs, (2) brain imaging to confirm CVT, and (3) additional laboratory tests and imaging to determine the underlying cause of CVT.

Clinical Manifestations of CVT

The clinical features of CVT are usually diverse and nonspecific, which adds to the difficulty in making a timely diagnosis. Clinical manifestations of CVT are attributed to two mechanisms: (1) elevation of overall intracranial pressure (ICP) and brain edema resulting from the obstruction of the cerebral venous sinus and cerebral blood outflow and (2) focal brain injury due to the local effects of the clot and venous infarction. Compared with other forms of stroke, the symptoms of CVT are usually slow in onset and progressive and may be bilateral. Abrupt onset is rare and is mostly seen in obstetrical and infectious cases.

Headache is the most common and earliest symptom of CVT affecting about 90% of cases and may be the only symptom in up to 25% of patients [8]. The headache is usually progressive

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Table 11.1 Risk factors for CVT

Risk category	Risk factor
Infectious	
	Infection of head and neck
	Central nervous system
	Other
Noninfectious	
Genetic	
	Protein C deficiency
	Protein S deficiency
	Factor V Leiden thrombophilia
	Prothrombin G20210A mutation
Acquired	
A. Sex-specific.	Pregnancy and postpartum states[a]
	Oral contraceptives[a]
	Hormone replacement therapy[a]
B. Disease related.	
Malignancy	Cancer
	Myeloproliferative neoplasms
Autoimmune disease	Systemic lupus erythematosus
	Antiphospholipid syndrome
	Behçet's disease
	Inflammatory bowel disease
	Sarcoidosis
Other disease	Thyroid disease
	Nephrotic syndrome
	Anemia
	Hyperhomocysteinemia
	Dehydration
	Central nerves system malformation
C. Mechanical injury.	Head trauma
	Lumbar puncture
	Neurosurgical operation
	Jugular vein catheterization
None identified	

[a]In female population

over days to weeks, but thunderclap headache has been reported in some cases. Other symptoms and signs of increased ICP, such as papilledema and transient visual obscurations, may manifest themselves later on. Seizures, focal or generalized, occur in ~40% patients and are usually secondary to a venous infarct. Altered level of consciousness may be seen in ~5% of cases and may be due to a postictal state or attributed to increased ICP. In addition, venous infarct(s) may result in focal neurological deficit in affected regions. These are variable, but hemiparesis is the most common. Rare presentations of CVT include tinnitus, vertigo, cranial nerve palsies, and cerebellar symptoms/signs. Coma, stupor, extensor spasms, or abulia may be seen with deep CVT leading to involvement of the basal ganglia and thalami.

Imaging of the Brain and Venous Sinuses

Imaging studies are key to establish the diagnosis of CVT in suspected cases.

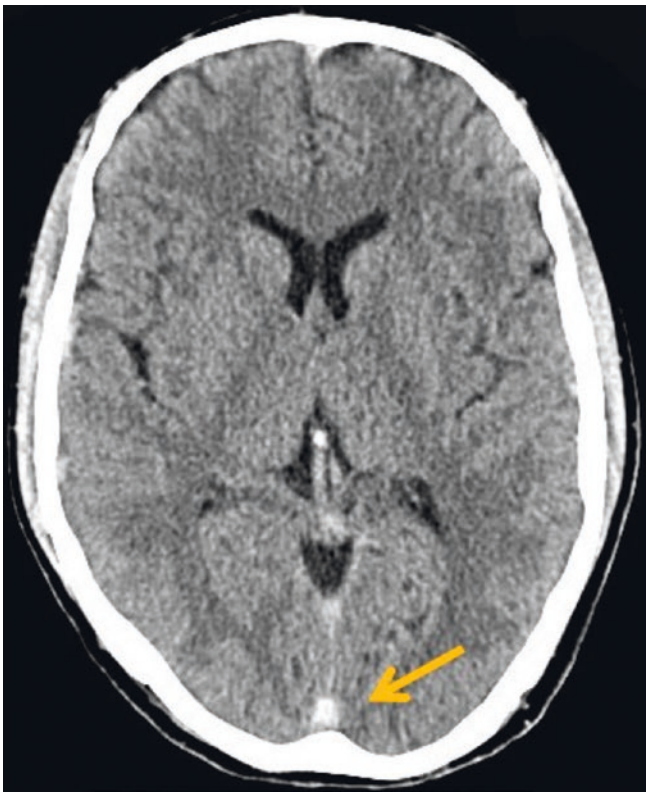

Fig. 11.1 Filled delta sign on non-contrast CT (arrow). The clot in the superior sagittal sinus causes increased density than normal

Computed Tomography (CT)

Non-contrast CT is usually the first imaging examination in these clinical scenarios due to its readiness in emergent settings and value in excluding other neurological conditions with similar signs and symptoms. However, radiological changes on non-contrast CT scans are too subtle to be diagnostic in most cases of CVT. Therefore, a negative CT result cannot entirely rule out the possibility of CVT. Indeed, initial CT scan is often interpreted as "normal" in 25–40% of patients with CVT [9, 10].

CT findings may include the following: changes in the mastoid or middle ear structures in patients with septic lateral sinus thrombosis; venous infarctions, which tend to be hemorrhagic and located in non-arterial or subcortical locations; and effacement of the sulci or slit-like ventricles due to brain edema or high ICP [11–13]. The most straightforward and direct evidence of CVT is to directly visualize the thrombus in the vein or sinus. On non-contrast CT scans, an acute clot can appear as a homogenous hyperdensity of a cortical vein or a cerebral sinus, mimicking a subarachnoid hemorrhage. In the cases of superior sagittal sinus CVT, the clot may emerge as a dense triangle due to the anatomic structure of superior sagittal sinus, which is referred to as the filled delta sign (Fig. 11.1). One of the drawbacks of non-contrast CT scans is that an acute clot can only be seen in the first

7–14 days. After that, the clot becomes isodense or hypodense and difficult to visualize [14].

Therefore, in subacute and chronic cases, contrast-enhanced CT scan and CT venography are recommended. On contrast-enhanced CT scans, the filling defect sign and empty delta sign [11] are equivalent to the above findings on non-contrast CT scans [12].

Magnetic Resonance Imaging (MRI)

MRI is the imaging modality of choice in CVT. Compared with CT, MRI is more sensitive in detecting parenchymal abnormalities, such as focal edema and infarctions, and the thrombus during the acute, subacute, and chronic stages [8]. The clot appears isointense on T1- and hypointense on T2-weighted images during the acute phase and gradually becomes hyperintense on both T1- and T2-weighted images by the second week [8, 10].

The main direct sign of thrombus on MRI is the absence of flow void within the affected venous sinus (Fig. 11.2), which is equivalent to the filled delta sign on non-contrast CT and filling defect sign on contrast-enhanced CT [8]. However, T1- and T2-weighted images have limitations, and false positives due to slow blood flow are not uncommon. While susceptibility-weighted MRI may allow direct visualization of deoxyhemoglobin in the thrombus as an area of signal loss/darkening within the affected sinus (Fig. 11.3), contrast-enhanced MRI and MR venography are always recommended [8, 15].

Venography

Non-contrast CT or MRI can be entirely normal in about 30% cases. Therefore, CT (CTV) or MR venography (MRV) are recommended when CVT is suspected, even when non-contrast CT or MRI are negative [8, 16]. The diagnostic value of CTV and MRV is equivalent; however, due to concerns about radiation and iodine contrast, MRV is the most widely used modality (Fig. 11.4). The 2D time of flight (TOF) is the most commonly used MRV technique (Fig. 11.5a). However, TOF MRV has limitations because flow gaps are not uncommon. The use of gadolinium-enhanced MRV is less likely to be affected by flow artifacts and when combined with the 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (Fig. 11.5b) is

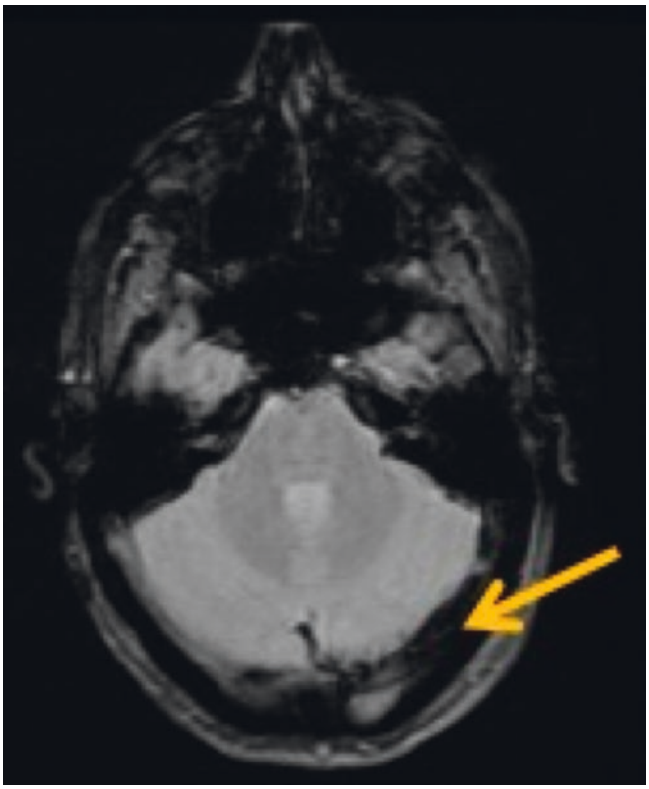

Fig. 11.3 Gradient echo T2∗ MRI showing susceptibility artifact within the left transverse sinus (arrow) consistent with sinus thrombosis

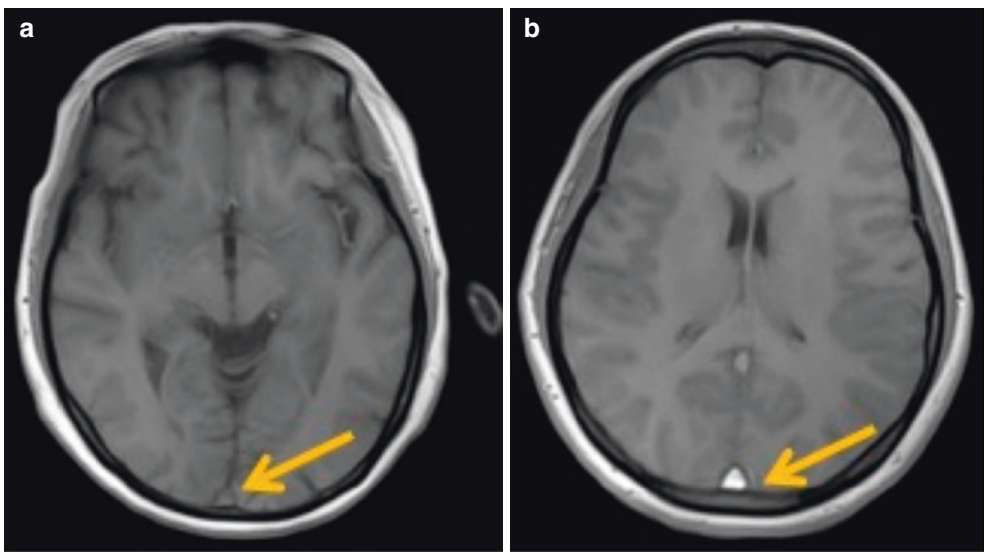

Fig. 11.2 MRI T1-weighted images of a 36-year-old man presenting with headache. **a** and **b** were obtained 6 days and 12 days after symptom onset, respectively. The clot in the superior sagittal sinus (arrows) appears isointense during the acute phase (**a**) and hyperintense during the chronic phase (**b**)

superior to TOF MRV particularly in complicated cases with anatomic variants [8].

The use of invasive digital subtraction angiography (DSA), the historical gold standard for diagnosing CVT, is declining due to the improvement in the sensitivity and specificity of noninvasive CTV/MRV. Nowadays, DSA use is often limited to patients in whom MRV/CTV is inconclusive and equivocal cases in which it is difficult to ascertain whether CVT detected on CTV/MRV is instead attributed to sinus hypoplasia or filling defects due to arachnoid granulations [8].

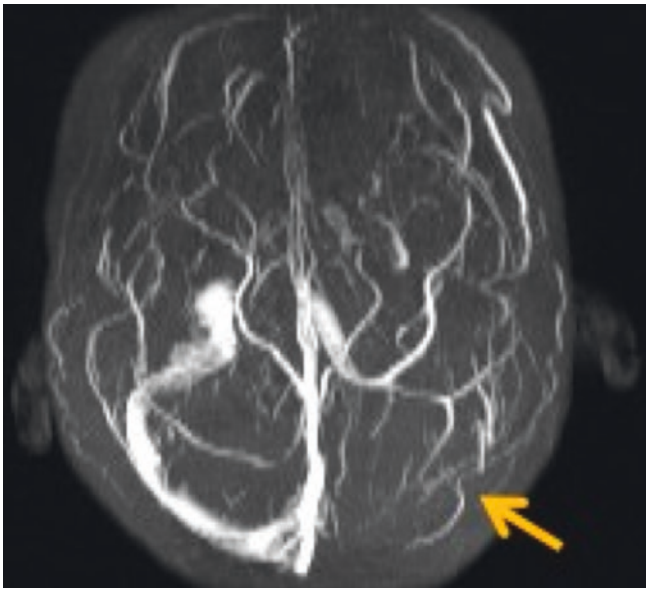

Fig. 11.4 A left transverse and sigmoid sinus thrombosis (arrow) confirmed by MRV

Blood Tests and Other Imaging Studies

The use of D-dimer as an alternative to imaging to exclude CVT diagnosis in low-risk patients has been debatable. Serum levels >500 μg/L have 91% specificity, 97% sensitivity, and 55% positive predictive value to detect CVT [17]. However, there are many causes for elevated D-dimer, and false-negative results may be seen in subacute or chronic cases, small clot burden, and cases presenting with isolated headache [8].

Laboratory tests are mostly helpful in determining the etiology of CVT (Table 11.1), including underlying infection, malignancy, hematological and inflammatory disorders, or prothrombotic conditions. Recommended initial tests include complete blood count, chemistry, sedimentation rate, and coagulations studies [8]. In cases where the cause of CVT remains undetermined after careful history and initial tests, testing for an inherited thrombophilia, including factor V Leiden, prothrombin gene mutation, antithrombin III

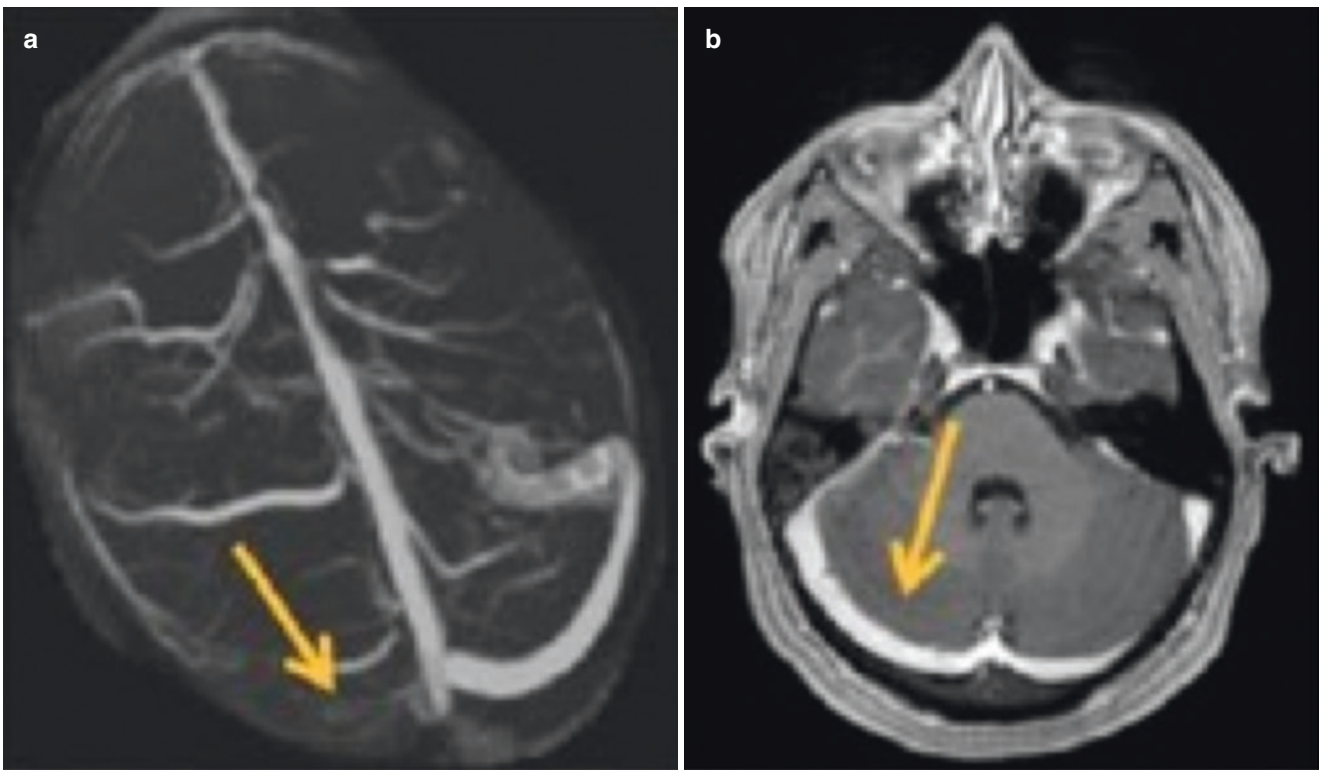

Fig. 11.5 (**a**) TOF-MRV shows lack of flow in the right transverse sinus (arrow). (**b**) MP-RAGE with gadolinium shows patency of the sinus (arrow)

deficiency, and protein C and S deficiency, should be considered. Ideally, testing should be done before initiation of anticoagulation and repeated 4–6 weeks later, particularly in patients whose initial workup is negative. Workup for an occult malignancy should be undertaken in those whose initial evaluation and thrombophilia testing are unrevealing.

Triage and Prognosis

Triage

Because of the diversity of causes and presenting symptoms, patients with CVT commonly encounter many specialists in different healthcare settings. Patients presenting with isolated headaches or nonlocalizing symptoms/signs of increased ICP are often encountered by family practitioners or internists as the first primary providers. This may prompt referral to a neurologist or local emergency department. Those presenting with neurological symptoms or signs are encountered by neurologists or emergency medicine physicians. Intensivists often encounter patients with CVT whose level of consciousness is impaired or are in coma and those who develop seizures or significant complications related to large hemorrhagic infarction, high ICP, and brain edema. Other specialties, such as hematologists, oncologists, and neurosurgeons, may be involved at different stages of the hospitalization and evaluation on a case-by-case basis.

Prognosis

Approximately one-quarter of patients deteriorate within several days after the diagnosis of CVT. Patients with depressed level of consciousness upon presentation are more likely to deteriorate. Early mortality is often attributed to herniation due to a large hemorrhagic infarct or massive brain edema, pulmonary embolism, or refractory status epilepticus. Predictors of mortality include altered consciousness, thrombosis of the deep venous system, and posterior fossa lesions. Observational studies report complete recovery in ~79% of patients, ~8% death rate, and 5% dependency rate (i.e., modified Rankin Scale score ≥3) after a median follow-up of 16 months [18].

Risk stratification scores have been developed to inform patients of their individual prognosis and to select those who might benefit most from aggressive treatments. In one model, 2 points are assigned for the presence of malignancy, coma, or thrombosis of the deep venous system and 1 point for male sex, presence of decreased level of consciousness, or intracranial hemorrhage. A cutoff score of ≥3 points indicates a higher risk of death or dependency at 6 months (c-statistic ~85%) [19]. Another study developed a risk score model that incorporated two more predictive variables: age >37 and infection. In this model, 5 points are assigned to male sex, 6 points for intracranial hemorrhage, 7 points for mental status disorder, 7 points for age >37, 10 points for Glasgow Coma score <9, 11 points for cancer, 11 points for deep CVT, and 12 points for central nervous system infection. The predictive value of a score <14 for good outcome (modified Rankin Scale score ≤2) is 0.96, whereas the predictive value of a score ≥14 for poor outcome is 0.39 [20].

Treatment

Acute Management

Anticoagulation

Acute anticoagulation is recommended, even in the presence of hemorrhagic infarctions, to prevent thrombus growth, pulmonary embolism, and deep vein thrombosis. This is based on the results of two randomized trials of intravenous unfractionated heparin (UFH) and subcutaneous low-molecular-weight heparin (LMWH), which included a total of 79 patients with CVT [21, 22] and showed no increase in the risk of intracerebral hemorrhage and a reduction in poor outcome and death with anticoagulation (RR 0.46; 95% confidence interval 0.16–1.3) [23]. A randomized trial comparing UFH vs. LMWH showed that LMWH was associated with higher rates of better clinical outcome at 3 months [24]. However, intravenous UFH might still be preferable in the acute setting if neurosurgical intervention is anticipated and rapid reversal of coagulopathy is needed.

Thrombolysis and Thrombectomy

There is insufficient evidence to recommend mechanical thrombectomy with or without intra-sinus thrombolysis as a first-line treatment for CVT. The Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) trial found that endovascular treatment (EVT) did not improve clinical outcomes and was recently terminated [3]. Furthermore, although the spontaneous recanalization rates of CVT approaches 85% after a few months, recanalization does not seem to be related to long-term outcomes. Therefore, EVT should not be routinely applied in cases with low risk for poor outcome and should be reserved for situations where significant neurological deterioration occurs despite intensive anticoagulation to facilitate recanalization and to reduce fatality [25, 26].

Symptom Management

Intracranial Hypertension

Isolated intracranial hypertension occurs in ~40% CVT cases [27]. The elevation of ICP is mainly due to CSF malabsorption. Thrombus in the superior sagittal sinus and lateral dural sinuses may impair arachnoid granulations, which therefore leads to reduced CSF absorption. Meanwhile, hemorrhage into the ventricles and severe brain edema may also lead to increased ICP by causing obstructive hydrocephalus. Intracranial hypertension may cause papilledema and visual field loss. Therefore, close monitoring of vision is necessary, and urgent therapeutic measures should be taken immediately when visual alteration is observed [28].

Although the optimal treatment for intracranial hypertension in CVT is inconclusive, acetazolamide 500–1000 mg/day can be considered, and therapeutic lumbar puncture, serial lumbar puncture, or a lumbo-peritoneal shunt is warranted when necessary [29, 30]. In life-threatening cases with intractable intracranial hypertension, decompressive hemicraniectomy may be considered [31]. Steroids are not recommended [32].

Seizures

Seizures occur in ~40% of patients with CVT and are associated with worse prognosis [33, 34]. Although prophylactic antiepileptic drugs are not recommended, early initiation of antiepileptic drugs is warranted after the first onset of one single seizure.

Treatment of Specific Conditions

Heparin-induced thrombocytopenia (HIT) may predispose to CVT [8]. HIT is a complication of UFH and typically occurs 4 to 10 days after exposure to UFH. It must be suspected when a patient who is receiving UFH is noted to have a decrease in platelet counts, particularly if the fall is >50% of the baseline count [35]. Confirming the diagnosis of HIT requires immunoassays to identify antibodies against heparin/platelet factor-4 (PF4) complexes and/or functional assays measuring platelet-activating capacity of PF4/heparin-antibody complexes [35]. If HIT is suspected, all heparin products including the use of UFH in flush catheters must be discontinued immediately. Alternative anticoagulants, typically a direct thrombin inhibitor such as argatroban, should be used instead [35].

In HIT patients, warfarin may cause microthrombosis, and in these patients international normalized ratio (INR) usually exceeds 4.0. Therefore, initiation of warfarin should be postponed until platelet count exceeds 150×10^9/L [36, 37]. Vitamin K should be given immediately if warfarin has already been given [38].

Long-Term Management

Oral Anticoagulation

Transition to oral anticoagulation is recommended for long-term management in order to prevent recurrent CVT or other venous thromboses. Traditionally, vitamin K antagonists (i.e., warfarin with target INR of 2.0–3.0) are often recommended. Novel oral anticoagulants (NOACs) present new options for long-term anticoagulation. Two cases series including a total of 22 patients who received NOACs after heparin therapy in the acute phase reported similar clinical benefits to warfarin [39, 40]. Given the nature and size of these studies, the use of NOACs for routine treatment of CVT requires further study and its use to treat CVT should be cautiously considered, especially as an alternative to UFH or LMWH during the acute phase [15].

The optimal duration for oral anticoagulation after CVT is uncertain. The American Heart Association/American Stroke Association guidelines recommend continuing anticoagulation for 3–6 months in patients whose CVT was provoked and related to reversible risk factors (e.g., due to the side effect of medical therapy), 6–12 months for those with idiopathic CVT, and lifelong for patients with recurrent CVT or irreversible severe prothrombotic conditions with high thrombotic risk, such as homozygous factor V Leiden, prothrombin gene mutation, and antithrombin III or protein C or S deficiencies [8].

Figure 11.6 summarizes a suggested flowchart for management of patients with suspected CVT.

Pregnancy

Women with a history of CVT are at increased risk for CVT recurrence during future pregnancies. The risk of CVT recurrence with pregnancy is ~1.2% and is highest during the third trimester and first 4 puerperium weeks. Therefore, prophylaxis with LMWH throughout a future pregnancy and at least 6 weeks postpartum is recommended [7, 41, 42].

Pharmacology

Heparin

Dose Bolus 80 units/kg (maximum 5000 units) + infusion 12 units/kg/h (maximum 1200 units/h) for normal body habitus or 1800 units/h for morbid obesity.

Monitoring schedule:

1. PTT should be checked at baseline, 6 hours after bolus or any rate change, and then daily, with a therapeutic target of 50–70 seconds.

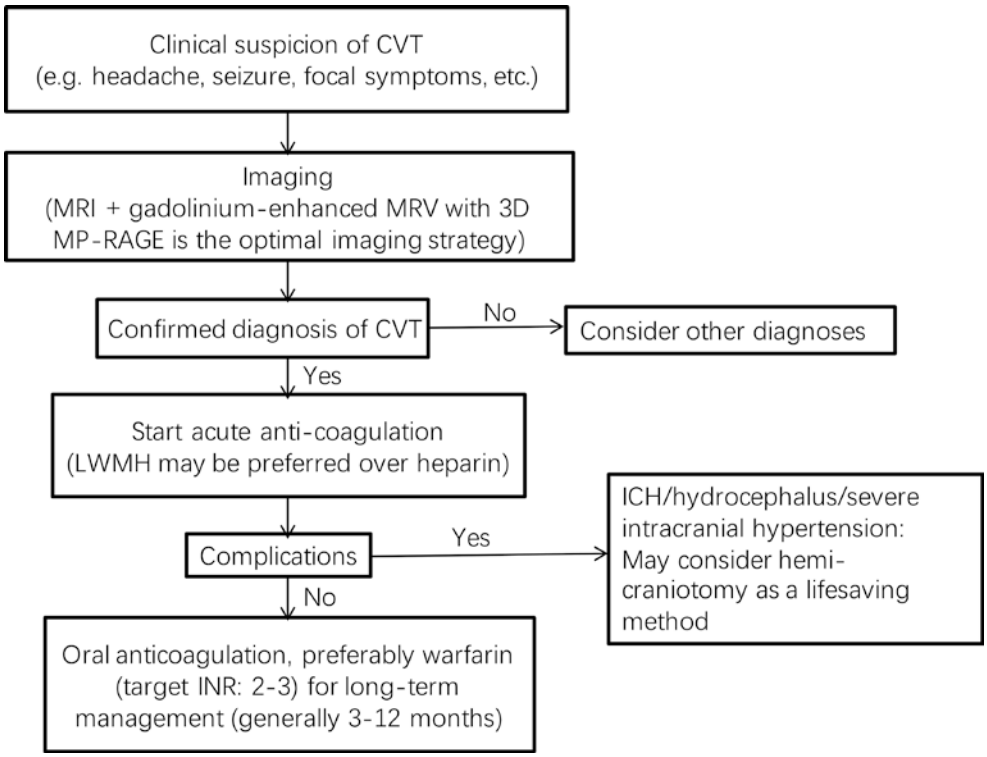

Fig. 11.6 Flowchart for suggested management of patients with suspected CVT

2. Platelets counts should be checked daily to monitor for HIT.
3. Hemoglobin and hematocrit should be checked every other day to monitor for bleeding.

Precautions:

1. Heparin should be discontinued immediately with suspicion of HIT.
2. Heparin should be prescribed with precaution during pregnancy because it increases the risk of maternal hemorrhage. Therefore, in pregnancy and postpartum, LMWH is preferred.

LMWH (Enoxaparin)

Dose 1.5 mg/kg per day or 1 mg/kg every 12 hours, subcutaneously.

Monitoring schedule:

1. Platelet counts should be checked daily to detect thrombocytopenia.
2. Anti-factor Xa level may be used to monitor the effect of enoxaparin in patients with severe renal impairment or underlying bleeding.

Precautions:

1. Warfarin should be initiated in conjunction with enoxaparin. Enoxaparin therapy should continue for at least 5 days and until therapeutic effects of warfarin has been achieved (INR 2.0 to 3.0).
2. In patients with severe renal impairment (creatinine clearance <30 ml/min), the dosage regimen is 1 mg/kg daily.
3. Enoxaparin must not be administered by intramuscular injection.
4. Lumbar puncture or other procedures should be performed at least 24 hours after the last dose, and the next dose should be delayed for at least 4 hours. In patients with creatinine clearance <30 ml/min, the procedure should be performed at least 48 hours after the last dose.

Warfarin

Dose Titrated from 2 to 5 mg/d to the therapeutic dosage that maintains the INR between 2.0 and 3.0.

Monitoring schedule:

INR should be monitored daily until stable in the therapeutic range. Subsequent INR should be obtained every 1–4 weeks.

Precautions:

1. INR should be monitored regularly.
2. Warfarin can infrequently cause tissue necrosis. In this situation, warfarin should be discontinued and replaced by alternative anticoagulants.
3. Warfarin is teratogenic and is contraindicated during pregnancy. If the benefit of taking warfarin outweighs the risk in pregnant women, the decision should be reviewed by the patient.
4. Acute kidney injury may occur in patients with previous renal insufficiency.
5. Warfarin may cause systemic atheroemboli and cholesterol microemboli. Once these phenomena are observed, warfarin should be discontinued and alternative anticoagulants should be considered.
6. Warfarin should not be used as initial therapy in patients with HIT but can be considered when platelets count returns to normal.

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Part III

Neurosurgical Emergencies

Management of Acute Traumatic Brain Injury

12

Sungho Lee, Aditya Vedantam, Claudia S. Robertson, and Shankar Gopinath

Initial Evaluation

Initial evaluation of acute TBI occurs in the emergency room as part of the trauma survey. Mechanism of injury, vital signs, Glasgow Coma Scale (GCS), pupillary exam, and any prehospital interventions should be clearly communicated by the emergency medical service providers upon the patient's arrival. In a patient with depressed GCS (<9) or signs of airway compromise, endotracheal intubation is performed. If the decision is made to intubate the patient in the emergency room, a quick neurological assessment should precede administration of paralytics in order to establish a baseline, when feasible. Injuries that impair ventilation in the short term, such as tension pneumothorax or massive hemothorax, are addressed urgently. Hemodynamic instability is best treated empirically with crystalloid and blood product transfusions. If there is an obvious open injury, attempts are made to temporarily control the bleeding.

Neurological evaluation is then performed, centered upon determining the patient's GCS, a simple scoring system for level of consciousness that is predictive of outcome [1]. Based on the GCS, TBI can be classified as mild (13-15), moderate (9-12), and severe (<9). Any confounding factors that can cloud the neurological status should be noted – including intoxication, narcotics, or hypoglycemia. In order to avoid secondary brain injury, avoidance of cerebral hypoxia and hypoperfusion is critical. If the patient is hemodynamically stable, the patient is then brought to the scanner for non-contrast computed tomography (CT) of the head and cervical spine as well as additional imaging when indicated. The findings of the CT head, in combination with the patient's neurological status, determine the need for emergent surgery. Therefore, CT head is one of the key decision points (see section titled "Key Decision Points").

Emergent Surgery

A large unilateral mass lesion with midline shift, effacement of the basal cisterns, and impending or obvious herniation requires emergent neurosurgical intervention (Fig. 12.1). Surgical Management of Traumatic Brain Injury guidelines recommend evacuation of subdural hematoma with >1 cm of width or >5 mm of midline shift as well as epidural hematoma >30 cc in volume (level III evidence) [2, 3]. Large contusions with associated clinical deterioration and open depressed skull fractures are also other indications for emergent surgery [4]. Nonetheless, surgical decisions are made based on the clinical status of the individual patient, and it is not advisable to rely solely on imaging findings. For subdural and epidural hematomas, craniotomy for evacuation of the hematoma is typically performed. In patients with significant cerebral edema, the bone flap is kept off and a lax duraplasty is performed to avoid the constricting effect of dura on the underlying brain. For contusions, craniotomy for evacuation of the mass lesion or various decompressive procedures are utilized. Large hemispheric hematomas or contusions with mass effect require a full frontotemporoparietal decompressive craniectomy, which according to the BTF guidelines should be greater than 15 cm in diameter (level IIA) [5].

Following surgery, the patient is admitted to the neurocritical care unit for postoperative care. An external ventricular drain (EVD) is usually placed intraoperatively, and intracranial pressures (ICPs) are managed accordingly in a tiered approach to be discussed later. If craniectomy is per-

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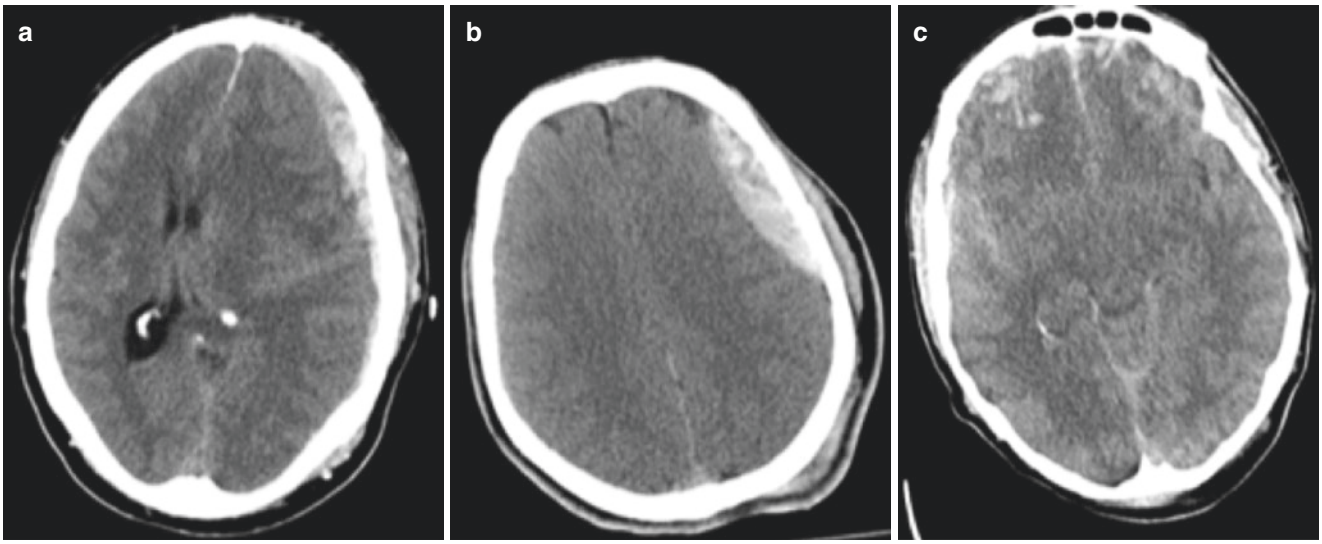

Fig. 12.1 Examples of mass lesions requiring surgical intervention are shown, including acute left convexity subdural hematoma measuring 1.8 cm in maximal thickness causing 1.7 cm of midline shift (**a**), acute left epidural hematoma exceeding 30 cc in volume (**b**), and bifrontal contusions causing medically refractory intracranial hypertension (**c**)

formed, the fullness of the flap provides an important gauge of ICP.

Management of TBI in the Neurocritical Care Unit

Initial Considerations

Once the patient arrives in the neurocritical care unit from the operating room or the emergency room, the basic tenets of critical care such as blood pressure management and mechanical ventilation are uniquely tailored toward the prevention of secondary brain injury (Fig. 12.2). One of the most fundamental goals of neurocritical care following TBI is avoidance of hypotension and resultant cerebral hypoperfusion. In patients with intact autoregulation, hypotension results in compensatory vasodilation, contributing to increased cerebral blood volume and ICP. If autoregulation is disrupted, hypotension produces ischemia, which is one of the most devastating contributors to secondary brain injury. Unsurprisingly, hypotension is one of the strongest predictors of morbidity and mortality following TBI [6].

The BTF guidelines therefore recommend maintaining a more aggressive systolic blood pressure (SBP) threshold in TBI patients than what is traditionally accepted for other types of critically ill patients (level III evidence) [5]. For patients 50–69 years old, the threshold is SBP ≥100 mm Hg; for patients 15–49 years old and those over 70 years old, the threshold is SBP ≥110 mm Hg. In order to achieve these goals, an arterial line is recommended to provide accurate measurements. Additionally, placement of central venous catheter allows large volume blood product transfusions, isotonic fluid resuscitation, and administration of vasopressors. Transducing central venous pressure can help gauge overall volume status and guide resuscitative efforts.

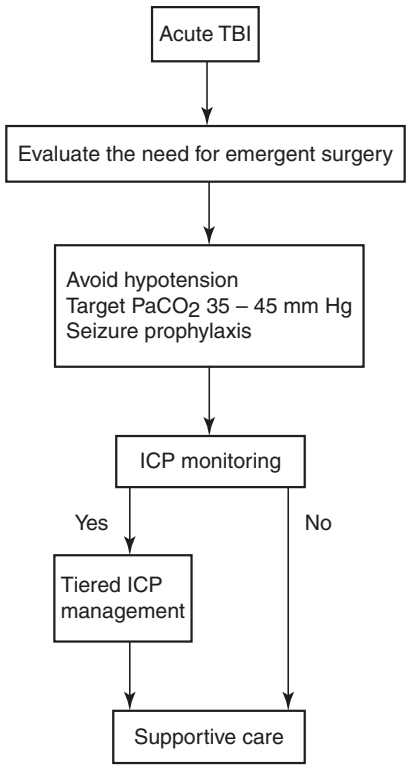

Fig. 12.2 Flow chart of acute TBI management

Mechanical ventilation strategies in TBI patients are aimed toward preventing hypercarbia, which contributes to vasodilation and increased ICP. Normal arterial partial pressure of carbon dioxide ($PaCO_2$) between 35 and 45 mm Hg should be maintained by titrating volume and respiratory rate. However, prolonged hyperventilation can exacerbate cerebral ischemia by reducing cerebral blood flow and should be avoided, except as a temporizing measure to reduce ICP in patients with impending cerebral herniation, for instance [7]. Nonetheless, in TBI patients with concurrent acute lung injury, the control of $PaCO_2$ often takes precedence over lung protection [8].

Intubated TBI patients require a careful approach to sedation and analgesia, as agitation and pain contribute to rises in ICP. Randomized clinical trials examining the clinical outcomes associated with the use of different sedatives and analgesics in TBI have found no compelling evidence to suggest the use of one agent over another [9]. In our practice, low-dose fentanyl infusions and short-acting sedative infusions (propofol or midazolam) are used, titrated to maintain a Richmond Agitation-Sedation Scale of −2. Neuromuscular blockade using cisatracurium, in conjunction with a sedative, may be considered in patients with persistently elevated ICP. However, the need for sedative infusions should be reevaluated frequently, and sedatives and analgesics should be withheld at least daily to perform a reliable neurological exam. In non-intubated patients with mild to moderate TBI, the use of narcotics and sedatives is minimized due to the risk of obscuring the neurological exam.

Apart from the judicious management of blood pressure and mechanical ventilation, early consideration should also be given to the prevention of post-traumatic seizures. Clinical seizures may be seen in 2.1–16.9% of TBI patients within 7 days of injury [10]. The rates of subclinical seizures are even higher, detected in over 30% of TBI patients undergoing continuous electroencephalography (EEG) monitoring [11]. Randomized clinical trials have shown that prophylactic anticonvulsants are able to prevent early (within 7 days of injury) but not late post-traumatic seizures (after 7 days of injury) [12]. Accordingly, loading doses of antiepileptics are administered followed by a 7-day course. The choice of a specific antiepileptic agent is at the discretion of the clinician as no one drug has been found to be superior to others. Intravenous (IV) formulations of phenytoin or levetiracetam are typically used, and we prefer the former due to its established efficacy in clinical trials, low cost, and ease of serum level monitoring. If patients have early post-traumatic seizures despite being on antiepileptics, the drugs may be continued beyond 7 days and stopped after discharge based on the physician's discretion. In patients with neurological deterioration not explained by CT imaging or other systemic causes, continuous EEG monitoring for 48–72 hours is reasonable [13].

ICP Monitoring

Following optimization of blood pressure, titration of ventilator settings and sedation, and initiation of seizure prophylaxis, the next consideration is to determine the need for ICP monitoring (see section titled "Key Decision Points"). Previous editions of the BTF guidelines recommended ICP monitoring for patients with severe TBI and abnormal admission CT head as well as in severe TBI patients with normal CT head with two or more of the following characteristics: age >40 years, unilateral or bilateral motor posturing, or SBP <90 mm Hg. However, these recommendations were mostly based on observational studies where ICP monitoring was routinely used without clinical equipoise. Indeed, a more recent study (BEST:TRIP) that randomly assigned severe TBI patients in a resource-constrained setting to treatments of intracranial hypertension based on invasive ICP monitoring versus imaging/clinical exam alone found no difference between groups in mortality or clinical outcome at 6 months [14]. Efforts to formalize the findings of this study into recommendations for intracranial hypertension management without invasive monitoring are currently under way. Nonetheless, ICP monitoring provides invaluable information regarding the treatment of intracranial hypertension, and a preponderance of literature supports its use to reduce short-term mortality (level IIA evidence) [5].

ICP monitoring, in conjunction with invasive blood pressure monitoring, also allows for the determination of cerebral perfusion pressure (CPP), which is calculated as the mean arterial pressure (MAP) – ICP. CPP represents the principal determinant of cerebral blood flow (CBF) and is maintained via cerebral autoregulation over a wide range of MAPs in the uninjured brain. However, in TBI patients with impaired autoregulation, close monitoring of CPP is essential to avoid dramatic changes in the CPP due to changes in the systemic blood pressure. Accordingly, the BTF recommends targeting CPP between 60 and 70 mm Hg in order to improve survival and promote favorable outcomes (level IIB evidence) [5]. However, targeting higher CPP goals of ≥70 mm Hg is associated with an increased risk of acute respiratory distress syndrome (ARDS) and should be avoided [15]. Therefore, stable blood pressure should be maintained via fluid resuscitation, use of vasopressors, blood product transfusions, and central venous pressure monitoring.

ICP monitoring is most often performed using an EVD or an intraparenchymal catheter. These devices are zeroed at the level of the tragus, connected to a pressure transducer, and provide real-time monitoring of ICP. EVDs are preferred over intraparenchymal catheters, as they allow for therapeutic cerebrospinal fluid (CSF) drainage in order to reduce ICPs and provide a more global estimate of the ICP. If continuous CSF drainage is utilized, some advocate for an addi-

tional intraparenchymal catheter to continuously monitor ICP concurrently. The current BTF guidelines favor continuous CSF drainage over intermittent use (level III evidence) and an ICP threshold of 22 mm Hg based largely on a recent retrospective study (level II evidence) [5].

ICP Management

ICP elevations have multiple causes, including cerebral edema, expanding mass lesions, altered CSF dynamics, cerebral venous obstruction, agitation, fever, and hypercarbia. Therefore, it is critical to approach the evaluation and treatment of raised ICP in a systematic manner. The ACS TQIP Best Practices propose a three-tiered approach to ICP management, which serves as a useful and practical guide in the neurocritical care unit [16]. In clinical practice, ICP management is often individualized based on the patient's clinical exam and imaging findings, and treatments from different tiers may be started concurrently. Nonetheless, these recommendations serve as a useful framework to methodically escalate care.

The first step is to ensure that the pressure transducer from the EVD or intraparenchymal catheter is zeroed at the level of the tragus and a good ICP waveform is observed. It is also important to note that the ICP waveform may be considerably dampened following a craniectomy. Elevating the head of the bed at 30 degrees and loosening constricting cervical collars or neck ties for endotracheal tubes improve cerebral venous outflow [17]. Up-titration or a bolus of sedative or analgesics may be necessary in agitated patients. Ventricular drainage of CSF can be performed in patients with EVDs until ICP is normalized between 20 and 25 mm Hg [16]. At times, clotted blood or brain matter may clog the external drainage catheter, which may need to be flushed distally. Concurrently, neurological exams to determine GCS and pupillary reactivity should be performed frequently to confirm any changes from baseline. If there is concern for expanding contusion or hematoma based on prior imaging and deterioration in neurological status, repeat CT head should be performed. If ICPs remain persistently elevated despite these above interventions, tier 2 treatment options can be initiated.

Hyperosmolar therapy is the mainstay of the second-tier approach to management of increased ICPs (see section titled "Special Pharmacologic Agents in Acute Management of TBI"). Mannitol is administered as intermittent boluses (0.25–1 mg/kg) IV, with frequent serum osmolality monitoring to avoid additional doses if serum osmolality exceeds 320 mOsm/L. Alternatively, intermittent boluses of hypertonic saline can be administered, with monitoring of serum sodium to avoid sodium >160 mEq/L. The patient should be temporarily hyperventilated to maintain $PaCO_2$ between 30 and 35 mm Hg [16]. A trial of neuromuscular blockade can also be tried, and if it successfully lowers ICP, a continuous infusion of neuromuscular blocking agent may be initiated as part of tier 3 therapy. Again, repeat CT head should be considered at this stage. If there is no improvement in ICP following these interventions, tier 3 treatments may be required.

Tier 3 therapeutic interventions are primarily based upon decompressive craniectomy or barbiturate coma [16]. Decompressive craniectomy is performed as a unilateral frontotemporoparietal craniectomy with expansile duraplasty in patients with a large unilateral lesion with mass effect and bifrontal craniectomy in patients without a large unilateral lesion. The Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury (DECRA) study randomized severe TBI patients with medically refractory ICP elevations to decompressive craniectomy plus standard care or to standard care alone within 72 hours of injury. While patients in the decompressive craniectomy group had significantly reduced ICP and fewer days in the ICU, they actually had worse 6-month outcomes [18]. In the more recent Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial, severe TBI patients were randomized to decompressive craniectomy only after having exhausted all tier 1 and tier 2 therapeutic options. While decompressive craniectomy resulted in lower mortality at 6 months, higher rates of vegetative state, lower severe disability, and upper severe disability were observed in the surgical group [19]. Therefore, decompressive craniectomy is a potential life-saving procedure, but quality of life is not necessarily improved, and outcomes are likely related to timing of surgery and patient selection (see section titled "Key Decision Points"). Continued ICP monitoring after decompressive craniectomy is additionally recommended to detect expansion of ipsilateral or contralateral lesions following surgery.

Barbiturate or propofol coma can be an alternative to decompressive craniectomy (see section titled "Special Pharmacologic Agents in Acute Management of TBI"). Both agents reduce cerebral metabolism but also produce hypotension, so they are relatively contraindicated in hypotensive patients, and vasopressors may be required during treatment [20]. Barbiturate therapy may be associated with increased risk of ARDS, infections, and coagulopathy, whereas long-term use of propofol can be associated with propofol infusion syndrome. Burst suppression may be monitored with continuous EEG, and daily levels of pentobarbital, if used, should be obtained. For patients who do not respond to barbiturate or propofol coma, early consideration should be given to decompressive craniectomy.

Supportive Care Following TBI

While the patient is undergoing tiered ICP management, other aspects of neurocritical care should not be ignored. In particular, an aggressive approach to managing fever and infection should be taken. Fever following TBI has been associated with increased risk of poor outcome by contributing to secondary brain injury and increased ICP [21]. Acetaminophen is the first-line treatment, and persistent fever requires use of cooling blankets or intravascular cooling catheters [22]. Cultures should be sent as early as possible and empiric IV antibiotics should be started until culture sensitivities result. On the one hand, respiratory infections are particularly common following TBI due to lack of a strong gag reflex and aspiration of stomach contents [23]. On the other hand, induced hypothermia as a neuroprotective strategy in TBI actually worsened outcomes in a large clinical trial, likely secondary to systemic side effects of hypothermia including coagulopathy, infection, and cardiac arrhythmias [24].

Early enteral nutrition has been shown to improve survival in severe TBI patients. The BTF guidelines recommend feeding patients to attain basal caloric replacement between 5 and 7 days following injury (level IIA evidence). Proton pump inhibitors should be started for TBI patients upon admission to the neurocritical care unit. Hypotonic fluids or dextrose-containing fluids should be avoided in acute TBI patients due to the risk of exacerbating cerebral edema. Hypertonic saline solutions should be considered early for hyponatremia as well. Hyperglycemia contributes to lactic acidosis in the injured brain and worsens cerebral hemodynamics, whereas hypoglycemia exacerbates secondary brain injury. Therefore, an insulin sliding scale should be instituted to maintain blood glucose between 80 and 180 mg/dL [25].

Deep vein thrombosis (DVT) is an important but difficult issue following TBI. On the one hand, almost all TBI patients have hemorrhagic lesions (intracranial hematomas or contusions), and early pharmacological prophylaxis carries the risk of progressive hemorrhagic injury [26]. On the other hand, the risk of DVT and its associated complications are dramatically reduced with pharmacological prophylaxis with low-molecular-weight heparin or low-dose unfractionated heparin [27–29]. The timing of pharmacological prophylaxis needs to be determined on an individual patient basis. The ACS TQIP guidelines advocate the use of the Berne-Norwood criteria that segregate the risk for spontaneous progression of hemorrhage with pharmacological prophylaxis into three categories [16]. With stable CT head findings at 24 hours that do not meet moderate- or high-risk criteria, it appears reasonable to initiate pharmacological prophylaxis. With progression of CT head findings at 24 hours or in patients who meet any of the moderate-risk criteria, pharmacological prophylaxis should be withheld for 72 hours. Retrievable inferior vena cava filters should be considered in patients in the high-risk category and be removed once pharmacological prophylaxis can be safely started.

Tracheostomy should be considered early in severe TBI patients who cannot be extubated early, because studies have shown that early tracheostomy is associated with shorter mechanical ventilation duration and length of stay [30, 31]. The ACS TQIP guidelines recommend tracheostomy within 8 days of injury in all TBI patients deemed unlikely to improve rapidly [16]. By this time, patients are less likely to be under active treatment for high ICPs or hemodynamically unstable, and the need for long-term airway protection is possible.

Conclusion

The main goal for acute care following TBI is the prevention of secondary injury. In order to achieve this goal, basic principles of critical care such as blood pressure management, mechanical ventilation, sedation, enteral nutrition, and sepsis management must be tailored to the unique needs of the TBI patient. ICP management should be approached in a systematic, tiered manner. The BTF and ACS TQIP guidelines provide a helpful framework, but they must be supplemented by clinical judgment and decision making.

Key Decision Points

Acute management of the TBI patient needs a multidisciplinary team, and several clinical decisions are required to ensure an optimal outcome. In the acute setting, evolution and recovery from the injury is a dynamic process that can change rapidly, sometimes requiring an urgent surgical or medical intervention. At admission, securing the airway and avoiding hypotension and hypoxia are the most important steps. Evaluation of the initial CT scan to determine the need for urgent surgical intervention is the next important decision point. Emergent surgical intervention to evacuate a mass lesion can relieve or prevent brain herniation and limit neurological damage. For patients who undergo ICP monitoring and demonstrate refractory intracranial hypertension, the clinician may have to decide on whether to proceed with decompressive craniectomy versus barbiturate coma for ICP treatment. Here, timing of the intervention and patient selection are key to optimizing clinical outcomes. Given the significant adverse systemic effects of barbiturates, particularly hypotension, only patients with a stable cardiorespiratory status should be selected for barbiturate coma. Timing of tracheostomy is another key decision point in the ICU course of a severe TBI patient. By day 8 after the injury, the clinician

should be able to determine if the patient can be extubated and can maintain a patent airway. Overall, there are a number of key decision points during the clinical course of the TBI patient where clinical judgment and established guidelines are utilized to limit secondary injury and assist neurological recovery.

Special Pharmacologic Agents in Acute Management of TBI

Mannitol

Mannitol is used for hyperosmolar therapy to treat cerebral edema after TBI. Mannitol is a sugar alcohol that is excreted by the kidneys. Mannitol creates an osmotic gradient across the blood-brain barrier and removes water from the interstitial spaces [32]. Additionally, mannitol increases blood volume and improves cerebral microcirculation [33]. Mannitol is administered as a rapid IV bolus of 0.25–1 g/kg every 6 hours. Serum osmolality and renal function should be monitored during mannitol therapy. Although mannitol is an effective hyperosmolar agent, it can have considerable adverse effects. Mannitol can induce acute renal failure, particularly in patients with preexisting renal disease, and when the serum osmolality is >320 mOSm/L [34]. Additionally, mannitol can cause hypernatremia, hypokalemia, metabolic acidosis, and transient hypotension.

Hypertonic Saline

Hypertonic saline (2–23.4% sodium chloride) has a higher tonicity than blood and creates an osmotic gradient across the blood-brain barrier. Although it acts similarly as mannitol, hypertonic saline does not produce diuresis. A bolus (30–60 ml) of hypertonic saline (23.4%) can rapidly reduce ICP and can be administered in the acute setting. Hypertonic saline (2–3%) can also be administered as an infusion (0.1–2 ml/kg/hour) for a target sodium of 145–155 mEq/L [35]. Adverse events associated with use of hypertonic saline include hyperchloremic acidosis, hypokalemia, congestive cardiac failure, cardiac arrhythmias, and pulmonary edema. Serum sodium needs to be monitored when patients receive hypertonic saline, since a serum sodium >160 mEQ/L can independently affect mortality after TBI [36].

Barbiturates

Barbiturates are used as medical treatment for refractory intracranial hypertension. The induction of a barbiturate coma can reduce critically high ICP after severe TBI [37]. Barbiturates also reduce cerebral metabolism [38] and have other cellular effects such as free radical scavenging and excitotoxicity inhibition [39]. The two most commonly used agents include pentobarbital and thiopental. One protocol for pentobarbital is an IV loading dose of 10 mg/kg over 30 minutes followed by three doses of 5 mg/kg and then a maintenance dose of 1 mg/kg/hour [40]. Pentobarbital levels are checked daily with a target of 30–50 μg/ml. Thiopental is administered as a loading dose of 10–20 mg/kg followed by a maintenance dose of 3–5 mg/kg/hour [41]. Continuous EEG monitoring can be performed during barbiturate therapy to document burst suppression. One adverse effect associated with barbiturate therapy is hypotension, and these patients often require vasopressors to maintain CPP [42]. Additionally, these patients are at greater risk for infections, coagulopathy, ARDS, and ileus. Overall, in deciding on initiating barbiturate coma, the benefits of ICP control should be weighed against the potential systemic complications of this therapy in severe TBI.

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Critical Care Management for Patients with Spinal Cord Injury

13

Zachary Pennington, A. Karim Ahmed, and Nicholas Theodore

Introduction

Spinal cord injury (SCI) is a complex condition defined by frequently irreversible damage to the spinal cord parenchyma, which may or may not be accompanied by damage to the osseoligamentous elements of the spine. Injury is classically secondary to a traumatic event, such as a motor vehicle collision, a fall, a sports-related injury, or a different high-impact event. Though SCI can occur at any level between the craniocervical junction and the conus medullaris, it is most often associated with damage to the cervical spine, and injuries to this region produce the most profound deficits. The mobile cervical spine is particularly vulnerable to injury, as it lacks the protection and rigid support that the rib cage affords the thoracic spine.

Management of traumatic SCI requires multidisciplinary care, beginning with rapid response teams who must quickly assess the patient's condition in the field and prepare him or her for safe transfer to a higher level of care. If the diagnosis of SCI is suspected in the field, the most expeditious method of transport is recommended to get the patient to a facility with expertise in treating these patients [1]. Care at inpatient centers includes the management of post-injury hypotension and posttraumatic compression of the spinal cord as well as stabilizing the patient for surgery. Secondary considerations include prophylaxis for venous thromboembolic events, decubitus ulcer formation, and infection. Care continues after discharge from the acute care hospital with physical rehabilitation and, in the most severe cases, permanent inpatient care, which is usually reserved for ventilator-dependent patients or those with concomitant severe traumatic brain injury. In this chapter, we briefly touch on the immediate management of SCI and then emphasize the complex critical care needs and controversies surrounding the management of these patients. We conclude with a brief discussion relating to prognosis and outcomes of patients with SCI.

Epidemiology and Background of Spinal Cord Injury

Frequency

The most recent estimates published by the National Spinal Cord Injury Center at the University of Alabama at Birmingham estimate that approximately 288,000 persons in the United States are afflicted by some form of SCI, with 17,700 new cases occurring each year (Table 13.1) [2]. Classically, affected persons have been young men in their 20s [3]; however, the average age at the time of injury has increased steadily since the 1970s and is currently 43 years old [2–4]. Similarly, the proportion of victims who are female has also increased [5]. Behind both of these statistics is an overall increase in the incidence of SCI as opposed to a simple shift in demographics [3, 6]. This change is driven by a rise in the prevalence of motor vehicle collisions precipitating SCI [3, 7–9].

Etiology

Multiple injury etiologies can result in SCI, but the most common are vehicular collisions, falls, sports-related injuries, violence, and self-harm (Table 13.1) [2, 3, 10–12]. The relative contribution of each etiology varies by patient age and by country. Falls are most common among those over the age of 45, increasing steadily with age, and motor vehicle collisions are most common among those younger than 45,

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Table 13.1 Select studies of spinal cord injury epidemiology and etiology in North America

Study	Incidence/prevalence	Etiology	
Chen et al. (2016) [5]	N/R	Vehicular	42.4%
		Falls	22.0%
		Violence	17.3%
		Sports	10.2%
		Medical/ surgical	2.7%
		Other	5.3%
Cripps et al. (2011) [10][a]	*P* = 39 per million Mortality in first-year status post-SCI = 7% Mortality in years 1–10 = 13%	Vehicular	47%
		Falls	20%
		Violence/ self-harm	15%
		Work-related	14%
		Sports/ recreation	11%
DeVivo et al. (1980) [124]	*P* = 906 per million	N/R	N/R
DeVivo, (2012) [3]	*I* = 40 per million per year *P* ≈ 844 per million	Vehicular	48.3%
		Fall	21.8%
		Violence	12.0%
		Sports	10.0%
		Other	7.9%
Ditunno et al. (1994) [125]	*I* = 38 per million per year *P* = 760 per million	Vehicular	45%
		Fall	22%
		Violence	16%
		Sports	13%
Ergas et al. (1985) [126]	*I* = 47 per million per year *P* = 1,009 per million	N/R	N/R
Griffin et al. (1985) [42]	*I* = 54.8 per million per year *P* = 473 per million	N/R	N/R
Harvey et al. (1990) [127]	*P* = 721 per million	N/R	N/R
Jackson et al. (2004) [12]	*I* = 40 per million per year *P* = 854 per million 54% with tetraplegia 45.3% with paraplegia	Vehicular	45.6%
		Fall	19.6%
		Violence	17.8%
		Sports	10.7%
		Other	6.3%
Kumar et al. (2018) [11]	*I* = 51.0 per million per year 50.08% cervical; 24.06% thoracic; 24.21% lumbosacral	Vehicular	41.6%
		Sports	8.6%
Lasfargues et al. (1995) [128]	*I* = 35.6 per million per year *P* = 787 per million	N/R	N/R
Lee et al. (2014) [15][a]	*I* = 38.4 per million per year 47% with paraplegia 53% with tetraplegia	Vehicular	47%
		Falls	22%
		Violence/ self-harm	16%
		Sports/ recreation	10%
National SCI Statistical Center (2018) [2]	*I* = 54 per million per year *P* = 884 per million	Vehicular	38.3%
		Fall	31.6%
		Violence	13.8%
		Sports/ recreation	8.2%
		Medical/ surgical	4.6%
		Other	3.5%
Noonan et al. (2012) [129]	*I* = 68 per million per year *P* = 2,525 per million	N/R	N/R
Savic et al. (2017) [4]	N/R	Vehicular	46.1%
		Fall	31.3%
		Sports	12.3%
		Hit by object	5.1%
		Violence	3.7%
		Other	1.5%

Abbreviations: *N/R* not reported, *P* prevalence, *I* incidence
[a]Derived from World Health Organization statistics

accounting for a progressively smaller proportion of cases with increasing patient age [13]. Injuries among the younger population are higher overall though, making motor vehicle collisions the most common cause of SCI among Americans.

The ability of a motor vehicle collision to cause SCI is likely due to the large forces routinely exerted on the spine during vehicular collisions, which are significantly greater than those seen in the other common etiologies. At greatest risk of injury in these collisions is the cervical spine as it (1) is relatively unrestrained compared to the thoracic and lumbar spines and (2) lacks the support of the rib cage and robust paraspinal musculature of the thoracolumbar spine. Consequently, cervical spine injury is associated with over 50% of patients with SCI after a motor vehicle collision [14], helping to explain the relatively high frequency of tetraplegia among SCI patients [12, 15]. These cervical cord injuries are commonly accompanied by bony injury and resultant cord compression. Accordingly, nearly half of patients (48.8%) will require acute surgical interventions as part of their treatment plan to decompress the spinal cord, realign the vertebral column, or both [14].

Acute Management of Spinal Cord Injury

The acute management of SCI can be separated into field management, transport of the patient to a higher level of care, and inpatient stabilization with medical and surgical interventions. Optimal management should consist of respiratory and hemodynamic monitoring in an intensive care unit [9] along with appropriate medical and/or surgical interventions. Most of the guidelines described in this chapter are derived from the 2013 recommendations made by a joint committee of the American Association of Neurological Surgeons and Congress of Neurological Surgeons [1, 16–35]. Evidence and recommendations were made based upon a modified version of the North American Spine Society Rating Schema for evaluating evidence level [36]. A review of the 2013 guidelines demonstrates that high-quality medical research on the topic of SCI management is too limited to support recommendations with level I or II data. Because of this, most recommendations are actually based on level III data. Table 13.2 lists the

Table 13.2 Level I or II recommendations for the treatment of traumatic spinal cord injury [1, 16–35]

Topic	Recommendations	
	Level I	*Level II*
Prehospital		
Prehospital immobilization [16]	None	All patients with documented or suspected cervical spine injury should have neck immobilized On-scene triage should be conducted by experienced EMS responders Immobilization is not required for a neurologically intact patient who is awake, alert, and oriented to name, location, and date (AAO×3) without neck pain or tenderness
Transportation [1]	None	None
Initial in-house management		
Clinical assessment [19]	Spinal cord Independence measure III should be used for assessment, care, and follow-up of SCI patients. International spinal cord injury basic pain data set should be used to assess pain in SCI patients	ASIA impairment scale and motor testing should be used for neurological examination of acute SCI patients
Radiographic assessment [21]	**AAO×3, asymptomatic**	
	No radiographic examination necessary Discontinue cervical immobilization	None
	AAO×3, symptomatic	
	Obtain high-quality CT of cervical spine. If CT unavailable, obtain 3-view C-spine radiographs (AP, lateral, odontoid views).	None
	Obtunded/unevaluable	
	Obtain high-quality CT of cervical spine. If CT unavailable, obtain 3-view cervical-spine radiographs (AP, lateral, odontoid views).	If normal CT, but high clinical suspicion of SCI, refer to clinician with greater experience in acute SCI treatment.
Closed reduction of fracture-subluxation [22]	None	None
Cardiopulmonary management [23]	None	None
Pharmacologic therapy [24]	Methylprednisolone administration is *not* recommended for patients with acute SCI GM-1 ganglioside administration is *not* recommended	None
DVT/VTE prophylaxis [18]	Prophylaxis against DVT/VTE in SCI patients. Use LMWH, rotating bed, or multimodal intervention. Alternatively, use heparin + compression stockings or electrical stimulator.	Do not use low-dose heparin as monotherapy. Do not use oral anticoagulants. Start VTE prophylaxis within 72 hours. Prophylaxis against DVT/VTE for ≥6 months.
Nutrition [20]	None	Use indirect calorimetry to determine caloric needs of SCI patient.
Management by injury		
Occipital condyle fracture [25]	None	Obtain CT to visualize injury.
Atlanto-occipital dislocation [26]	Obtain CT to determine condyle-C1 interval in pediatric patients with suspected AO dislocation.	None
Atlas fractures [28]	No	None
Axis fractures [27]	None	Consider surgical stabilization if type II odontoid fracture in patient ≥50 years old
Combination atlas-axis fractures [29]	None	None
Os odontoideum [30]	None	None
Subaxial fracture [31, 32]	None	None
Central cord syndrome [33]	None	None
SCIWORA [35]	None	None
Vertebral artery injury [17]	Obtain CT angiogram in patients with C-spine trauma that meets Denver screening criteria for vertebral artery injury	None

Abbreviations: *EMS* emergency medical services, *AAO×3* awake, alert, and oriented, *SCI* spinal cord injury, *ASIA* American Spinal Injury Association, *CT* computed tomography, *AP* anteroposterior, *DVT* deep vein thrombosis, *VTE* venous thromboembolism, *LMWH* low-molecular-weight heparin, *AO* atlanto-occipital, *SCIWORA* spinal cord injury without radiographic abnormality

relevant level I and II recommendations for the management of a patient with acute SCI. If there is insufficient evidence to make recommendations regarding the timing of surgery, the adage "Time is spine" is widely used [9, 37].

Field Management

The first step in the treatment of a patient with acute SCI is safely expediting their transfer to a higher level of care. This involves determining whether the patient is stable enough to move from the site of injury and, if not, implementing interventions necessary to stabilize him or her for transfer. Failure to do the latter is thought to precipitate up to 25% of all SCI, underlining the importance of high-quality field management in the care of patients with SCI [38].

The first step in verifying a patient's clinical stability is to evaluate the "ABCs". That is, check his/her *a*irway for obstruction, look for signs of spontaneous respirations (*b*reathing), and ascertain whether he/she has a palpable pulse (*c*irculation) [9]. This brief assessment is used to evaluate all trauma patients for potentially correctable life-threatening issues. Once these have been addressed, consideration is given to rapidly transporting the patient to a trauma center. Patients should also be evaluated briefly for alertness and orientation to name, location, and date (awake, alert, and oriented times three; also known as AAO×3). The responses to these questions are important when assessing a patient for a traumatic brain injury, which occurs frequently in traumatic injury and often accompanies SCI. Those patients who are coherent and oriented can be questioned about axial neck pain and the circumstances surrounding their injury. Patients who are neurologically intact and who deny axial neck pain, distracting injuries, or circumstances consistent with an injury to the spine can be transferred to the nearest trauma facility without cervical immobilization [16]. Such patients, especially those involved in high-velocity collisions, should still be evaluated at a trauma hospital where the possibility of associated injuries can be assessed. Those who report axial neck or back pain or those with a suspected SCI should be immobilized with an appropriate rigid cervical orthosis and placed on a backboard before being transferred to the nearest trauma center for neurological and radiological evaluation [1, 39]. Exact protocols vary by emergency medical services region, but total spinal immobilization is universally recommended, though prior systematic reviews have failed to document high-quality evidence to suggest that this intervention prevents or reduces long-term neurological injury [40]. The type of cervical collar used for immobilization appears not to alter outcomes significantly, so field providers are encouraged to use the collar with which they are most familiar [38].

Transit

Only low-quality evidence exists describing transport of patients with SCI to higher levels of care [1]. Despite this, recommendations are quite strong in terms of timing; patients with SCI *should be moved to the next level of care as soon as they are stable enough for transport*. Types of transportation include ambulance, plane, and helicopter; the chosen mode should be whichever allows for the most expeditious movement of the patient to a center with experience treating acute SCI. That said, transfer to a higher level of care should not be substantially delayed for medically unstable patients if they are waiting to be transported to a specialized spinal cord treatment center.

Injury Assessment

Once the patient is stabilized, care can turn to the assessment of the SCI. SCI can be classified by either the level of vertebral body injury or the level of SCI. The degree of concordance between the two is high in the upper cervical spine and steadily decreases as one moves caudally due to differences in the postnatal growth rates of the spinal cord and bony spine. The level of the injured vertebra(e) is most important when considering surgical intervention, as it identifies that region of the spine that might require decompression, stabilization, or realignment. The neurological level is more important than the vertebral level when articulating the severity of the injury.

Neurological Assessment

In general, injuries that are more cephalad beget greater functional disability and are associated with poorer long-term survival and greater permanent disability [3, 4, 41–49]. However, clinicians treating SCI must use a standardized description of the neurological injury, which provides normative information regarding injury prognosis. Currently, the gold standard for injury assessment is the American Spinal Injury Association (ASIA) Impairment Scale, with which all trauma providers should be familiar (Table 13.3) [3, 4, 41–49]. This scale grades the extent of SCI based upon motor output in the C5–T1 and the L2–S1 myotomes (each graded on the familiar 0–5 manual motor testing scale), the presence or absence of a sensory level (based on pinprick and light touch sensation in the C2–S4/5 dermatomes), and rectal tone. Those with full strength and no sensory or rectal findings are graded as *ASIA E*; those with 0/5 motors, with a documented sensory level, and with no rectal tone are *ASIA A* [50]. Injuries intermediate to these extremes are classified as *ASIA B* (0/5 motors, sensory level, rectal tone intact),

Table 13.3 American Spinal Injury Association (ASIA) impairment scale and motor scoring system [9]

ASIA impairment scale					
Grade	Description				
E	*Normal*. Sensation and motor function preserved in all segments				
D	*Motor incomplete*. Strength of key muscle functions is ≥3/5 on manual motor testing in ≥50% of groups below the injury level				
C	*Motor incomplete*. Preservation of motor function for voluntary anal contraction *or* patient meets criteria for ASIA B with sparing of motor function such that ≥50% of groups below injury level are <3/5 on manual motor testing				
B	*Sensory incomplete*. Sensory but not motor function preserved below the level of neurological injury *and* no motor function is present ≥3 levels below the level of neurological injury				
A	*Complete injury*. No sensory/motor function preserved in S4–S5 segments				
ASIA motor scoring system: muscle groups					
Upper extremity			*Lower extremity*		
Root	**Muscle group**	**Movement**	**Root**	**Muscle group**	**Movement**
C5	Biceps brachii	Elbow flexion	L2	Iliopsoas	Hip flexion
C6	Wrist extensors	Wrist extension	L3	Quadriceps	Knee extension
C7	Triceps	Elbow extension	L4	Tibialis anterior	Foot dorsiflexion
C8	Finger flexors	Flex middle finger	L5	Extensor hal. Long.	1st digit dorsiflexion
T1	Hand intrinsics	Abduct fifth digit	S1	Gastrocnemius	Foot plantar flexion
Manual motor testing scale					
Grade	*Interpretation*		*Grade*	*Interpretation*	
5	Full strength		2	Active movement with gravity removed	
4	Active movement against resistance		1	Flicker or trace contraction	
3	Active movement against gravity		0	No contraction/total paralysis	

ASIA C (<3/5 strength in most groups below injury, sensory intact, rectal tone present), or *ASIA D* (≥3/5 strength in most groups above the level of injury, sensory intact, rectal tone present) [51]. The ASIA International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) worksheet can be found here: https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet/.

In addition to sensorimotor impairment, damage to the cervical and high thoracic spinal cord may compromise autonomic nervous system output, causing diaphragm paralysis (injuries at or above the level of the phrenic nerve cell bodies, C3–C5) and complete loss of sympathetic tone (via loss of descending input to cell bodies situated in the T1–L2 segments) [9]. Loss of sympathetic tone is especially germane to the acute medical management of SCI patients as it produces spinal or neurogenic shock, which is characterized by hypotension, bradycardia, a widened pulse pressure, and a distributive-type circulatory shock. In this state, occasional outflow from the unregulated sympathetic nerves can trigger reflex spinal sympathetic stimulation with subsequent vasoconstriction and intermittent hypertension. In turn, parasympathetic output is increased at levels above the injury, worsening vasodilation and hypotension, a clinical phenomenon known as *autonomic dysreflexia*—most common in injuries above the T7 level [52, 53]. This condition is discussed in greater detail below.

Radiographic Assessment

After assessing the neurological status of the patient, the next step in management is acquisition of cervical spine imaging. In the setting of suspected or confirmed head trauma, patients should undergo rapid head computed tomography (CT) to rule out intracranial pathology [54, 55]. This may be accompanied by concomitant imaging of the cervical spine. In the absence of suspected head trauma, the imaging algorithm is dictated by the patient's neurological status. Based upon level I evidence provided by the National Emergency X-Radiography Utilization Study Group, patients who are awake, not intoxicated, neurologically asymptomatic, and have no distracting injuries do not require cervical spine imaging or continued immobilization [56]. Patients who are awake but who demonstrate signs of neurological injury should undergo high-quality CT to characterize the bony injury. If high-quality CT is unavailable, 3-view (i.e., anteroposterior, lateral, odontoid views) radiographs of the cervical spine should be acquired, and the patient should be transferred to a facility capable of evaluating intracranial injury. Some authors [9] also recommend high-quality CT of the thoracic and lumbar spine, given the possibility of concurrent thoracic and/or lumbar injuries that may be masked by neurological dysfunction secondary to cervical spine injury [8]. Acquisition of dynamic radiographs with flexion and extension views may be considered in persistently symp-

tomatic patients, as they may be useful in diagnosing underlying instability.

CT and radiography are limited in their ability to assess soft tissue damage, such as that resulting from trauma to the intervertebral discs, vertebral ligaments, and neural structures. For this reason, urgent magnetic resonance (MR) imaging of the spine is also recommended in patients with persistent neurological injury [9, 57]. Short T1 inversion recovery (STIR) sequences provide the best assessment of the soft tissue injuries, especially to the spinal cord, since injury-related edema and tissue disruption both appear as T2 hyperintensities [14]. Many of these changes frequently resolve within the first 48 hours of injury, underlining the importance of expediting MR acquisition in patients with persistent neurological injury [38]. Additionally, MR allows for the identification of intracanalicular disk fragments that might injure the cord upon application of traction, so some providers recommend acquiring MR before traction is used [9].

For patients who are comatose or whose examination results are inconsistent, the default management strategy should be to assume cervical spine injury and take steps to rule out this injury. Consequently, patients in this last category should undergo high-quality CT of the entire neuraxis to rule out both intracranial pathology and multilevel injury [38].

Classification Systems

In an effort to standardize radiographic classification of cervical spine injury and to streamline management of these patients, several classification systems have been devised for cervical spine injury. Anatomically, injuries can be classified as occurring at the atlanto-occipital junction, atlantoaxial junction, or subaxial spine.

Atlanto-occipital injuries involve trauma to the skull base, atlas (C1), or ligamentous structures of the occipitocervical junction. Skull base trauma can be categorized into three classes: class I injuries comprise comminuted fractures of the occipital condyle, class II injuries include basilar skull fractures, and class III injuries describe avulsion fracture of the alar ligaments [38]. Atlas trauma is similarly divided into three classes: type I injures result from fracture of the dorsal arch, type II injuries from lateral mass fracture on one side, and type III injuries—so-called Jefferson fractures—from three or more fracture sites around the atlantal ring. Lastly, compromise of the occipitocervical ligamentous complex may be associated with atlanto-occipital dislocation, an often-fatal complication seen in roughly 1% of patients presenting with cervical spine trauma [58].

Fractures of the axis (C2) are especially common among elderly patients [59]. Among this population, the greatest burden of disease is caused by fractures of the odontoid process, which account for nearly 90% of cases of axis trauma [59]. Axis fractures are divided into three classes based upon the level of the fracture: type I fractures consist of avulsion fractures at the tip, type II fractures occur through the waist of the dens, and type III fractures involve the body of the axis [60]. Among young and middle-aged adults, Hangman's fractures—fractures through the bilateral *pars interarticularis*—are also relatively common [59]. These injuries are significantly more destabilizing than odontoid fractures and are graded based upon the degree to which the dissociated segments remain apposed to one another [61]. Type I fractures involve less than 3 mm of displacement, type II injuries involve >3 mm displacement with >11° of angulation in the odontoid, and type III fractures are associated with bilateral C2/3 facet dislocation. Thankfully, the vast majority of axis fractures are not associated with a concomitant neurological injury.

For injuries of the subcervical spine, the most common scoring system is the subaxial cervical spine injury classification (SLIC) system developed by the AOSpine Classification Group (Table 13.4) [62]. Under this system, injuries are graded with respect to morphology and any associated neurological deficit. A similar system was developed for the thoracolumbar spine, which also incorporates damage to the posterior ligamentous complex (Table 13.5) [63]. Both systems have been validated by their authors [64] and by independent groups [65, 66]. Recently, updated versions of these classification systems have been published [64, 67–71],

Table 13.4 The subaxial cervical spine injury classification (SLIC) system

Characteristic	Points
Morphology	
No abnormality	0
Compression	1
Burst	+1 (2)
Distraction (e.g., facet perch, hyperextension)	3
Rotation/translation (e.g., facet dislocation, unstable teardrop, or advanced-stage flexion-compression injury)	4
Neurological status	
Intact	0
Root injury	1
Complete cord injury	2
Incomplete cord injury	3
Continuous cord compression in setting of neuro deficit	+1
Score	**Management**
< 4	Nonoperative treatment
4	Operative vs. nonoperative
≥ 5	Operative treatment

The data presented in this table are republished with permission from Vaccaro et al., 2007 [62]

Table 13.5 The thoracolumbar injury classification and severity score (TLICS)

Characteristic	Points
Morphology	
No abnormality	0
Compression	1
Burst	+1 (2)
Translational/rotational	3
Distraction	4
Integrity of the posterior ligamentous complex	
Intact	0
Suspected/indeterminate injury	2
Injured	3
Neurologic status	
Intact	0
Nerve root	2
Cord, conus medullaris	
Complete	2
Incomplete	3
Cauda equina	3
Score	**Management**
<4	Nonoperative treatment
4	Operative vs. nonoperative
≥5	Operative treatment

The data presented in this table are republished with permission from Vaccaro et al., 2005 [63]

though their utility is less well-established than the original systems.

All of the abovementioned systems are based on the bony injury observed in the traumatized region, which demonstrates the need for high-quality CT in the evaluation of patients presenting with traumatic SCI. However, as described earlier, many injuries may be limited to spinal cord and soft tissue trauma, which is only recognizable on MR imaging. Furthermore, some have suggested that the degree of permanent deficit is related to the extent of cord injury. One classification system that uses cord signal changes on MR imaging to classify cord injury is the Brain and Spinal Cord Injury Center (BASIC) score [72]. This internally validated metric uses T2-weighted imaging to grade spinal cord lesions based upon the extent of T2 signal hyperintensity and presence (or absence) of spinal cord hemorrhage. Though limited in its ability to guide the decision to stabilize, it does appear to predict a patient's neurological recovery to a reasonable degree of accuracy.

Hemodynamic Pathophysiology and Therapeutic Interventions After Acute Spinal Cord Injury

As discussed above, acute SCI is often accompanied by hemodynamic instability owing to decreased sympathetic tone and autonomic dysreflexia. Therefore, all patients with acute SCI should receive continuous hemodynamic monitoring in an intensive care unit. Key to management is maintaining sufficient perfusion of the cord, with a target systolic blood pressure of ≥100 mm Hg and a mean arterial pressure of 85–90 mmHg [23]. Target oxygen saturation is ≥90% to prevent cord ischemia, as parenchymal hypoxia has been associated with greater neuronal death and is consequently likely to decrease the odds of neurological recovery [73]. These targets should be kept for a period of 5–7 days, at which point insufficient evidence exists to affirm their efficacy. Maintaining mean arterial pressure above 85 mm Hg can be accomplished via a combination of volume repletion with crystalloids and colloids (in patients with signs of volume depletion) and/or vasopressors, including dopamine (1–20 μg/kg/min), dobutamine (5–15 μg/kg/min), epinephrine (1–10 μg/min), norepinephrine (1–20 μg/min), or phenylephrine (10–100 μg/min) [57]. Norepinephrine followed by dopamine is the preferred regimen for lesions above the T7 segment, due to their combined chronotropic and inotropic effects (i.e., required to address loss of sympathetic output through the thoracic cardiopulmonary nerves), whereas pure vasoconstrictors such as phenylephrine are preferred for lesions at T7 or below [57].

Autonomic Dysreflexia

Paradoxically, acute hypertension is also a concern in patients with injury above the level of T6, as such injuries can produce a condition known as *autonomic dysreflexia*. Concern for autonomic dysreflexia is raised in patients with traumatic SCI who demonstrate acute elevations in systolic blood pressure (>20–30 mmHg) with associated bradycardia [74]. It is most common in the chronic phase of those with complete tetraplegia secondary to high cervical injuries (which disrupt descending vasomotor pathways), but it has also been noted in the acute setting. Treatment consists of prophylaxis and control of hypertension (target systolic blood pressure ≤150 mmHg) [75].

The most commonly used means of prophylaxis is periodic urinary catheterization since urinary bladder distension and irritation is the most common trigger of autonomic instability. In cases where urinary catheterization fails, level I evidence supports interventions aimed at decreasing efferent stimulation, including botulinum toxin injection into the detrusor muscle [76–78], intravesical resiniferatoxin injection [79, 80], and/or an oral anticholinergic [81]. Sacral denervation procedures may also be indicated in refractory cases; however, this is supported by only low-quality evidence [82].

Control of blood pressure in patients with autonomic dysreflexia begins with nonpharmacologic management, including removal of constrictive clothing and elevating the patient

to a seated position. Blood pressure should be checked every 5 minutes until the event has resolved. In patients for whom this is ineffective at terminating the episode, administration of an antihypertensive agent should be considered. No specific agent is recommended, but regimens previously suggested to be effective include nifedipine (10 mg; bite and swallow; level II evidence), nitrates (level V evidence; no clinical evidence), captopril (25 mg sublingual; level IV evidence), terazosin (level IV evidence), and prazosin (0.5–1 mg bid/tid PO; level 1 evidence). Monitoring of blood pressure and heart rate should be continued for at least 2 hours after symptom resolution [57].

Diaphragm Paralysis and Ventilatory Support

Patients with high cervical injuries (C1–C4) often present with respiratory insufficiency (36–83% of cases) secondary to loss of phrenic nerve input; concomitant head trauma may also contribute to respiratory insufficiency [83]. Consequently, all patients with suspected cervical spine injury should be evaluated for respiratory support and intubation [84]. Goals for respiratory management focus on maintaining adequate oxygenation of cord and peripheral tissues [85]. In patients breathing spontaneously, supplemental oxygen should be provided as needed, and patients should be encouraged to take deep breaths to avoid atelectasis (incentive spirometry is useful in this regard). Adequate analgesia should also be provided to facilitate deep respirations without depressing respiratory drive.

In patients requiring ventilatory support—that is, those with vital capacity below 15 mL/kg, increased $PaCO_2$, or inspiratory pressure ≥ -14.5 mmHg— ventilation and tracheostomy should be considered early, especially when prolonged intubation is anticipated. Ventilatory targets for these patients are similar to those established for head injury: $PaCO_2$ should be maintained in the range of 26–30 mm Hg [83, 85, 86]. Though some groups have recommended 0 mm Hg end-expiratory pressures to avoid air trapping, evidence supporting this is insufficient, and it is recommended that patients receive tidal volumes of 10–12 mL/kg and positive end-expiratory pressures of 5–7 cm H_2O. The use of positive end-expiratory pressure should be evaluated carefully in patients with concomitant traumatic brain injury because of the theoretic potential to increase intracranial pressure. Some evidence suggests that tidal volumes greater than 20 mL/kg may decrease the time to wean, but the strength of this evidence is moderate at best.

Weaning patients with SCI from the ventilator should be done via progressive ventilator-free breathing, in other words, gradual increases in respirator-free time, starting with FiO_2 of 10% above respirator baseline and 5 minutes of disconnection per hour [83]. If the patient reaches 48 hours without ventilator support and achieves an inspiratory pressure < -15 mm Hg, discontinuation of the ventilator may be considered. Alternatively, if the patient has been ventilator-dependent for more than 72 hours, tracheostomy should at least be considered to establish a definitive airway. Tracheostomy is also more comfortable for the patient and allows for improved pulmonary hygiene [57].

Respiratory insufficiency in patients with SCI is associated with an increased risk of respiratory infection [83], which is the most common cause of mortality among patients with SCI [47]. This is especially true for those with lesions above the mid-thoracic level: these patients have lost innervation of most expiratory musculature, which is responsible for effective coughing and clearing of airway secretions [83]. This is compounded by increased respiratory secretions in patients with autonomic dysfunction. In these patients, secretions should be regularly cleared via postural/gravity-assisted drainage and manually assisted coughing (i.e., chest compressions as the patient attempts to cough). Percussion or vibration of the thorax may also facilitate secretion clearance. In patients with cervical spine instability or thoracic trauma, manual-assisted coughing should be avoided until the patient is cleared for these maneuvers by the spinal surgeon, due to the risk of further injury secondary to application of mechanical forces to the chest wall.

Steroid Use

Acute SCI can itself be divided into primary and secondary injury phases [9]. The primary injury phase is the injury that occurs secondary to physical insults to the cord and nerve roots: namely, contusion, transection, and laceration with or without persistent compression [9]. This damage occurs at the time of injury and is at present irreversible. The second phase of injury is that which occurs in the hours to days following the injury and is mediated by a combination of oxidative and inflammatory damage. It is this second-phase damage that pharmacological treatment of traumatic SCI seeks to lessen or reverse.

The most widely evaluated medication used in the treatment of acute SCI is high-dose intravenous methylprednisolone. Methylprednisolone is purported to work by reducing cord swelling and inflammation, two of the primary mediators of secondary injury (via free-radical production) and glial scarring. Three large clinical trials called the NASCIS trials [87–91] evaluated the clinical efficacy of intravenous methylprednisolone. Except for a secondary analysis of the NASCIS II demonstrating a minor improvement in motor scores, no significant difference was observed in terms of neurological recovery among patients receiving methylprednisolone and those receiving placebo treatment [92].

Reanalysis of these results by an independent third party noted several inconsistencies in the data analysis, calling into question the motor improvement noted by the NASCIS II authors. These discrepancies included the authors' decision to report only right-sided motor scores, despite collecting bilateral motor scores, and to arbitrarily divide patients receiving methylprednisolone within 8 hours of injury from those treated more than 8 hours post-injury [90, 91]. Furthermore, the documented motor score differences were clinically meaningless as measured by the ASIA Functional Impairment Measure (FIM) [90], and methylprednisolone significantly increased the risk of adverse effects [93] (specifically gastrointestinal hemorrhage and wound infection).

For these reasons, the 2013 American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injury recommended against the routine use of methylprednisolone for patients with acute cervical SCI, as the likelihood of an adverse event far exceeds the likelihood of any therapeutic improvement. Contradictory guidelines developed by AOSpine suggested a 24-hour infusion of high-dose methylprednisolone (30 mg/kg bolus + 5.4 mg/kg/hours × 23 hours) to SCI patients presenting within 8 hours of injury [94]. The AOSpine group reached this recommendation through meta-analysis of three randomized controlled trials and one prospective trial [87, 92, 93, 95, 96], which found a moderately superior improvement among methylprednisolone-treated patients without a concomitant rise in complication rates. Notably, the group acknowledged this to be a weak recommendation and did not include the results of either NASCIS I or NASCIS III in their meta-analysis. Furthermore, the authors acknowledged that, although their included evidence supported a statistically significant improvement in motor function, it is unknown whether this translates to a clinically meaningful benefit.

Consequently, we believe that the preponderance of evidence suggests *there is little to no neurological benefit to be gained from administering methylprednisolone in patients with acute SCI*. However, if a patient presents within 8 hours of injury and has a low risk for complications (e.g., a younger patient without medical comorbidities), there might be a small clinical benefit as suggested by a recent meta-analysis [97]. Most groups agree that there is no benefit to methylprednisolone administration more than 8 hours after an acute injury.

Evidence for other pharmacological interventions is currently limited. The antibiotic minocycline [98] has shown some ability to improve neurological recovery and is undergoing a phase II clinical trial (NCT01828203). A phase III clinical trial of riluzole (NCT01597518) is also currently underway. To date, no definitive results are available from either trial.

Traction

In patients with acute cervical SCI, traction has been a well-studied, valuable adjunct in the treatment of pathology where there is misalignment secondary to a fracture, dislocation, or combination of the two. Barring any ligamentous injury at the craniocervical junction, traction can generally be used in awake patients and is most commonly applied via Gardner-Wells tongs or a halo ring. It should be noted that there is a theoretical risk of worsening deficit following traction; however, in the overwhelming majority of cases, it can provide immediate realignment of the spinal column with decompression of the spinal cord [22].

Prior to application of traction, CT of the cervical spine is evaluated to rule out injury at the level of the craniocervical junction. The patient is treated with a nonsedating pain medication (e.g., morphine, fentanyl) and muscle relaxant (diazepam) and is then placed supine [99]. Pin sites are scrubbed with 70% alcohol followed by povidone/iodine, and the pins are treated with bacitracin gel. Pins should be placed at the external auditory meatus, or in the case of jumped facets (with the intention of inducing flexion correction), 3 cm posterior to the external auditory meatus. In cases where a halo ring is being used for traction, the anterior pins should be placed 1 cm above the orbital rim and the posterior pins should be placed over the mastoid [99].

After application of initial traction, fluoroscopy and radiography are used intermittently to evaluate for correction of the injury and to prevent over-distraction at the craniocervical junction. Traction should be discontinued if the patient is unable to tolerate the procedure, demonstrates neurological deterioration, or displays evidence of over-distraction on radiography. If the patient remains neurologically intact and tolerates the procedure, traction may be progressively increased in 5- to 10-lb increments, with new radiographs/fluoroscopy images acquired after each weight increase. Traction should be increased progressively until the fracture is reduced (approximately 5–10lbs/cervical level), the patient is unable to tolerate the procedure, or the patient demonstrates neurological deterioration [100]. If the fracture is reduced, a halo vest or other cervical orthosis can be applied to maintain the correction. Traction can also be maintained until surgery, if indicated. Although there is a paucity of high-quality evidence to support the use of traction in the setting of acute cervical spine injury, a recent review reported that closed reduction with Gardner-Wells tongs or a halo ring is successful in reducing the spinal deformity in 80–90% of cases [57].

Surgical Intervention

Surgical intervention for acute traumatic SCI consists of neural element decompression, correction of deformity, and

stabilization across the injured region. Prolonged compression of the spinal cord after trauma contributes to worsening secondary injury by generating ongoing parenchymal ischemia, presumably through compression of the cord vasculature. This is supported both by extensive primary research [37, 101–103] and by several meta-analyses [104–107], which have demonstrated significantly better neurological outcomes for patients who underwent surgical decompression within 24 hours of injury. In fact, some of these studies have recommended that decompression takes place within 8 hours of injury (or as soon as possible) for optimal outcomes [107, 108]. In addition to achieving improved neurological outcomes, Bourassa-Moreau et al. [109] and Carreon and Dimar [110] both demonstrated that early decompression (i.e., within 24 hours of injury) was associated with lower rates of pneumonia and urinary tract infection. Pursuant to these results, most surgeons (≥80%) currently recommend rapid decompression (≤24 hours) for patients with complete or incomplete SCI, with most (72.9%) recommending decompression within 6 hours, if possible, for patients with incomplete SCI [111].

In addition to surgical decompression, some evidence suggests that duraplasty with or without drainage of cerebrospinal fluid may aid in neurological recovery. Evidence supporting its use is limited to animal studies [112]. In a porcine model, mean arterial pressure elevation with cerebrospinal fluid drainage was associated with significant improvements in spinal cord perfusion compared to mean arterial pressure management alone [112]. This evidence supports a Monro-Kellie-like model of spinal cord fluid dynamics, wherein residual elevation in intrathecal pressure decreases spinal cord perfusion pressure, increasing hypoxia and neuronal damage secondary to free radical production [113].

Concomitant spinal fixation with instrumentation is recommended for patients with mechanically unstable injuries or for patients in whom multilevel decompression may cause iatrogenic destabilization. The selection of approach and stabilization levels is ultimately up to the treating surgeon with multiple factors being taken into consideration. In general, all deformities should be corrected and fixated, instrumenting at least one (and sometimes more) level above and below the unstable segment. For occipitocervical instability, this means fixation from the skull into the subaxial spine, using a combination of an occipital plate and lateral mass fixation, or wiring with a malleable titanium rod in pediatric patients. Similarly, for patients with isolated subaxial spine trauma, lateral mass fixation is most commonly used. Here the main caveat is that fusion should extend past the cervicothoracic junction in patients demonstrating instability of the low subaxial spine to prevent progressive cervicothoracic deformity. For isolated atlantoaxial instability, posterior fusion with transarticular or a lateral mass screw technique can be quite effective [114, 115]. Lastly, anterior odontoid screw fixation can be effective for select younger patients with type II odontoid fractures and no evidence of concurrent injury to the posterior osseoligamentous complex.

Other Considerations

Decubitus Ulcers

Although more worrisome in the chronic setting, decubitus ulcers are a complication seen in a 10–30% of patients with SCI and are associated with healthcare costs of $1.2 to $1.3 billion annually [116]. Ulcers most commonly present on the buttocks (31%), lateral thighs (26%), and sacrum (18%) [9] and can be prevented with daily skin cleaning, inspection, and frequent rotation of the patient throughout the day. When sores develop, they should be cleaned thoroughly with aseptic technique and debridement of necrotic tissue where necessary.

Venous Thromboembolism

Deep venous thrombosis and pulmonary embolism are two common complications seen in 40% or more of patients with SCI [39]. The current recommendation is to implement venous thromboembolism prophylaxis with low-molecular-weight heparin (40 mg SQ qday) along with conservative measures, including compression stockings and/or serial compression devices. Vena cava filters are not recommended as a routine prophylactic measure but can be considered for select patients in whom anticoagulation fails or who are not candidates for anticoagulation and/or mechanical devices [18]. In all patients with SCI, early mobilization and rehabilitation may also help to reduce the risk of venous thromboembolism.

Sphincteric Dysfunction

Most patients with acute SCI develop bladder and bowel dysfunction. Neurogenic bladder may be addressed with intermittent Valsalva maneuver in a select minority of patients but most require intermittent sterile catheterization to drain the bladder. Failure to treat neurogenic bladder results in accumulation of urine in the renal pelvis with resultant hydronephrosis and the potential for chronic renal failure, which historically has contributed significantly to mortality among SCI patients [57].

The posttraumatic bowel similarly requires intervention to promote passage of stool, which can be accomplished with dietary modification, rectal stimulation when necessary, and stimulant laxatives (e.g., senna, bisacodyl, sodium picosulfate). In patients with permanent bowel dysmotility, colostomy may be recommended. However, consideration of colostomy requires in-depth discussion with the patient and is almost never required [39]. One additional clinically important gastrointestinal sequela of SCI is the acute stress

ulcer, also known as a *Cushing ulcer*. Patients should receive antisecretory agents for prophylaxis against this clinical entity in the acute setting; proton pump inhibitors (e.g., omeprazole 20–40 mg PO qday) are first-line treatments [57]. If these lesions become symptomatic, patients should have a nasogastric tube placed to facilitate ulcer healing, along with resuscitation with blood or intravenous fluids to address the hypovolemic state (1:1:1 packed red cells:fresh frozen plasma:platelets is preferred).

Infection

Spinal cord injury denervates the spleen and other secondary lymphoid organs. This is thought to contribute to the post-injury immunodeficiency seen in SCI patients. Immunodeficiency increases the risk of a clinically significant infection in patients, especially those with compromised respiratory function [52, 53].

Prognosis and Outcomes of Patients with Spinal Cord Injury

Prognosis of patients with acute SCI revolves around two main concerns: survival and neurological recovery, which can be thought of as the "quantity and quality of life." The latter is strongly predicted by the severity of injury at diagnosis, with over 97% of patients who were *ASIA D* at diagnosis being ambulatory at 1 year postoperatively, compared to a mere 8% of patients who were *ASIA A* at diagnosis [117]. Other factors, including younger age at the time of injury (patients younger than 65 years vs. patients 65 years and older) and greater lower extremity motor strength immediately post-injury, have been demonstrated to positively predict ambulation in multivariable analyses [3, 46, 50]. These factors are also associated with an increased ability to complete post-injury rehabilitation, raising the question of whether older, more severely injured patients generally are less able to recover or whether worse baseline function prevents completion of rehabilitation and subsequently inhibits recovery. At present, the evidence is insufficient to disentangle these two possibilities. However, it is obvious that the poor condition of some SCI patients contributes to the substantial costs of traumatic SCI. Cao et al. reported that direct costs of treatment are directly related to injury severity. For example, among patients with high cervical spine injury, direct costs for those with *ASIA D* injuries were reportedly $359,783, compared to $1,102,403 for patients who were *ASIA A* [2, 118]. These differences persist following discharge, imposing a significant financial burden upon patients and family members [2, 119–122].

Patients with SCI also have lower life expectancies than persons without. As with functional disability and care cost, actuarial survival is highly dependent on the age at injury and the extent of neurological injury [2]. Young patients with mild injury (e.g., *ASIA D*, age 20) have almost normal life expectancies (interval life expectancy 52.9 vs. 59.6 yr), whereas elderly patients (age > 60) with ventilator-dependent injury have drastically abridged life expectancies (3.7 vs. 23.2 yr) [2]. Regardless of grade and age at the time of injury, the strongest predictor of long-term survival appears to be surviving at least 1 year after the injury [3, 42]. During the first post-injury year, death most commonly results from medical complications (e.g., pneumonia and other respiratory diseases) rather than from the neurological injury itself [47]. Of course, the severity of the neurological injury undeniably contributes to mortality risk and to the likelihood of a prolonged inpatient stay [3, 4, 42, 44, 45, 48, 49]. Consequently, there is an almost exponential increase in mortality with increasing injury severity. To this end, it is likely that the significant improvement in overall mortality following SCI seen over the past three decades [3, 48] is at least in part due to the significant improvements in intensive care unit mortality [123]. Current investigations seek to further improve both life expectancy and neurological recovery after SCI, as there is still much room for improvement.

Conclusions

Traumatic SCI is an increasingly common clinical entity that requires multimodal management. Implementation of care must be performed in an expedient fashion and should be customized to include surgical decompression and/or stabilization, medical management of cardiopulmonary function, and post-injury rehabilitation based upon the unique characteristics of the patient and the injury. At present several contested issues remain, most notably the use of high-dose methylprednisolone during the acute injury phase. Similarly, several interventions have been universally recommended (e.g., surgical decompression), but they are supported only by poor-quality evidence. Moving forward, it is incumbent upon practitioners in neurosurgery and critical care medicine to procure data to investigate current interventions and to establish truly evidence-based treatment protocols.

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Treatment of Oncologic Emergencies in the Neurocritical Care Unit

14

Jeffrey S. Ehresman and Chetan Bettegowda

Management of Intracranial Pressure

Overview

Both metastatic disease and primary brain tumors can lead to emergent cases of increased intracranial pressure (ICP). These tumors can cause cerebral edema, further increasing the ICP. Intracranial tumors are inherently dangerous due to the fixed volume of the skull of approximately 1400–1700 mL [1]. In a healthy adult, 80% of this volume will be brain parenchyma, 10% will be cerebrospinal fluid (CSF), and 10% will be blood. The Monro-Kellie doctrine states that when one of these components is altered or a new lesion is present, the remaining components are displaced and ICP increases if a volume threshold is reached [2].

In adults, ICP is normally ≤15 mm Hg. Increasing pressure above 20 mm Hg defines intracranial hypertension (ICH). Although the volume of the brain parenchyma is relatively fixed, CSF is able to move into the spinal arachnoid space and cerebral venous blood volume can be decreased through increased drainage or vasoconstriction. If these volume compensations cannot adequately account for the presence of a new lesion, ICP begins to increase [3]. The compensation of decreasing cerebral blood flow (CBF) is limited by its effect of reducing cerebral perfusion pressure (CPP). This decrease can eventually lead to an ischemic state, which can cause poor outcomes for the patient [1].

In addition to the increase of volume due directly to a mass, cancer can increase ICP through different mechanisms that require consideration. "Pseudoprogression" is the term used to describe the increase in ICP after a patient undergoes radiation for a mass lesion and vasogenic edema ensues [4]. This can be differentiated from actual tumor progression through serial imaging as pseudoprogression would not continue to increase in volume over time [4]. Furthermore, blockage of any CSF outflow tract will cause this fluid to build up, and its compensatory displacement cannot occur [3]. Both of these mechanisms mimic the mass effect of a lesion and can therefore lead to similar presentations.

One major consequence of acutely increased ICP beyond the compensation threshold is herniation of the brain parenchyma [5]. The three types of herniations that often occur are subfalcine, uncal, and tonsillar herniations. Subfalcine herniation refers to the compression of the anterior cerebral artery inferior to the falx cerebri, uncal herniation refers to the compression of the midbrain and ipsilateral oculomotor nerve by the uncus, and tonsillar herniation refers to the downward compression of the brainstem through the foramen magnum [3]. Each of these herniations is responsible for separate patient presentations and will be discussed in the following section.

Presentation

The most common presenting symptom of increased ICP in patients with brain tumors is a headache similar to the non-throbbing tension-type. Unlike tension-type headaches, headaches from tumors are often worsened when the patient bends over [6]. The severity of the headaches can vary, with some patients describing it as "the worst headache of my life" that was not relieved by common analgesics [7]. These acute onsets headaches could be due to hemorrhage or obstructive hydrocephalus caused by tumors and can be noted by phenomena called plateau waves. Plateau waves are defined as acute elevations in ICP that often surpass 40 mm Hg for over 5 minutes [8]. These severe headaches may also be accompanied by transient neurologic deficits that can falsely present as orthostatic hypotension since moving to the standing position can decrease level of con-

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sciousness [9]. Furthermore, plateau waves lasting more than 30 minutes can cause irreversible damage due to the lack of CBF [10].

Headaches may be accompanied by other symptoms of mass effect including nausea, vomiting, papilledema, abducens nerve palsy, and transient neurologic deficits [6]. Headaches that occur in a patient with no prior history of headaches or headaches that abruptly change pattern are particularly worrisome, although keep in mind that brain tumors are present in patients with isolated headaches less than 1% of the time [11, 12]. As previously stated, these deficits may be brought on from standing or other triggers that increase ICP such as coughing or sneezing. Impairments of consciousness often present as patient lethargy [13].

The most severe presentations of elevated ICP occur from herniation of the brain. These most often occur after acute increases in ICP when volume compensations are not adequate. A few signals that herniation is likely are the Cushing's reflex, Cheyne-Stokes respiration, or acute impairments in consciousness [14]. Cushing's reflex refers to hypertension, bradycardia, and abnormal breathing patterns as a response to increased ICP [15]. Cheyne-Stokes respiration is characterized by pronounced fluctuations in breathing that cycle between deep breathing and temporary pauses in breathing [16]. Both of these signs, as well as consciousness impairments, require emergency attention [13].

Compression of the anterior cerebral artery from subfalcine herniation can lead to contralateral leg weakness and potentially bladder incontinence [4]. Uncal herniation may cause compression of the oculomotor nerve and the midbrain. A patient with an oculomotor nerve palsy will likely present with a "blown pupil" as the parasympathetic fibers are located on the outer portion of the oculomotor nerve. Further compression can then cause a "down and out" eye accompanied by ptosis, both on the ipsilateral side. Ipsilateral hemiparesis may occur as the midbrain is pressed against the contralateral cerebral peduncle. The posterior communicating arteries may also be compressed, which could lead to a stroke in the occipital lobe [17]. Tonsillar herniations can lead to devastating outcomes when the brainstem is compressed, leading to reticular activating system damage or pontine hemorrhage. Levels of consciousness can be greatly impaired, and patients with pontine hemorrhage may lose all motor function except upward gaze and eyelid movements as in the classic locked-in syndrome [18].

Hospital Course and Management

When a patient's clinical presentation demonstrates the previously listed symptoms, the patient should be managed medically in the hyperacute setting with hyperventilation, steroids, and osmotherapy. Hyperventilation should be the initial treatment, and it is performed through intubation with the patient sedated. The goal is to reduce pCO_2 to 25–30 mm Hg in order to cause vasoconstriction in the cerebral vessels, although this decreases CBF, so the duration of hyperventilation must be balanced with the risk of ischemic damage [19].

Once hyperventilation has been initiated, the patient should be started on steroids and osmotherapy. Dexamethasone is the preferred corticosteroid and is used to reduce ICP by decreasing vasogenic edema. This mechanism is especially effective when ICP elevations are caused by mass lesions. Based on a level 3 recommendation, patients with acute ICP emergencies should receive a bolus of 10–20 mg and be maintained on 8–16 mg per day as seen in Table 14.1 [20]. This should then be tapered over a 2-week period unless the patient remains symptomatic, requiring a lengthened duration of the steroid [21]. One contraindication to note is when CNS lymphoma is also on the differential, as this corticosteroid may lyse the B lymphocytes and confound the biopsy. In this case, osmotherapy should be used without concurrent corticosteroid use until the biopsy is performed [12].

Osmotherapy is used with dexamethasone and can either be in the form of 20–25% mannitol or hypertonic (23.4%) saline [22, 23]. By increasing the osmolarity of the blood, a gradient is formed across the blood-brain barrier to reduce water in the intracranial space [13]. This therapy has the potential to acutely reverse ICP to avoid or alleviate brain herniation. However, caution should be used because a rebound effect has been observed after frequent doses are administered, which could exacerbate the elevated ICP [23]. Furthermore, osmotherapy is only effective until the brain builds up enough "idiogenic osmoles" to reverse the osmolarity gradient and draw fluid back across the blood-brain barrier [24].

Once these immediate treatments are given, imaging is needed to look for the cause of elevated ICP. In emergency situations, a non-contrast CT should be performed in order to rule out hemorrhage. Once this is ruled out or the patient is stable, magnetic resonance imaging (MRI) should be the next step to evaluate the cause of increased ICP. T2 fluid-attenuated inversion recover (FLAIR) images can demonstrate the vasogenic edema and mass effect present by suppressing the CSF signal, while T1-contrast-enhanced images represent the gold standard by providing clear and high-resolution images of the mass lesion present [12, 25].

If the cause of elevated ICP is found to be due to a mass lesion and immediate ICP-lowering treatments do not reverse the acute presentation, neurosurgical intervention becomes warranted [25]. This can involve an entire resection or a partial debulking to decrease mass volume, and the extent of resection will largely be due to the intracranial location of the tumor [13]. Furthermore, CSF can be reduced through the placement of a ventriculostomy, especially when the mass lesion is causing obstructive hydrocephalus [25].

Table 14.1 Common pharmacological agents used in the NCCU

Pharmacological agents			
Elevated intracranial pressure			
Drug	**Dosing**	**Route**	**Key side effects**
20% mannitol solution	Bolus of 1 g/kg, repeat with 0.25–0.5 g/kg as needed every 6–8 hours	Intravenous	"Rebound" increase in ICP Hypernatremia Pulmonary edema
Hypertonic (23.4%) saline	Bolus of 30 mL	Intravenous	Central pontine myelinolysis (rare) Acute heart failure Pulmonary edema
Dexamethasone (also used in intratumoral hemorrhage)	Loading dose of 10–20 mg, maintained on 8–16 mg per day, then tapered over a 2-week period	Oral or intravenous	Insomnia Essential tremor GI complications Steroid myopathy Opportunistic infections
Pituitary tumor apoplexy			
Drug	**Dosing**	**Route**	**Key side effects**
Hydrocortisone	100 mg IV or IM followed by 50–100 mg IM every 6 hours or 100–200 mg IV with 2–4 mg/hour through IV infusion	Intravenous and intramuscular	Nausea Headache Dizziness Opportunistic infections Hyperglycemia (rare)
Status epilepticus			
Drug	**Dosing**	**Route**	**Key side effects**
Lorazepam	4 mg fixed dose and repeat if no termination of seizure activity	Intravenous (use intramuscular midazolam if no venous access)	Drowsiness Cognitive impairment Respiratory depression Hypotension
Fosphenytoin	15–20 mg/kg phenytoin equivalents (PE) infused at 100 mg PE/minute	Intravenous or intramuscular if no venous access	Hypotension Arrhythmias CNS adverse effects Local dermatological reactions
Valproic acid	20–40 mg/kg infused at 5 mg/kg/min	Intravenous	Nausea/vomiting Drowsiness Thrombocytopenia Pancreatitis Hepatotoxicity
Lacosamide	200–400 mg IV bolus	Intravenous	Visual changes Nausea/vomiting Ataxia
Levetiracetam	40–60 mg/kg	Intravenous	Behavioral changes Somnolence Headache Stevens-Johnsons syndrome (rare)
Phenobarbital	20 mg/kg infused at 30–50 mg/min	Intravenous	Cardiorespiratory depression Visual changes Effects of CYP450 induction Paradoxical hyperactivity (children)

Pituitary Tumor Apoplexy

Overview

Pituitary tumor apoplexy (PTA) is the phenomenon that occurs when the blood supply to the pituitary is acutely interrupted. This blood supply includes the superior and inferior hypophyseal arteries for the anterior and posterior pituitary glands, respectively [26]. If a pituitary adenoma grows rapidly enough, it may physically disrupt the blood supply, and this can lead to either hemorrhage or necrosis of the tissue. Furthermore, pregnancy, peri- or postsurgical hypotension, vasospasm, and head trauma can lead to apoplexy [12, 27].

The incidence of these episodes is relatively rare and incidence ranges from 0.6% to 7% of pituitary adenomas [27–29]. The most common pituitary tumors associated with PTA are nonfunctioning macroadenomas, prolactinomas, and growth hormone-secreting macroadenomas [30]. These tumors may extend into the suprasellar region and impinge

upon the optic chiasm as well as laterally to affect the structures of the cavernous sinus [27]. These cavernous structures include cranial nerves (III, IV, V_1, V_2, VI) and the internal carotid artery [31].

Presentation

The most common presentation of PTA is acute headache. It is speculated that these severe headaches can be due to several factors, including trigeminal nerve involvement, dural stretching, or meningeal irritation. The headaches are often retro-orbital and deep and are usually unique to any previous headaches [27]. These headaches may also be severe enough to be accompanied by nausea and vomiting, or even mental disturbances in the most severe cases [12].

As mentioned previously, cranial nerves can be affected in PTA, which can present with visual disturbances. The oculomotor nerve (cranial nerve III) is the most common cranial nerve deficit and is present in approximately 50% of patients. This can be observed as ptosis and "blown" pupils [32]. Bitemporal hemianopsia may also arise in patients if the pituitary tumors grow superiorly enough to make contact with the optic chiasm [31]. However, the rates of visual alterations may be lower in modern practice than what the literature states since many studies include patients that were treated before MRIs were widely available, with more delayed diagnoses and larger tumors [33, 34].

Since PTA episodes are most often reported in cases of macroadenomas, endocrinopathies are often present in patients. Approximately 80% of patients with PTA have at least one sign of anterior pituitary hormone dysfunction; the most common is adrenocorticotropic hormone (ACTH) dysfunction, present in nearly 70% of PTA cases. This regulates the cortisol production axis, and deficiency can therefore present as hypotension or hyponatremia [32]. Less common hormone deficiencies can include thyrotropin and gonadotropin. Conversely, prolactin may be increased from either prolactinomas or stalk compression due to interruption of its dopamine-signaled constitutive inhibition [35]. While anterior pituitary dysfunction is relatively common in PTA, the posterior pituitary gland is rarely affected with only 5% of patients presenting with symptoms of diabetes insipidus [34].

Hospital Course and Management

Traditionally, CT scans were performed when patients presented with signs of PTA to look for evidence of sellar hemorrhage. However, a recent study found that hemorrhage was only identified in 42% of patients with PTA [34]. MRI was able to detect hemorrhage in 89% of patients while also allowing for the evaluation of the health of the surrounding tissue [34]. Furthermore, MRI allows subacute and chronic apoplexy to be observed to a much greater extent than CT [27]. Therefore, an urgent brain MRI is indicated when signs of PTA are present unless an MRI is contraindicated in a patient. In these cases, high-quality CT scans with and without contrast are warranted [27]. MR angiograms may be utilized when vasospasm or aneurysms are assumed to be contributing precipitants of PTA [27]. Furthermore, CT scans may be performed in order to exclude subarachnoid hemorrhage (SAH) and meningitis as these conditions can present with similar signs [33].

The greatest cause of morbidity and mortality after PTA episodes is acute adrenal insufficiency due to pituitary damage [33]. Therefore, 100 mg intravenous (IV) or intramuscular (IM) hydrocortisone should be given to combat this effect along with IV fluids to maintain electrolyte balance. This should be followed by hydrocortisone 50–100 mg IM every 6 hours or 100–200 mg IV bolus with 2–4 mg/hour continuous IV infusion [33]. Hydrocortisone should be continued orally after discharge until it is clear that adrenal function is stabilized [27]. An urgent blood endocrine panel should also be obtained in order to assess the need to supplement other hormone deficiencies [33, 34].

While early decompression has been the traditional treatment for PTA, there is growing evidence that conservative treatment involving sole medical management can lead to similar outcomes in select patients [33, 36, 37]. Early decompression is most often indicated when patients present with severe ophthalmological alterations. This is currently the preferred treatment when visual deficits are progressive and not improved with initial medical therapy [34]. In patients who did not present with visual symptoms or their symptoms decreased with medical therapy, conservative approaches of medical management can lead to complete resolution of symptoms. However, as many studies have pointed out, direct comparisons between these two treatments cannot be made since treatment decisions were based on the presentation of individual cases. Therefore, this selection bias should not be overlooked, and sole medical management should only be opted for when progressive neuro-ophthalmological symptoms are not present and symptoms are decreasing in severity [33, 34, 36, 37]. This treatment paradigm is in agreement with the Society for Endocrinology UK guidelines for the management of pituitary apoplexy [38].

Acute Tumor Hemorrhage

Overview

The incidence of intratumoral hemorrhage has been reported to range between 1% and 10% in previous studies, and this includes both primary and metastatic brain tumors [39, 40].

The vast majority of these hemorrhages occur in patients with previously discovered brain tumors, while only 4% of patients had intracerebral hemorrhages caused by unsuspected brain tumors [40].

The two primary brain tumors most associated with intracranial hemorrhage are glioblastoma multiforme (GBM) and oligodendrogliomas [41]. GBMs are the most common primary brain tumor in adults and are known for their very destructive nature. Although oligodendrogliomas are less invasive, these tumors contain retiform capillaries that are known to hemorrhage [42]. Of metastatic brain tumors, melanoma, lung, renal, choriocarcinomas, and papillary thyroid carcinomas have had the highest rates of intracerebral hemorrhages [23, 43].

Presentation

The presentation of intratumoral hemorrhage is very similar to the presentation common in intracranial hemorrhage patients without brain tumors [44]. The two most common presenting signs include hemiparesis and headaches, both occurring in nearly half of patients [43]. These are followed by encephalopathy, nausea and vomiting, seizure, and coma in the most severe cases [43]. However, one difference between brain tumor patients and the general population is that intracranial hemorrhages in tumor patients are primarily intraparenchymal instead of subdural or subarachnoid [26].

Hospital Course and Management

When hemorrhage is suspected in a patient, an urgent MRI is indicated unless one is not immediately available. In that case, an immediate non-contrast CT scan is indicated. This is supported by Class I, Level A evidence from the American Stroke Association [45]. Brain tumor hemorrhages are often suspected when an intracerebral hemorrhage (ICH) is present in an atypical location, there are multiple hemorrhages, or if an enhancing mass is seen near the bleeding site [23]. A baseline severity score, such as the original ICH score, must also be given when initially evaluating a patient with a suspected ICH (*Class I; Level of Evidence B*) [45]. This grading scale includes variables such as age, ICH volume, location of hemorrhage, presence of intraventricular hemorrhage, and score on the Glasgow Coma Scale [45]. If suspicion for the presence of a tumor remains, "a CTA, CT venography, contrast-enhanced CT, contrast-enhanced MRI, magnetic resonance angiography and magnetic resonance venography, and catheter angiography can be useful to evaluate for underlying structural lesions including vascular malformations and tumors" (*Class IIa; Level of Evidence B*) [45]. An MRI also allows one to search for alternative causes of hemorrhage such as ischemic stroke with hemorrhagic conversion, venous sinus thrombosis, or amyloid angiopathy [44].

Once an intratumoral hemorrhage is confirmed, corticosteroids can be given to alleviate any vasogenic edema present [23]. However, corticosteroids should not be given solely to reduce ICP after intratumoral hemorrhage (*Class III; Level of Evidence B)* [45]. Consideration should then be given to whether the tumor can be surgically removed [41, 43]. The International Surgical Trial in Intracerebral Hemorrhage (STICH) found that lobar hemorrhages trended toward better surgical outcomes, although this finding was nonsignificant [46]. However, if there are multiple tumors or a tumor is unresectable, whole-brain radiation may be the next option [44]. If an intratumoral hemorrhage bleeds excessively and a clot forms, the clot may be subject to surgical evacuation. However, this should only be performed if the clot is causing progressive symptoms or is superficially located because the STICH and STICH II trials found that early evacuation did not improve patient outcomes [46, 47].

Although short-term outcomes of patients with intratumoral hemorrhage are similar to non-cancer patients with intracerebral hemorrhage, long-term outcomes are often worse due to the underlying malignancy. Navi et al. observed a 78% mortality at 1 year, likely because intratumoral hemorrhages often occur late in the course of malignancy [43]. However, patients with intracerebral hemorrhage due to cancer-related coagulopathies had worse outcomes than patients with intratumoral hemorrhages, as the former patients often had larger hemorrhages and involvement of multiple intracranial compartments [43, 44].

Status Epilepticus in Tumor Patients

Overview

Patients with both primary and metastatic brain tumors have a relatively high rate of seizures, likely due to the mass effect of the surrounding cortex [12]. Seizures most often begin as partial seizures due to the location of the tumor, and only a portion of these will become generalized seizures. Dysembryoplastic neuroepithelial tumors (DNETs) and gangliomas are associated with the highest rates of seizures (80–100%), with these tumors most often arising in children [48]. These tumors likely carry a high risk of seizures due to their frequent localization in the temporal lobe, which is an epileptogenic area along with the insula and cortex [49]. Interestingly, 60–85% of lower-grade gliomas have been found to lead to seizures compared to only 30–60% of glioblastomas [50]. This may be due to the fact that the survival period in patients with low-grade gliomas is much longer [51]. Seizures from brain metastases occur at a lower frequency than each of the above-mentioned primary brain

tumors, carrying only a 20–35% seizure incidence [51, 52]. Metastases from melanomas have the highest incidence of seizures (67%), likely due to its hemorrhagic nature [51].

Although seizures in patients with brain tumors are most often self-limited and short-lasting, those that do transform into status epilepticus (SE) become emergencies [12]. SE is defined as a continuous seizure lasting greater than 5 minutes, or multiple seizures occurring consecutively without return to baseline [53]. SE is associated with a 20% 30-day mortality, and between 15% and 22% of brain tumor patients with epilepsy progress to SE [54, 55].

In addition to seizures being caused by mass effect, several cancer therapies have been known to cause seizures through a phenomenon known as posterior reversible encephalopathy syndrome (PRES). These therapies include bevacizumab, sorafenib, cyclophosphamide, l-asparaginase, cisplatin, and gemcitabine [56]. Therefore, PRES must be ruled out when brain tumors are being investigated as the cause of seizures.

Presentation

Patients may present with different subtypes of seizures, including simple partial seizures, complex partial seizures, and focal seizures with secondary generalization [23, 51]. Patients may also present with focal weakness in an extremity after they experience an epileptic episode, known as postictal paralysis (Todd's paralysis) [57]. Some patients progress to SE in the absence of convulsions, also called nonconvulsive status epilepticus (NCSE). Patients with NCSE may present with abnormal eye movements, nonspecific personality changes, myoclonic jerks, or altered mental status [23, 57]. Furthermore, SE may arise at different periods throughout the neoplastic process. Cavaliere et al. found that 29% of SE in brain tumor patients arises at tumor presentation, 23% during tumor progression, and 23% in patients with stable brain tumors [54].

Hospital Course and Management

When a brain tumor patient presents with SE, medical therapy should be immediately given and the airway must be secured. Patients should initially be given lorazepam 4 mg IV (a benzodiazepine) to terminate the SE unless IV access is not possible, and then IM midazolam is substituted [58]. If SE is not terminated, another dose of 4 mg lorazepam (or IM midazolam) should be given [3, 59]. Electrocardiogram and vital sign monitoring should also be initiated upon diagnosis of SE, and blood samples should be tested for glucose, electrolytes, antiepileptic drug (AED) levels, and toxic agents. If SE is not terminated after benzodiazepine administration, phenytoin (a second-line agent) should be given at 15–20 mg/kg. If phenytoin does not terminate SE, third-line agents include phenobarbital, valproic acid, lacosamide, and levetiracetam [3, 60]. These treatments are based on the Guidelines for Status Epilepticus by the Neurocritical Care Society and should be followed regardless of whether the cause of SE is a brain tumor [60]. Although epileptic attacks are more frequent with low-grade gliomas, high-grade gliomas are associated with AED refractoriness with a 60% failure rate of terminating after first-line benzodiazepines [55]. However, when seizures progress to SE in brain tumor patients, this tumor-associated form of SE is paradoxically easier to treat with first-line benzodiazepines than SE in the general population [55].

When treating SE in cancer patients, it is important to be aware of drug-drug interactions between SE therapies and chemotherapeutic agents. For example, several older-generation anticonvulsants are hepatic cytochrome P450 inducers (phenytoin, carbamazepine, phenobarbital) that can reduce levels of drugs that use the same metabolic pathway, such as dexamethasone [12]. For this reason, newer antiepileptic drugs (levetiracetam, lamotrigine, lacosamide) are often used as they carry less risk of drug interactions [61, 62]. The opposite can also occur where hepatic cytochrome P450 inhibitors (valproic acid) can increase the levels of chemotherapeutic agents (cisplatin, etoposide), which can lead to bone marrow toxicity [63]. Furthermore, although these AEDs are helpful in the situations previously discussed, there is a lack of evidence in their prophylactic use to decrease risk of new seizures [64].

Once SE is terminated, imaging should be performed to search for the cause of the seizures. A CT scan may be performed in an emergent situation to look for obvious hemorrhage or mass effect, but an MRI is optimal for a more detailed evaluation of the cause of SE. MRI can more accurately display the number and size of masses as well as whether progression of a known tumor has caused SE [23]. Seizures in brain tumor patients may not always be convulsive, and this makes electroencephalography (EEG) a useful tool in order to look for seizure activity when NCSE is suspected [65]. An EEG also allows one to observe if a patient returns to baseline after a seizure in order to rule in/out SE [7, 23, 49].

Lastly, once SE is terminated and a brain mass is identified as the cause, surgical resection may be performed if feasible. Chang et al. analyzed 332 patients who underwent surgical resection for low-grade gliomas and found that 67% were seizure-free after surgery and that gross total resections achieved the best seizure outcomes [66]. Therefore, surgical resection should remain an option in treating these patients, and this should be discussed with the multidisciplinary neuro-oncological care team.

Patient Flow Upon Admission

Upon admission to the NCCU, the vital signs of brain tumor patients need to be stabilized immediately. This should be followed by a physical examination and comprehensive laboratory studies. The patient should undergo appropriate monitoring including electrocardiogram, blood pressure, oxygen saturation, hematologic laboratories, liver and kidney function tests, blood and urine osmolality, and body temperature [67]. This should be followed by a detailed neurological examination assessing mental status, cranial nerves, sensorimotor function, reflexes, and coordination if possible.

As discussed in the previous sections, ICP, CPP, and CBF should be continually monitored, and the team should consider whether invasive ICP monitoring is necessary as this could also allow for CSF drainage if required [68]. EEG monitoring is also supported for patients in the NCCU based on Class II and III evidence, Type C recommendation from the American Society of Neurophysiological Monitoring [69]. In addition to these monitoring techniques, selection of MRI or CT scans should depend on the urgency of symptoms and the type of pathology expected.

Pain severity and degree of sedation should also be evaluated in the NCCU. Pain severity should be assessed according to the numerical ranking score from 0 to 10, with 0 representing no pain and 10 representing excruciating pain. However, the patient may be incapacitated and unable to give a response. Therefore, patient behaviors such as facial expressions must be evaluated and combined with the physiological functions already being monitored (heart rate, blood pressure) [67]. These parameters can also be used when assessing the degree of sedation and can be applied to several scoring systems including the Ramsay Score, Riker Sedation-Agitation Score, and the Bispectral Index Scale. These scores, combined with respiratory and cardiovascular functioning, can inform the type and quantity of analgesics required for the patient while a treatment plan is being formed and delivered [70].

Summary

This chapter outlines the most common presentations, hospital courses, and management routes of patients with elevated ICP, pituitary tumor apoplexy, acute tumor hemorrhage, and status epilepticus. An understanding of these emergencies, as well as others not discussed in this chapter, will allow the NCCU team to give the best care to patients by delivering the most efficient evaluation, diagnosis, and treatment. While several NCCU guidelines have been established to allow for better, more standardized patient care, more are needed to ensure optimal care is being given in each NCCU.

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Neurosurgical Emergencies

15

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Spontaneous Intraparenchymal and Intraventricular Hemorrhage

Presentation and Initial Management

Spontaneous intracerebral hemorrhage (ICH), or hemorrhagic stroke, is an emergency for which neurosurgical intervention plays a role in a subset of cases. The diagnosis is suspected in patients with acute-onset altered mental status, depressed consciousness, elevated systolic blood pressure, and headache. It is confirmed and distinguished from ischemic stroke with non-contrast head computed tomography (CT) or magnetic resonance imaging (MRI) (Fig. 15.1; American Heart Association (AHA)/American Stroke Association (ASA) Class I recommendation, Level A evidence) [1–4]. The neurosurgical team is typically consulted emergently on presentation so that an evaluation can be performed and recommendations can be made in conjunction with the emergency department, stroke team, and intensivists.

Assessment and control of airway, breathing, and circulation should be performed as in all emergencies. Intubation is often required due to the inability of the patient to protect his or her airway. Continuous cardiopulmonary monitoring is standard, and blood pressure should be closely controlled. Current recommendations suggest a systolic blood pressure goal range of 140–180 mmHg given a recent randomized controlled trial (RCT) showing no benefit of a lower target on death or disability and a higher rate of renal complications (ACC/AHA Class III, Level A) [4–6]. This is in contrast to prior guidelines based on RCT data suggesting that immediate blood pressure lowering to <140 mmHg was safe and might slow hematoma growth and lead to better functional outcomes [4, 7–10]. Prophylactic anticonvulsants are not recommended in this setting (AHA/ASA Class III, Level B) unless there are clinical seizures (AHA/ASA Class I, Level A) or change in mental status with signs of seizure on EEG (AHA/ASA Class I, Level C) [4, 11–14].

Initial management of high intracranial pressure (ICP) should include elevation of the head of bed, hyperosmolar therapy, hyperventilation, and sedation [4, 15]. The clinical exam should be followed serially to assess for signs of worsening ICP and response to therapy. Invasive ICP monitoring can be considered in patients with Glasgow Coma Scale (GCS) ≤8, clinical evidence of transtentorial herniation, or significant intraventricular hemorrhage (IVH) or hydrocephalus (AHA/ASA Class IIb, Level C) [4]. The goal of monitoring should be to maintain cerebral perfusion pressure (CPP)—the difference between MAP and ICP—above 50–70 mmHg (dependent on status of cerebral autoregulation, AHA/ASA Class IIb, Level C) and ICP below 20–22 mmHg [4, 16–18]. In general, these guidelines are based on data from severe traumatic brain injury (TBI) as there is less evidence for ICP management in spontaneous ICH [19–21]. Corticosteroids should not be used (AHA/ASA Class IIb, Level B) [4, 22].

Determining Etiology

ICH can be classified as either primary (80–85% of cases) or secondary (15–20%) [4, 23, 24]. Primary ICH is typically caused by hypertension (usually in the basal ganglia) or amyloid angiopathy (typically lobar in location). Secondary

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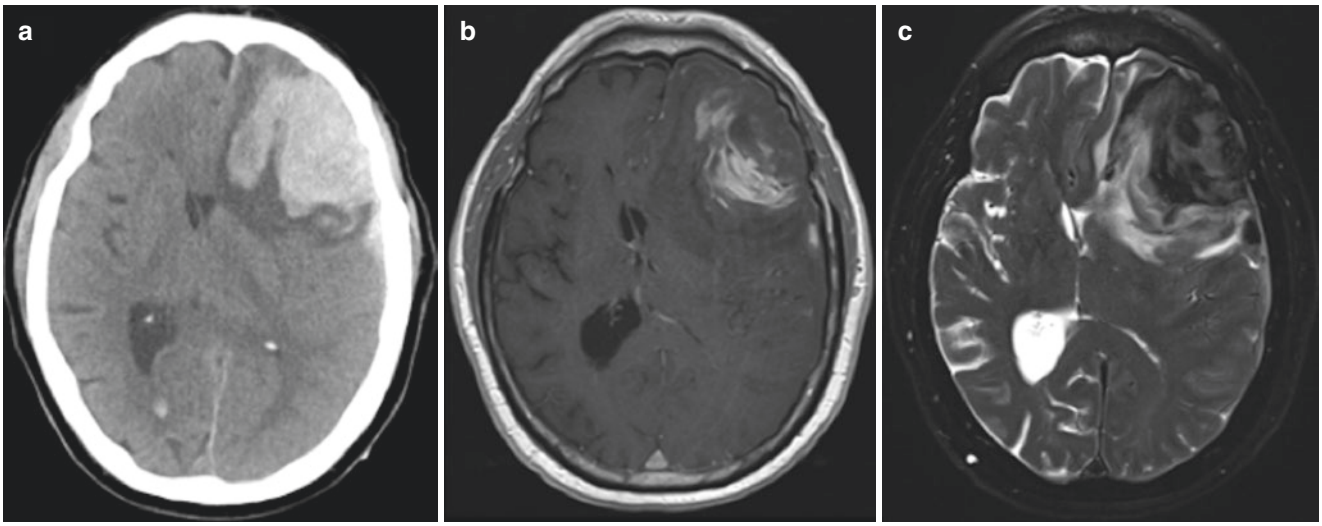

Fig. 15.1 Spontaneous intracerebral hemorrhage. Large acute left frontal lobar intraparenchymal hemorrhage with surrounding edema resulting in significant mass effect, effacement of the left lateral ventricle, and rightward midline shift. Underlying diagnosis thought likely to be amyloid angiopathy. (**a**) Non-contrast axial plane head CT on the day of presentation. (**b**) Gadolinium-enhanced axial plane T1 MRI brain and (**c**) T2 MRI brain approximately 2 days after the hemorrhage

ICH can occur from cerebral aneurysms, vascular malformations, coagulopathy and anticoagulant use, tumors, vasculitis, venous thrombosis, sympathomimetic drugs, or hemorrhagic conversion of ischemic infarction.

For most patients with ICH, CT angiography or MR angiography is recommended (AHA/ASA IIb, Level B) and is typically done as soon as the patient is stable [4, 25–28]. Contrast-enhanced CT or MRI, CT or MR venography, and catheter angiography may also be useful to evaluate for underlying structural lesions (ASA/AHA Class IIb, Level B) [4, 29–32]. Certain underlying etiologies may need to be urgently addressed, such as cerebral aneurysm, vasculitis, and venous thrombosis. Nearly all will require blood pressure control and medical management of ICP. Knowing the etiology of the ICH may also influence surgical decisions. If an aneurysm is present and surgically accessible, then clipping and evacuation may happen concurrently. In contrast, vascular malformations are often managed medically in the acute setting, with surgical intervention performed once recovery has occurred. Workup of the underlying lesion should not delay the placement of an external ventricular drain (EVD) if deemed urgently indicated. However, for the reasons mentioned, diagnosing the underlying lesion is likely to inform discussions regarding surgery.

Reversal of Antiplatelets and Anticoagulants

Initial history and workup should include assessing for history of platelet dysfunction, coagulopathy, and recent antiplatelet or anticoagulant use. Platelet count, international normalized ratio (INR), and partial thromboplastin time (PTT) should be checked urgently on initial evaluation. If the patient is known or found to have severe thrombocytopenia or coagulopathy due to a factor deficiency, the appropriate replacement therapy of platelets or coagulation factors should be administered (AHA/ASA Class I, Level C) [4].

While antiplatelets should be discontinued immediately, platelet transfusion after ICH in patients with a history of long-term use is generally not recommended if the patient is not undergoing surgical intervention (Neurocritical Care Society (NCS)/Society of Critical Care Medicine (SCCM) conditional recommendation, low-quality evidence) as its usefulness is uncertain (AHA/ASA Class IIb, Level C) [4, 33–44]. For patients with a history of aspirin or adenosine diphosphate (ADP) receptor inhibitor use undergoing neurosurgical intervention, platelet transfusion is suggested (NCS/SCCM conditional recommendation, moderate-quality evidence) [35, 44]. However, this suggestion does not extend to nonsteroidal anti-inflammatory drug (NSAID) or glycoprotein IIb/IIIa (GpIIb/IIIa) inhibitor use (NCS/SCCM conditional recommendation, very low-quality evidence) [44, 45].

In addition to antiplatelet medications, all classes of anticoagulants should be discontinued immediately (NCS/SCCM good practice statement) [44]. In general, there is good evidence for correction of coagulopathy and reversal of anticoagulants in this setting. For those taking vitamin K antagonists (e.g., warfarin), they should receive factor replacement and vitamin K to correct their INR (AHA/ASA Class I, Level C) [4, 46, 47]. Prothrombin complex concentrate (PCC) should be considered over fresh frozen plasma

(FFP) as it may act more rapidly and has fewer complications (AHA/ASA Class IIb, Level B) [4, 48–57]. In those receiving a heparin infusion at the time of ICH, protamine sulfate should be used for reversal (AHA/ASA Class IIb, Level C) [4, 58]. Other anticoagulants should be reversed based on institutional policies. Activated factor VII is not recommended in ICH patients (AHA/ASA Class III, Level C) [4, 59–67]. When indicated, rapid reversal of platelet and coagulation abnormalities is essential for safely performing neurosurgical procedures.

Hydrocephalus and Role for Ventricular Drainage

IVH is a reported component in 36–50% of ICH and is associated with worse outcomes [68–74]. Ventricular extension is usually secondary to the intraparenchymal process but can often comprise the more substantial component of the hemorrhage [69, 75]. The acute concern with intraventricular extension is hydrocephalus, which is also associated with worse outcomes [72–74]. Traditionally, IVH and hydrocephalus have been treated with external ventricular drainage. However, there is limited evidence of efficacy [73, 76]. In general, the practice at our institution is to place a ventricular drain in patients with evidence of ventricular outflow obstruction on imaging and clinical signs of symptomatic hydrocephalus. In particular, it should be considered in patients with decreased level of consciousness (AHA/ASA Class IIa, Level B) [4]. Instillation of fibrinolytics through ventricular catheters may be considered to hasten clot dissolution, but efficacy and safety are uncertain, as is the efficacy of endoscopic IVH evacuation (AHA/ASA Class IIb, Level B) [4, 18, 77–91]. Since these most recent guidelines, the CLEAR III trial was published [92]. In this study, 500 IVH patients were randomized to irrigation through a routine EVD with either alteplase or saline (control). The primary efficacy endpoint of good outcome as measured by the modified Rankin Scale (mRS; ranges from 0, no symptoms, to 6, deceased) was not significantly different between groups. The alteplase group had a lower 180-day case fatality (14% vs. 29% in saline group, $p = 0.006$) but a greater proportion of patients with mRS 5 (17% alteplase vs. 9% saline, $p = 0.007$). The safety endpoints of ventriculitis and symptomatic bleed were similar in both groups. A ventricular catheter is typically not placed at our institution solely for the purpose of administering intraventricular alteplase.

Role for Surgery

There is little evidence to consistently support surgical intervention for supratentorial ICH, and the role of surgery in this setting remains controversial. The rationale for surgery is to decrease ICP, prevent herniation, and reduce mass effect. Based on current evidence, surgery should be considered a life-saving measure and does not appear to affect functional outcomes [92–94].

For supratentorial hemorrhages without neurological deterioration, the usefulness of surgery is uncertain (AHA/ASA Class IIb, Level A) [4, 93–96]. If there is neurological deterioration, evacuation can be considered as a life-saving measure (AHA/ASA Class IIb, Level C) [4]. If the patient is in a coma, has a large hematoma with significant midline shift, or has elevated ICP refractory to medical management, decompressive hemicraniectomy with or without hematoma evacuation may reduce mortality (AHA/ASA Class IIb, Level C) [4, 97–101]. The Surgical Treatment of Intracerebral Hemorrhage (STICH) trial randomized 1033 patients with spontaneous ICH to either early (<24 h) surgical evacuation or medical management [93]. In the early surgery group, 26% of patients had a favorable primary endpoint on the Glasgow Outcome Scale compared to 24% in the initial medical management group ($p = 0.414$). Subgroup analyses suggested benefit for those with superficial lobar hemorrhage within 1 cm of the surface. To further explore this subgroup, the STITCH II trial randomized 601 patients with superficial hemorrhages 10–100 mL in size to either early surgery or initial medical management [94]. The rate of unfavorable outcome was similar in both groups (59% surgical vs. 62% medical, $p = 0.367$).

Hematomas that are moderate-sized and within 1 cm of the cortical surface are typically considered the best surgical candidates, as opposed to deep lesions or those that are either so massive as to already be devastating or so small that the risk of surgery outweighs any potential benefit [93]. The optimal timing of surgery is also unclear. There may be harm in operating too early (<4 h) due to higher risk of rebleeding but also loss of benefit in operating too late (>21 h) [94, 102–105]. New minimally invasive clot evacuation techniques using stereotactic or endoscopic aspiration have shown uncertain benefit (AHA/ASA Class IIb, Level B) [4, 99, 106–111]. Most recently, the Minimally Invasive Surgery with Thrombolysis in Intracerebral Hemorrhage III (MISTIE III) trial randomized 499 patients with ICH >30 mL to either minimally invasive intervention with thrombolysis or standard medical care [112]. At 1 year, the proportion of patients who achieved the primary endpoint of good functional outcome (mRS 0–3) was not significantly different between groups (45% vs. 41%, $p = 0.33$).

It is imperative to have a goals-of-care discussion with the patient and his/her family as quickly as possible when surgery is being considered. When making the decision for surgical intervention, it must be clear that while this treatment may save the patient's life, it may not improve functional status. The patient's long-term outcome may include severe

dependence and disability. If the patient is unable to make decisions, the family must be encouraged to rely on the patient's previously expressed wishes regarding goals for quality of life after catastrophic illness.

The role for surgery is somewhat clearer when ICH occurs in the posterior fossa. Cerebellar hemorrhage with neurologic deterioration, brainstem compression, or hydrocephalus from ventricular obstruction requires clot evacuation as soon as possible (AHA/ASA Class I, Level B) [4, 113–115]. Initial treatment with ventricular drainage alone rather than surgery for hematoma evacuation is not recommended (AHA/ASA Class III, Level C) [4, 115].

If the decision for surgery is made for either a supratentorial or posterior fossa hemorrhage, the patient should first be stabilized from a cardiopulmonary standpoint. Medical management of ICP should happen concurrently, and any platelet or coagulation factor deficiencies should be addressed. Again, there is no clear benefit of early surgery compared to surgery at time of neurological deterioration (AHA/ASA Class IIb, Level A) [4]; therefore, medical optimization should be a priority.

ICU Course

Postoperatively, the patient should undergo a non-contrast head CT and return to the ICU with neurologic exams every hour by trained nursing staff. Any further deterioration should be evaluated by the neurosurgical and neurointensive care teams and an additional head CT should be obtained to assess for edema, rebleeding, herniation, or other signs that care needs to be escalated either medically or surgically.

Patients for whom nonoperative management is selected should receive the same early aggressive monitoring and care. Deciding upon "do not attempt resuscitation" (DNAR) should be delayed until at least the second full day of hospitalization (AHA/ASA Class IIa, Level B) [4], unless such an order was already in place at the time of hemorrhage [116–120]. DNAR status should be distinguished from "goals of care" as the latter may not limit appropriate medical and surgical interventions unless otherwise explicitly indicated (AHA/ASA Class III, Level C) [4, 8, 119, 121–124].

Depending on the size of the hemorrhage, extent of edema and hydrocephalus, use of ventricular drainage, cardiopulmonary status, and other medical comorbidities, patients may require days to weeks of critical care monitoring and management. Otherwise, healthy patients with good neurologic status, stable imaging for 24 h, no concern for hydrocephalus, and no need for hypertonic saline for an elevated sodium goal may transfer to the floor as soon as hospital day 2 or 3. On the other hand, if there is continued concern for depressed level of consciousness, worsening bleed or edema on imaging, worsening hydrocephalus, or the patient has significant medical comorbidities, then the ICU stay should be prolonged. Mechanical ventilation and use of hypertonic saline to manage edema are frequently the last requirements that must be weaned before transfer. The ICU stay may also be lengthened by non-neurologic complications such as pulmonary embolism and myocardial infarction.

Nontraumatic Subarachnoid Hemorrhage

Presentation and Initial Management

The most common etiology (approximately 80%) of nontraumatic subarachnoid hemorrhage (SAH) is aneurysmal SAH [125]. The presenting symptom of aneurysmal SAH is typically "worst headache of life," which is unable to be clinically distinguished from migraine or tension-type headache and is preceded by a sentinel headache in 10–43% of patients [125–128].

After ensuring control of airway, breathing, and circulation, patients should undergo emergent non-contrast head CT to make the diagnosis (Fig. 15.2a). A high index of suspicion should be maintained for all patients with sudden onset of severe headache, as SAH is a frequently misdiagnosed emergency (AHA/ASA Class I, Level B) [126, 129–133]. Non-contrast head CT has a sensitivity of close to 100% within 3 days of hemorrhage, but lumbar puncture should be performed for patients with nondiagnostic CT in whom the clinical suspicion is high for SAH (AHA/ASA Class I, Level B) [126, 134, 135]. MRI may also be useful in the setting of a negative CT but does not obviate lumbar puncture (AHA/ASA Class IIb, Level C) [126, 136–138]. Initial clinical and radiographic evaluation and grading should be performed with validated scales (AHA/ASA Class I, Level B) [126], and a neurosurgeon should be consulted emergently [139, 140]. All nontraumatic SAH patients should initially be admitted to the ICU.

After diagnosis, high-quality CT angiography (CTA) is typically performed in an urgent fashion to assess the cerebral vasculature and can be highly sensitive (Fig. 15.2b) [141–143]. In cases where CTA is inconclusive, or further anatomic detail is needed for treatment planning, digital subtraction angiography (DSA) is recommended (AHA/ASA Class IIb, Level C) [126, 143–147]. Even with a high-quality CTA showing an aneurysm, the authors still typically obtain DSA for further lesion characterization and treatment planning [147–153].

Medical management should include continuous cardiopulmonary monitoring in the ICU. Before treatment of the aneurysm, blood pressure should be controlled with a titratable agent to balance risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (AHA/ASA Class I, Level B) [126]. The optimal systolic blood pressure ceiling is not well established, but the latest

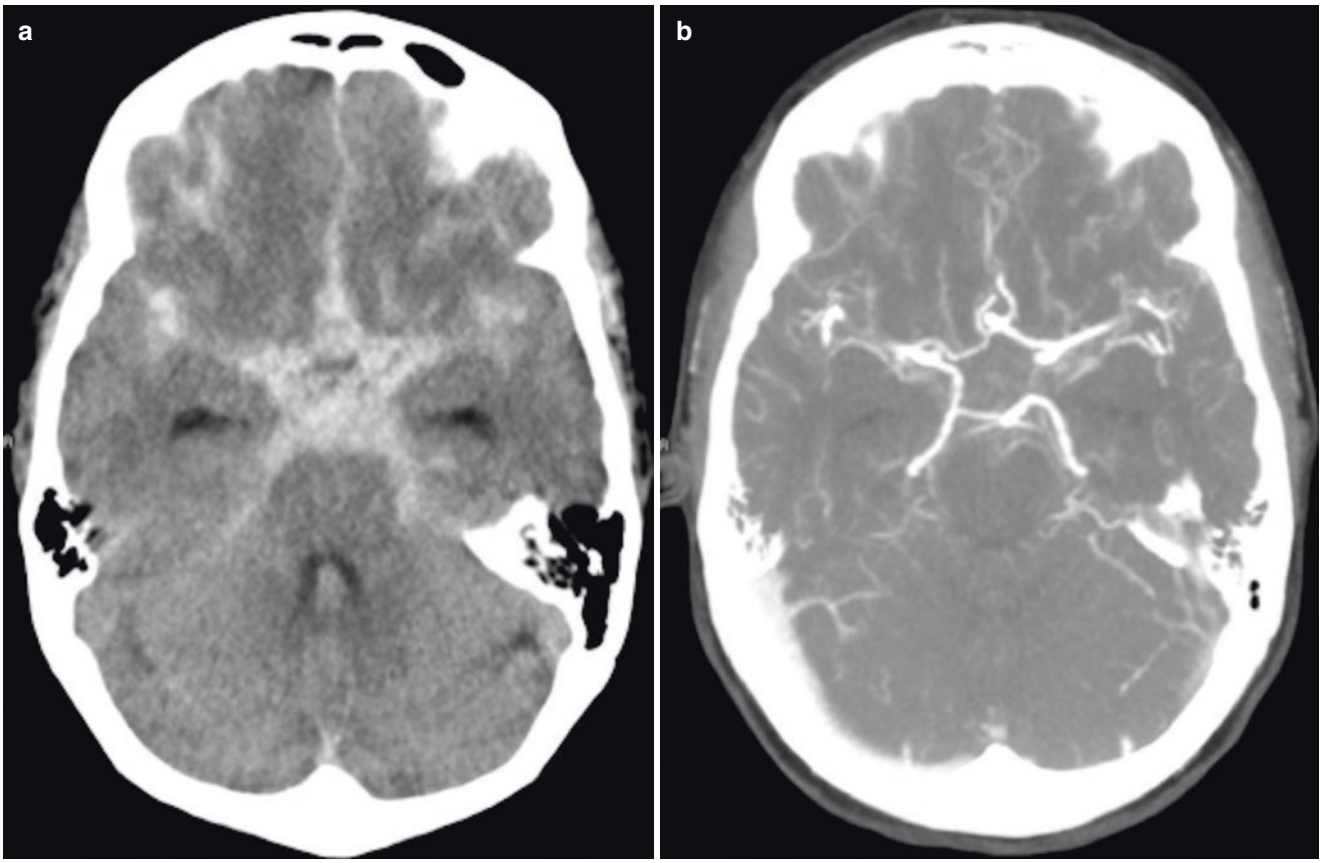

Fig. 15.2 Aneurysmal subarachnoid hemorrhage. (**a**) Non-contrast axial plane head CT showing diffuse subarachnoid hemorrhage in the basal cisterns, sulci of the bilateral cerebral hemispheres, and along the falx cerebri. There is intraventricular hemorrhage in the fourth ventricle and resultant hydrocephalus, seen here as enlargement of the temporal horns of the lateral ventricles. (**b**) Axial plane CT angiogram of the head from the same patient showing a saccular aneurysm of the anterior communicating artery, which is the likely source of this hemorrhage

guidelines suggest <160 mmHg (AHA/ASA Class IIa, Level C) [126, 154]. Prophylactic hypervolemia before angiographic vasospasm is no longer recommended (AHA/ASA Class III, Level B), but instead the goal should be to maintain euvolemia and normal circulating blood volume to prevent delayed cerebral ischemia (DCI; AHA/ASA Class I, Level B) [126, 155]. Oral nimodipine should be given to all patients with aneurysmal SAH (AHA/ASA Class I, Level A) [126] for 21 days (NCS high-quality, evidence, strong recommendation) [156, 157]. The authors also typically start seizure prophylaxis (AHA/ASA Class IIb, Level B) [126] with levetiracetam and administer IV dexamethasone (4 mg every 6 h) for 24 h after presentation to help with meningeal inflammation.

Acute Hydrocephalus

Acute hydrocephalus is a common complication of SAH and can be both obstructive from intraventricular extension and communicating from CSF reabsorption obstruction at the arachnoid granulations. Symptomatic hydrocephalus in this setting should be managed with external ventricular or lumbar drainage (AHA/ASA Class I; Level B) [126, 158–161]. The authors typically elect to place ventricular drains in patients who present with ventriculomegaly and casting or near casting of the third or fourth ventricle or in whom progressive ventriculomegaly corresponds to progressive neurologic decline. We also consider ventricular drain placement in patients who will be under general anesthesia for prolonged periods of time for endovascular aneurysm treatment and for whom there is concern for impending hydrocephalus.

Securing the Aneurysm or Lesion

The aneurysm should be secured by surgical or endovascular means as early as possible (ideally within 24 h) to reduce the risk of rebleeding (AHA/ASA Class I, Level B) [126], and obliteration should be complete whenever possible (AHA/ASA Class I, Level B) [126, 154, 162–165]. A secure aneurysm also makes permissive or augmented hypertension—which is beneficial if vasospasm and DCI occur—safer given that higher systolic blood pressures may be a risk factor for rebleeding. There is some evidence that endo-

vascular coiling is preferred to surgical clipping in those who are candidates for either procedure (AHA/ASA Class I, Level B) [126, 166], although specific aneurysm treatment should be determined by experienced surgeons and endovascular specialists on a case-by-case basis (AHA/ASA Class I, Level C) [126]. The International Subarachnoid Aneurysm (ISAT) trial randomized 2143 patients with ruptured intracranial aneurysms to neurosurgical clipping or endovascular coiling [166]. There was a lower rate of death or dependence in the endovascular group (23.5%) compared to the surgical clipping group (30.9%, $p = 0.0001$). Subsequently, the Barrow Ruptured Aneurysm Trial (BRAT) randomized 472 subarachnoid hemorrhage patients to either endovascular therapy or surgical clipping and reported a lower rate of poor outcome (mRS >2) in the endovascular group (23.2%) compared to the surgical group (33.7%, $p = 0.02$) [167]. For middle cerebral artery (MCA) aneurysms, especially those associated with large (>50 mL) intraparenchymal hematomas, microsurgical clipping may be preferable given that evacuation of a large temporal hematoma at the time of surgery can improve mass effect and edema [168–172]. Endovascular treatment should be strongly considered for older patients (>70 years), those with poor World Federation of Neurological Surgeons (WFNS) grade at presentation (IV/V), and those with basilar apex aneurysms (AHA/ASA Class IIb, Level C) [126, 168, 173, 174].

Vasospasm and Delayed Cerebral Ischemia

After securing the aneurysm and managing hydrocephalus, the primary neurologic focus of SAH patients is preventing and treating vasospasm and DCI. The window for this phenomenon is typically 4–21 days after hemorrhage [175]. Vasospasm is an angiographic finding, whereas DCI is a clinical finding that may lead to ischemic stroke [176]. Importantly, the cerebral territories affected by radiographic vasospasm do not always correspond to the areas of ischemic symptoms [176, 177], and recognition of this paradox is integral to the most recent practice guidelines.

As mentioned earlier, maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI (AHA/ASA Class I, Level B) [126, 155]. Patients at high risk are ideally monitored in the ICU (NCS very low quality, strong) [178]. Transcranial Doppler (TCD) studies are typically performed daily at the authors' institution to screen for vasospasm (AHA/ASA Class IIa, Level B; NCS moderate-quality, strong) [126, 178]. However, we do not usually act on TCD or radiographic evidence of vasospasm alone. Heavier reliance is placed on the clinical exam and on either progressive global decline or new focal neurologic deficits since TCDs have been shown to be an unreliable marker of DCI [179–181]. If these symptoms occur, CTA and CT perfusion or DSA imaging are usually obtained to look for radiographic vasospasm and areas of perfusion deficit, particularly in patients who do not respond to induced hypertension (AHA/ASA Class IIa, Level B; NCS high quality, strong) [126, 178, 180, 182, 183]. With evidence of DCI, blood pressure augmentation is employed unless elevated at baseline or cardiac status precludes it (AHA/ASA Class I, Level B; NCS moderate quality, strong) [126, 155, 178, 184]. If response to induced hypertension is not sufficient, we typically perform urgent DSA and treat angiographic vasospasm with angioplasty and/or intra-arterial vasodilators (AHA/ASA Class IIa, Level B; NCS moderate quality, strong) [126, 178, 185–187]. Unsecured aneurysms not thought to be the source of hemorrhage should not influence decisions on blood pressure augmentation (NCS moderate quality, strong) [178].

ICU Course

All patients with SAH should initially be admitted to the ICU. The risk of re-rupture is 4–14% in the first 24 h, and providers should be vigilant for this occurrence [162, 163]. Given the delayed onset of vasospasm/DCI, we typically monitor patients in the ICU for at least 10–14 days after securing the aneurysm, even in patients with a good clinical grade at presentation. Patients with moderate-to-high clinical grade will likely require a longer ICU stay, typically for some combination of mechanical respiratory support, control of hydrocephalus, ICP monitoring and management, depressed level of consciousness, seizures, hyponatremia, and treatment of DCI. Medical comorbidities may also complicate the disease course, and cardiac complications are common in SAH. Prolonged ICU stays, however, can increase the risk for hospital acquired infections, which may require additional critical care.

Epidural Hematoma

Presentation and Initial Management

Cranial epidural hematomas (EDH) form in the potential space between the dura and the skull. They usually occur as a result of trauma such as traffic accidents, falls, and assaults, with skull fractures present in 75–95% of cases (Fig. 15.3) [188]. The skull fracture caused by trauma lacerates either an artery (in 85% of cases) or a dural sinus (15% of cases) [189]. EDH after trauma often co-occurs with traumatic SAH, hemorrhagic contusions, diffuse cerebral edema, and subdural hematomas (SDH) [189]. EDH should be distinguished from SDH as the management can be quite different.

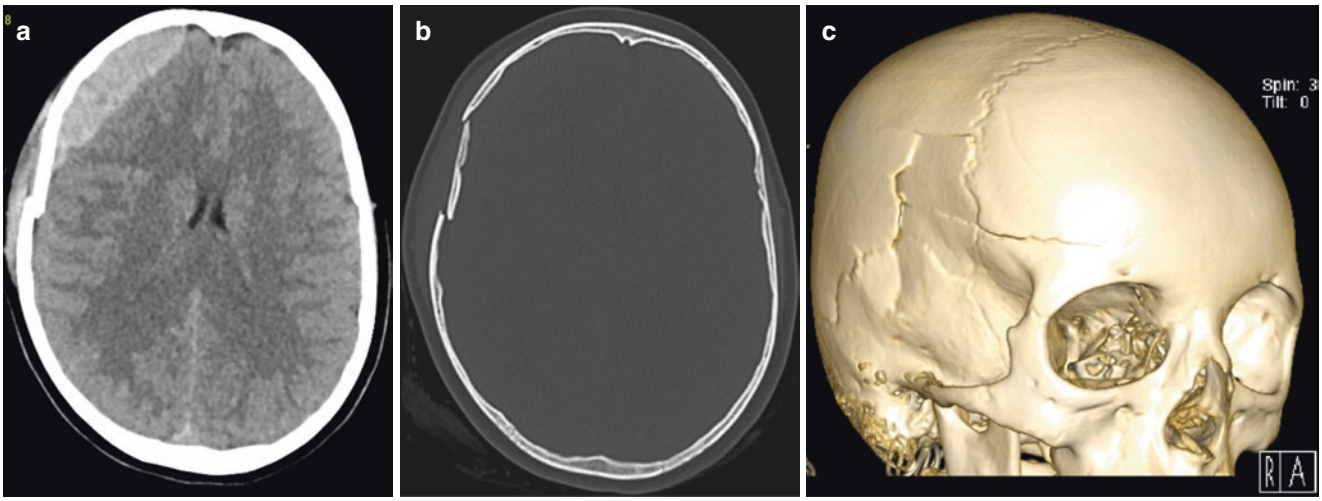

Fig. 15.3 Epidural hematoma. (**a**) Non-contrast axial plane head CT showing a right frontal epidural hematoma. (**b**) Bone window of the same axial plane head CT showing overlying depressed skull fracture. (**c**) Three-dimensional skull reconstruction re-demonstrating complex fracture overlying the epidural hematoma. A lacerated branch of the middle meningeal artery was found underlying the fracture and was the likely source of hemorrhage

EDH does not cross suture lines and is therefore more likely to have a lentiform shape on head CT, whereas SDH can cross suture lines and often has a crescent shape [190].

Upon presentation after trauma, patients are typically assessed and managed using the Advanced Trauma Life Support (ATLS) protocol. Non-contrast head CT makes the diagnosis. Neurosurgery should be consulted emergently. It is important to obtain a baseline neurologic exam before sedation or intubation when possible. Suspicion for elevated ICP on clinical exam or on imaging should be aggressively addressed with medical therapy. History of antiplatelet use, anticoagulant use, and coagulopathy should be obtained concurrently with laboratory evaluation of platelet count and coagulation factors. Any quantitative or qualitative dysfunction should be addressed emergently.

Determining Need for Surgical Intervention

Open craniotomy for evacuation is the traditional mainstay of treatment for acute EDH. Surgical management through open craniotomy allows for more complete evacuation and potential identification and ligation of the bleeding vessel or sinus [189]. An expert panel published guidelines in 2006 recommending surgical evacuation for all adult patients with acute EDH volume > 30 cm^3 regardless of GCS [189]. As for timing, the panel strongly recommended that patients with acute EDH in coma (GCS <9) with pathologic anisocoria undergo surgical evacuation as soon as possible (within 90 min) [189, 191, 192].

Nonoperative management can be considered in those patients with EDH volume < 30 cm^3 *and* with <15 mm thickness *and* with <5 mm midline shift (MLS) if GCS >8 and there are no focal deficits [189, 193–196]. These patients should be monitored closely in an ICU with follow-up imaging in 4–6 h intervals until stability and again at least 24 h from initial imaging if stable [197, 198]. Any decline in neurologic exam or growth of hematoma on interval imaging should prompt consideration for surgery. Notably, deterioration and growth can occur quickly, particularly when the bleeding vessel is an artery.

The decision to manage nonoperatively is also supported by comorbid medical conditions or concurrent injuries. For example, patients with platelet dysfunction and coagulopathy secondary to liver failure are at high risk for surgical complications, and the surgical team might be more inclined to manage these cases nonoperatively. If the patient is comatose or sedated, an ICP monitor can be placed to help guide medical management and determine the need for surgical intervention down the line. If there is significant cerebral edema or suspicion that edema may progress from TBI, decompressive hemicraniectomy instead of simple craniotomy can be performed for evacuation.

Considerations in the Posterior Fossa

In the posterior fossa, space is more limited, and smaller hematomas can be more devastating. EDHs in this compartment are more likely to be due to venous sinus injury. Compression of adjacent venous sinuses or the fourth ventricle can cause global cerebral edema and acute obstructive hydrocephalus. Mass effect in this region can also rapidly cause brainstem compression and cardiorespiratory compro-

mise. For these reasons, posterior fossa EDH is typically more aggressively surgically managed.

ICU Course

Patients should receive a postoperative non-contrast head CT to evaluate for extent of evacuation and then return to the ICU. Neurologic exams should be performed every hour to monitor for rebleeding and for developing signs of concurrent diffuse edema from TBI. Otherwise healthy patients with isolated EDH who receive prompt and adequate evacuation can have a relatively good prognosis. In one prospective study of 107 patients, mortality was only 5%, and 89% of patients made a good recovery or had only mild-moderate residual deficits [199]. In a retrospective review of 139 patients, mortality was 9%, 46% had a good recovery, and 31% were moderately disabled [200]. Patients with advanced age, medical comorbidities, other traumatic injuries, and other neurologic injuries may require a longer ICU stay. With more severe TBI, even after hematoma evacuation patients will likely require ICP monitoring with a parenchymal sensor or ventricular drain as well as medical ICP management, all of which will likely prolong the ICU course.

Subdural Hematoma

Presentation and Initial Management

Subdural hematoma (SDH) is a common neurosurgical condition defined as bleeding into the space between the dura mater and arachnoid mater. SDH can be either acute (<14 days) or chronic (>14 days) and either traumatic or nontraumatic. The inciting trauma may have been trivial and unrecognized, especially in patients with advanced age and history of antiplatelet or anticoagulant use. As with EDH, traumatic SDH commonly presents concurrently with other intracranial lesions, including hemorrhagic contusions, traumatic SAH, and skull fractures [201–204]. Patients typically present immediately after trauma that involves notable head injury or if the trauma was minor, they may present several days to weeks later with altered mental status, headache, or focal neurologic deficit from a progressive lesion [202–207]. Diagnosis is made with non-contrast head CT.

Initial management after trauma should always start with the ATLS protocol. If the patient is unable to protect his or her airway or does not have adequate respiratory drive, he or she should be intubated. With radiographic or clinical suggestion of increased ICP or herniation, aggressive medical measures should be undertaken: elevation of the head of bed, hyperventilation, sedation, and hyperosmolar therapy. However, it should be noted that many ICP-lowering interventions have the potential to increase the size of the SDH since decreasing parenchymal edema may increase the size of the subdural space. The guidelines for management of TBI are discussed in detail elsewhere in the chapter. Trauma patients should also undergo appropriate screening for and management of extracranial injuries that also may be life-threatening.

As with all intracranial hemorrhages, the team must rapidly determine if there is a history of platelet dysfunction or coagulopathy, or if the patient is taking antiplatelets or anticoagulants. These should be corrected or reversed emergently to lower the risk of further hemorrhage, although this benefit should always be weighed against the risk of stopping antiplatelets or anticoagulants if they are needed for another medical indication (e.g., atrial fibrillation, coronary stent).

Determining the age and etiology of SDH can be important for subsequent management decisions. Acute SDH will usually follow head trauma and will appear hyperdense to brain parenchyma on non-contrast CT [208]. If the SDH is subclinical or is conservatively managed, it will begin to age. As the acute SDH ages, it will become first isodense to brain parenchyma (days to weeks) and eventually will approach the hypodense appearance of CSF (weeks to months) [208]. In cases where the hematoma persists, a capsule may form around it [209]. It is not uncommon for patients with chronic SDH to present with an "acute-on-chronic" SDH—an acute hemorrhage mixed in with, or layered on, a chronic collection (Fig. 15.4) [210]. This may occur spontaneously or from new trauma. On CT, there will be typically be a hyperdense acute component layered on the more subacute or chronic isodense or hypodense component [211]. Alternatively, blood of different ages can be mixed and result in an isodense collection [211].

Subdural collections may also form and progressively enlarge due to decreased ICP or brain atrophy. A frequent cause of subdural hematoma/hygroma from this mechanism is overdrainage of CSF from a ventricular shunt or lumbar drain. Initial treatment in these patients should be to discontinue drainage. External drains should be clamped, and permanent shunts should have programmable valves adjusted to decrease drainage. Nonprogrammable shunts may need surgical ligation or valve exchange.

Indications for Surgery

Expert panel guidelines were released in 2006 recommending surgery for acute SDH with clot thickness >10 mm or midline shift >5 mm regardless of GCS [204, 212–217]. They also recommended surgery for comatose patients (GCS

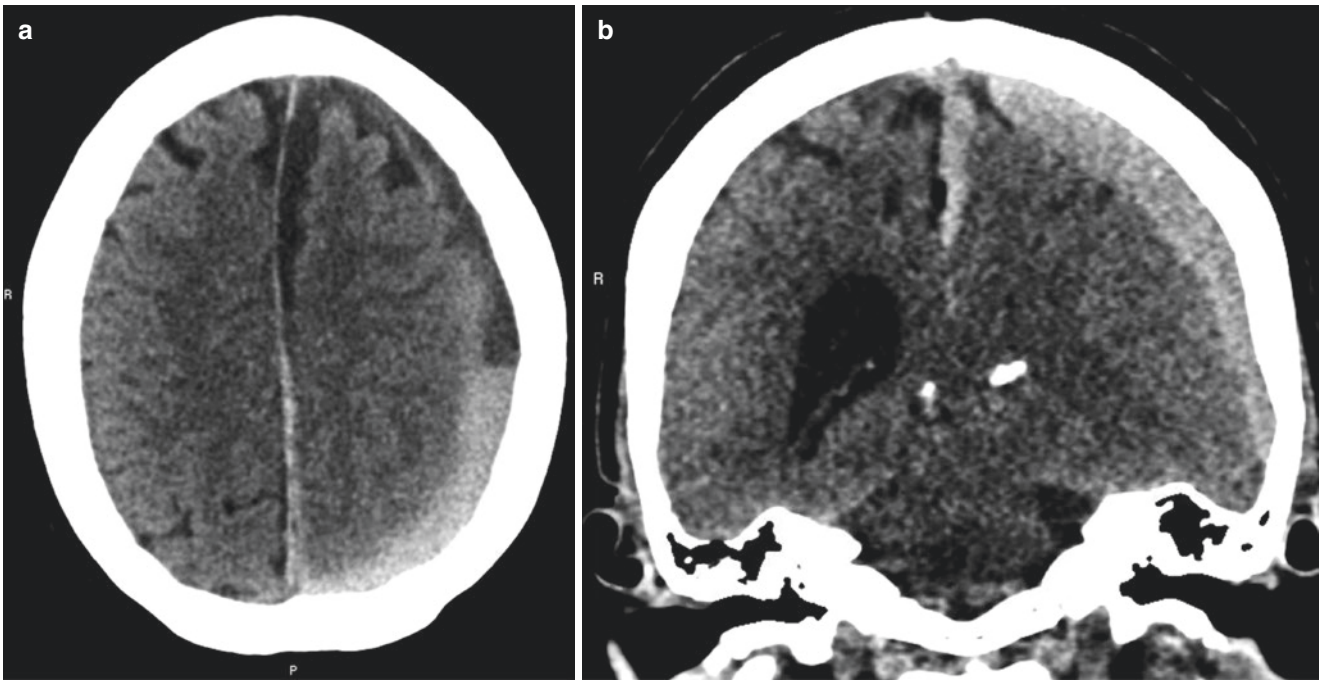

Fig. 15.4 Acute-on-chronic subdural hematoma. (**a**) Non-contrast axial plane head CT showing a mixed density left frontoparietal subdural collection representing an acute-on-chronic subdural hematoma. Hyperdense acute blood is seen layering posteriorly with a fluid-fluid level separating it from the more hypodense chronic collection anteriorly. (**b**) Non-contrast coronal plane head CT of the same patient showing the acute component of the subdural collection with mass effect on the underlying brain parenchyma. There is also an acute interhemispheric subdural hemorrhage

<9) with acute SDH <10 mm and midline shift <5 mm and any of the following: GCS decreased ≥2 points between time of injury and hospital admission, asymmetric or fixed and dilated pupils, or ICP >20 mmHg [204, 212, 216]. Surgery as soon as possible (e.g., after anticoagulation has been reversed) is strongly suggested for patients meeting these criteria [192, 212, 218–220].

Dogmatic guidelines are, of course, not a substitute for clinical judgement. For instance, if a SDH of >10 mm is encountered in a patient who otherwise has a near-normal GCS, we may defer surgery as long as the neurological exam does not decline or interval imaging does not show hematoma growth. Acute SDH typically requires a craniotomy for evacuation, whereas the more chronic, liquefied SDHs may be evacuated effectively with burr hole drainage alone. The possibility of rebleeding after evacuation is worth noting, so allowing more time (e.g., for the effect of novel oral anticoagulants to diminish, after stabilizing extracranial injuries) may decrease this risk after surgery. For "acute-on-chronic" and progressive chronic SDH, the threshold for surgery at higher GCS levels or in those without focal deficits is often lower given they have proven refractory to conservative management already. More recent data has suggested the possibility of middle meningeal artery embolization as a means of treating SDH, but further studies are needed [221].

ICU Course

Patients not receiving emergent operations are typically admitted to the ICU until radiologic and clinical stability. An interval head CT without contrast should be obtained ~6 h after initial imaging. With progressive hemorrhage, additional scans should be obtained every 6 h until stability [197]. Patients should receive close neurologic and cardiopulmonary monitoring. There is a high rate of clot expansion and neurologic decline requiring surgical evacuation in initially conservatively managed patients [197, 215, 216]. Severe TBI patients may also develop refractory ICP elevations even with small SDH, and in these situations, it may be justified to perform concurrent decompressive hemicraniectomy with SDH evacuation.

Postoperative patients should also be admitted to the ICU. Often, a drain will be left in the subdural space for several days to prevent reaccumulation, which is more common with chronic collections [222–224]. Chronic SDH patients and those with brain atrophy are typically kept flat for the first 12–24 h, which is thought to promote brain re-expansion, and then elevated based on follow-up CT imaging. Patients with severe TBI, medical comorbidities, respiratory failure, older age, and persistent altered mental status (especially in older patients) will likely require a longer ICU stay

than patients with an isolated acute SDH. Typically, 24–48 h of clinical and radiologic stability is needed before transfer from the ICU to the floor.

Severe Traumatic Brain Injury

Presentation and Classification

TBI is a structural injury and/or physiologic disruption in brain function as a result of blunt trauma, acceleration or deceleration forces, or exposure to blast [225]. TBI patients most commonly present after falls, motor vehicle accidents, pedestrian impacts, and assaults. TBI should be suspected in any of these scenarios or with any history of external force causing head injury resulting in neurologic deficits, confusion, amnesia, or alteration in consciousness. Patients should be triaged and managed according to the ATLS algorithm, as they often have extracranial injuries that can be more life-threatening.

Emergent non-contrast head CT should be obtained in all patients suspected to have moderate-severe TBI (Fig. 15.5). TBI can present with a variety of intracranial pathologies visible on CT, including traumatic SAH, EDH, SDH, hemorrhagic parenchymal contusions, intraventricular hemorrhage, and skull fractures. The cervical spine is typically imaged with CT in patients with suspected TBI, and all patients with suspected TBI should be assumed to have a cervical spine injury until proven otherwise and provided appropriate precautions (i.e., cervical collar).

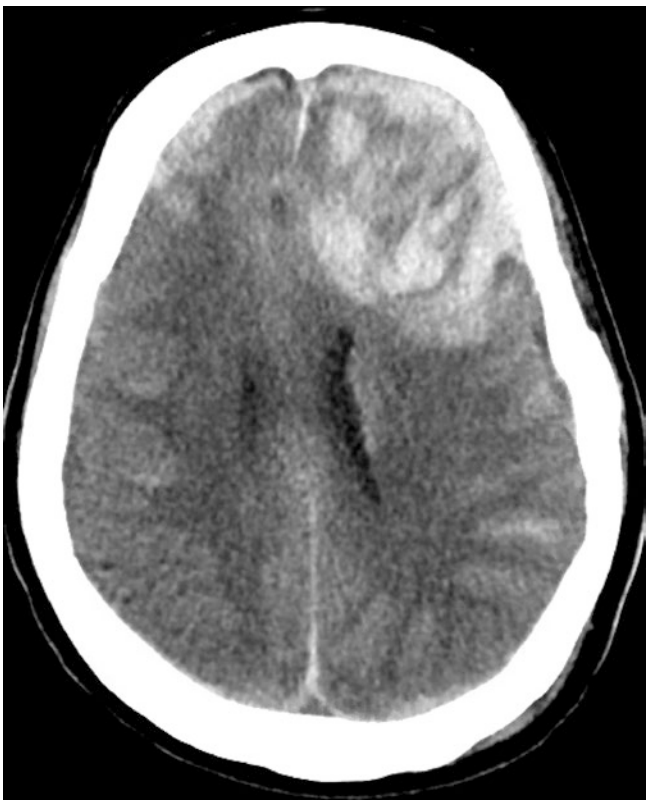

Fig. 15.5 Severe traumatic brain injury. Non-contrast axial plane head CT showing a large left frontal hemorrhagic parenchymal contusion after head impact. There is also a smaller right frontal parenchymal contusion, bilateral extra-axial hemorrhages, and scattered cortical subarachnoid hemorrhages

TBI can be classified as mild, moderate, or severe [225]. Severe TBI—the focus of this section—requires at least one of (a) >24 h of loss of consciousness, (b) >7 days of post-traumatic anesthesia, or (c) best GCS < 9 within the first 24 h [225]. Structural imaging can be normal or abnormal.

ICP Monitoring and Management

While TBI may present with intracranial lesions that meet the criteria for urgent surgical evacuation (e.g., large EDH causing herniation, large SDH causing significant midline shift), often no individual lesion is severe enough to address surgically. In these cases, management should be tailored to the neurologic exam and ICP. The Brain Trauma Foundation (BTF) recommends ICP monitoring in all salvageable patients with GCS 8 or less after resuscitation and an abnormal CT scan (e.g., hemorrhage, contusions, edema, herniation, compressed basal cisterns) [226]. ICP should also be monitored invasively in severe TBI patients with normal CT scans if two or more of the following are present at admission: age >40 years, unilateral or bilateral motor posturing, or systolic blood pressure <90 mm Hg [226]. Information from ICP monitoring should be used to direct management in order to reduce in-hospital and 2-week post-injury mortality (BTF level IIB evidence) [226]. Of note, these criteria for ICP monitor placement remained in the BTF fourth edition guidelines with the caveat that they do not meet current standards of evidence [227–232]. We typically place ICP monitors following these criteria and, in general, in any severe TBI patient whose neurologic exam cannot be reliably followed due to confounding variables (e.g., heavy sedation for ventilator synchrony, extremity injuries obscuring motor exam, etc.).

For patients without hydrocephalus or risk of it, we usually place parenchymal ICP monitors rather than a ventriculostomy catheter. In general, parenchymal monitors are easier to place and are thought to present lower risk to the patient. Ventriculostomy catheters, though, can provide the ability for therapeutic CSF drainage. ICP levels above 22 mmHg should be treated, as values above this threshold are associated with increased mortality (BTF level IIB) [226, 233]. However, a combination of ICP values, clinical exam, and brain CT findings should be used for making management decisions (BTF level III) [226, 234–236]. CPP should be maintained above a goal of 60–70 mmHg (BTF level IIB) [226, 233, 237].

However, this should be weighed against the risk of respiratory failure secondary to use of fluids and vasopressors to meet an elevated CPP goal (BTF level III) [226, 238, 239]. In general, attempts should be made to lower ICP to improve CPP as compared to augmenting MAP. Management of severe TBI using these CPP monitoring guidelines is recommended to decrease 2-week mortality (BTF level IIB) [226, 233, 237].

Indications for Surgery

Surgical intervention can be considered for a variety of scenarios in the setting of TBI. Specific recommendations for surgical intervention for extra-axial hematomas, skull fractures, and penetrating trauma are discussed in detail elsewhere in this chapter. Hemorrhagic parenchymal contusions are common and often contribute significantly to increased ICP and mass effect causing shift and herniation [240–244]. Large lesions associated with elevated ICP refractory to medical therapy, progressive deterioration, or significant mass effect can be evacuated by craniotomy [245]. Patients with GCS 6–8 with frontal or temporal contusions >20 cm^3 with >5 mm midline shift and/or cisternal compression may be treated operatively as well [245]. It has also been recommended that patients with lesions >50 cm^3 undergo surgery [245]. Even after craniotomy and evacuation, many of these patients eventually require craniectomy for decompression [241, 243, 245, 246]. For this reason, decompressive craniectomy is becoming more frequently performed at the outset, while the aggressive evacuation of contusions by craniotomy alone is less common. This approach was shown to result in better outcomes [247].

ICP can be effectively controlled with decompressive craniectomy; however, the benefits and indications for this procedure are controversial [248–254]. Frontotemporoparietal hemicraniectomy has traditionally been considered for unilateral hemispheric swelling and bifrontal craniectomy for diffuse bilateral swelling; however, hemicraniectomy is often performed for generalized swelling as well. In general, these procedures should be thought of as life-saving measures that may not affect functional outcome. For this reason, the decision for decompression should rely heavily on a discussion with the family regarding the patient's previously expressed wishes for quality of life. Decompression should be performed in those patients for whom the family understands that, although the procedure may prevent death, the patient may remain severely neurologically debilitated if they survive [254]. The neurosurgical and neurointensive care teams should also thoroughly consider clinical variables such as patient age, comorbidities, and extent of non-neurosurgical trauma that may make meaningful recovery less likely.

The BTF does not recommend bifrontal craniectomy for improving outcomes in severe TBI patients without mass lesions who have medically refractory ICP elevation >20 mmHg, although they acknowledge that it does effectively reduce ICP and minimize days in the ICU (Level IIA) [226, 255]. The Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension (RESCUEicp) randomized 408 patients with TBI and refractory ICP (>25 mmHg) to decompression or ongoing medical care [254]. The rate of death at 6 months was lower in the surgical (26.9%) versus medical group (48.9%, $p < 0.001$), but the rates of vegetative state (8.5% vs. 2.1%) and severe disability (37.3% vs. 22.4%) were higher in the surgical arm. The rate of moderate disability and good recovery were similar between groups.

Deciding upon craniectomy may be made easier if there is a surgically addressable hematoma contributing to high ICP, neurologic deficits, or neurologic decline. For example, hemicraniectomy can be performed to both evacuate a subdural or epidural hematoma and at the same time decompress the generalized pressure increase causing elevated ICP in severe TBI. If hemicraniectomy is performed, it should be large (>12 × 15 cm or 15 cm in diameter), which reduces mortality and improves neurologic outcomes as compared to smaller decompressions (BTF Level IIA) [226, 256, 257].

Traumatic Subarachnoid Hemorrhage

One of the most frequent neurosurgical consults is for traumatic SAH—often small but sometimes quite significant. There is typically no role for surgical intervention for traumatic SAH; however, one must ensure that the SAH was secondary to the trauma and did not lead to it. For example, spontaneous SAH can cause loss of consciousness and lead to fall with additional intracranial and extracranial pathologies that may make it seem as if the SAH was secondary to trauma. Compared with aneurysmal SAH, traumatic SAH tends to occur in the convexity as opposed to the basal and sylvian cisterns. If there is doubt, vessel imaging should be performed to rule out an underlying vascular lesion, as the treatment of traumatic versus spontaneous SAH is vastly different and the mortality from aneurysmal rehemorrhage is significant if not secured.

ICU Course

Patients with severe TBI should be admitted to the ICU and may require days to weeks of critical care. Initial care—after addressing the "ABCs"—should focus on managing ICH, which may require reversal of anticoagulation or antiplatelet agents and monitoring ICP. Serial imaging should be obtained until stability, usually in 6 h intervals. Hemorrhagic

contusions often appear in a delayed fashion and progress in the first few days. A worsening exam may warrant invasive ICP monitoring, and refractory ICP elevations may trigger surgical decompression. Decompensation thought due to epidural or subdural hematoma may also warrant surgical intervention. Constant multidisciplinary communication is required when there are extracranial injuries being managed by other specialists. Patients are typically ready for ICU discharge when they are no longer requiring mechanical ventilation (although many require tracheostomy), ICP has normalized and monitoring or intervention is no longer required, intracranial hemorrhages are stable, and any comorbid medical conditions are stabilized.

Skull Fractures

Presentation and Initial Management

Skull fractures should be suspected in any traumatic head injury patient, especially underlying scalp lacerations. Every trauma patient should first be assessed and stabilized according to the ATLS protocol. Those with facial and skull base fractures must be intubated with great care so as not to inadvertently enter the cranial cavity. Extensive facial injury may necessitate emergent tracheostomy or cricothyroidotomy. Scalp lacerations can cause marked blood loss and may either be a cause of hemorrhagic shock or require attention during the "circulation" phase of the primary survey. Significant bleeding should be controlled, but scalp lacerations should not be probed. Non-contrast head CT is the imaging modality of choice (Fig. 15.6).

Skull fractures are categorized as linear, depressed, or basilar. The highest morbidity and mortality occurs from depressed skull fractures, basilar skull fractures with CSF leak, and fractures involving the middle meningeal artery [258–261]. Temporal bone fractures often cause extra-axial hematoma due to the relationship to the middle meningeal artery and relatively decreased thickness of the temporal bone. Frontal bone fractures are often associated with frontal lobe contusions and dural tears. Fractures overlying dural sinuses are also at very high risk for major hemorrhagic complications. Vascular imaging with CT or MR arteriography/venography may be useful.

In general, linear skull fractures with no bone displacement have minimal to no clinical significance unless they injure the middle meningeal artery or a major venous sinus. If there is no underlying hemorrhage or brain injury, no specific intervention is needed for these fractures. These patients should be observed in the emergency department for 4–6 h and discharged if there are no significant extracranial injuries and there is adequate supervision at home [262]. If there is underlying hemorrhage, emergent neurosurgery consultation should be obtained.

Depressed skull fractures occur when one segment of the skull is driven below the level of the adjacent segment, potentially injuring brain parenchyma and vascular structures. These fractures are classified as open if there is an overlying scalp laceration. Patients with depressed fractures are at increased risk for infection and seizures, so prophylactic antibiotics and antiepileptic agents are often administered [260, 261, 263–265]. Tetanus immunization should also be given if indicated.

Role of Surgical Intervention

Guidelines were released in 2006 recommending that open fractures depressed greater than the thickness of the cranium undergo operative intervention to prevent infection

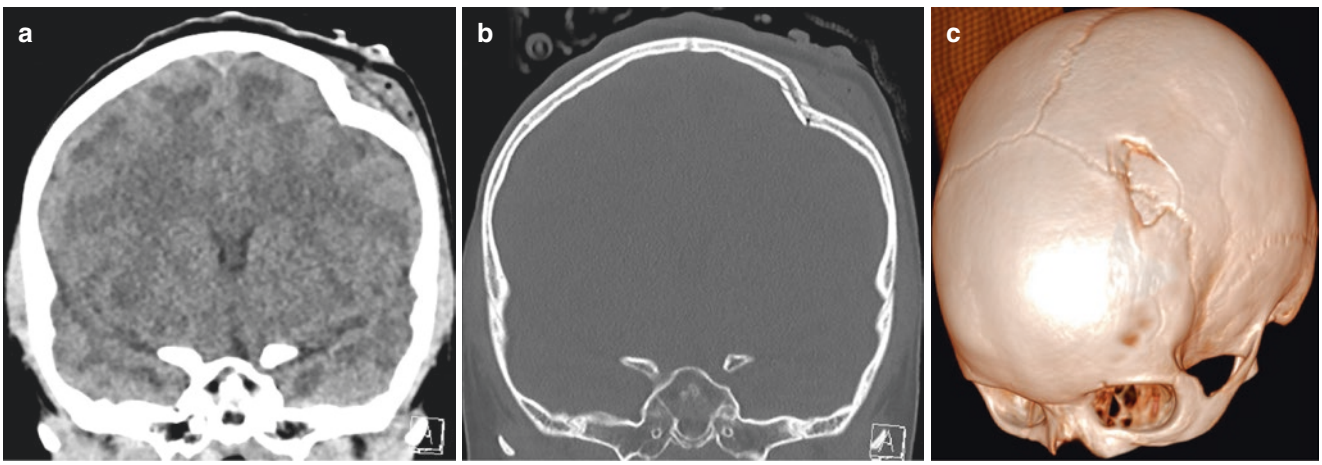

Fig. 15.6 Depressed skull fracture. Non-contrast coronal plane head CT (**a**) brain window and (**b**) bone window showing a traumatic left frontal complex, open, depressed skull fracture in a pediatric patient involved in a motor vehicle accident. (**c**) Three-dimensional reconstruction

[266]. Surgery should be performed as soon as possible to prevent infection and to decompress if there is mass effect from the bone or underlying hematoma. However, depressed fractures without clinical or radiographic evidence of dural penetration, significant intracranial hematoma, depression greater than 1 cm, frontal sinus involvement, gross cosmetic deformity, wound infection, pneumocephalus, or gross wound contamination may be managed nonoperatively [260, 266, 267]. Closed depressed skull fractures can also be managed nonoperatively if uncomplicated [266].

If there is concurrent hemorrhage with the skull fracture, a thorough history must be obtained to determine if the patient is taking antiplatelets or anticoagulants. Laboratory testing of platelet count, INR, and PTT should be performed. Any quantitative or qualitative deficiency should be addressed. Skull fracture patients with moderate or severe TBI may have elevated ICP that should be managed as discussed elsewhere in this chapter.

Skull base fractures present their own unique challenges. CSF leak is a frequent complication, and basilar skull fractures also carry a risk for underlying hemorrhage and compression of neural structures, including brain parenchyma and cranial nerves. The evidence for use of antibiotic prophylaxis for basilar skull fractures, with or without CSF leak, is inconclusive [268].

ICU Course

All patients with depressed skull fractures should initially be admitted to the ICU. Those managed nonoperatively should be followed with serial imaging. Progressive hematoma growth or concurrent intracranial pathologies may eventually warrant surgical intervention. Postoperatively, patients should be admitted to the ICU and undergo follow-up imaging. These patients may develop delayed or progressive ICH. They may also develop elevated ICP and should be managed by following the TBI guidelines discussed previously. Patients with fractures involving a venous sinus are at risk for sinus thrombosis and must be monitored closely for this complication and subsequent cerebral edema, hydrocephalus, and hemorrhage [269]. Altered mental status, especially in older patients, is common, and patients should be monitored for possible seizure as these patients are high risk. Cases of depressed skull fracture without other significant intracranial or extracranial injury may need only 1–2 days in the ICU and are usually stable for transfer to the floor with 24–36 h of stable imaging and neurologic exams. Those with severe TBI will require days to weeks of critical care.

Penetrating Injuries

Presentation and Initial Management

Penetrating head trauma represents a particularly morbid and often fatal condition. Up to two-thirds of patients die before reaching the hospital [270–273]. Firearms are the most common cause of penetrating head trauma, a majority of which are secondary to suicide attempts and gang violence [270, 271, 273, 274]. The identification of penetrating head trauma in patients presenting after suicide attempt will likely be obvious; however, in cases of assault with multiple extracranial sites involved, it may require a thorough survey. Knives, screwdrivers, and arrows are other common penetrating objects.

Initial management should follow the ATLS protocol. Intubation and mechanical ventilation are often necessary when patients demonstrate lack of airway protection and/or respiratory effort. With facial trauma or concern for skull base fractures, one should be cautious of inadvertently entering the cranial cavity with the endotracheal tube, gastric tube, or anything else inserted into the naso- or oropharynx. With extensive facial trauma, emergent tracheostomy might be necessary in order to secure the airway. Scalp lacerations can cause profuse bleeding that should be controlled with staples, sutures, or Raney clips. Lacerations can be irrigated for exploration but should not be probed. A thorough survey of entry and exit wounds should be performed, with hair clipping and irrigation as necessary. Any penetrating objects, such as knives, should be left in place. The tetanus vaccine, prophylactic antibiotics, and antiepileptic medications should be given. Aggressive hemodynamic resuscitation is typically needed, which should begin with isotonic saline and progress to vasopressors, if needed. Many patients will require blood product transfusions.

A focused neurologic exam should be performed, preferably before sedation, to determine GCS and any focal deficits. This is critical, along with head imaging and assessment of concurrent injuries, to determine subsequent steps in management. Non-contrast head CT is the imaging modality of choice once the patient is initially stabilized (Fig. 15.7). Penetrating injuries may cause a variety of intracranial pathologies, including EDH, SDH, SAH, intraparenchymal hemorrhage, intraventricular hemorrhage, hemorrhagic contusion, and venous sinus injury. They may also cause both simple (linear) and complex (depressed, comminuted) skull fractures.

Aggressive measures are likely to be needed during initial resuscitation if there are signs of elevated ICP on CT imaging. This may include hyperventilation, elevating the head of bed,

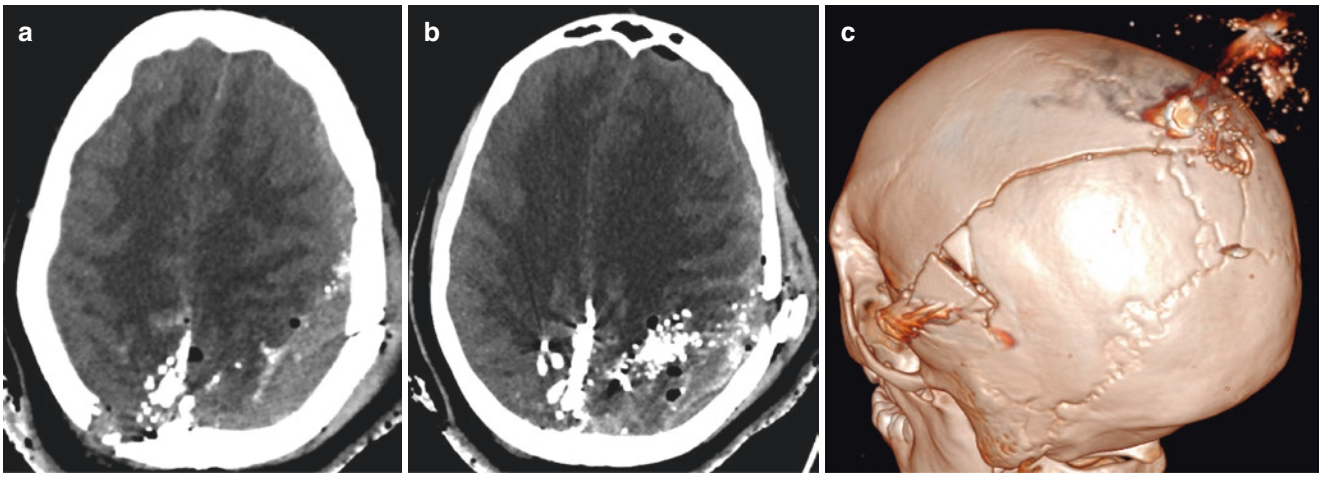

Fig. 15.7 Penetrating brain trauma. Non-contrast axial plane head CT showing bullet trajectory (**a**) entering through the superior right parietal calvarium and (**b**) traveling to the left temporal lobe with significant deposition of ballistic fragments and parenchymal disruption along the tract. There are associated comminuted fractures at both sites, hemorrhagic contusions along the tract, left convexity extra-axial hemorrhages, and likely disruption of the superior sagittal sinus. (**c**) Three-dimensional reconstruction in the same patient

maintaining cervical venous drainage, hypertonic saline, and sedation. Mannitol should be used with caution in the trauma patient as it may precipitate or worsen hypotension.

Role of Neurosurgical Intervention

The neurosurgical service should be consulted in all cases of penetrating head injury. A multidisciplinary decision must then be made regarding emergent neurosurgical intervention. Many patients, despite aggressive resuscitation, will meet either brain or cardiac death criteria. In these situations, further neurosurgical intervention is futile. If the patient does not meet these criteria and there is a low-velocity penetrating object still in place, the patient should be taken to the operating room for directly visualized removal, debridement, and closure. If the penetrating trauma is secondary to a bullet or other high-velocity object, the decision can be more difficult.

In general, a penetrating missile—whole or in fragments—does not necessarily need to be removed. Aggressive debridement and pursuit of missile fragments into brain parenchyma can cause more harm than benefit and is now typically avoided [275–277]. Even with aggressive debridement, fragments are often left behind and have a relatively low chance of causing a cerebral abscess [278, 279]. Instead, focused, superficial debridement of necrotic brain tissue and easily accessible fragments is recommended [280, 281]. Surgery is also usually considered for associated trauma-related lesions: depressed skull fracture, EDH, SDH, intraparenchymal hematoma, cerebral edema, CSF leak, and decompressive craniectomy for refractory ICP elevation. The indications for surgical intervention for these lesions are similar in penetrating brain injury patients; however, there is likely to be more parenchymal injury, potentially affecting overall prognosis and diminishing the benefit of intervention.

CSF leaks do need to be addressed aggressively; prevention of leak can be more important than debridement in limiting infection, morbidity, and mortality [278, 279]. This involves focused debridement, irrigation, watertight dural closure (when possible), and meticulous scalp flap closure. If an air sinus is breached, it should be operatively addressed to prevent leak and fistula formation [282, 283]. Decompressive craniectomy is often performed overlying the site of injury if the bone is comminuted or if there is high likelihood of significant underlying edema.

Neurosurgical intervention may also be warranted to address or repair vascular injury. Damage to major vascular structures should be suspected based on anatomic location of the penetrating injury or associated fractures. The dural venous sinuses are at particular risk, as are the carotid and vertebral arteries. CT angiogram +/− venogram of the head and neck is the imaging modality of choice after penetrating trauma. For venous sinus injuries, open surgery may be required for repair. Arterial injuries may require endovascular sacrifice of the vessel, in some cases allowing for safe removal of the penetrating object [284].

ICU Course

All penetrating brain injury patients should be admitted to the ICU. Patients will likely need ongoing management of ICP and interval head imaging as their clinical course progresses. TBI guidelines for monitoring and managing

ICP can be applied. ICP monitors should be considered in those with poor post-resuscitation neurologic exams or in whom an exam is not possible due to sedation. ICP >22 mmHg should be treated to lower mortality, and CPP should be kept above 60–70 mmHg (BTF Level IIB) [226]. Information from frequent neurologic exams, interval CT imaging, and overall clinical picture should be used to periodically reassess the need for surgical intervention. Surgery may be needed in settings of delayed hemorrhage, progressive hematoma, worsening edema, previously unrecognized CSF leak, and refractory ICP elevation. CSF leak may require ventriculostomy or lumbar drainage if unable to be repaired primarily.

Patients typically require ICU care for days to weeks. Patients should receive at least 7 days of anticonvulsant prophylaxis. Rates of both early and late post-traumatic epilepsy are high. Central nervous system (CNS) infections are common, and patients should receive prophylactic antibiotics, typically a cephalosporin, such as cefepime or ceftriaxone, with vancomycin [276, 282, 285–290]. Many patients require mechanical ventilation and are slow to recover consciousness, if at all. Transfer from the ICU usually occurs after ICP normalization without ongoing treatment and liberation from intubation and mechanical ventilation, although eventual tracheostomy is common.

Acute Hydrocephalus

Presentation and Etiologies

Hydrocephalus is a pathological derangement in the CSF pathway that can occur with or without ventriculomegaly. Hydrocephalus can either be acute or chronic and can be the result of an obstruction of ventricular system outflow (non-communicating hydrocephalus) or a decrease in the absorption of CSF into the bloodstream (communicating hydrocephalus). Oftentimes, however, there is a component of both pathophysiologic mechanisms. The concern with acute hydrocephalus, the focus of this section, is increased ICP and its sequelae, including herniation.

Acute hydrocephalus in the adult population is seen most often in settings of intraparenchymal/intraventricular hemorrhage, SAH, infection, malfunction of existing ventricular shunts, and mass lesions causing obstruction (e.g., tumor, abscess, lymphoma) [160, 291–293]. With intraventricular hemorrhage, it is especially important to recognize risk for acute hydrocephalus when there is obstruction of the third or fourth ventricle by blood [294–297]. Mass lesions can cause acute hydrocephalus by obstructing the third ventricle, cerebral aqueduct, or fourth ventricle via two mechanisms: from mass effect of the lesion itself or from its surrounding edema [298]. Intraventricular mass lesions, such as colloid cysts, may also cause acute obstruction [299–301]. While patients with ICH are often symptomatic from the parenchymal damage of the initial bleed, those with oncologic or infectious mass lesions may present with acute obstructive hydrocephalus as their first symptom.

By itself, acute hydrocephalus most commonly presents with headache and alteration in level of consciousness. In cases of spontaneous ICH and mass lesions, there may also be focal neurologic deficits related to the location of the lesion. Non-contrast head CT will establish the diagnosis (Fig. 15.8). The neurosurgical service should be consulted emergently for evaluation, and the patient's airway should be protected if level of consciousness is depressed. These patients can deteriorate rapidly and should be closely monitored.

CSF Diversion

The mainstay of treatment for acute hydrocephalus is CSF diversion [295, 298, 299, 302, 303]. In the acute setting in a decompensating patient, this is typically performed with an EVD placed either in the emergency department, ICU, or operating room. Before a ventricular drain can be placed, any platelet dysfunction or coagulopathy needs to be identified and corrected. History of antiplatelet or anticoagulant use should be obtained from the family or medical record in parallel with laboratory testing of platelet count, INR, and PTT. Platelets below 100,000 are usually supplemented with platelet transfusion and, similarly, recent antiplatelet administration may be reversed with platelet transfusion. Anticoagulant use must be rapidly reversed with the appropriate pharmacologic agents. This process can often be the rate-limiting step in placing a much-needed ventriculostomy. Patients undergoing ventricular drain placement should ideally be intubated and sedated so that there is no movement during the procedure.

After placing the ventricular drain, the opening pressure should be noted and a non-contrast head CT obtained to confirm the position of the catheter and screen for any hemorrhage associated with placement. Ideally, the tip of the catheter should terminate in the third ventricle by passing from the lateral ventricle through the foramen of Monro. Some adjustment may be necessary if the catheter is placed too deeply or in the wrong trajectory [304, 305]. Intraparenchymal hemorrhage along the catheter tract occurs in a minority of cases but is usually not clinically significant [306]. If this occurs, an interval non-contrast head CT should be obtained in ~6 h to ensure stability of the hemorrhage. Epidural and subdural hemorrhage may also occur upon ventriculostomy placement and may require evacuation depending on size, magnitude of midline shift, and progression on interval follow-up imaging. The ventriculostomy catheter

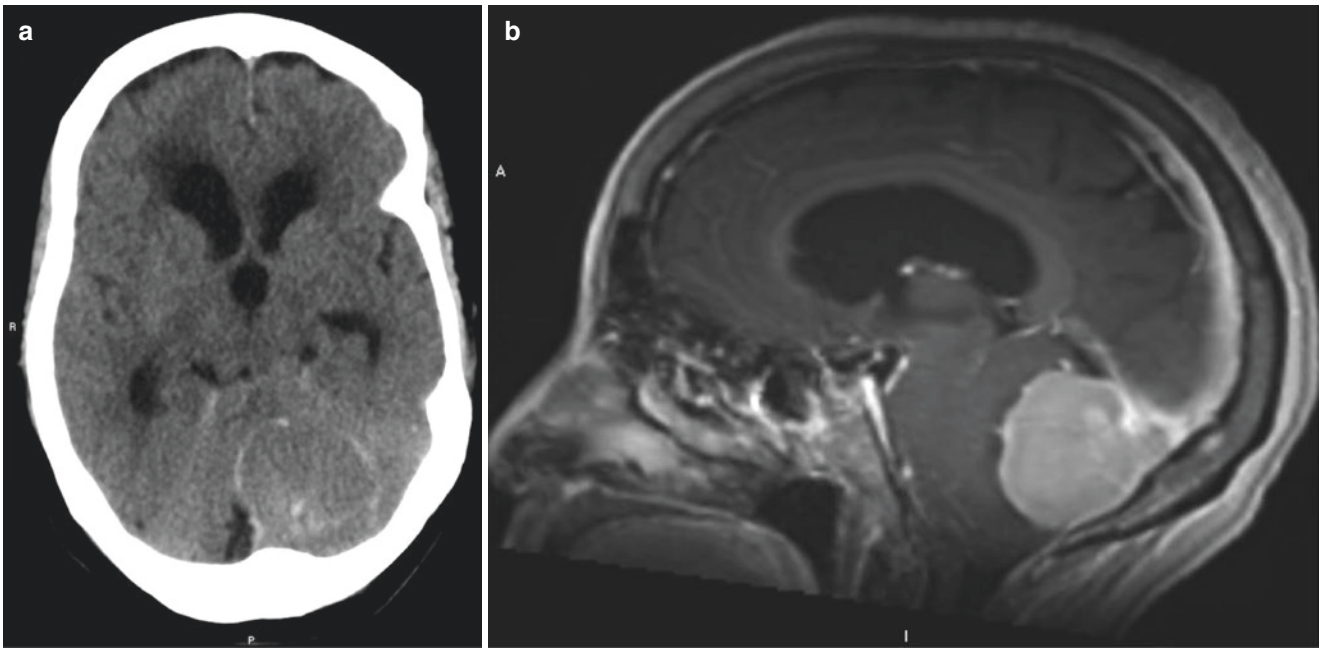

Fig. 15.8 Obstructive hydrocephalus. (**a**) Non-contrast axial plane head CT showing a large, round, well-circumscribed isodense mass in the posterior fossa causing effacement of the fourth ventricle and resultant ventriculomegaly. (**b**) Sagittal plane gadolinium-enhanced MRI brain of the same patient showing a homogenously enhancing extra-axial posterior fossa mass causing significant mass effect on the cerebellum and brainstem and obstructing CSF outflow through the fourth ventricle

pressure sensor should be transduced and monitored. The initial drainage pressure threshold is usually set to 10–20 mmHg and then subsequently titrated to imaging and clinical exam. Of note, overdrainage can cause SDH formation.

The Neurocritical Care Society released guidelines in 2016 for EVD management [307]. Several recommendations are worth mentioning: do not routinely collect CSF (conditional recommendation, low-quality evidence), do not routinely change catheter sites (strong recommendation, moderate-quality evidence), and wean the EVD as quickly as possible to minimize infection risk (good practice statement) [307].

Role of Surgery

Placement of a permanent ventricular shunt is also an option for acute hydrocephalus, although it is less commonly employed. In the setting of hemorrhage or infection, a permanent shunt would be at high risk of failure due to blood product and/or protein obstruction of the catheter. It is also inadvisable to place hardware in the setting of active infection. If the cause of the hydrocephalus is readily reversible, such as a posterior fossa tumor that will be soon resected, a permanent shunt is likely not needed, and a temporary drain is more appropriate. External ventricular drainage also affords the ability to monitor ICP and make frequent adjustments to the drainage threshold. For these reasons, a permanent ventricular shunt is usually only placed for chronic hydrocephalus.

Lesions in the posterior fossa are at particularly high risk for causing acute non-communicating hydrocephalus from obstruction of the fourth ventricle. As mentioned, intra- or periventricular mass lesions are common culprits. In many instances, an EVD is placed to temporize acute decompensation until surgical treatment of the lesion reverses the obstruction and normal CSF outflow resumes. For posterior fossa ischemic stroke, ventriculostomy is recommended for resultant obstructive hydrocephalus but only as a temporizing measure prior to decompressive craniectomy (AHA/ASA Class I; Level C) [308]. If the lesion is not surgically accessible, temporary drainage may need to be transitioned to permanent shunting. More easily accessible cerebellar mass lesions may be taken directly to the operating room for resection and decompression, which can relieve the hydrocephalus and obviate the need for CSF diversion. Patients with intra-axial and/or extra-axial hemorrhages secondarily causing hydrocephalus in the posterior fossa may also go directly to surgery for decompression with or without hematoma evacuation. The reasoning behind more aggressive surgical intervention for posterior fossa pathology is the higher risk for brainstem compression. Edema from cerebellar ischemic stroke can also cause obstructive hydrocephalus and represents another scenario where urgent surgical decompression may relieve both CSF outflow and brainstem compression.

Ventricular Shunt Malfunction

Acute hydrocephalus also commonly occurs in patients with chronic hydrocephalus in the setting of ventricular shunt malfunction. The time course and severity of acute exacerbation depend on the original etiology of hydrocephalus and the degree of malfunction. Patients with congenital and non-communicating hydrocephalus tend to more rapidly decompensate with shunt failure. A complete failure will also cause more rapid symptoms than situations in which flow through the shunt is diminished but still present. Non-contrast head CT is obtained if shunt malfunction is suspected, and ventricular size is compared to prior imaging. If the patient's ventricles are larger and he or she is acutely symptomatic, he or she will likely need an emergent revision of their shunt to replace the malfunctioning component.

Surgery for exploration and shunt revision or replacement is preferred in these patients over placement of a new EVD. If the ventricles are the same size as prior imaging when the shunt was thought to be working, a shunt tap or lumbar puncture may be performed to determine ICP. It is important to note that not all shunted patients will develop ventriculomegaly when their shunt has failed, despite increased ICP. It's also worth noting that many patients with communicating hydrocephalus who have had a shunt for many years can become "shunt dependent." When their shunt fails, they can rapidly decompensate despite initially having only a mild or insidious onset of hydrocephalus before shunt placement. This is thought to occur because they eventually lose their remaining capacity for natural CSF absorption as that role was replaced by the shunt.

In cases of acute hydrocephalus when infection causes shunt malfunction, the patient should be taken to the operating room for removal of the entire existing system and for EVD placement (IDSA strong recommendation, moderate-quality evidence) [309]. The patient is then treated with antibiotics for 1–2 weeks before a new shunt is placed and the drain removed. Treatment duration is usually a decision made in conjunction with the infectious diseases service.

ICU Course

All patients requiring external ventricular drainage should be admitted to the ICU for drainage monitoring and titration. These patients will require ICU care until either the underlying cause for hydrocephalus has been addressed or until a permanent shunt has been placed. Patients presenting with hydrocephalus from shunt malfunction secondary to infection will require ICU care if they have an EVD in place of their previous hardware. Often, the infectious diseases team recommends 2 weeks of antibiotics before placement of new permanent shunt. If the shunt system was externalized instead of replaced with an EVD, many of these patients will not require ICU care unless there is concurrent sepsis, persistent altered mental status, or significant medical comorbidities. Patients who undergo shunt revision surgery for malfunction in the absence of infection typically have new permanent shunt systems placed and do not require ICU level of care unless there is ongoing altered mental status or medical comorbidities. Regardless, it may be wise to monitor patients who had presented with significant decompensation in the ICU postoperatively for at least 24 h.

Cerebral Edema and Ischemic Stroke

Presentation and Etiologies

Cerebral edema often complicates neurosurgical pathologies and can precipitate the need for acute neurosurgical intervention. Focal edema is frequent with tumor, hemorrhage, and ischemia. However, diffuse cerebral edema is also common but presents its own unique challenges and considerations. Diffuse edema can occur from the above pathologies when massive or multifocal. It can also be seen in the setting of ischemic stroke, meningitis, encephalitis, venous sinus thrombosis, hepatic encephalopathy and other metabolic derangements, and TBI (discussed above).

The presentation of diffuse cerebral edema is that of symptoms of increased ICP, which can include headache, nausea, vomiting, confusion, depressed level of consciousness, and abducens palsy. In advanced stages, herniation syndromes and brainstem compression ensue. Hemispheric edema may have near normal ICP but instead cause symptomatic decline from shift of midline structures. Non-contrast head CT should be obtained emergently if this diagnosis is suspected. CT will typically show signs of diffuse edema (e.g., loss of sulci and gyri, loss of gray-white differentiation, relative parenchymal hypodensity) or midline shift and may demonstrate evidence of herniation. However, imaging without these findings does not exclude elevated ICP.

Therapies should be titrated based on the patient's presumed diagnosis and clinical exam, in particular, his or her level of consciousness and any focal neurologic deficits. Intracranial hypertension can be temporized and sometimes reversed with elevation of the head of bed, ensuring patency of cervical venous outflow, hyperventilation, mannitol bolus, and hypertonic saline bolus. Sedation can also be used, but it may obscure the neurologic exam. Peritumoral vasogenic edema can be treated with a bolus of dexamethasone, although this will be less useful in the hyperacute setting.

If the patient is comatose (GCS <9) after resuscitation or if sedation is required, invasive ICP monitoring may be indicated to guide management. An EVD allows for both accurate monitoring of ICP and therapeutic drainage of

CSF. Placement of ventriculostomy catheters can be difficult with small ventricles and may carry a higher risk for hemorrhage than other monitoring modalities. For these reasons, intraparenchymal sensors are often used for ICP monitoring in the absence of hydrocephalus. CPP (MAP minus ICP) is ideally maintained above 60–70 mmHg, with reduction in elevated ICP attempted before vasoactive augmentation of a normal MAP.

Evidence for ICP monitoring outside of TBI and stroke is limited. For cerebral edema in the setting of liver failure, the major concern for invasive monitoring is hemorrhage due to coagulopathy [310–314]. The role of ICP monitoring remains unclear in these patients and is potentially outweighed by the risk [310, 315–319]. Hemorrhage in the setting of ICP monitor placement may also be of concern in other patients with edema from metabolic derangements or in patients with platelet deficiency/dysfunction. Clinicians should carefully weigh the risks and benefits of ICP monitor placement. ICP monitoring has been reported in bacterial meningitis [320–327], encephalitis [327–329], and venous sinus thrombosis [330].

Role of Surgery

For brain tumors, resection can be performed with or without decompressive craniectomy to treat refractory edema causing elevated ICP or shift, as discussed elsewhere in this chapter. For ischemic stroke and other causes of more diffuse cerebral edema without a mass lesion, the surgical option is typically decompressive craniectomy and is usually reserved as a life-saving measure. Decompressive craniectomy with duraplasty is highly effective in reducing ICP but, in many cases, may not affect functional outcome or may result in a surviving patient with complete dependence for activities of daily living.

Decompressive hemicraniectomy has been less well studied in causes of refractory cerebral edema other than ischemic stroke and trauma. There are, however, numerous case reports and retrospective series of decompression with good outcomes for refractory edema from meningitis [320–323, 325, 327, 331, 332], herpes encephalitis [327, 329, 332–343], other meningitides/encephalitides [342, 344–347], cerebral venous thrombosis [348–362], diabetic ketoacidosis [363–365], and acute disseminated encephalomyelitis [366–371]. There is rarely a role for surgical intervention in cerebral edema from hepatic failure.

Supratentorial Ischemic Stroke

Ischemic stroke from acute occlusion of the internal carotid artery (ICA) and/or proximal MCA may lead to life-threatening cerebral edema. Patients with ICA or proximal MCA occlusions should be identified as being at high risk for malignant edema (AHA/ASA Class I; Level B) [308]. Younger patients are at higher risk due to lower intracranial compliance [372–376]. On CT, frank hypodensity within the first 6 h, involvement of greater than or equal to one-third of the MCA territory, and early midline shift are useful predictors of edema (AHA/ASA Class I, Level B) [308, 377–392]. A rapid fulminant course can also be predicted by MRI diffusion-weighted imaging volume ≥ 80 mL within the first 6 h (AHA/ASA Class I, Level B) [308, 385, 393, 394]. These high-risk patients should be monitored in an ICU or stroke unit (AHA/ASA Class I, Level C), and neurosurgery should be consulted [308].

Neurologic deterioration from edema usually occurs between 72 and 96 h after the ischemic event [395]. Noncontrast head CT (Fig. 15.9) should be obtained serially to monitor size of infarction and progression of cerebral edema and mass effect (AHA/ASA Class I, Level C) [308]. As opposed to more diffuse bilateral cerebral edema, deterioration from large ischemic stroke may occur with a normal ICP [396, 397]. Displacement of midline structures is thought to be the cause of clinical deterioration. For this reason, routine

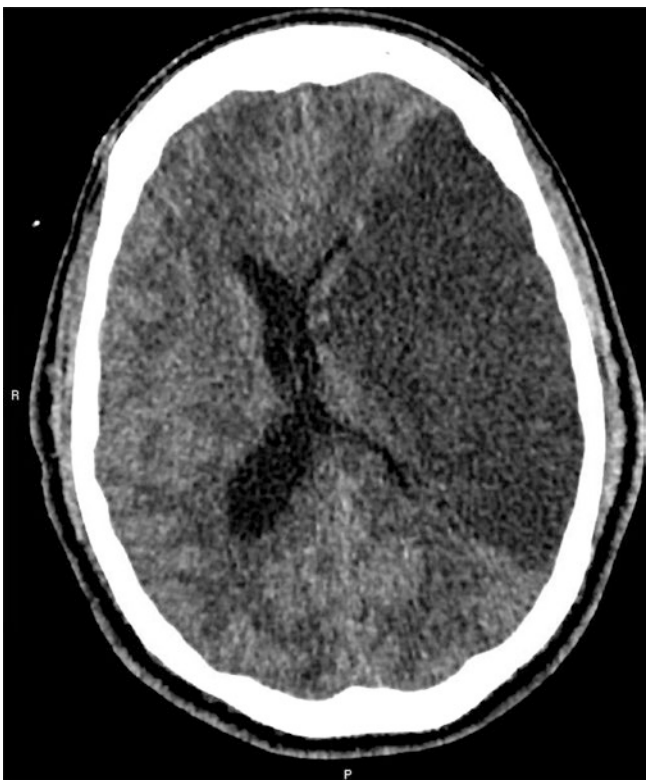

Fig. 15.9 Left middle cerebral artery territory ischemic infarct. Noncontrast axial plane head CT showing a large, left-sided middle cerebral artery territory hypodensity consistent with ischemic stroke. There is secondary edema causing mass effect, effacement of the left lateral ventricle, and midline shift. This patient ultimately required decompressive hemicraniectomy

ICP monitoring is not indicated in hemispheric ischemic stroke (AHA/ASA Class III, Level C), including ventriculostomy [308]. Instead, clinicians should monitor the neurologic exam, particularly the level of arousal, pupillary dilation, and motor responses, for signs of deterioration (AHA/ASA Class I, Level C) [308, 373, 383, 393, 398–403].

Deteriorating patients should undergo interval CT imaging to evaluate the degree of edema and to rule out any new area of ischemia or hemorrhagic conversion. Seizure as a cause of exam decline should also be investigated. Osmotic therapy is the mainstay of treatment, either with mannitol, hypertonic saline, or both (AHA/ASA Class IIa, Level C) [308]. We usually use a 0.25–1.0 g/kg bolus of mannitol in hyperacutely decompensating patients without renal contraindications or hypotension and/or a 23.4% saline bolus if serum sodium concentration is less than 150–155 mEq/L [339, 387, 404, 405]. An elevated sodium goal should be maintained if the patient declined at a previously lower range (i.e., if he/she declined in the range 140–150 mEq/L, increase the goal range to 150–160 mEq/L). Increased serum sodium concentration can be maintained with a combination of hypertonic saline (2% or 3%) boluses and infusions.

Refractory neurologic decline in the form of decreasing level of consciousness due to progressive cerebral edema should trigger consideration for decompressive craniectomy (AHA/ASA Class IIa, Level A) [308]. Decompressive craniectomy with dural expansion is an effective life-saving intervention within the first 48 h after stroke in patients under 60 years of age and is recommended by the latest guidelines (AHA/ASA Class I, Level B) [308, 406–410]. Efficacy for patients >60 years of age (AHA/ASA Class IIb, Level C) and > 48 h after stroke onset (AHA/ASA Class I, Level B) is less certain, but strong consideration for this procedure is recommended in these populations [308, 411].

It is critical to note that, while this is a life-saving procedure, patients will likely be left severely debilitated. Decompression has minimal effect on functional outcome, and rarely are survivors able to perform activities of daily living without assistance [409]. For this reason, the patient's primary team should inform the family that half of surviving patients with massive hemispheric infarctions, even after decompression, are severely disabled and one-third are fully dependent (AHA/ASA Class IIb, Level C) [308, 412]. A decision should then be made based on the patient's previously expressed goals for quality of life after catastrophic illness. Medical comorbidities often factor in to this decision as well.

Cerebellar Ischemic Stroke

Cerebellar ischemic stroke manifests and is managed differently than ICA/MCA supratentorial ischemic stroke. Presentation can be variable, including dizziness, vertigo, nausea, vomiting, speech changes, gait changes, coordination difficulty, and abnormal eye movements. Initial volume of infarct is more important than affected vessel [413]. Serial non-contrast head CT should be used for monitoring edema and mass effect (AHA/ASA Class I, Level C) [308]. Key radiologic markers for progression are fourth ventricular effacement, basal cistern compression, brainstem deformity, hydrocephalus, tonsillar herniation, and upward herniation [413].

Similar to supratentorial ischemic stroke, the level of consciousness is the major indicator of neurologic decline due to edema [413–415]. Patients should be monitored for level of arousal and new brainstem signs (ASA/AHA Class I, Level C) [308]. Maximal medical therapy, including osmotic therapy, should be employed to manage worsening edema. In contrast to supratentorial lesions, however, cerebellar stroke patients may develop elevated ICP due to obstructive hydrocephalus. Therefore, standard measures of ICP management may be more effective. Ventriculostomy is recommended in declining patients if hydrocephalus develops but should not obviate subsequent decompressive craniectomy (AHA/ASA Class I, Level C) [308, 416].

Family discussions are also critical for patients with cerebellar infarcts when surgical intervention is being considered. The team may discuss with family members that not only is decompressive craniectomy life-saving, but the outcomes may be good (AHA/ASA Class IIb, Level C) [308, 417–419]. In two of the largest retrospective series looking at functional outcome after suboccipital decompression, 35–40% of patients lived functionally independent on follow-up at >1 year [417, 419]. Brainstem infarction was a significant poor prognostic factor. Age, medical comorbidities, and the patient's previously expressed wishes should still be weighed heavily. With family consent and neurologic deterioration despite maximal medical therapy, suboccipital craniectomy is recommended for decompression (AHA/ASA Class I, Level B) [308, 416–419].

ICU Course

Patients with cerebral edema treated without surgery will require ICU care until normalization of ICP and treatment of their underlying disease process. Osmolar therapy and other measures to lower ICP may be needed for days to weeks. For patients with ischemic stroke, peak edema occurs around day 3–5; high-risk patients should therefore be monitored in an ICU or specialized stroke unit until after this period. They should also receive serial imaging with non-contrast head CT to document regression or at least stabilization of the progression of edema. Many patients with depressed levels of consciousness will require intubation and mechanical ventilation, which must be weaned before transfer to the floor.

Patients who underwent craniectomy will usually have adequate normalization of ICP, even with some progression of edema. However, providers should be vigilant for postoperative complications including hemorrhage.

Intracranial Epidural Abscess and Subdural Empyema

CNS infections can present in a variety of forms by a range of organisms. Cranial epidural abscesses and subdural empyemas represent two infectious conditions that often require urgent surgical intervention. Cranial epidural abscesses are overall rare, more classically occurring in younger patients secondarily from otitis or sinusitis [420]. In the adult population, cases are seen in the setting of either trauma or recent intracranial, transnasal, or transmastoid surgery. The presentation is typically subacute and consists of nausea, vomiting, fever, and headache. It can progress to altered mental status, seizures, and focal neurologic deficits. The diagnosis is usually made after cranial imaging, preferably gadolinium-enhanced MRI [421]. Empiric antibiotics should be started and neurosurgical consultation obtained. If the patient is stable and the surgery will be performed semi-electively in the next day or two, holding antibiotics is often considered to increase the diagnostic yield of culture. The recommended empiric antibiotic regimen is vancomycin, ceftriaxone, and metronidazole [422]. Lumbar puncture is not recommended [423, 424]. Most cases do require surgical management, usually in the form of a craniotomy or craniectomy to allow for adequate drainage and debridement [420]. Infected bone should be removed [423, 425]. Given the frequent relationship to sinusitis or otitis, otolaryngology consultation may also be warranted [424].

Subdural empyema is a more common entity with similar presentation and etiologies. However, the clinical syndrome is often more severe [426, 427]. Subdural empyema most commonly occurs after a neurosurgical procedure but also can occur from sinusitis, mastoiditis, and in the setting of meningitis with a preexisting subdural hematoma or hygroma [426–430]. Management involves broad-spectrum antibiotics and, in the majority of cases, urgent surgical intervention [423, 428]. Both CT and MRI are useful for diagnosis. Imaging may show concurrent cerebritis and thrombosis [421, 426]. Lumbar puncture is contraindicated [431]. In cases with significant adjacent brain edema, hemicraniectomy may be needed for both evacuation and decompression [429]. Urgency is usually dictated by the extent of neurologic deficit, magnitude of ICP, and degree of midline shift and herniation. Patients with subdural empyema can decline rapidly [423, 428]. In cases where spread is suspected from an adjacent sinus or otologic structure, the otolaryngology team should be involved for source control at the time of neurosurgical evacuation [424].

These patients should be monitored in a critical care setting before and after surgical intervention. Before transfer to a lower level of care, the patient should be stabilized from a neurologic standpoint, and systemic risk of sepsis should be adequately mitigated. Surgical site drains may be left in the evacuation cavity, and close interval follow-up imaging may be obtained to screen for persistence of infection and reaccumulation. Patients may require multiple evacuations and debridements. Seizures are a common complication [429, 431].

Pituitary Apoplexy

Presentation and Initial Imaging

Pituitary apoplexy is sudden, symptomatic hemorrhage into the pituitary gland, usually into a pituitary adenoma. It can manifest with variable symptomatology, but the syndrome is classically defined by severe headache, nausea, altered mental status, visual dysfunction, and hypopituitarism [432–438]. Pituitary apoplexy should be present in the differential for all individuals with acute, severe headache. Suspicion should be further increased by visual field or acuity deficits from optic nerve involvement and diplopia from oculomotor involvement [439]. Hypopituitarism can become life-threatening when adrenocorticotropic hormone (ACTH) deficiency occurs, which can lead to adrenal insufficiency and hypotension.

The patient should be stabilized hemodynamically, and CT should be obtained emergently followed by MRI for confirmation (Society for Endocrinology level III evidence, grade B recommendation) [440]. Neurosurgery, endocrinology, and ophthalmology consultations should be obtained and the patient moved to the ICU for medical management. Medical stabilization should include intravenous fluid administration, balancing electrolytes, and laboratory assessment of endocrine dysfunction (Society for Endocrinology level III, grade B) [440]. Diabetes insipidus (DI) is a rare feature [441]. Empiric steroids should be strongly considered for hemodynamic instability, altered level of consciousness, reduced visual acuity, and severe visual field deficits (Society for Endocrinology level IV, grade C) [440]. Formal visual field testing should also be performed early.

Role for Surgery

Urgent neurosurgical intervention should be considered for all patients with neurologic symptoms and evidence of hypopituitarism. Transphenoidal resection of the pituitary gland

along with the adenoma and hematoma is the preferred approach, either endoscopically or microscopically [442–444]. Although there is some support in the literature for conservative management and delayed surgery, many authors report better neurologic outcomes with early surgery [434, 437, 439, 440, 442, 444–451]. In general, the presence of visual deficits, depressed GCS, and ophthalmoplegia more strongly favor urgent surgery as compared to conservative management or delayed elective surgery [452]. The Society for Endocrinology guidelines recommend surgery for patients with severe neuro-ophthalmologic signs such as severely reduced visual acuity, severe and persistent or deteriorating visual field defects, or declining level of consciousness (level III, grade B) [440]. However, they also state that ocular paresis because of the involvement of cranial nerves III, IV, or VI in the cavernous sinus in the absence of visual field defects or reduced visual acuity is not in itself an indication for immediate surgery (level III, grade B), as these symptoms in isolation may resolve spontaneously with non-operative management [434, 440, 449, 453]. In all, the decision to undergo surgery should be made in a multidisciplinary fashion in conjunction with the patient and family's wishes. If not performed urgently, surgery should typically be performed within 7 days of symptom onset (Society for Endocrinology level III, grade B) [434, 437, 440, 451, 454].

ICU Course

These patients should return to the ICU after surgery and be treated similarly to elective postoperative pituitary resection patients. Endocrinology should be consulted for assistance with management. If not already started, the patient should be given standing hydrocortisone. To monitor for DI, patients should have regular checks of serum sodium and urine specific gravity with strict measurement of urine output. Depending on institutional criteria, vasopressin or desmopressin may be needed. The patient should also have frequent neurologic exams, with particular attention to visual fields, visual acuity, and extraocular movements. Clear drainage from the nose or into the throat may indicate CSF leak, which may require further surgery. Many centers administer prophylactic antibiotics in all postoperative transphenoidal surgery patients. Typically, 1 or 2 days are spent in the ICU postoperatively, which can be lengthened by endocrinologic complications such as DI and less commonly by neurologic complications or operative site hemorrhage.

Brain Tumors

Presentation and Initial Workup

Most brain tumors do not present as neurosurgical emergences. However, they may present emergently due to hemorrhage, hydrocephalus, increased ICP, and mass effect causing neurological deficits or herniation syndromes. These clinical syndromes can present with a variety of symptoms, including headache, nausea, vomiting, confusion, depressed level of consciousness, aphasia, and other focal neurologic deficits. Patients with more severe disease may present comatose with signs of herniation. Comatose patients should be intubated for airway protection or if there is lack of adequate respiratory drive. Emergent non-contrast head CT should be obtained, and the imaging findings should be correlated with the clinical presentation (Fig. 15.10). If there is evidence of raised ICP, this should be treated aggressively with medical interventions while awaiting neurosurgical

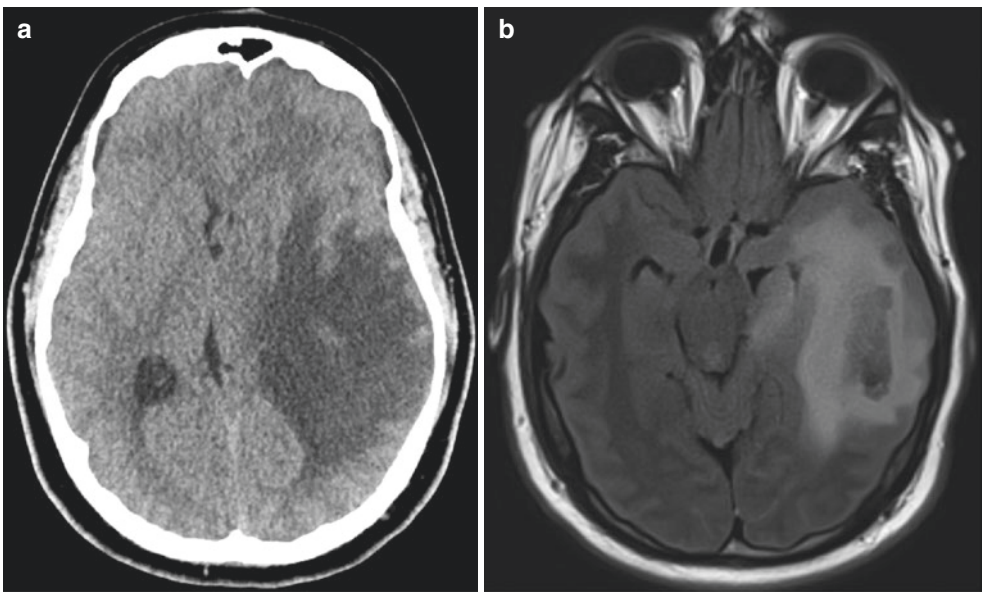

Fig. 15.10 Supratentorial brain tumor. (**a**) Non-contrast axial plane head CT showing large left parietotemporal hypodensity concerning for underlying tumor with surrounding vasogenic edema causing mass effect and midline shift. (**b**) T2 fluid-attenuated inversion recovery (FLAIR) axial plane brain MRI from the same patient showing significant edema and mass effect causing medialization of the uncus and midbrain/brainstem compression

evaluation. Brain tumor patients may also present with seizures, in which case the clinical exam may not match imaging findings.

Tumor-Associated Hemorrhage

Brain tumors, especially metastases, often present as intraparenchymal hemorrhages [455–457]. Depending on the amount of hemorrhage, the underlying tumor may be obscured on imaging. For this reason, initial management of these tumors is the same as any intraparenchymal hemorrhage, which is discussed in detail separately in this chapter. Blood pressure should be strictly controlled. Qualitative and quantitative platelet dysfunction should be investigated through history and laboratory studies. Coagulopathy should also be investigated and corrected as appropriate. Medical management of ICP should be aggressive. If the patient can tolerate, CT or MR angiography should be performed to evaluate for an underlying vascular lesion [4]. CT angiography offers the advantage of speed and is typically performed first at our institution. However, if the patient is stable enough to tolerate the longer exam, MR angiography can be done concurrently with gadolinium-enhanced MRI, which is the study of choice to diagnose and characterize an underlying tumor or lesion.

Managing Edema and Mass Effect

While the mass effect of the tumor itself can be substantial, oftentimes the edema surrounding the mass is the symptomatic culprit. The amount of edema is dependent on the underlying pathology and can progress much more rapidly than the tumor itself, particularly in the setting of hyponatremia. Peritumoral edema not only augments the tumor's mass effect and increase in ICP, but it also causes dysfunction of the affected edematous parenchyma. Symptomatic edema should be treated with dexamethasone. Typically, a 10 mg IV bolus is administered, followed by 4–6 mg IV every 6 h. Doses of up to 10–20 mg IV every 6 h can be used if the edema is severe and inadequately responding to lower doses. Although steroids are typically not given for spontaneous ICH, they can be used if there is significant suspicion for underlying tumor.

If the edema is causing acute decompensation from elevated ICP or midline shift, mannitol and hypertonic saline will more rapidly address the edema than steroids. Mannitol should be used cautiously if there is hypotension or concern for renal failure. Loop diuretics can be used to augment the effects of mannitol but can contribute to both renal failure and hypotension. We also use a range of hypertonic saline preparations depending on the specific clinical scenario. In the hyperacutely decompensating patient with signs of herniation, a bolus of 23.4% sodium chloride can be administered. Boluses of sodium chloride at 3% and 2% concentrations can also be used in 250 and 500 cc increments. An elevated sodium goal (e.g., 140–150 mEq/L or 145–155 mEq/L) is then usually maintained if edema is symptomatic with 3% or 2% sodium chloride used as a continuous infusion. Of note, 0.9% sodium chloride has 154 mEq/L of sodium and may also be adequate depending on the patient's underlying renal function. In the acutely herniating patient, we often use all of the above—steroids, mannitol, and hypertonic saline—in conjunction with hyperventilation and other standard maneuvers for managing ICP.

Hydrocephalus

Brain tumors can cause acute hydrocephalus through intraventricular obstruction and extraventricular compression. Obstruction by extraventricular compression usually occurs at the third ventricle, cerebral aqueduct, or fourth ventricle and can be due to either the tumor itself or surrounding edema. Decompensation can happen quickly when CSF outflow is blocked. Acute hydrocephalus in this scenario will usually be evident as ventriculomegaly on non-contrast head CT, as will the location of compression. Corticosteroids should be administered immediately. The receding edema may reopen the obstructed CSF outflow. However, in patients with depressed level of consciousness, urgent ventriculostomy is warranted along with medical measures for managing ICP. Ideally, the patient is stabilized by nonsurgical means so that emergent surgery is not necessary and can be done on a more semi-elective, planned basis.

Intraventricular tumors may also obstruct CSF outflow and cause acute hydrocephalus. This occurs commonly with fourth ventricular tumors and colloid cysts of the third or lateral ventricles. For intraventricular tumors, there is minimal contribution of edema to the obstructive process so corticosteroids are likely to be less effective. Instead, ventriculostomy is the intervention of choice to manage hydrocephalus and stabilize the patient while further workup and surgical planning is ongoing.

Indications for Urgent Surgery

In general, emergent surgery for brain tumors is avoided if possible. Medical management of ICP, corticosteroids, and ventricular drainage can often stabilize the patient or even reverse neurologic decline. Ideally, the patient is temporized until MRI with contrast and adequate surgical planning can be performed during hours when experienced staff are available. In cases where a tumor presents as a large intraparen-

chymal hemorrhage, the hematoma will likely obscure the underlying tumor, and clinical decision-making should proceed according to the ICH guidelines discussed separately in this chapter. For supratentorial ICH lesions, hemicraniectomy with or without hematoma evacuation should be considered in cases with neurologic deterioration as a life-saving measure (AHA/ASA Class IIb, Level C) after discussion with the family or healthcare decision-makers [4]. ICH lesions within 1 cm of the cortical surface are generally the best candidates for clot evacuation [94]. A stronger argument for surgical resection of the hematoma could likely be made if the team has good reason to believe there is an underlying tumor, since the tumor could be biopsied or resected concurrently.

Tumors that are associated with hemorrhage in the cerebellum can also be obscured and should be treated by the ICH guidelines if that is the case. The AHA/ASA guidelines state that for cerebellar hemorrhage with neurologic deterioration, brainstem compression, or hydrocephalus from ventricular obstruction, clot evacuation should be performed as soon as possible (AHA/ASA Class I, Level B) [4]. Also, initial treatment with ventricular drainage alone rather than surgery for hematoma evacuation is not recommended (AHA/ASA Class III, Level C) [4].

In situations where a tumor is causing notable neurologic dysfunction or decline from mass effect without hemorrhage or hydrocephalus, medical management should be maximized. If the patient continues to decline neurologically, including further depression in level of consciousness or a new focal neurologic deficit, surgery for decompression with or without tumor debulking/resection should be strongly considered.

ICU Course

Patients presenting with new acute neurologic deficits, symptomatic hydrocephalus, midline shift, or risk for impending herniation should be admitted to the ICU for initial monitoring, workup, and management. Many patients will have significant improvement with steroids only, which can reverse or improve new deficits and shift. Patients should receive frequent neurological exams and undergo serial imaging to assess for progression or stabilization of mass effect or hydrocephalus. Patients requiring ventricular drainage will need ICU care until definitive shunting or surgical resection. After permanent shunting with correction of hydrocephalus or resection with improvement of mass effect, patients typically require only 1–2 additional days of ICU monitoring. Patients presenting with massive ICH will likely require a longer ICU stay, in part due to the need for intubation and mechanical ventilation. Providers should also be vigilant for signs of hemorrhage into the resection cavity complicating the postoperative course.

Conclusion

Management of neurosurgical emergencies represents a persistent challenge for the healthcare system. Critical decisions must be made quickly, and precise and swift care coordination among many provider teams is required. All providers involved need to be knowledgeable of the management pathway for each of the most common emergencies. In general, stabilization of airway, breathing, and circulation should be accomplished first. In trauma scenarios, the ATLS protocol should be followed, and suspicion for neurologic injury should not distract from screening and management of extracranial injuries that may be more acutely life-threatening. An accurate neurological exam is critical for further decision-making and should be obtained before sedation or administration of a paralytic agent, if possible. ICP should be aggressively addressed first by medical means while further surgical intervention is planned. Knowledge of pharmacological or medical platelet or coagulation cascade dysfunction is critical to nearly all neurosurgical emergencies as it may affect management or require rapid correction.

The decision for surgical intervention continues to increase in complexity as we focus more on functional outcomes instead of simply improving survival. While many neurosurgical interventions can reverse the course of neurological injury, recent data continues to demonstrate that often our traditional interventions can be life-saving but do not actually improve functional outcomes. Thus, the patient's previously expressed wishes regarding quality of life after catastrophic illness should be assessed via the patient's family to guide surgical decision-making. The neurosurgeon and other providers should be familiar with—and accurately apply—currently accepted prognostic factors from the literature to each patient in order to decide who would best and least benefit from surgery. Most importantly, further research is needed to better delineate patient subgroups who may benefit from current neurosurgical interventions and also to discover new techniques that may provide improvement in functional outcomes.

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Part IV

Neurological Emergencies

Treatment of Infectious Meningitis and Encephalitis in the Neurocritical Care Unit

16

Christine E. Yeager, Lauren Koffman, and Thomas P. Bleck

Introduction

Infections of the central nervous system (CNS) are a common problem that physicians often encounter in their practice. CNS infections can mimic other CNS pathologies and can have vague, nonspecific presentations that cause diagnostic challenges. Rapid diagnosis is imperative, as they typically carry a higher morbidity and mortality compared with infections in other organ systems [1]. Treatment can be challenging, as pharmacologic agents must be able to cross the blood–brain barrier and may require different medication dosing regimens [2]. A significant proportion of CNS infections do not have identifiable pathogenic organisms [3], but as technology advances, detection may become possible, faster, and more accurate. In addition to the primary infection, many pathogens can cause severe complications with long-term neurologic sequelae and impact activities of daily living. Throughout this chapter, there will be documentation regarding the level of evidence supporting each recommendation, and while the newer Infectious Diseases Society of America (IDSA) guidelines have adopted the GRADE methodology with the strength of recommendation followed by the level of evidence, some of the older guidelines used a different style, which is explained in Table 16.1.

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Meningitis

Meningitis is an infection of the membranes lining the brain and can cause significant morbidity and mortality [4]. This section discusses bacterial, viral, and fungal meningitides. In the absence of neurosurgical manipulation or a cerebrospinal fluid (CSF) leak, a pathogen typically spreads hematogenously to the CNS and invades the blood–brain barrier [5]. The host immune response is unable to control infection within the CNS, in particular in the subarachnoid space, and the inflammatory response to the infection is actually responsible for some of the symptoms associated with meningitis [6].

Bacterial

Background

In developed nations, the use of vaccines has altered the most commonly seen pathogens associated with meningitis

Table 16.1 Grading system previously used by the Infectious Diseases Society of America for ranking recommendations in clinical guidelines

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from >1 properly randomized, controlled trial
II	Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experiences, descriptive studies, or reports of expert committees

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[1, 2]. Today the most commonly identified pathogen in bacterial meningitis is *Streptococcus pneumoniae*, although its incidence has been reduced by the introduction of the 7 valent pneumococcal conjugate vaccine [1, 2, 4]. This is the predominant pathogen in all age groups except in those younger than 1 month, where *S. agalactiae* (group B strep) is the most common pathogen in bacterial meningitis [7]. *Neisseria meningitides* is second most common in adults, followed by group B strep, *H. influenzae*, and *Listeria monocytogenes* [1]. Other pathogens such as *Haemophilus influenzae* and *Staphlococcus aureus* may be seen when there is an underlying non-CNS pathology (e.g., otitis, sinusitis, endocarditis) [4].

The incidence of *H. influenzae* meningitis was significantly reduced in the 1990s after the advent of Hib conjugate vaccine for infants [1]. In 2006-2007, the US incidence of bacterial meningitis was 1.38 cases per 100,000 population [1]. The incidence in the UK and Western Europe is 1–2 cases per 100,000 people per year [2], and in endemic areas such as the Sahel region of Africa, also known as the meningitis belt, the incidence can be as high as 1000 cases per 100,000 people per year [2]. Bacteria can access the meninges through several mechanisms: hematogenous spread via bacteremia (*N. meningitides* and *S. pneumoniae*), direct extension from otitis media or sinusitis, and direct inoculation via neurosurgical procedures [2].

Healthcare-associated meningitis is most commonly associated with neurosurgical patients, and the predominant organism identified in these cases is *Staphylococcus aureus* [8, 9]. Risk factors for the development of healthcare-associated meningitis include the presence of an external ventricular drain (EVD), craniotomy surgical case length, persistent CSF leak/drainage, and superficial surgical site infection after a neurosurgery [9, 10]. One strategy often employed is the use of prophylactic antibiotics in the perioperative period, specifically against *S. aureus* – a strategy that is weakly supported in the literature [8]. The CSF parameters for the diagnosis of meningitis in patients who have had neurosurgical manipulation differ from CSF parameters in patients diagnosed with community-acquired meningitis [11]. Generally, treatment of EVD-related meningitis is based on a trend in the CSF parameters in addition to clinical findings concerning for meningitis [11].

Diagnosis

The classic meningitis triad is altered mental status, nuchal rigidity, and fever, but only 50–67% of patients have all three findings; almost all cases will have at least two [2, 6]. When there is concern for bacterial meningitis, blood cultures and a lumbar puncture must be performed. If there is any delay in obtaining CSF, empiric treatment must be initiated. If there is concern for a focal neurologic deficit, evidence of increased intracranial pressure on examination, or known immunodeficiency, then computed tomography (CT) head should be performed prior to lumbar puncture (Level B-II) [7]. The gold standard for the diagnosis of bacterial meningitis is CSF analysis [2]. CSF typically demonstrates pleocytosis with neutrophilic predominance, a glucose concentration less than 2/3 that of serum glucose, and an elevated protein concentration [4, 7, 12]. Some patients may not have an elevated white blood cell count, such as the immunosuppressed, and this can indicate a poor prognosis [2]. Opening pressure may be high and should always be assessed along with a closing pressure measurement.

Gram stain and culture of CSF permit identification of the pathogen in 60–90% of cases as well as antibiotic susceptibility [2, 4]. If empiric antibiotic therapy was started prior to the lumbar puncture, the likelihood of pathogen identification by gram stain or culture is reduced by 44% [2]. One study showed that of patients who underwent a lumbar puncture within 4 h of starting antibiotics, 73% had a positive CSF culture; however if the procedure was performed beyond this time, the sensitivity dropped to less than 11% [13]. This has led to the consideration of other testing methods to identify a pathogenic organism. Latex agglutination was developed for more rapid detection of a bacterial pathogen; however, its use has been less supported more recently and is not routinely recommended at this time (Level D-II). There is some utility in using latex agglutination in patients with a negative CSF gram stain (Level C-II) or in patients pretreated with antibiotics and a negative gram stain and CSF culture (Level B-III) [7]. The limulus lysate assay was developed as another potential means to detect a pathogen, specifically in those with suspected gram-negative meningitis [14]; however, this test was shown in some studies to have a low sensitivity and does not distinguish between specific gram-negative organisms [7]. It is not recommended for routine use in patients with meningitis (Level D-II) [7]. Pathogen-specific polymerase chain reaction (PCR) has been shown to have a high sensitivity of 87–100% and specificity of 98–100% [1]. There is some evidence suggesting that PCR can be utilized in patients with a negative CSF gram stain and high suspicion of bacterial meningitis (Level B-II) [7].

Newer methods of detecting multiple pathogens at once have been developed including multiplex PCR, 16 s PCR, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF), and whole genome sequencing [2]. Multiplex PCR uses conventional PCR but contains primers and probes for several pathogens allowing for testing for many pathogens at the same [3]. All bacteria contain 16 s rRNA; therefore, the 16 s PCR has been shown to be sensitive and specific for the diagnosis of bacterial meningitis (sensitivity 92% and specificity 94%) [2]. Another

method of identifying microorganisms is MALDI-TOF, which essentially uses the protein mass of the organism to identify the pathogen [2, 15]. This method has been shown to lead to more rapid identification of an organism, but it is not currently included in the guidelines for the diagnosis of bacterial meningitis [2, 15].

Other laboratory studies that may assist in diagnosing meningitis include CSF lactate, C-reactive protein, and procalcitonin (PCT). CSF lactate has been shown to differentiate between bacterial and viral meningitis with good sensitivity and specificity when lactate is greater than 4.2 mmol/L [7], but only in patients who were not previously treated with antibiotics [16]. Additionally, CSF lactate does not provide further information regarding organism identification and is not recommended for patients with community-acquired bacterial meningitis (Level D-III) [7]. CSF lactate may have a role in diagnosing bacterial meningitis in postoperative neurosurgical patients or in those with an EVD. It has been shown to be helpful in these populations because CSF cell counts are abnormal in these patients even without infection, making CSF analysis difficult. It is recommended that in this population of patients, if CSF lactate is >4.0 mmol/L, the initiation of empiric antibiotics should be considered (Level B-II) [7]; however, CSF lactate alone has been shown to not be a reliable marker of CNS bacterial infection and should be considered in the context of the patient [17]. Serum C-reactive protein concentrations have a strong negative predictive value, and can be useful in patients with CSF parameters consistent with meningitis but a negative gram stain (Level B-II) [7]. Serum PCT is found in healthy individuals at levels that are below a detectable limit and increases significantly in patients with bacterial infections [18]. It has been shown to be an effective biomarker for bacterial meningitis [19]; however, due to lack of ready availability at clinical laboratories, regular use of it is not been recommended at this time (Level C-II) [7].

Imaging is not required to diagnose meningitis. In special scenarios, computed tomography (CT) of the head should be obtained prior to a lumbar puncture including in adults with an immunocompromised state, history of CNS disease, new-onset seizure, papilledema, abnormal level of consciousness, and/or a focal neurologic deficit (Level B-II) [7]. In uncomplicated meningitis, CT head is often normal, but it can help evaluate for predisposing causes such as sinusitis, middle ear or mastoid infection, or fractures [20]. Magnetic resonance imaging (MRI) is normal in half of cases, but it may show pial enhancement, enhancement of the subarachnoid spaces (Fig. 16.1), or fluid-attenuated inversion recovery (FLAIR) changes suggestive of an underlying meningeal process [20]; these findings are not specific for bacterial meningitis. While imaging may not be useful in diagnosing bacterial meningitis, it can be used to evaluate neurologic sequelae, to be discussed later.

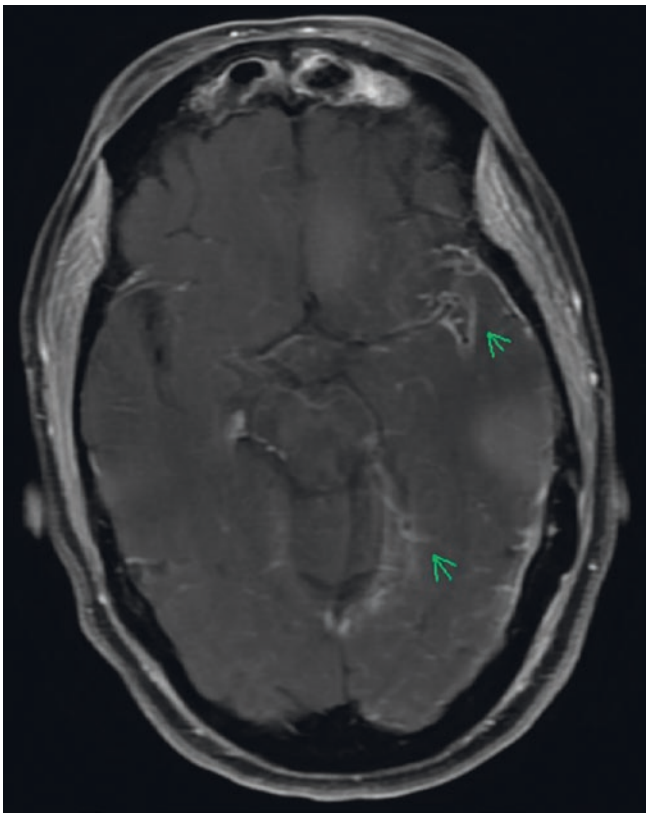

Fig. 16.1 Meningeal enhancement noted on MRI T1 axial post-contrast image in a 74-year-old male with suspected bacterial meningitis (arrows). No pathogen was identified as CSF studies were obtained after antibiotic administration

Management

Meningitis is a neurologic emergency, and although there is inadequate evidence to support specific guidelines on an interval between initial assessment and administration of empiric therapy, it is generally recommended to start therapy as soon as possible. Empiric treatment of meningitis for patients 2–50 years old is vancomycin plus a third-generation cephalosporin (Level A-III); for patients greater than 50 years old or thought to be immunocompromised, ampicillin should be added (Level A-III) [7]. Antibiotics can be changed based on pathogen identification and susceptibility results.

Animal studies showed that antibiotic-induced cell lysis can lead to inflammation in the subarachnoid space, which was thought to worsen outcomes [21]. A large randomized controlled trial showed that the percentage of patients with an unfavorable outcome or death was significantly reduced in patients who had received adjunctive dexamethasone, specifically those with pneumococcal meningitis [21]. Initially the literature showed worse hearing-related outcomes in patients who received dexamethasone [21]; however, a meta-analysis showed that hearing outcomes were better in patients who received adjunctive dexamethasone when compared to those who received placebo [22]. Based on the evidence available,

it is recommended that in adults with suspected or proven pneumococcal meningitis, dexamethasone should be started at a dose of 0.15 mg/kg Q6H for 2–4 doses with the first dose being administered 10–20 min before or at the same time as the first dose of antimicrobial therapy (Level A-I) [7]. It can be considered in all adults who are being started on empiric therapy for presumed meningitis as the pathogen is not always readily identified at antibiotic initiation (Level B-III) [7]. Adjunctive dexamethasone should not be given to adult patients who have already had antimicrobial therapy administered (Level A-I) [7]. The recommendation for the use of adjunctive steroids in bacterial meningitis has recently been questioned by recent literature, as a retrospective analysis showed increased incidence of delayed cerebral ischemia in patients who received adjunctive steroids [23]. Further studies are necessary to better evaluate this association.

Complications of bacterial meningitis have been studied extensively and include arterial and venous infarcts (Fig. 16.2), cerebral edema, hydrocephalus, intracerebral hemorrhage (Fig. 16.3), ventriculitis (Fig. 16.4), vasculopathies (Fig. 16.5), empyema, seizures, brain abscesses (Fig. 16.6) [20, 24], and cavernous sinus thrombosis (Fig. 16.7). A mild transient hydrocephalus is the most

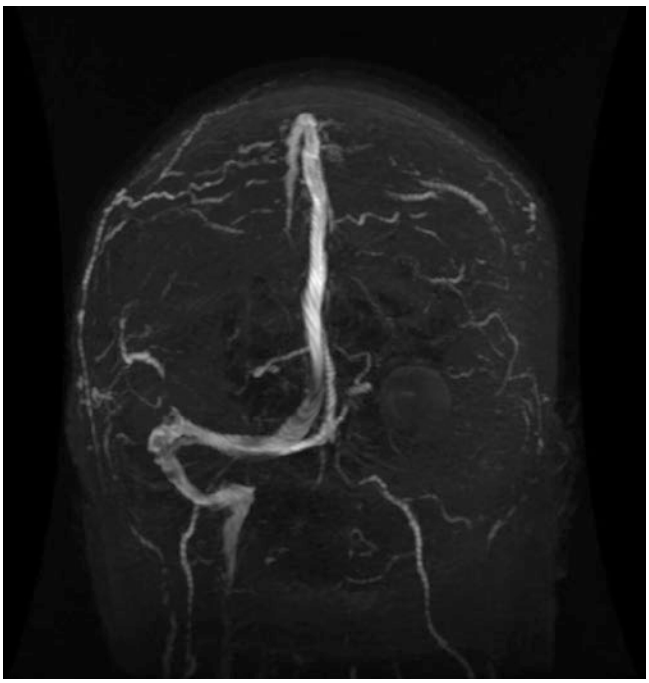

Fig. 16.2 MR venogram showing a transverse sinus thrombosis in a patient with bacterial meningitis

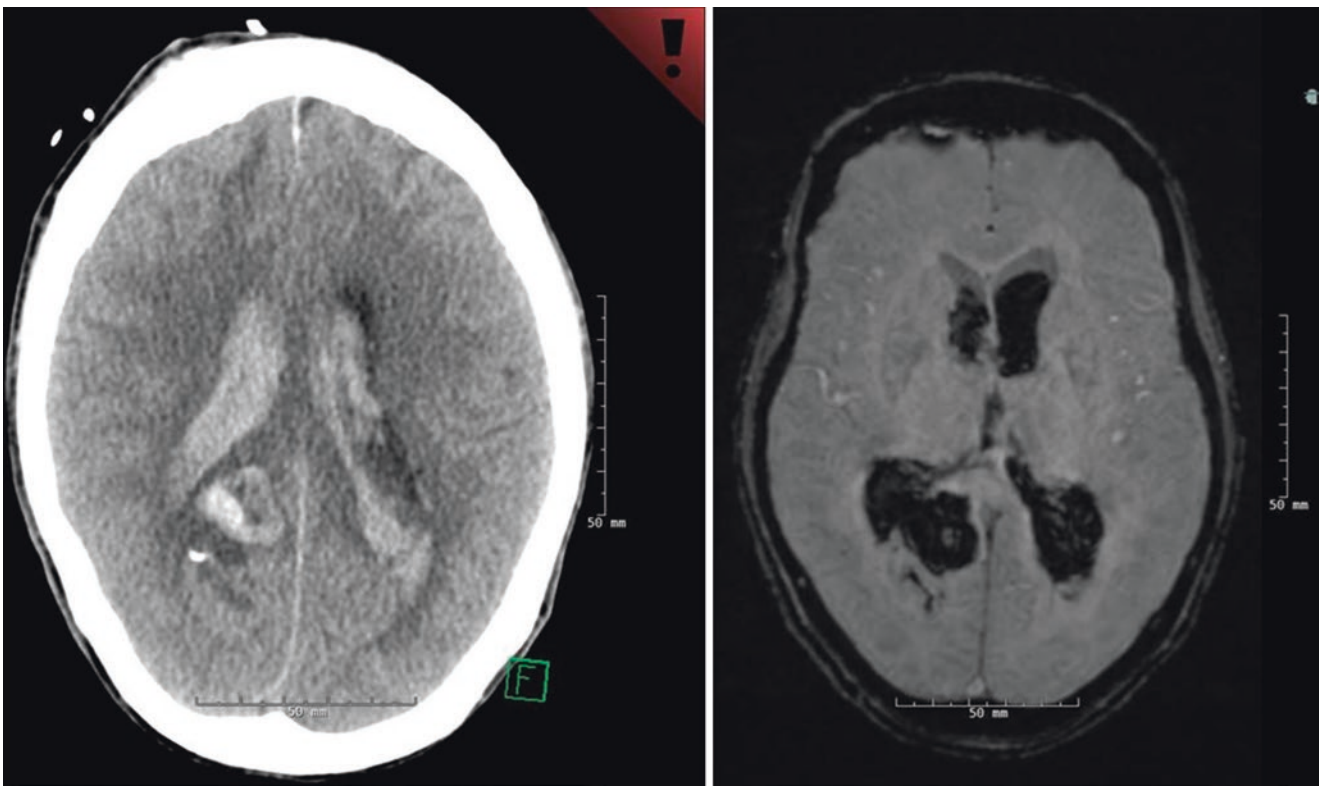

Fig. 16.3 A 58-year-old with HSV encephalitis. (Left) CT head without contrast shows a hyperdensity in right posterior parietal parasagittal region representing an intracerebral hemorrhage in addition to intraventricular hemorrhage. (Right) MRI susceptibility-weight image in which the black areas correspond to the areas of hemorrhage

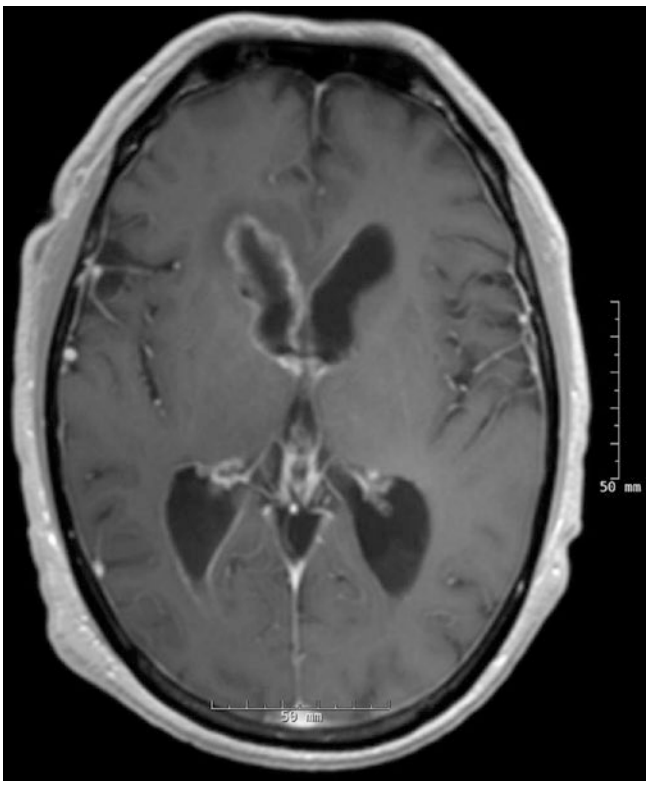

Fig. 16.4 MRI T1 axial post-contrast image demonstrates ventriculitis in a 72-year-old with culture-negative but presumed bacterial meningitis

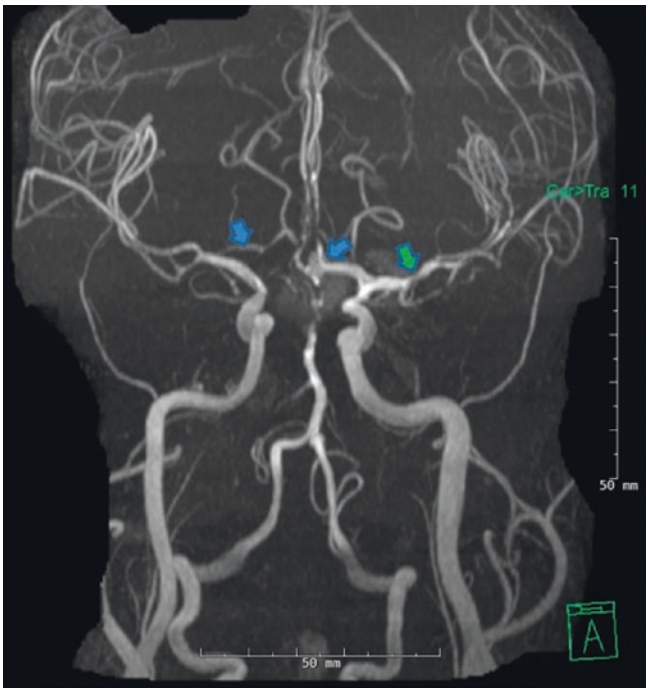

Fig. 16.5 MR angiogram showing moderate-to-severe vasospasm in bilateral proximal A1 segments (blue arrows) and left MCA (green arrow) in a 57-year-old with viral encephalitis

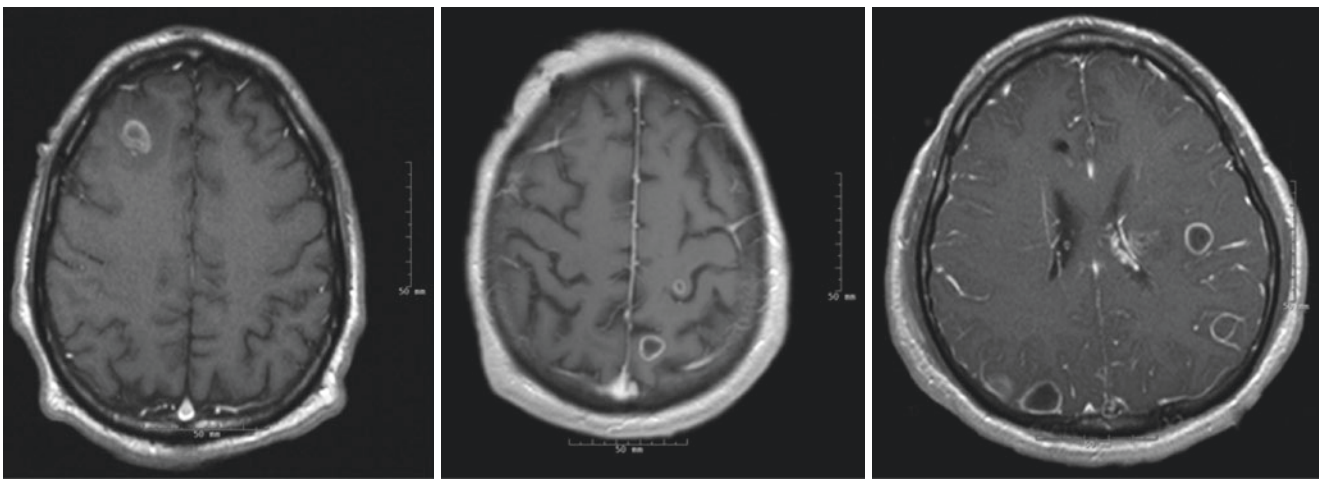

Fig. 16.6 MRI T1 axial post-contrast images show the classic findings of brain abscesses with ring-enhancing lesions in a 26-year-old. 16sRNA was positive for *Streptococcus intermedius*

common complication in meningitis [20] but typically does not require permanent shunting [24]. Some of these complications may require further interventions including repeat lumbar puncture, follow-up imaging, or neurosurgical intervention. One long-term complication of pneumococcal meningitis that can occur in both adult and pediatric populations is hearing loss [2, 22].

Viral

Background

The most common form of meningitis is viral, with the most commonly identified pathogens including enteroviruses [25], herpesviruses, and, in many parts of the world, arboviruses [3]. The incidence of viral meningitis is often

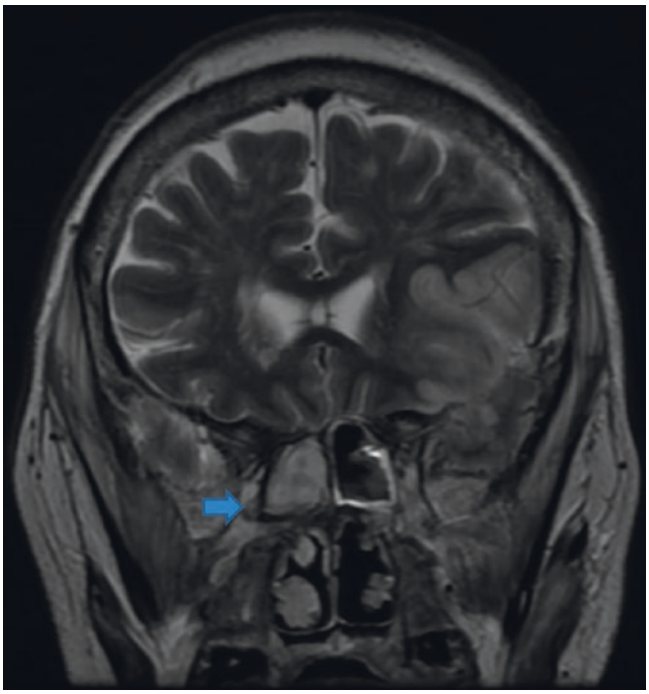

Fig. 16.7 MRI T2 coronal image shows a cavernous sinus thrombosis in a patient with bacterial meningitis. Note the hyperintensity in the cavernous sinus (arrow)

underrepresented due to under-reporting or lack of recognition, but the annual incidence has been estimated to be between 0.26 and 17 cases per 100,000 persons [3]. Viral meningitis can present similarly to bacterial meningitis with patients complaining of headache, neck stiffness, and photophobia [3]. Most often, viruses spread to the CNS via hematogenous spread; however, herpes simplex, rabies, and varicella zoster (VZV) travel to the CNS via neuronal spread [26] in a retrograde manner [27].

Enteroviruses are typically acquired by fecal-oral contamination or less commonly via respiratory droplets [25]; they include echoviruses, coxsackieviruses, and polioviruses [25]. These viruses are found worldwide, although polioviruses have largely been eradicated in developed parts of the world due to vaccination [25]. Peak incidence is typically in the summer months, thought to be secondary to sparse clothing and warm weather that facilitates fecal-oral spread [3, 25]. Risk factors for enteroviral meningitis include young age, immunodeficiency, and lower socioeconomic status secondary to lack of sanitation [25, 28]. In addition to the typical meningitis clinical syndrome, coxsackie meningitis can present with a rash over the hands, feet, and mouth [25].

Herpes simplex viruses (HSV) are the most common causes of endemic viral meningitis in adults [29], with the most frequently detected being herpes simplex virus type 2 (HSV-2) and VZV [3]. HSV-2 is sexually transmitted and remains an important pathogen; despite an increased focus on barrier methods and education, more than 20% of the US population older than 12 years of age were noted to be infected with HSV-2 in 2003 [30]. Rarely, patients can develop recurrent meningitis, also known as Mollaret meningitis, which is typically attributed to HSV-2; there have been case reports of recurrent meningitis involving Epstein-Barr virus (HHV-4) and HSV-1 [29] also. Recurrence is rare, and the estimated prevalence is 2.2/100,000 population [31].

Arboviruses are normally found in specific regions and are transmitted to hosts via insect bites by mosquitos, ticks, biting flies, mites, and nits [32]. The peak incidence tends to be in summer months when mosquitos are most prevalent [33]. Although most infections by arboviruses are subclinical, meningitis occurs particularly with West Nile virus, Tick-borne encephalitis virus, and Toscana virus [3]. The newly re-emerged Zika virus can cause a meningoencephalitis and is becoming a rising worldwide concern due to the recent outbreaks [32]. Arboviruses typically start with a flu-like illness, which progresses to nausea, vomiting, and neck stiffness [32]. West Nile is one of the more commonly seen arboviruses in the US, and although the majority of infections are asymptomatic, a small proportion present with a fever and flu-like symptoms and an even smaller proportion with neuroinvasive disease [33]. Of those patients with neuroinvasive disease, the infection can manifest as meningitis, encephalitis, and/or acute flaccid paralysis [33].

Mumps virus is another viral cause of meningitis, and it has been increasing in recent years due to decreasing rates of vaccination [34]. The Center for Disease Control (CDC) has indicated that the number of mumps cases in the USA alone increased from 229 in 2015 to 6366 in 2016 and to more than 5600 in 2017 [35]. Mumps is known to cause acute onset of unilateral or bilateral parotitis that occurs 2–3 weeks after initial exposure to the virus; however, not all patients have this symptom and some can present with respiratory symptoms, low-grade fever, and headache [34]. Meningitis can occur in 5–10% of all patients but is rarely fatal and typically self-limited [36]. It is one of the few viral meningitides (along with herpes simplex and lymphocytic choriomeningitis viruses) that can cause remarkable hypoglycorrhachia.

Diagnosis

As with any concern for potential CNS infection, a lumbar puncture is crucial. CSF analysis typically shows a normal to mildly elevated opening pressure, a lymphocytic pleocytosis, a moderately raised protein, and a mildly reduced glucose, although not to the same degree as bacterial meningitis [3]. Viral culture is often not helpful in the diagnosis of viral meningitis as it can be time-consuming and sensitivity is very low [37]. Serologic studies can be considered in the diagnosis of some viral infections, but they typically are also time-consuming and have limited specificity [37]. Epstein-Barr virus (EBV) is a member of the herpes family and is an exception, as the presence of immunoglobulin M (IgM) is

very suggestive of an acute infection. Serologic studies are the most available method of diagnosing an arboviral infection [37]. The presence of IgM antibodies directed against a specific arbovirus in the CSF is diagnostic of neuroinvasive disease, and a fourfold change in specific immunoglobulin G (IgG) antibody 2–3 weeks after presentation is also diagnostic [37]. For West Nile virus in particular, it is recommended to check CSF IgM, as PCR is only 60% sensitive [38]. However, the IgM response to West Nile can last up to 500 days, which may lead to some diagnostic uncertainty. PCR for specific arboviruses is becoming more common, but it is still not readily available at most institutions [37]. However, the gold standard of diagnosing viral meningitis is still virus-specific PCR, and this should be performed to rule in viral meningitis versus bacterial when available (Level B-II). This can be falsely negative if performed too early or if the amount of virus is very low [3]. Multiplex PCR can be utilized as well. Unlike viral encephalitis, there are no imaging findings that are specific to viral meningitis, so imaging findings are not essential for diagnosis.

Management

For most types of viral meningitis, there is no specific treatment. In the 1990s, pleconaril was considered for the treatment of enteroviral meningitis [3], as it is designed to stop RNA virus replication and the infection cycle [39]. It was a promising drug as it displayed oral bioavailability above 70% [39] and achieved high CSF concentrations; however, it only showed a slight reduction in the duration of headaches in patients with viral meningitis [3]. Some experts support the use of pleconaril in neonates and agammaglobulinemic patients [37]. Acyclovir is efficacious in herpes viruses, specifically in herpes encephalitis and genital herpes disease; however, there is no clear evidence supporting its use in herpes virus meningitis [3] since there have been no randomized control trials or other studies to help guide clinical decision-making. Overall, the mainstay of treatment of viral meningitis is symptomatic management and supportive care. Patients should be empirically started on antibiotics when there is clinical concern for bacterial meningitis; these can be discontinued when the CSF gram stain is negative and culture has shown no growth in 24–48 h. Most patients with viral meningitis recover quickly with little to no sequelae, so there is some argument as to whether development of a specific treatment is even warranted.

Fungal

Background

Fungal meningitis is not common; however, it is associated with significant morbidity and mortality. Unlike viral and bacterial meningitis, fungal meningitis presents as a subacute to chronic meningitis, with symptoms progressing over 2–4 weeks [40]. Fungal meningitis typically manifests secondary to a systemic infection with hematogenous spread, but trauma or surgery can also cause seeding [41, 42]. Common fungal pathogens that cause meningitis include *Cryptococcus*, *Coccidioides*, and *Histoplasma* species [41]. Other opportunistic fungal pathogens should be considered when the host is immunocompromised or there is breakdown of the blood–brain barrier [42]. Fungal pathogens are typically endemic to particular geographic regions; however, with air travel, different pathogens must always be considered. It is important to obtain a thorough risk factor history including travel history, animal exposure, and occupational exposure. Some examples include the association between *Cryptococcus* with avian droppings, and histoplasmosis can be seen in patients who were spelunking due to bat guano exposure [40].

Cryptococcal meningitis is one of the most common causes of adult meningitis worldwide, especially in areas where human immunodeficiency virus (HIV) is endemic [43]. HIV is the major risk factor for cryptococcal meningitis and is associated with 79% of cases [41]. However, cryptococcal meningitis can also occur in other forms of immunosuppression such as in transplant patients and in those with hematopoietic malignancies, autoimmune disease, genetic immunodeficiency syndromes, corticosteroid use, sarcoid, and age-related immunosenescence [44, 45]. It can occur in patients without readily identified immunosuppression as well, and these account for 13–18% of all cryptococcal meningitis cases [46]. Patients without immunosuppression may be difficult to diagnose as presentation may be indolent and lack the typical features such as fever or meningeal signs [44]. Greater than 50% of all patients with cryptococcal meningitis will develop intracranial hypertension related to hydrocephalus [40].

Coccidioidal meningitis has been increasing in incidence over time and is seen in the southwestern US. Disseminated coccidioidomycosis occurs after dust exposure, and approximately 33–50% of those with disseminated disease develop meningitis [41]. Any patient with a prior history of coccidioidomycosis who presents with signs concerning of meningitis must be evaluated with CSF studies. Coccidioides meningitis is a life-threatening disease and without treatment is almost 100% fatal [47, 48]. There are also significant complications associated with this disease that can be life-threatening, including hydrocephalus, CNS vasculitis, cerebral ischemia, vasospasm, and hemorrhage [47].

Histoplasma is a dimorphic fungus that is endemic around the Ohio and Mississippi River basins, and meningitis can occur after exposure to soil contaminated by bird or bat stool [44, 49]. Histoplasmosis is contracted via inhalation of spores and typically presents with pulmonary symptoms, but it can spread hematogenously to the CNS [50]. Among patients with disseminated histoplasmosis, 5–10% develop

CNS disease [44]; however, isolated CNS involvement can be seen as well [51].

Although not as common, *Aspergillus* is another fungal pathogen that can cause meningitis. *Aspergillus* has a predilection for invading the tissue and vasculature, and this risk increases with higher levels of immunosuppression, especially in those with neutropenia, hematologic malignancies, end-stage AIDS, transplant recipients, and those requiring corticosteroids [44]. Mucorales (disease caused by which is called mucormycosis) is another angioinvasive mold that infects the same patient population but is not responsive to voriconazole, which is often used for the treatment of aspergillus [44]. In addition to the immunosuppressed, mucorales can also infect uncontrolled diabetics [44]. Mucorales should always be considered when aspergillus is in the differential; however, its clinical picture is typically rhinocerebral disease with the involvement of the sinuses and less often meningitis [44].

Diagnosis

CSF evaluation for fungal meningitis should include an opening pressure, cell count with differential, glucose and protein concentrations, gram stain, India ink, and fungal culture [42]. Specific serologic testing can be performed also. Opening pressure is important to obtain as elevated intracranial pressure can be a poor prognostic sign in cryptococcal meningitis [42, 44]. CSF parameters typically show hypoglycorrhachia and an elevated protein concentration. The nature of the pleocytosis can sometimes be an indicator of the pathogen; for example, polymorphonuclear cells can be indicative of aspergillus or blastomycosis, while eosinophils may indicate *Coccidioides* [42]. The presence of pleocytosis depends on the immune status of the patient, as those who are immunosuppressed may not be able to generate the suspected immune response [42, 44].

CSF culture is the gold standard for the diagnosis of cryptococcal meningitis but is time-consuming, and sensitivity decreases when fungal burden is low [52]. India ink is still a commonly used tool for the diagnosis of *Cryptococcus*; however, it also has a sensitivity of only 86% and this is also reduced when fungal burden is low [52]. CSF serological studies testing for *Cryptococcus* antigens should always be performed in conjunction with CSF culture because these tests can make the diagnosis prior to the final culture results and may be positive when cultures are negative [42].

The diagnosis of coccidioidal meningitis is based on positive serologic testing (IgM or IgG) or CSF culture [47, 48]. A positive CSF culture for *Coccidioides* species is diagnostic but has a low sensitivity of about 25% [53]. The pleocytosis noted in coccidioidal meningitis is typically in the double digits to hundreds, with typically a lymphocytic predominance [53].

Similar to *Cryptococcus*, CSF culture is the gold standard for the diagnosis of histoplasmosis meningitis, but it is not a sensitive test and often yields false-negative results [54]. False-negative results may be secondary to difficulty isolating small numbers of yeast organisms, so at least 10 mL of CSF is needed for culture to increase the sensitivity [51]. Ancillary testing can be performed with antigen testing from CSF, urine, or serum, but while the antigen titers can be helpful, there is significant cross-reactivity with other dimorphic fungi [40].

Imaging findings in fungal meningitis are related to the complications of the pathogen itself. CT can be used as an initial screening tool and may show findings of hydrocephalus (Fig. 16.8) or hemorrhage; however, MRI is the preferred modality due to its superior evaluation of the brain parenchyma [55]. In addition to the typical findings of meningitis, MRI can show the vascular complications of fungal meningitis including vasculitis, mycotic aneurysm formation, cerebral hemorrhage, and ischemic infarction [55].

Aspergillus can have many abnormal imaging findings in addition to leptomeningeal enhancement, including a solitary mass lesion (aspergilloma), cavernous sinus thrombosis, and multiple abscesses [40].

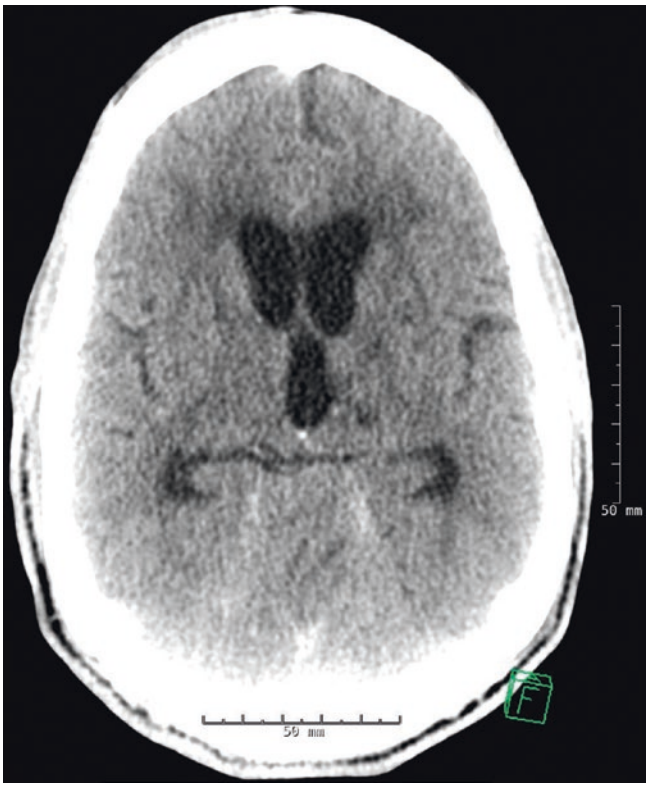

Fig. 16.8 CT head without contrast shows hydrocephalus as a result of cryptococcal meningoencephalitis

Management

For cryptococcal meningitis, the mainstay of treatment is amphotericin B with flucytosine [56]. Treatment in HIV-positive patients is broken into three stages: induction, consolidation, and maintenance. The recommended dosing of amphotericin is 0.7–1 mg/kg/day intravenous (IV) with flucytosine 100 mg/kg/day orally in 4 divided doses per day for at least 2 weeks to complete the induction stage, followed by fluconazole 400 mg/day orally for a minimum of 8 weeks (Level A-1) [57, 58]. Liposomal amphotericin B can be substituted for patients with renal dysfunction or those at risk for renal impairment at a dose of 3–4 mg/kg/day IV. Secondary induction and consolidation regimens can be considered based on availability and tolerance. Amphotericin or liposomal amphotericin B can be considered alone for 4–6 weeks (Level A-II) [57]. Another regimen that can be considered is amphotericin B at 0.7 mg/kg/day IV plus fluconazole 800 mg/day orally for 2 weeks, followed by fluconazole 800 mg/day orally for a minimum of 8 weeks (Level B-I) [56, 57]. The evidence for fluconazole plus flucytosine, fluconazole alone, or itraconazole alone is much less supportive and, in general, these regimens are discouraged [57]. Maintenance or suppressive therapy is recommended with fluconazole 200 mg daily (Level A-I), but itraconazole can be considered at 200 mg twice per day orally with consistent drug level monitoring (Level C-I) [57]. A similar regimen can be considered for organ transplant recipients, but since they are often more predisposed to renal dysfunction, it is recommended that liposomal amphotericin B be utilized. Typically the maintenance or suppressive regimen is fluconazole 200 mg–400 mg daily for 6–12 months rather than indefinitely as for HIV–infected patients (Level B-II) [57]. For patients who are not immunosuppressed, the recommended treatment regimen is amphotericin B 0.7–1.0 mg/kg/day IV plus flucytosine 100 mg/kg/day orally in four divided doses for 4–6 weeks depending on neurologic complications. Consolidation is completed with fluconazole 400 mg per day orally for 8 weeks (Level B-II) [57]. Maintenance is then completed with fluconazole 200 mg daily orally for 6–12 months (Level B-III) [57]. In the past, intrathecal or intraventricular amphotericin B had been considered for refractory disease and only in a salvage setting [58]; however, presently its use is discouraged (Level C-III) [57]. Persistence and relapse of the disease requires re-evaluating measures to decrease immunosuppression (antiretroviral therapy, decreasing immunosuppressant agents, etc.), and if those measures are optimized, induction therapy can be restarted (Level B-III) [57].

Cryptococcal meningitis is often complicated by elevated intracranial pressures [44]. A baseline lumbar puncture with opening pressure should be obtained, and if the opening pressure is >25 cm H_2O, it is recommended that CSF drainage be performed to reduce the opening pressure by 50% or to a normal pressure of <20 cm H_2O (Level B-II) [57]. Persistent elevated intracranial pressure with symptoms should be treated with repeat lumbar puncture daily, and temporary lumbar drains or a ventriculostomy can be considered if the need continues (Level B-III) [44, 57]. Treatment of elevated intracranial pressure with mannitol (Level A-III) and acetazolamide has been shown to be ineffective and can worsen the outcome (Level A-II) [44, 57].

An important consideration for cryptococcal meningitis is the paradoxical immune response that can occur, resulting in immune reconstitution inflammatory syndrome (IRIS). For isolated elevated intracranial pressure in cryptococcal meningitis, corticosteroids are generally discouraged [44, 57]; however, for increased intracranial pressure related to IRIS, prednisone 0.5–1.0 mg/kg/day or dexamethasone at higher doses can be considered (Level B-III) [57].

For coccidioidal meningitis, while many antifungal agents are effective, treatment is typically fluconazole or itraconazole [48]. Fluconazole has been shown to be effective orally with a dose of 400 mg daily; however, many clinicians favor beginning therapy with 800 mg–1200 mg per day (strong recommendation, moderate evidence) [47, 53]. Itraconazole is typically dosed 400 mg–600 mg per day [48]. In patients with refractory disease, salvage therapy with voriconazole or posaconazole can be used [47, 48]. Due to a high relapse rate and delay in neurologic sequelae, therapy should continue with an azole medication indefinitely (strong recommendation, moderate evidence) [47, 53]. A late complication that can occur is spinal arachnoiditis, which is better treated with intrathecal amphotericin. IV amphotericin B is typically not used in coccidioides meningitis due to poor bioavailability across the blood–brain barrier, but in the past, intrathecal amphotericin was the mainstay of treatment [47, 48, 53]. Hydrocephalus can occur early in the disease course, and initial treatment should be medical therapy with repeated lumbar punctures (strong recommendation, low evidence) [53]. Many of these patients will not have resolution of their hydrocephalus, so early MRI imaging and neurosurgical consultation for permanent shunt placement is recommended (strong recommendation, moderate evidence) [53].

The suggested treatment of histoplasmal CNS disease is liposomal amphotericin B 5 mg/kg/day for a total of 175 mg/kg given over 4–6 weeks, followed by itraconazole 200 mg two to three times a day for at least 1 year (Level B-III) [59]. Monitoring with repeat lumbar punctures and CSF analysis for *Histoplasma* antigen levels, white blood cell count, and antibody titers can help determine the duration of therapy [50]. Fluconazole has been considered as an alternative to itraconazole as it achieves higher CSF levels; however, animal studies have shown it to be less effective than itraconazole [50]. Ongoing monitoring of itraconazole trough levels

and CSF *Histoplasma* antigen are recommended as well. Voriconazole or posaconazole have been suggested as salvage therapies; however, there is little or no evidence currently to support their use [51]. In the case of immunosuppression, lifelong suppressive therapy may be necessary [50, 51].

The mainstay of treatment for invasive CNS aspergillosis is voriconazole (Level A-II) [44]. The standard treatment is 6 mg/kg IV every 12 h for 1 day (or two doses) followed by 4 mg/kg IV every 12 h (Level A-I) [60]. Oral therapy can be considered as well with a dose of 4 mg/kg day or typically 200 mg every 12 h (Level B-III) [60]. The duration of treatment is not well defined and is recommended for at least 6–12 weeks for immunocompetent patients and for the duration of immunosuppression in immunosuppressed patients [60]. Caspofungin is often used in combination with voriconazole; however, there is insufficient data to support this [60]. Other agents may be considered if a patient is intolerant or refractory to voriconazole, and these include itraconazole (dose not defined), posaconazole 200 mg four times a day, or liposomal formulations of amphotericin 3–5 mg/kg IV daily (Level B-III) [60].

As noted previously, although mucorales is often in the same differential as aspergillus, it is not responsive to voriconazole. Treatment of mucorales is based on a three-step approach: often aggressive debridement is needed in addition to antifungal therapy and correction of immunosuppression (Level A-II) [44, 61]. The antifungal agent of choice when dealing with CNS involvement of mucorales is liposomal amphotericin B (Level B-II) [44, 61, 62]. The dosage for CNS involvement is recommended as at least 5 mg/kg/day for at least 6–8 weeks [61]. Posaconazole can be considered in cases refractory to amphotericin B or in those who do not tolerate it (Level B-II) [44, 61]. The recommended dosing of posaconazole is 400 mg twice daily with monitoring of serum drug levels [61].

Encephalitis

Encephalitis is an acute febrile illness including any combination of neurologic signs or symptoms including convulsions, delirium, confusion, stupor, coma, aphasia, hemiparesis, reflex asymmetry, involuntary movements, ataxia, myoclonic jerks, nystagmus, ocular palsies, and facial weakness [63]. It has also been defined as an inflammation of the brain with clinical neurologic dysfunction [38].

It is imperative to distinguish between infectious encephalitis and post-infectious/post-immunization encephalitides, as treatment and prognosis vary significantly [26]. In most cases of infectious encephalitis, a pathogen is not identified; however, the majority of the identified infectious cases are usually viral [4]. In the US, the most common causes of viral encephalitis are HSV [64], West Nile virus, and enteroviruses [27]. As noted in the section regarding viral meningitis, viruses typically invade the CNS via hematogenous spread or neuronal spread (traveling retrograde from the nerve endings).

When approaching a patient with suspected encephalitis, a thorough history is important in order to ascertain risk factors, recent illness or vaccination (concerning for post-infectious encephalitis), and clinical clues that point to a certain diagnosis [38]. Epidemiological clues can also help point to a specific pathogen [38, 65]. Physical examination can also reveal clues that may be helpful in diagnosis. Rashes can be helpful; for example, those associated with chickenpox or following a dermatomal pattern raise concern for VZV. Additionally, the rash seen with coxsackieviruses can involve the hands, feet, and mouth [65]. The constellation of neurologic deficits can also point to different pathogens [65]. Ultimately, the diagnostic tests obtained will vary based on clinical suspicion.

CSF studies are the mainstay of the diagnostic work-up for a patient with suspected encephalitis. Serologic studies for specific pathogens are generally recommended, and nucleic acid amplification tests such as PCR should be performed on all CSF specimens obtained to help rule in a certain pathogen (Level A-III) [38]. Specifically, HSV PCR should be performed on CSF samples of patients with suspected encephalitis (Level A-III) [38]. Viral cultures are not routinely recommended. Regardless of the suspected pathogen, acyclovir should be started in all patients with suspected encephalitis until further results are obtained (Level A-III) [38].

It is reasonable to send serum studies to assist in ascertaining an etiology of encephalitis. Cultures of body fluid specimens (blood, stool, sputum, nasopharynx) other than CSF can be obtained with some evidence to support their use (Level B-III); however, positive results do not necessarily indicate the etiology of the encephalitis, as unrelated shedding from a prior infection can occur [37, 38]. Biopsies and histopathological specimens of brain parenchyma are generally recommended (Level A-III) if possible to obtain. Serum serologic testing can be considered with evidence to support their use (Level A-III), and serum PCR studies can also be considered (Level B-III).

Herpes Simplex Virus

HSV encephalitis is one of the most important causes of viral encephalitis in developed countries due to its frequency, high mortality, long-term morbidity, and potential for treatment [66]. Despite high HSV-1 seropositivity in

young healthy adults, HSV encephalitis incidence is only 2.3 per million people per year [67]. Clinical manifestations of HSV encephalitis include low-grade fever, altered mentation, bizarre behavior, and sometimes expressive aphasia [68]; however, these are not specific to HSV and can be seen with other etiologies [27] making diagnosis difficult on clinical findings alone. Another clinical manifestation often seen in HSV encephalitis is seizures, which occur in 40% of cases [27, 68]. Peripheral blood studies are not particularly useful; for example, either leukocytosis or a normal white blood cell count can be seen [68]. CSF studies, MRI, and electroencephalogram (EEG) provide better information for a diagnosis [68]. Most often, there is a CSF pleocytosis and an elevated CSF protein concentration, but these parameters can be normal in 5% of cases [69, 70]. The diagnosis is established by HSV PCR, which has been shown to have a sensitivity of 96.5–98.3% and a specificity of 100% [71, 72]. False-negative PCR results can occur if obtained within the first 1–3 days of infection or after treatment has commenced, and a repeat sample should be considered [68].

EEG can show lateralized periodic discharges over the temporal lobes, but this finding is only 60% sensitive and 80% specific [68]. CT has given way to MRI in terms of the imaging modality favored in HSV encephalitis [73]. MRI demonstrates abnormalities in the majority of HSV encephalitis cases and most typically displays FLAIR/T2 abnormalities indicative of inflammatory edema in the temporal lobe (Fig. 16.9) followed by the insula, frontal lobe, thalamus, and parietal lobe [27, 70]. It was previously thought that hemorrhage was commonly seen in HSV-1 encephalitis; however, it is rarely noted and some studies have shown that it may be more common in HSV-2 CNS infection [27]. Abnormalities noted on MRI often enhance with contrast and occasionally show restricted diffusion [70].

The mainstay of treatment for HSV encephalitis is acyclovir; the recommended dose is 10 mg/kg IV every 8 h for 14–21 days (Level A-I) [38, 65]. The dose should be reduced in patients with pre-existing renal impairment. There is no evidence to support adjunctive use of valacyclovir [74]. Corticosteroids have been considered as adjunctive therapy but have yet to be supported by significant evidence and are not used routinely in patients with HSV encephalitis [65, 75]. Time to initiation of acyclovir has been shown to be a predictor of outcome [73]. Whenever any sort of encephalitis is being considered, acyclovir should be initiated and can be stopped after CSF HSV encephalitis has been ruled out. Other problems that can occur with HSV encephalitis are seizures (the most common associated complication), elevated intracranial pressure, and respiratory failure requiring intubation [70].

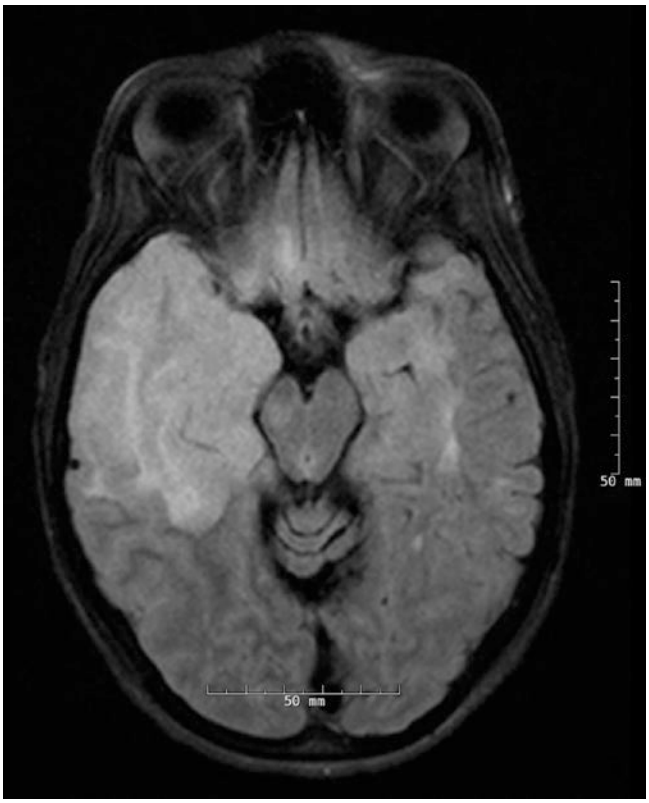

Fig. 16.9 MRI FLAIR axial image shows hyperintensity in the right temporal lobe in a patient with HSV encephalitis

Other Encephalitides

Encephalitis can be caused by non-viral etiologies such as bacteria, fungi, inflammatory/autoimmune processes, and even protozoa. In terms of viral etiologies, herpesviruses other than HSV-1 can be considered. Aside from acyclovir for the treatment of HSV-1, there is no strong evidence for other antimicrobial interventions. Table 16.2 shows the recommended treatment of other herpes viruses with the level of evidence supporting their use [38].

Other specific antivirals can be considered for different viral pathologies. Ribavirin can be considered for measles virus (Level C-III) or Nipah virus (Level C-III) [65]. Pleconaril, as noted in the section on viral meningitis above, was considered a promising agent for the treatment of enteroviruses but fell out of favor due to lack of strong evidence though can be considered in patients with enteroviral encephalitis (Level C-III) [28, 39, 65]. If the suspected pathogen is influenza virus, then oseltamivir can be considered (Level C-III) [38]. If the patient has HIV, it is strongly recommended that highly active antiretroviral therapy (HAART) be given (A-II) [38]; however, antiretroviral therapy may be delayed if the patient has an

Table 16.2 Treatment recommended for herpes virus encephalitides

Herpes virus type	Recommended treatment	Level of evidence	Notes
Herpes simplex	Acyclovir	A-I	10 mg/kg IV every 8 h in patients with normal renal function for 14–21 days
Varicella-zoster	Acyclovir	B-III	10–15 mg/kg IV every 8 h for 10–14 days
	Ganciclovir (corticosteroids)	C-III	5 mg/kg every 12 h can be considered as an alternative (if there is a vasculitic component, it is stronger evidence for steroid use (B-II) [65])
Epstein-Barr	Corticosteroids	C-III	Acyclovir is not recommended; steroids only after weighing risks and benefits
Cytomegalovirus	Ganciclovir plus foscarnet	B-III	5 mg/kg IV every 12 h for 3 weeks plus foscarnet 60 mg/kg IV every 8 h or 90 mg/kg IV every 12 h
			Cidofovir is not recommended
HHV-6	Ganciclovir plus foscarnet	C-III (B-III∗)	Treatment regimen not defined as limited evidence
			∗In immunosuppressed patients
Herpes B virus	Valacyclovir	B-III	1 g orally every 8 h for 14 days
	Ganciclovir	B-III	5 mg/kg IV every 12 h for minimum 14 days
	Acyclovir	C-III	12.5–15 mg/kg IV every 8 h for 14 days

opportunistic infection and there is an elevated risk of developing IRIS [76].

Autoimmune encephalitis is beyond the scope of this chapter but should be considered whenever the diagnosis of encephalitis is entertained.

Admission to the Neurocritical Care Unit

Several CNS infections can have significant complications that require admission to a neurocritical care unit. Airway, breathing, and circulation are the most important initial assessments of any patient. In patients with neurologic infections, obtundation leading to inability to protect the airway can mandate intubation requiring intensive care unit (ICU) level of care. It is important to choose induction agents carefully based on the patient's pathology, as succinylcholine has been shown to increase intracranial pressure in brain tumors though this may not be true for all CNS pathologies [77].

As described previously, hydrocephalus could potentially require frequent lumbar punctures, CSF diversion via an EVD or lumbar drain, and/or close monitoring for potential elevations in intracranial pressure. Elevated intracranial pressure has been shown to be a poor prognostic sign in infectious meningitis, and although it has been suggested that intracranial pressure monitors be used in meningitis, there is still limited evidence to support this [78]. While in bacterial meningitis permanent drain placement is rarely needed, it more often occurs in cases of fungal meningitis.

Seizures are commonly seen in CNS infections, especially HSV encephalitis. ICU admission may be required for prolonged EEG monitoring [27]. A patient in status epilepticus may need ICU admission for mechanical ventilation and EEG monitoring while undergoing treatment with anesthetic agents [27]. Antiseizure agents are not routinely started for prophylaxis, but there should be a low threshold to exclude seizures using EEG.

Less commonly, infection (usually bacterial or fungal) can cause vasculopathy. Arterial cerebrovascular complications including ischemic stroke can occur in up to one fifth of patients with bacterial meningitis [79]. Stroke syndromes related to fungal infections (aspergillosis and mucormycosis) are rare, but they can occur due to the angioinvasiveness of these pathogens [44]. If there is suspicion for parainfectious vasculopathy, transcranial Doppler (TCD) or CT angiography can be performed to evaluate for vasospasm [80]. If vasospasm is present, cerebral angiography and potentially intra-arterial therapy with calcium channel blockers may be beneficial. Daily TCDs may be useful to monitor for worsening vasospasm. These patients should have close neurologic monitoring because of the increased risk for progressive vasospasm and subsequent infarcts.

Both bacterial and fungal CNS infections can cause abscesses, and while these can be treated with antimicrobial therapies, there may be a need for neurosurgical intervention to drain the lesions and obtain a sample for gram stain and culture. In the appropriate clinical context, one should also consider evaluating for infective endocarditis, which can cause abscesses, embolic infarctions, and mycotic aneurysms.

Pharmacology

See Table 16.3 for recommended dosing and potential side effects of antimicrobial therapies.

Table 16.3 Pharmacology for infectious meningitis and encephalitis

Drug name	Dosage	Duration	Route of administration	Side effects/toxicity
Bacterial meningitis[a]				
Vancomycin	30–45 mg/kg every 8–12 h	10–14 days (pneumococcal)	IV	Nephrotoxicity, ototoxicity, thrombophlebitis, neutropenia, hypotension/flushing (rare)
Ceftriaxone	2 g every 12 h	7 days (*N. meningitides, H. influenzae*)	IV	Hypersensitivity, elevated INR (rare), hemolytic anemia, pancreatitis
Ampicillin	2 g every 4 h	21 days (*L. monocytogenes*)	IV	Hypersensitivity, rash, tongue and mouth soreness
Viral meningitis				
Acyclovir	10 mg/kg every 8 h	10–14 days	IV	Renal failure, agitation, delirium, tremors, hallucinations
Fungal meningitis				
Cryptococcus				
Amphotericin B (induction)	0.7–1 mg/kg/day	2 weeks	IV	Nausea, vomiting, chills, fever, rigors, renal injury, thrombocytopenia
Liposomal amphotericin B (induction)	3–4 mg/kg/day	2 weeks	IV	Anaphylaxis, infusion reactions, nausea, chills, electrolyte abnormalities
Flucytosine (induction)	100 mg/kg/day (divided into 4 doses)	2 weeks	Oral	Cardiotoxicity, confusion/delirium, ataxia, pruritus, abdominal pain
Fluconazole (consolidation)	400 mg/day	8 weeks	Oral	QTc prolongation, dizziness/seizure, hepatotoxicity, hypersensitivity, rash
Fluconazole (maintenance)	200 mg/day	Indefinitely	Oral	
Coccidioides				
Fluconazole	800 mg to 1200 mg/day initially, then 400 mg /day	Indefinitely	Oral	
Itraconazole	400 mg to 600 mg/day	Indefinitely	Oral	CNS depression, heart failure, hearing loss, hepatotoxicity, hypersensitivity, neuropathy
Histoplasma				
Liposomal amphotericin B	5 mg/kg/day	Over 4–6 weeks (to achieve total treatment dose of 175 mg/kg)	Oral	
Itraconazole (follows Liposomal amphotericin B therapy)	200 mg two to three times per day	At least 1 year	Oral	
Aspergillus				
Voriconazole	6 mg/kg twice daily for two doses, followed by 4 mg/kg	6–12 weeks	IV	Nausea, vomiting, headache, diarrhea, visual disturbance
Voriconazole	4 mg/kg/day or 200 mg every 12 h	6–12 weeks	Oral	
Mucorales				
Liposomal amphotericin B	5 mg/kg/day	6 to 8 weeks	Oral	
Posaconazole	400 mg twice daily	6 to 8 weeks	Oral	Hypertension, peripheral edema, tachycardia, rash, headache, diarrhea
Viral encephalitis				
Herpes simplex virus				
Acyclovir	10 mg/kg every 8 h	14–21 days	IV	Neurotoxicity (confusion, tremor, hallucination), renal failure

[a]Treatment for bacterial meningitis can be narrowed based on the identified pathogen and susceptibilities [7]. *CNS* central nervous system, *INR* international normalized ratio, *IV* intravenous

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Autoimmune Encephalitis in the Intensive Care Unit

17

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Introduction

Autoimmune encephalitis, a rapid, progressive encephalopathy that is secondary to an autoimmune response directed against the brain, is associated with significant morbidity, and often requires evaluation and treatment in the ICU not only for the underlying inflammatory response but also for its medical and neurological sequelae. In this chapter, we will discuss the epidemiology, clinical presentation, diagnostic approaches, and treatment options for autoimmune encephalitis as well as its sequelae, with particular focus on management and triage issues encountered by the intensivist.

Definition

Encephalitis is defined as neurologic dysfunction due to inflammation of the brain with the cerebral cortex or deep gray matter nuclei frequently involved. Infectious encephalitides have historically been the most common; however, autoimmune encephalitides have become increasingly recognized and described [1, 2].

Autoimmune encephalitides include not only those syndromes due to a primary autoimmune response but also those that are paraneoplastic. Similar to other paraneoplastic neurological syndromes, paraneoplastic autoimmune encephalitis results when systemic immune responses to peptide antigens of the tumor respond to similar to peptides found in the brain [3, 4]. Paraneoplastic autoimmune encephalitis occurs remotely from a known cancer or metastasis and can precede the detection of an associated cancer or cancer recurrence by years [3].

Since the original description of paraneoplastic autoimmune encephalitis, and particularly over the past two decades, autoimmune encephalitides have been identified and described in the absence of cancer. These primary autoimmune encephalitis syndromes are typically the result of immune responses directed against cell surface proteins (e.g., neurotransmitter receptors) [5]. For the purposes of this chapter, we will consider both paraneoplastic and non-paraneoplastic autoimmune encephalitis together.

Epidemiology

Autoimmune encephalitis is seen in a broad age range but most commonly affects young people. The annual incidence of encephalitis is up to 12.6 per 100,000 individuals [1, 6, 7], 20–30% of whom have an underlying autoimmune etiology [6, 7]. One recent population-based study found the prevalence of autoimmune encephalitis as 13.7 per 1000,000 individuals, comparable to all infectious encephalitides [2]. These observations may still be underestimates if we consider that as many as 50% of encephalitis patients have an unknown etiology [6, 7] and that the paraclinical findings associated with various autoimmune encephalitides included in recent consensus clinical criteria may be transient or of varied sensitivity [5]. Interestingly, new immune activating therapies introduced for oncological purposes are influencing the incidence of autoimmune encephalitis [8]. Although the clinical profile of encephalitic syndromes may suggest autoimmune causes, some clinical presentations may not immediately raise concerns for autoimmune encephalitis. For instance, new onset refractory status epilepticus (which may occur without cognitive or behavioral changes) may appear to be solely epileptic; however, over one third of these cases are found to be due to autoimmune encephalitis [9]. With improved identification of autoantibodies through refined testing practices and assay advances, the development and application of consensus clinical criteria, and the description of novel autoantibody-associated autoimmune encephalitis

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syndromes over the past decade, the incidence of autoimmune encephalitis is anticipated to continue to rise [1, 2].

Patients with autoimmune encephalitis commonly require care in an ICU [10, 11]. In one retrospective series at a tertiary referral center, 55% of patients meeting consensus clinical criteria for possible autoimmune encephalitis were admitted to the neurocritical care unit [10]. Patients particularly at risk for ICU admission are those who had a longer duration of symptoms before hospitalization and anemia, likely a marker of systemic inflammation [12]. Seizures (including status epilepticus), subacute cognitive decline, and respiratory failure are the most common indications for neurocritical care [10–13]. Almost 70% of patients with autoimmune encephalitis have critical care needs at some point during their initial hospital stay [14], with ICU stays greater than 4 days observed in 44% of patients in one series [13]. As discussed below, patients with autoimmune encephalitis are at risk for a variety of neurological and medical complications, with a mortality rate up to 40% in the ICU [11, 13].

Clinical Presentation

In general, the clinical presentation of autoimmune encephalitis is rapid in both onset and progression. Consensus clinical criteria were recently developed to promote the early identification of patients with autoimmune encephalitis and facilitate early initiation of immunosuppressive therapy [5]. These criteria require a subacute and progressive encephalopathy, typically over the course of days to weeks (as opposed to the months or years commonly seen in those with neurodegenerative disorders) [5]. Prodromal symptoms, such as headache and nonspecific respiratory or gastrointestinal illnesses, may precede the development of encephalopathy [15–17].

This characteristic subacute clinical presentation includes progressive deficits in working memory, altered mental status (i.e., change in level of consciousness, lethargy, and/or personality change), and/or psychiatric symptoms over a course of less than 3 months [5]. These symptoms may be accompanied by other neurological symptoms or examination findings suggesting involvement of the central nervous system [5]. Some symptoms and findings may provide clues for specific autoimmune encephalitis syndromes, such as faciobrachial dystonic seizures, neuromyotonia, and orofacial dyskinesia with new-onset psychosis being linked to the specific antibodies anti-leucine-rich glioma-inactivated 1 (anti-LGI1), anti-contactin-associated protein 2 (anti-CASPR2), and anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibodies, respectively (Table 17.1) [18–20].

The clinical presentations of anti-NMDAR encephalitis and anti-LGI1 encephalitis deserve particular mention, as they are the most commonly described autoimmune encephalitides (Tables 17.2 and 17.3). This is likely the product of the recent detailed descriptions of these respective syndromes as well as the specificity of the respective antibodies to each syndrome. The clinical presentation of anti-NMDAR encephalitis is characterized by a viral illness-like prodrome of fever and/or headache followed over the course of days to weeks by personality changes (e.g., agitation, paranoia), short-term memory loss, and abnormal movements (e.g., ballismus, catatonia, choreoathetosis, dyskinesias, and/or dystonia) [21]. Patients can subsequently progress to develop generalized or partial-onset seizures and status epilepticus, depressed levels of consciousness, central hypoventilation, and dysautonomia. The majority of patients are female and in the second to third decades of life. With that said, the age range of cases extends from early childhood through the late elderly years, with anti-NMDAR encephalitis manifesting among males more commonly in the first through second decades [20]. Across all age groups, behavioral change is the most common first symptom, while seizures are prevalent [20]. This may be why anti-NMDAR encephalitis is frequently initially misdiagnosed as a psychiatric disorder [22, 23]. Movement disorders are common among patients less than 12 years in age, less so among those who are older [20]. Only 38% of patients are found to have an underlying malignancy at the time of initial presentation, most often an ovarian teratoma (94%) although a variety of other malignancies have been reported such as extraovarian teratomas and cancers of the lung and breast [20].

Anti-LGI1 encephalitis accounts for 40% of patients seropositive for antibodies directed against the voltage-gated potassium channel (anti-VGKC) complex. Of the remaining patients, 10% have anti-CASPR2 antibodies and 50% are seronegative for both anti-LGI1 and anti-CASPR. The "double negative" anti-VGKC seropositive population is heterogeneous in terms of syndromes, cancer association, and response to immunosuppression, possibly reflecting immune responses to other proteins associated with the VGKC complex that have yet to be characterized, limiting its value as a specific marker of autoimmune neuroinflammation [24].

Patients with anti-LGI1 encephalitis most commonly present in their sixth to eighth decade with limbic encephalitis. Anti-LGI1 encephalitis is characterized by short-term memory loss, seizures, and psychiatric symptoms, with evidence of a combination of medial temporal lobe inflammation, temporal lobe epilepsy or dysfunction, or intrathecal inflammation. A large subset of patients (13%) present without evidence of brain inflammation by magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) analysis [25]. Faciobrachial dystonic seizures (FBDS) have been described preceding the development of short-term memory loss and encephalopathy suggestive of limbic encephalitis by weeks to months in

Table 17.1 Autoantibodies in autoimmune encephalitis

Antibody	Antigen class	Syndromes and associated neurological findings	Frequency of cancer	Main cancer type	Response to immunotherapy
Limbic encephalitides					
AMPA receptor [68]	Synaptic receptor	Limbic encephalitis, epilepsy, nystagmus	65%	Thymoma, small-cell lung carcinoma	71% with partial ($N = 10$) or good response ($N = 5$) after treatment with immunotherapy and oncologic therapy as appropriate ($N = 21$)
Amphiphysin [69]	Intracellular	Limbic encephalitis, stiff-person syndrome, more general encephalitis, subacute cerebellar degeneration, myelopathy, subacute sensory neuronopathy, peripheral neuropathy	79%	Small-cell lung carcinoma, breast, thymoma	Among patients with various syndrome who were anti-amphiphysin seropositive, various first-line therapies used with 80% improving who received corticosteroids ($N = 5$), 50% of those who received IVIG ($N = 4$), none with plasmapheresis ($N = 4$). 60% treated with oncologic therapy improved ($N = 20$)
CASPR2 (contactin-associated protein 2) [19]	Cell surface	Limbic encephalitis, Morvan syndrome, neuromyotonia	20–50%	Thymoma	52% with partial and 39% with complete recovery after treatment with various combinations of first-line immunotherapy ($N = 23$)
CV2/CRMP (collapsing response mediator protein) 5 [70–72]	Intracellular	Limbic encephalitis, more general encephalitis, chorea, subacute cerebellar degeneration, cranial neuropathies, uveitis, optic neuritis, retinopathy, myelopathy, subacute sensory neuronopathy, autonomic neuropathy, peripheral neuropathy	87%	Small-cell lung carcinoma, thymoma, uterine sarcoma, prostate small cell carcinoma	Limited to case series of various syndromes (mostly movement disorders). Range of response to immunotherapy 13–50%, primarily intravenous methylprednisolone. The primary focus of care is on oncological therapy
$GABA_B$ receptor [73]	Synaptic receptor	Limbic encephalitis, epilepsy, cerebellar ataxia	50%	Small-cell lung carcinoma	33% with a complete response and 40% with partial response to immunotherapy alone; 13% with a complete response and 13% with partial response to immunotherapy and oncological therapy (13%; $N = 15$)
GAD 65 (65 kDa glutamic acid decarboxylase) [74]	Intracellular	Limbic encephalitis, stiff-person syndrome, cerebellar ataxia, autoimmune epilepsy, brainstem and more general encephalitis, myelopathy, large fiber peripheral neuropathy, autonomic neuropathy	15%	Small-cell or non-small-cell lung carcinoma, thymoma or thymic carcinoma, testicular seminoma, thyroid neoplasia, breast adenocarcinoma, gastrointestinal carcinomas, renal cancer, lymphoma, myeloma	Across all neurological phenotypes of GAD65 autoimmunity, approximately 50% of patients improve with immunotherapy
Hu (ANNA1) [75]	Intracellular	Limbic encephalitis, brainstem encephalitis, more general encephalitis, subacute cerebellar degeneration, myelitis, sensory neuronopathy, autonomic neuropathy, peripheral neuropathy	84%	Small-cell or non-small-cell lung carcinoma, prostate cancer, gastrointestinal cancer	Clinical improvement or stabilization in 38% treated with oncological therapy with or without immunotherapy ($N = 80$) and in 21% treated with immunotherapy alone ($N = 34$)
LGI1 (leucine-rich glioma-inactivated 1) [25]	Cell surface	Limbic encephalitis, faciobrachial dystonic seizures, abnormal sleep behavior	5–10%	Thymoma	50% improve with first-line immunotherapy, and 71% at 24 months had a good outcome ($N = 48$)

(continued)

Table 17.1 (continued)

Antibody	Antigen class	Syndromes and associated neurological findings	Frequency of cancer	Main cancer type	Response to immunotherapy
Ma1 or Ma2 [76]	Intracellular	Limbic encephalitis, brainstem encephalitis, hypothalamic encephalitis, mesencephalic encephalitis, subacute cerebellar degeneration	>95%	Ma 1: various lung cancers; Ma2: testicular cancer, seminomas	With various immunotherapy regimens, 36% improved and 46% were stable ($N = 24$)
Other encephalitides					
MOG (myelin oligodendrocyte glycoprotein) [77, 78]	Cell surface	Acute disseminated encephalomyelitis (ADEM), neuromyelitis optica, optic neuritis, myelitis	0%	None	Varies by presentation, with brainstem encephalitis and encephalitis least common (14% total). MOG antibodies may be transiently present in postinfectious disorders such as ADEM. Based on data from patients with optic neuritis and those with myelitis ($N = 62$), complete recovery in 35–52%, partial response in 40–65%
NMDA receptor [20]	Synaptic receptor	Anti-NMDA receptor encephalitis with anxiety, psychosis, epilepsy, extrapyramidal disorder, hypoventilation, central dysautonomia	Varies with age and sex; 38% across the population	Ovarian teratoma	Of those treated with first-line immunotherapy alone or with teratoma resection, 50% improve at 4 weeks. Of those not improved at 4 weeks and then given second-line therapy, 67% with a complete or mild disability at 24 months ($N = 472$)
Dopamine 2 receptor [79]	Synaptic receptor	Basal ganglia encephalitis, Sydenham chorea	0%	None or unknown	Limited case series with 7 patients treated with immunotherapy, either corticosteroids or corticosteroids with IVIG, 5 with clinical improvement. Suggestion that more aggressive IV methylprednisolone + IVIG has a better outcome
Aquaporin 4 [80]	Cell surface	Encephalitis, neuromyelitis optica (NMO), optic neuritis, myelitis	0%	None	Rarely, NMO patients may present with encephalopathies or encephalitis syndromes. Overall, patients with NMO respond well to immune therapy. 53% who received first-line immunotherapy (IV methylprednisolone alone or followed by plasmapheresis if limited response to corticosteroids) without motor disability ($N = 15$)
DPPX (dipeptidyl-peptidase-like protein 6) [81]	Cell surface	Encephalitis, psychiatric symptoms, diarrhea, tremor, nystagmus, hyperekplexia, ataxia, progressive encephalomyelitis with rigidity and myoclonus (PERM)	<10%	Lymphoma	44% with complete or near complete recovery, 33% with a mild disability after immunotherapy ($N = 9$)
$GABA_A$ receptor [31]	Synaptic receptor	Encephalitis, epilepsy, cerebellar ataxia	<5%	Thymoma	28% complete, 72% partial clinical improvement after immunotherapy and oncologic therapy ($N = 21$)
mGluR5 [82]	Synaptic receptor	Encephalitis	55%	Hodgkin's lymphoma, small-cell lung cancer	55% with complete recovery and 45% with partial recovery following treatment with immunotherapy ($N = 4$), immunotherapy and oncologic therapy ($N = 4$), oncological therapy alone ($N = 2$), or none ($N = 1$)

Table 17.2 Case series of anti-NMDAR encephalitis

Anti-NMDAR encephalitis												
Study	No	Age (−/+)	ICU (%)	Psych (%)	Cog (%)	Se (%)	SE (%)	RSE (%)	Mov (%)	Dys (%)	Int (%)	Mort (%)
Titulaer et al. Late-onset encephalitis. Multicenter multination study. Spain, 2013 [83]	31	52 (45–84)	27 (87)	31 (100)	26 (84)	4 (13)	–	–	21 (68)	13 (42)	10 (32)	5 (16)
Titulaer et al. Treatment and prognosis for long-term outcomes. Multicenter multination study. Spain, 2013 [20]	577	21 (0.33–85)	435 (77)	238 (65)[a]	288 (85)[a]	230 (68)[a]	–	–	241 (71)[a]	166 (49)[a]	139 (41)[a]	7 (5)[a]
Chi et al. Risk factors for mortality in encephalitis. Single center single nation study. China, 2017 [58]	96	24.5 (9–71)	13 (14)	87 (90.6)	15 (16)	77 (80)	29 (30)	13 (14)	–	6 (6)	13 (14)	11 (12)
de Montmollin et al. Adults with encephalitis in UCI. Multicenter multination study. France, 2017 [30]	76	24 (20–31)	133 (72)	–	31 (41)	30 (39)	34 (45)	28 (37)	–	2 (3)	59 (78)	7 (4)
Wang et al. Encephalitis in pediatric population. Single center single nation study. China, 2017 [65]	51	8 (0.33–14)	7 (14)	30 (55)	26 (51)	34 (67)	14 (27)	–	–	12 (24)	7 (23)	0
Gable et al. Encephalitis in pediatric population. Multicenter single nation study. USA, 2017 [29]	24	10.5 (2–18)	10 (54)	16 (66)	–	16 (66)	–	–	19 (79)	13 (54)	8 (33)	1 (4)
de Bruijn et al. Neuropsychological outcome in pediatric population. Multicenter single nation study. Netherlands, 2018 [84]	28	14 (1–17)	13 (46)	27 (96)	26 (93)	24 (86)	–	–	24 (86)	15 (24)	4 (14)	–
Ho et al. Encephalitis in pediatric population. Multicenter single nation study. China, 2018 [85]	15	12 (1–17)	10 (67)	14 (93)	14 (93)	–	–	12 (80)	5 (33)	2 (13.3)	–	
Granata et al. Movement disorders in Pediatric encephalitis. Single center single nation study. Italy, 2018 [86]	18	12.4 (12–17.5)	1 (6)	5 (28)	16 (89)	17 (94)	–	–	18 (100)	7 (41.1)	–	1 (6)
Zhang et al. Late-onset encephalitis. Single center single nation study. China, 2018 [87]	18	51.5 (45–78)	1 (6)	73 (60)	5 (4)	2 (11)	1 (6)	1 (6)	6 (33)	6 (33)	3 (17)	1 (6)
Mueller et al. Genetic predisposition in encephalitis. Multicenter multination study. Germany, 2018 [88]	96	30.3 (17–44)	44 (42)	88 (92)	–	70 (73)	–	–	43 (45)	37 (39)	–	–

ICU intensive care unit, *Psych* psychiatric, *Cog* cognitive, *Se* seizures, *SE* status epilepticus, *RSE* refractory status epilepticus, *Mov* movement disorders, *Dys* dysautonomia, *Int* intubation/hypoventilation, *Mort* mortality

[a]Only adults' data was included

anti-LGI1 encephalitis. These immunotherapy (rather than antiepileptic) responsive seizures are very brief (on the order of seconds), frequent (median of 50 times per day in one series) unilateral or bilateral jerking movements of the arm and ipsilateral face more often than leg [18, 26]. High emotion or auditory or visual stimuli are triggers for FBDS in 28% of patients [26]. In those patients with anti-LGI1 encephalitis presenting with FBDS, earlier treatment with immunotherapy predicted improved outcomes in terms of cognition, disability, and seizure control [18, 19]. As has been observed in patients with antibody responses directed at cell surface proteins, anti-LGI1 is not strongly associated with a particular cancer, with only 7% of patients found to have a malignancy [26].

The subsequent diagnostic evaluation of a patient with suspected autoimmune encephalitis is directed not only at supporting a diagnosis of autoimmune encephalitis and its sequelae to permit rapid treatment but also at assuring the absence of other etiologies of a subacute and progressive encephalopathy, particularly infectious encephalitides. When evaluating a patient with suspected autoimmune encephalitis, it is crucial to be mindful that the diagnosis of autoimmune encephalitis is clinical, incorporating clinical presentation with paraclinical findings, and is not solely dependent on the detection of an autoantibody.

Table 17.3 Case series of anti-LGI encephalitis

Anti-LGI1 encephalitis									
Study	No	Age (−/+)	ICU (%)	Psych (%)	Cog (%)	Se (%)	SE (%)	Dys (%)	Mort (%)
Finke et al. Cognitive deficits and structural hippocampal damage in encephalitis. Multicenter single nation study. Germany, 2017 [89]	30	65.7 (12.3)	–	11 (37)	30 (100)	28(93)	–	–	1(3)
Gao et al. Clinical characterization of autoimmune LGI1 antibody limbic encephalitis. Single center single nation study. China, 2016 [90]	10	51.5 (27–75)	–	2 (20)	9 (90)	10(100)	1(10)	–	2(20)
Celicanin et al. Autoimmune encephalitis associated with LGI1 ab. Denmark, 2017 [91]	16	62 (29–84)	–	5 (31)	10 (63)	6(38)	–	4(25)	1(6.2)
Irani et al. Faciobrachial dystonic seizures precede limbic encephalitis. Multicenter multination study. UK, 2011 [26]	29	64 (36–83)	1 (3)	–	19 (66)	26(77)	–	5(19)	–
Mueller et al. Genetic predisposition in encephalitis. Multicenter multination study. Germany, 2018 [88]	54	62.7 (51–74)	4 (7)	31 (57)	–	41(76)	–	6(12)	–

ICU intensive care unit, *Psych* psychiatric, *Cog* cognitive, *Se* seizures, *SE* status epilepticus, *Dys* dysautonomia, *Mort* mortality

Diagnostic Evaluation

Diagnostic studies incorporated in the evaluation for possible autoimmune encephalitis include autoantibody testing along with common and widely performed paraclinical diagnostics: CSF studies, electroencephalography, and brain MRI. We will consider each briefly in turn as well as the developing role of brain fluorodeoxyglucose-positron emission tomography (FDG-PET) as a diagnostic modality. In addition, the evaluation includes assessing for occult malignancy in the event that the encephalitis is a paraneoplastic syndrome.

Antibody Testing

Several autoantibodies have been described in association with autoimmune encephalitis (Table 17.1), each serving as either a marker of an autoimmune response or in a direct pathogenic capacity [4, 27]. Patients with possible autoimmune encephalitis should be tested for the presence of antibodies not only in the serum but also in the CSF [5]. This advisement is made since in some, but not all, autoimmune encephalitis syndromes (e.g., anti-NMDAR encephalitis), CSF antibody assays are more sensitive than those in the serum [5, 20, 25]. CSF antibody testing allows for greater specificity as it is not uncommon for multiple antibodies to be detected in the serum, with only one antibody detected in paired CSF that more likely reflects the underlying immune response [5]. Thus, CSF antibody testing has a lower rate of false-positive and false-negative results than testing in the serum alone [5].

CSF Testing

In addition to antibody testing, CSF testing plays an essential role in the initial management of a patient suspected to have autoimmune encephalitis, both to support the possibility of this diagnosis and to evaluate for other potential diagnoses. Moderate lymphocytic-predominant CSF pleocytosis (>/= 5 white blood cells/milliliter) is a criterion incorporated in the most recent consensus clinical criteria; however, this finding may depend on syndromic timing. Late in the disease course, no abnormalities may be noted in the CSF except for an elevated protein level. Elevated CSF to serum immunoglobulin G index and intrathecal oligoclonal bands are also supportive, though not diagnostic, of an intrathecal autoimmune response. It is, however, important to note that CSF glucose at a depressed level relative to serum would be more suggestive of an infectious etiology than autoimmune encephalitis.

Electroencephalography (EEG)

EEG findings are also included in the consensus criteria, namely, temporal lobe slowing (bilateral or unilateral) and electrographic seizures ranging from focal to generalized and including nonconvulsive and convulsive status epilepticus that may be refractory [5, 9, 28]. Otherwise, EEG itself is variable in its sensitivity across the autoimmune encephalitides, with slowing and disorganized activity being the most frequent findings [5]. Some rare electrographic findings have been described in specific syndromes, such as extreme delta brush in anti-NMDAR encephalitis; however, such findings appear to be the exception rather than the rule [29].

MRI

Although brain MRI is an important diagnostic tool in the evaluation of encephalitis, around 75% of cases of autoimmune encephalitis do not demonstrate abnormalities on MRI. Clinical consensus criteria include T2/FLAIR (fluid-attenuated inversion recovery) hyperintensities of the medial temporal lobes or multifocal T2/FLAIR hyperintensities of the gray matter, white matter, or a combination of the two – suggestive of demyelination or inflammation (Fig. 17.1) [5]. The most frequently affected areas are the frontal cortex, basal ganglia, thalamus, temporal lobe, cerebellum, and insula [29, 30]. The sensitivity of such abnormalities vary, from 93% when evaluated for among patients otherwise meeting the consensus criteria for probable or definite autoimmune encephalitis in one series to approximately half of patients with anti-NMDAR encephalitis and 10–20% of patients with anti-LGI1 encephalitis presenting with FBDS [2, 18, 20]. In addition, such findings can be mild, transient, associated with only subtle contrast

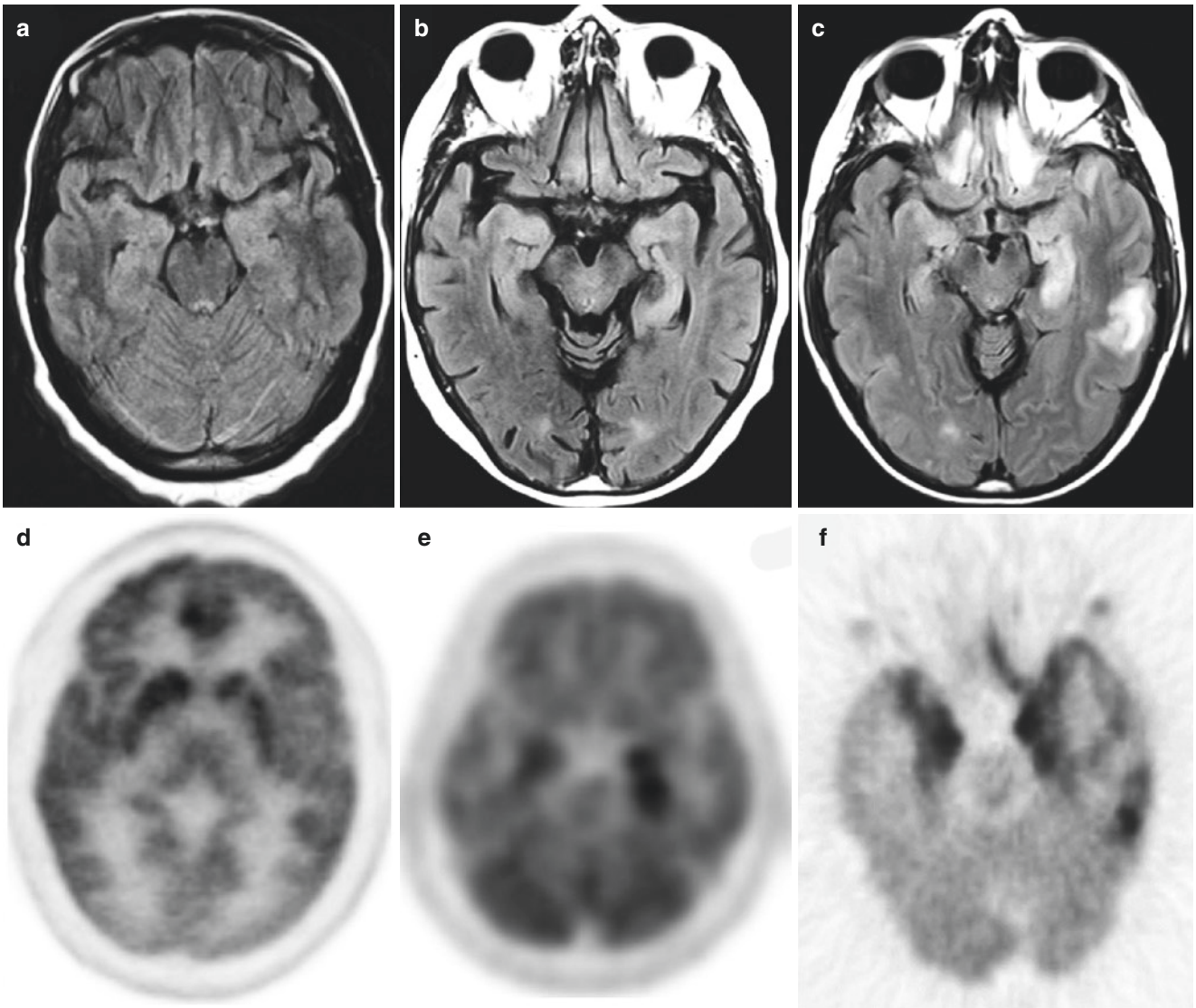

Fig. 17.1 Examples of brain MRI and FDG-PET findings in autoimmune encephalitis. Brain MRI: (**a**) Subtle T2 hippocampal T2/FLAIR hyperintensities in a patient in the acute phase of anti-NMDAR encephalitis. (**b**) T2/FLAIR hyperintensities in the bilateral medial temporal lobes of a patient in the acute phase of anti-LGI1 encephalitis. (**c**) Multifocal T2/FLAIR hyperintensities involving the left more so than right hippocampi and gray and subcortical white matter of the temporal lobes in a patient with anti-GAD65 encephalitis. Brain FDG-PET/CT: (**d**) Marked cortical hypometabolism in the same patient with anti-NMDAR encephalitis. (**e**) Areas of hypermetabolism of the bilateral hippocampi in the same patient with anti-LGI1 encephalitis. (**f**) Areas of hypermetabolism in the bilateral medial temporal lobes in the same patient with anti-GAD65 encephalitis

enhancement, or even asynchronous (some appear while others disappear) in appearance, as has been recently described in anti-$GABA_A$ receptor antibody-associated encephalitis [31]. A common late finding, particularly in the subset of autoimmune limbic encephalitides, is the development of mesial temporal lobe sclerosis [18, 31, 32]. Selective involvement of diencephalic structures or brainstem is characteristic of some autoimmune encephalitides such as those associated with Ma-Ta antibodies [4].

FDG-PET

Though included in early descriptions, such as that for anti-NMDAR encephalitis, dedicated brain FDG-PET imaging has recently attracted growing interest as a potential diagnostic and monitoring test in autoimmune encephalitis [33–35]. Hypermetabolism by FDG-PET of the medial temporal lobes is included in the clinical consensus criteria for definite limbic encephalitis but not those for autoimmune encephalitis in general [5]. Case series reporting a gradient of occipital hypometabolism to frontotemporal hypermetabolism in anti-NMDAR encephalitis, hypermetabolism of the basal ganglia and medial temporal lobes in anti-LGI1 encephalitis, and normalization of these abnormalities with improvement in functional status suggest an expanded utility of FDG-PET in the evaluation and clinical monitoring of patients with autoimmune encephalitis [26, 35]. As the clinical value of brain FDG-PET is evaluated in the future, it will be important for researchers and clinicians to be mindful that abnormal patterns of cerebral metabolism on FDG-PET also have been well-described in neurodegenerative syndromes that can present with subacute cognitive decline, such as posterior cerebral atrophy and Lewy body dementia, which are both associated with occipital hypometabolism [36]. In addition, treatments commonly prescribed to patients in the acute phase of autoimmune encephalitis, such as corticosteroids and antiepileptic medications, have been observed to alter cortical metabolism [37, 38].

Biopsy of Brain Tissue

A biopsy of brain tissue is not generally used to diagnose autoimmune encephalitis for several reasons. Neuropathological findings such as infiltration by lymphocytes or microglia activation are frequently nonspecific and nondiagnostic. Also, one study found that brain biopsy contributed to diagnosis in only 8% of patients with autoimmune encephalitis [39]. Finally, antibody testing as described above yields more specific diagnoses and is noninvasive.

Evaluation for Occult Malignancy

As autoimmune encephalitis is considered a classic paraneoplastic syndrome, the clinical evaluation of a patient suspected to have this condition entails an assessment for an occult malignancy [40]. Some tumors produce peptides that are similar to those found in the nervous system, leading to immune cross-reactivity and paraneoplastic neurological syndromes. In particular, the immune system reacts against tumors leading to the development of cytotoxic and antibody-mediated responses directed not only at the tumor but also against the nervous system. In 80% of cases, neurological manifestations develop before the cancer diagnosis [41]. Paraneoplastic disorders usually develop during the early stages of cancer, so the tumor may be difficult to find. If detected, an antibody can guide monitoring for strongly associated tumors. A patient should be followed with regular diagnostic imaging to screen for an occult malignancy at regular intervals for 4 years. Studies have shown that after this time, the likelihood of detecting cancer is low [42].

Differential Diagnostic Considerations

The preceding discussion focused on the diagnostic value of each respective study for autoimmune encephalitis. In parallel, other diagnostic possibilities should be simultaneously evaluated for and eliminated as potential diagnoses. Differential considerations for a subacute, rapidly progressive encephalopathy include infection (e.g., encephalitis or meningoencephalitis due to *herpes simplex virus*, *varicella zoster virus*, human immunodeficiency virus (HIV), *enterovirus*, *Cryptococcus*, syphilis, and prion disease), encephalopathy due to systemic disease (e.g., sepsis, organ failure, vitamin deficiency, electrolyte abnormalities), rheumatologic and systemic autoimmune disease (e.g., systemic lupus erythematosus), illicit (e.g., ketamine) or prescribed (e.g., anticholinergic, neuroleptic, serotonergic) drug toxicity or withdrawal, metabolic disorder (e.g., mitochondrial and urea cycle disorders), cerebrovascular disease (e.g., recurrent ischemic stroke), cancer (e.g., primary and secondary brain cancers), and seizure (e.g., nonconvulsive status epilepticus) [5, 43, 44]. A detailed clinical history with brain imaging by MRI, CSF analysis, and EEG can be invaluable in the early period of hospitalization to rapidly sift through this broad differential as well as gather information to support the diagnosis of autoimmune encephalitis.

This diagnosis should be made based on the clinical presentation, and diagnostic evaluation should not be reserved for those with a detected commercially testable antibody nor

applied to those who respond to systemic immunotherapy. From a practical perspective, antibody testing may not always be readily accessible and, if performed, the results may take weeks to return. In addition, there is a growing catalog of described antibody-associated autoimmune encephalitis syndromes, some of which are not testable at the commercial laboratory level. Thus, failure to detect an antibody in the serum or CSF does not exclude the possibility of autoimmune encephalitis in the appropriate clinical scenario but rather argues for the testing of serum and CSF in a neuroimmunological referral center. With that said, false-positive antibody results can occur. Finally, a variety of conditions respond by varying degrees to systemic immunosuppression, such as corticosteroids in the treatment of primary and secondary cancers of the brain as well as neurosarcoidosis. Together, these points emphasize the importance of the clinical presentation and a careful evaluation to identify those with autoimmune encephalitis.

As early recognition and initiation of immunotherapy appear to be associated with improved clinical outcome in autoimmune encephalitis, the diagnostic evaluation is directed at identifying those patients who may have autoimmune encephalitis, assessing for other encephalitis etiologies (particularly infectious), screening for occult malignancy, initiating immunotherapy with escalation as needed, and managing sequelae of the encephalitis syndrome. We will now turn to immunotherapy and the management of autoimmune encephalitis sequelae commonly encountered in the ICU.

Immunotherapy

As autoimmune encephalitis is relatively rare, guidelines for immunotherapeutic management are lacking. No controlled prospective clinical trials have been conducted to determine efficacy of treatments in autoimmune encephalitis. At the present, most of the treatments rely on extant understanding of disease mechanisms, expert opinion based on clinical experience and case series, and a few relatively small prospective trials. When considering acute immunotherapy options, it is important to consider the patient's comorbidities and phase of illness at presentation. Serological status, if known, may guide agent selection and prognostication of recovery. It is essential to mention that delay in therapy initiation could worsen outcomes [45].

First-line immunotherapies for autoimmune encephalitis include intravenous (IV) corticosteroids (typically methylprednisolone), intravenous immunoglobulin (IVIG), and plasmapheresis (PLEX) (Table 17.4). Second-line therapies commonly used include rituximab and cyclophosphamide (Table 17.4), while mycophenolate and azathioprine are typically reserved for maintenance of immunosuppression after the acute phase of the illness. Patients seropositive for autoantibodies directed at cell surface proteins tend to respond well to antibody-directed therapies (i.e., IVIG and PLEX). These typically follow or accompany courses of IV corticosteroids. Consideration for selection of IVIG versus PLEX relies on patient status and active additional medical concerns [46, 47].

Corticosteroids are a helpful class of medications in a variety of autoimmune disorders, but their prolonged use is associated with multiple comorbidities including insulin resistance, diabetes mellitus, osteopenia, and increased risk for opportunistic infections. IVIG may be associated with a higher risk for chemical meningitis, hyperviscosity, and thrombotic syndromes. In addition, IVIG occasionally triggers headache, flushing, chest tightness, fever, chills, myalgias, fatigue, dyspnea, back pain, nausea, vomiting, diarrhea, and tachycardia and infrequently acute renal failure, neutropenia, autoimmune hemolytic anemia, skin reactions, and arthritis. PLEX can result in decreased arterial blood pressure, arrhythmias, sensations of cold with temporarily elevated temperature, paresthesias, and rarely life-threatening conditions (e.g., shock, hypotension, persistent arrhythmias, hemolysis) [48–50].

Immune absorption (IA) is an alternative therapy to PLEX, although this medication is not yet available in many countries, including the United States. Studies have suggested an at least equivalent efficacy of IA compared to PLEX [51, 52]. IA allows rapid and selective elimination of antibodies, making this medication an excellent option. IA produces an immediate intravascular reduction of antibody and immune complex concentration as well as antibody redistribution that causes subsequent immunomodulatory changes. While PLEX is a nonselective medication and associated with a reduction in coagulation factors, IA is selective and has fewer adverse effects. In a retrospective analysis of 30 patients with autoimmune encephalitis treated with PLEX or IA, 65% improved after PLEX and 100% after IA [51]. Furthermore, a retrospective analysis of 13 patients with autoimmune encephalitis treated with IA showed that 85% had improvement of their symptoms; however, this efficacy could not be completely attributed to IA because most patients were treated with concomitant corticosteroids [53].

When a detected antibody is directed to an intracellular protein, therapies directed at the cell-mediated immune response rather than immunomodulatory therapies are advocated [46, 47]. In the acute setting, therefore, cyclophosphamide plays an important role in suppressing the cytotoxic response with the aim of reducing the extent of neuronal injury due to the cell-mediated immune response [46, 47].

No guidelines exist to otherwise guide the selection of first-line immunotherapy nor subsequent escalation to

Table 17.4 Common acute immunotherapies for autoimmune encephalitis

Therapies	Initial treatment regimen	Time to response	Pretreatment management	Side effects
First-line				
Intravenous methylprednisolone	1000 mg daily for 3–5 days	Days to weeks with benefit for weeks	Assess for hypertension, baseline serum glucose and electrolytes, close glucose monitoring and consideration for insulin adjustments in known diabetics	Insomnia, psychiatric symptoms, hyperglycemia (close glucose monitoring with sliding scale insulin advised), electrolyte abnormalities, fluid retention, hypertension, peptic ulcer (gastric ulcer prophylaxis advised), Cushing syndrome, cataracts, infection, osteoporosis, avascular necrosis (patients should be advised of risk and monitored for), addisonian crisis in setting of rapid withdrawal
Intravenous immunoglobulin[a]	0.4 g/kg/day for 5 days	Days to weeks with benefit for approximately a month	Consider IgA-level assessment; premedication with acetaminophen and diphenhydramine	Headache, aseptic meningitis, thromboembolic events, acute renal failure, anaphylaxis in those who are IgA deficient
Plasmapheresis	5 exchanges, typically an exchange every other day. Schedules vary by institution	Days to weeks with benefit for months	Plasmapheresis catheter placement of adequate caliber, assessment to assure no active infection	Hypotension, electrolyte imbalance. With central line, infection, hemorrhage, thrombosis, and pneumothorax are risks
Second-line				
Rituximab[a]	1000 mg weekly for 2 weeks, or 375 mg/m^2 body surface area weekly for 4 weeks	Weeks	Screening for hepatitis B and C, screening for tuberculosis	Allergic reaction, opportunistic infection, reactivation of tuberculosis or hepatitis B
Intravenous cyclophosphamide[a]	500–1000 mg/m^2 monthly for 3–6 months	Weeks	Baseline complete blood cell count, liver function tests, serum creatinine. Assure adequate hydration over 24 h prior to dose (2–3 L), normal saline 500 mL intravenous 1 h prior to a dose, prochlorperazine or ondansetron as nausea and vomiting prophylaxis, mesna for hemorrhagic cystitis prophylaxis	Nausea, vomiting, alopecia, mucositis, hemorrhagic cystitis, infertility, myelosuppression

[a]Can be used in both acute and maintenance phases of treatment

second-line treatments in the acute phase. Second-line treatments are typically considered once the period of anticipated response (around 2 weeks) to first-line treatment has passed as well as in severe presentations [20]. With that said, there is evidence to suggest a role for rituximab, a monoclonal antibody against CD20, as second-line immunotherapy for both seropositive and seronegative autoimmune encephalitis, with tolerability and improved outcomes observed [54, 55]. Furthermore, studies have shown good efficacy of rituximab in patients with IgG4 subtype antibodies, and IgG4 antibodies predominate in anti-LGI1 and anti-CASPR2 encephalitis.

The most common side effects of rituximab are infusion-related reactions, infections, tiredness, and nausea; however, in general, it is a medication with a good safety profile. On the other hand, cyclophosphamide can potentially cause infertility among other side effects. Therefore, the collection of eggs and sperm and the administration of GnRH agonists in women are recommended [56].

Complications of Autoimmune Encephalitis in the ICU

As already stated, a large percentage of encephalitis patients require ICU admission. The most common reasons for ICU care in autoimmune encephalitis are altered mental status requiring intubation, status epilepticus/refractory status epilepticus, severe hyperkinetic movements, respiratory failure, autonomic dysfunction, and increased intracranial pressure (Tables 17.2 and 17.3). ICU level care, which is

presumably linked to higher costs, is strongly associated with long-term outcome [39]. A recent study in a tertiary referral hospital showed that intensive care charges are around $173,000 vs. $50,000 for autoimmune encephalitis patients who do not require ICU admission [11]. In addition, the mortality rate of ICU-admitted patients ranges between 12% and 40% [13, 39, 57]. The main causes of death are severe pneumonia, multiple organ dysfunction syndromes, and refractory status epilepticus [58].

Status Epilepticus (SE) and Refractory Status Epilepticus (RSE)

SE is a frequent, and sometimes the only, manifestation of autoimmune encephalitis. SE represents the principal cause for ICU admission and may evolve into RSE [58, 59]. Studies have reported generalized, nonconvulsive, partial, and complex seizures. In a cohort of patients with autoimmune encephalitis, 28% of patients suffered from SE for 7 or more days and required on average 5 antiepileptic medications [15].

SE treatment in autoimmune encephalitis centers on the use of antiepileptic medications for seizure control as well as immunosuppression [60]. There are validated protocols for seizure control in SE that include IV lorazepam, diazepam, and phenytoin or intramuscular midazolam or rectal diazepam as first-line therapy (Class I). Valproate and levetiracetam are second-line options (Class I–III), and IV sedative medications such as pentobarbital, propofol, or midazolam are used in case of failure of first- and second-line therapies. If seizures are uncontrolled, topiramate and phenobarbital can also be considered. Of note, phenobarbital is associated with more adverse effects such as hypotension and a high mortality rate. In addition, once infectious etiologies have been eliminated, first-line immunotherapy as per the discussion above should be rapidly initiated. In case of severe seizures, a vagus nerve stimulator or surgical resection of the seizure focus may be necessary [61]. Early diagnosis and treatment of SE/RSE are associated with better neurological outcomes and fewer relapses [62].

Another alternative for uncontrolled seizures with poor response to antiepileptic medications is the ketogenic diet (KD). This is a high-fat and low-carbohydrate diet that induces ketone bodies and has been effective in drug-resistant epilepsy in children and adults. The KD has been used in patients with anti-NMDAR encephalitis with success, and it is thus a potential therapy option [63]. A recent study in a tertiary referral center showed seizure control in 73% of patients with super-refractory SE after 2 days of the diet. At discharge, 67% were alive and the majority recovered to their baseline [64].

Elevated Intracranial Pressure

Intracranial hypertension is a well-known indication for ICU admission in patients with autoimmune encephalitis. Elevated intracranial pressure has been reported (in 34.4% and 21.5% of patients) in only two cohorts of patients with anti-NMDAR encephalitis [58, 65]. Given these reported frequencies, it is interesting that this condition has not been more widely reported, perhaps because it has not been previously identified as a predictor of poor prognosis or mortality. Given the potential for additional brain injury in the setting of persistent intracranial hypertension, further studies are necessary for evaluating the impact of this finding in patients' outcomes as well as its possible correlation with a specific syndrome. Acute management of elevated intracranial pressure may include interventions such as head of bed elevation, hyperventilation with normal oxygenation, careful blood pressure management, hyperosmolar or hypertonic saline therapy, IV corticosteroids, or neurosurgical interventions depending on etiology and clinical status.

Dysautonomia

Autonomic dysregulation has been reported in 25–45% of patients with autoimmune encephalitis. Children are frequently less affected than adults. Common dysautonomic manifestations include fever without infection, hypoventilation or hyperventilation, tachycardia or bradycardia, blood pressure crises, diarrhea, hypersalivation, and erectile dysfunction. The presence of autonomic instability is a predictor of poor response to first-line immunotherapy. In addition, autonomic dysfunction appears to be associated with disease progression, particularly in anti-NMDAR encephalitis.

The underlying mechanism of autonomic instability is not clearly understood. Cardiac function is the result of a careful balance between the bradycardiogenic parasympathetic and the positive chronotropic sympathetic system [20]. An experimental study showed several brain regions that could potentially affect cardiac autonomic outflow such as the insula, anterior cingulate cortices, and amygdala, areas commonly involved in limbic encephalitis. Also, cardiac autonomic discharges can synchronize with epileptogenic activity triggering a lethal bradyarrhythmia or asystole [66].

Therefore, careful monitoring is necessary in all cases of autoimmune encephalitis. Dantrolene, external and internal cooling, pacemakers, mechanical ventilation, and hypertensive medications have been used in the management of dysautonomia in autoimmune encephalitis. In addition, temporary pacemakers have a Class I recommendation in

cases of asystole, symptomatic bradycardia with hypotension that is not responsive to atropine, and bifascicular block. Certainly some patients require a permanent pacemaker as autonomic instability can last for several weeks or months [20, 66].

Need for Mechanical Ventilation

Mechanical ventilation is a common complication in patients with autoimmune encephalitis. In a recent study, 57% of patients were intubated for approximately 1 month on average [15]. Some required tracheostomy (68%) and others developed ventilator-associated pneumonia (57%) [15]. Reasons for mechanical ventilation include depressed level of consciousness, respiratory insufficiency, absent airway protection reflexes, hypoventilation, pneumonia, and sedation in psychosis or SE. Reported complications of mechanical ventilation are pneumonia, need for pleural drainage, and acute respiratory distress syndrome (ARDS).

Triage and Administrative Considerations for Patients with Autoimmune Encephalitis

With these complications in mind, the triage of a patient with autoimmune encephalitis is dependent not only on their neurological status but also on their overall medical status. In the emergency department setting, management begins with the clinical survey of airway, breathing, circulation, and glucose status. With the identification and treatment of potential vital sign-related issues, management progresses to the initial diagnostic evaluation including diagnosing autoimmune encephalitis and considering alternative diagnoses discussed earlier in this chapter. Patients may be treated empirically for some of these etiologies while awaiting diagnostic results (e.g. IV acyclovir for herpes simplex encephalitis while awaiting CSF test results). In addition, emergency room providers must assess for decreased or altered level of consciousness as well as their potential etiologies (e.g., seizure, elevated intracranial pressure due to cerebral edema). The management of each of these will likely continue through to triage to the ICU [67].

Intra- and inter-facility transfer discussions are founded on an understanding of a patient's cardiovascular, pulmonary, and neurological status, with emergent management (e.g., mechanical ventilation, treatment of SE) initiated before transfer.

Disposition from the emergency room or ICU varies by institution; however, it primarily depends on independence from mechanical ventilation, cardiovascular stability, normalization of intracranial pressure, and resolution of SE. Subsequent discharge from the hospital is most commonly to an acute or subacute rehabilitation center for recovery, particularly for those who required prolonged ICU care.

Discussions regarding posthospital care should be held beginning at the time of admission, with plans made to address clinical issues as they arise, resolve, or persist throughout the course of hospitalization. The decision to transition from the acute care setting to rehabilitation or home is made upon completion of the diagnostic evaluation and treatment, which requires inpatient care. One should be mindful that the period of recovery following an episode of autoimmune encephalitis is on the order of weeks to months and is facilitated by directed physical, occupational, speech and language, and cognitive therapy. Psychiatric co-management may also be required for those patients with psychiatric symptoms (e.g., psychosis), which will require longitudinal care. A critical factor in disposition planning is close hospital follow-up of not only diagnostic results and clinical recovery but also the identification and management of potential sequelae such as epilepsy.

Given the complexities entailed in managing patients with autoimmune encephalitis, their clinical care is collaborative and multidisciplinary. Intensivists, neurologists and neurological subspecialists, medical specialists, psychiatrists, and physiatrists have essential roles to play in collaboration with nursing staff, therapists, and pharmacists. The epoch of inpatient care can last weeks to months, with understandable strain on not only patients but also on their families and other loved ones. Social work, palliative care, and spiritual/chaplaincy services also play important roles in the care of patients with autoimmune encephalitis and their families throughout the hospitalization and during the transition to the outpatient setting.

Prognosis

Factors associated with poor neurologic outcomes are delay in administering immunotherapy, longer ICU stay, need for mechanical ventilation, intrathecal inflammation, severe sepsis, medical comorbidities, need for tracheostomy, and malignancy [30]. Furthermore, prognosis depends on the antibody subtype, with better prognosis for cases involving cell surface antigens and worse prognosis for those associated with paraneoplastic disorders and intracellular antigens.

Our understanding of the long-term neurobehavioral outcomes in autoimmune encephalitis is limited; some preliminary observations are hopeful, while others are sobering. In one large study of long-term outcomes of 77 patients with autoimmune encephalitis treated at a single tertiary center, 53% had a "good" functional outcome (modified Rankin Score $\leq$2). However, in detailed interviews, while 85% of patients were employed prior to developing autoimmune encephalitis, only 42% were employed afterward; in addi-

tion, only 50% reported independence in traveling within their community, and 46% were responsible for their own finances [10]. In addition to these functional and practical aspects of recovery, patients commonly reported symptoms of fatigue, emotional lability, short-term memory loss, and difficulty with concentration years after the initial episode of autoimmune encephalitis [10]. Much work remains to characterize the outcomes and sequelae of autoimmune encephalitis in order to guide refinements to initial and longitudinal management of patients with this disorder.

Future Directions

There are still aspects of autoimmune encephalitis that remain unresolved, including the correlation of time to diagnosis and administration of immunotherapy versus outcomes and the elucidation of new serum, CSF, and radiological biomarkers that predict outcomes or measure disease activity. In addition, the role of brain FDG-PET in the diagnosis and prediction of outcomes needs to be clarified. Further studies are needed to determine a correlation between antibody titers and outcomes as well as the role of autonomic dysfunction and underlying malignancy in specific antibody subtypes. Work to thoroughly evaluate and clarify management strategies such as first-line versus second-line therapies, individual therapies, and new immunotherapies is also needed. Additionally, a detailed knowledge of postencephalitis sequelae is crucial to understand and attempt to ameliorate the impact on quality of life after the acute period.

Conclusion

Autoimmune encephalitis is a diverse category of primary autoimmune and secondary paraneoplastic syndromes that have gained increased attention over the past two decades. The diagnosis of autoimmune encephalitis is clinical, with outcomes dependent on early initiation of immunotherapy. Intensivists play a central role in the management of these patients, particularly in light of frequently associated complications such as SE, cardiovascular instability, and need for mechanical ventilation. ICU-level management is also critical given the high rate of mortality among patients with autoimmune encephalitis and to help optimize their outcomes.

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The Care of Patients with Neuromuscular Disease in the Neurocritical Care Unit

18

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Introduction and Epidemiology

There are few acute neuromuscular disorders managed on the neurology wards and even fewer requiring ICU level of care. Rapidly progressive weakness leading to concern for respiratory failure is the main reason for observation (and often respiratory support). Two major diseases in this group include Guillain-Barré syndrome (GBS) and myasthenia gravis (MG). In addition, amyotrophic lateral sclerosis (ALS) can require ventilatory support at the terminal stage of the disease, if requested by the patient. Further, critically ill patients who have had a prolonged stay in medical and surgical intensive care units (ICUs) are at risk of developing severe weakness due to critical illness polyneuropathy (CIP) and/or critical illness myopathy (CIM). Entities such as acute myopathy syndromes, vasculitic neuropathies, West Nile myelitis, or even tick paralysis can rarely present as rapidly progressive neuromuscular failure. In developing countries, tetanus and botulism remain prevalent (Table 18.1) [1, 2].

MG is the prototypical autoimmune disorder involving the neuromuscular junction. Incidence is reported at anywhere between 2 and 20 per million per year [3] with no significant change over the past 50 years. It varies significantly among age, gender, and ethnic groups and more often affects young women and older men [4].

Myasthenic crisis is arbitrarily defined as an acute exacerbation of underlying MG characterized by respiratory failure usually requiring noninvasive or invasive ventilatory support. Bacterial or viral infections, reduction of cholinergic or immunosuppressive medications, or initiation of corticosteroids are the most common precipitating triggers of myasthenic crisis. Other risk factors include thoracic or abdominal surgical procedures, pregnancy, or use of neuromuscular-blocking agents such as aminoglycosides. About one-fifth of patients experience crisis in their lifetime, which tends to occur in the first few years of disease onset [5].

Myasthenic patients are also at risk for cholinergic crisis due to excessive use of cholinergic drugs, presenting with *s*alivation, *l*acrimation, *u*rination, *d*efecation, *g*astrointestinal upset, and *e*mesis, known by the mnemonic "SLUDGE syndrome."

GBS or acute inflammatory demyelinating polyneuropathy is a self-limiting condition. It is the most common etiology of flaccid paralysis in the United States with an estimated incidence of 10 per million per year, which has remained unchanged over the last few decades [6–8]. GBS is often preceded by a respiratory or gastrointestinal tract infection. The prevailing immunopathogenic hypothesis of GBS is molecular mimicry triggered by a recent infection, generating an autoimmune humoral and/or cell-mediated response against the ganglioside epitopes or myelin proteins. In a subgroup of patients, the inflammation causes macrophage invasion of axons without demyelination [9], referred to as acute motor axonal neuropathy (AMAN). The most common antecedent pathogens of GBS are *Campylobacter jejuni* [10], cytomegalovirus [11], influenza virus [12], Epstein-Barr virus, and *Mycoplasma*

Table 18.1 Unusual causes of acute weakness and respiratory failure

Tick paralysis (children)
Botulism
Tetanus
Organophosphate poisoning
Fish poisoning (tetrodotoxin)
Snake bite
Vasculitis
Hypophosphatemia
Hypokalemia/hyperkalemia
Hypermagnesemia
Acute porphyria

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pneumoniae. No preceding illness can be identified in 30–40% of patients [13].

Triage

Neuromuscular disorders may affect the respiratory system directly as a result of impairment in mechanics or indirectly via oropharyngeal dysfunction causing inability to clear secretions. These mechanisms (respiratory pump failure, inability to adequately open the airway tract, and a poor cough) can lead to an emergent situation requiring transfer of the patient to the ICU. In order to better assess and triage patients with neuromuscular failure, a basic understanding of respiratory anatomy and physiology is of utmost importance.

The respiratory pump can be divided into inspiratory and expiratory muscle groups. The main muscles of inspiration include the diaphragm, the external intercostal muscles, the sternocleidomastoid muscles, and the scalene muscles. The major driving force for inspiration is provided by contraction of the diaphragm, which pushes the abdomen downward and forward. This force has to overcome the respiratory load (including the elastic resistance of the chest wall, resistance to inspiratory flow, and elastic resistance and positive pressure in the lungs) to draw air into the lung and if not will lead to alveolar collapse of distal segments (Fig. 18.1). This movement increases the volume of the chest cavity and creates a pressure difference between the thorax and abdomen. In healthy adults, the diaphragm's contraction can produce airway pressures of up to 150–200 cm H_2O during maximal inspiratory effort. The diaphragm is innervated by the right and left phrenic nerves (which originates from cervical nerves 3–5). External intercostal muscles are the other important muscles of inspiration; they pull the ribs forward and upward, increasing both the anteroposterior and lateral diameters of the chest cavity. These muscles are innervated by intercostal nerves (which originate from thoracic spinal nerves). It is important to note that patients with injuries to the lower cervical and thoracic spinal cord can breathe on their own, as inspiration is primarily dependent on the diaphragm, and paralysis of intercostal muscles has no significant effect on respiration. Accessory muscles of inspiration such as the scalene and sternocleidomastoid muscles (innervated by cervical nerves 3–8 and cranial nerve 11, respectively) do not contract during normal breathing; however, they actively contract during exercise and in the event of respiratory obstruction or diaphragmatic weakness [14–16].

Unlike inspiration, expiration is mainly passive and relies on thoracic cage recoil. However, active exhalation occurs with hyperventilation and exercise. The main muscles of expiration include the abdominal wall muscle group (rectus abdominis, internal oblique, external oblique, and transversus abdominis, innervated by thoracic nerves 7–12) and internal intercostal muscles (innervated by thoracic nerves 1–12). Contraction of abdominal wall muscles increases

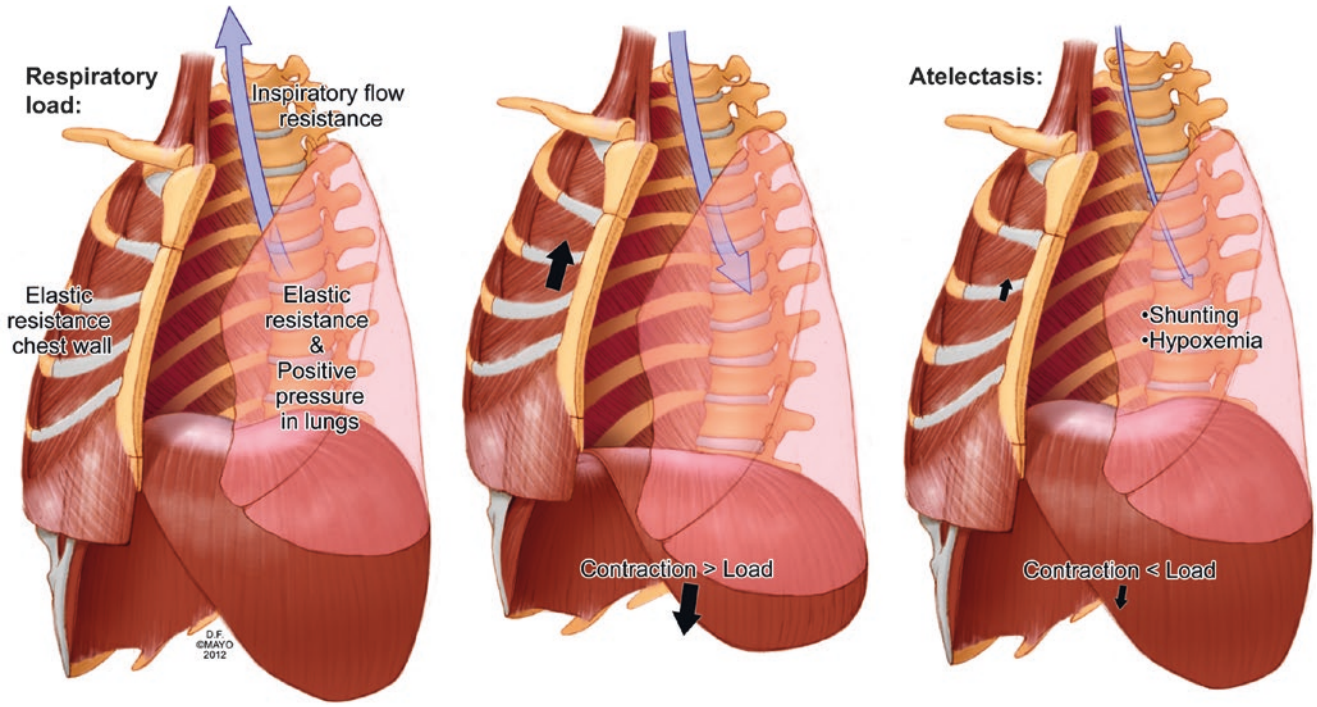

Fig. 18.1 Inspiratory load is determined by several factors (left and center of diagram). Mechanisms of atelectasis (right side of diagram). (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved)

intra-abdominal pressure, leading to diaphragmatic elevation during expiration. Moreover, these muscles are critical for strong coughing, and their weakness may result in failure to clear secretions [17].

As mentioned earlier, oropharyngeal dysfunction can also lead to respiratory failure through pooling of secretions and microaspiration. Muscles of the palate, pharynx, and larynx function in a timely and orchestrated manner with respiratory muscles to maintain adequate ventilation. In most of the neuromuscular disorders, both muscle groups are affected; however, oropharyngeal involvement usually precedes respiratory pump failure.

It is crucial for neurologists on the wards to be able to recognize patients at risk of imminent neuromuscular failure so that timely triage and management can be arranged. In most cases, respiratory failure occurs in a predictable sequence: diaphragmatic and intercostal muscle weakness leading to the compensatory use of accessory muscles, which will eventually lead to hypoventilation and hypercapnia. Hypoxemia usually appears last and thus should not be used to gauge respiratory status in patients with neuromuscular weakness. Weakness leads to shallow breathing and poor gas exchange, with resultant hypercapnia. Hypercapnia, in turn, triggers the medullary respiratory center, causing compensatory tachypnea with transient correction of PCO_2. It is not uncommon to find patients in imminent neuromuscular failure with tachypnea but normal PCO_2. Assuming normal brain and lung function, correction of hypercapnia can occur until respiratory muscle strength has decreased to 25–30% of normal.

There are also certain clues during the bedside examination that help with assessment. During exhalation, the diaphragm moves up, pushing air out of the lungs and causing the chest to contract. Paradoxical breathing, also known as thoracoabdominal asynchrony, reverses this pattern: during inspiration, the chest contracts, and during expiration it expands, pushing the abdomen down and out. Other signs include an inability to speak in full sentences (staccato speech) and nasal voice.

Patients with neuromuscular failure exhibit decreased forced vital capacity (FVC), particularly when supine. A fall in the FVC by more than 25% when the patient lies down specifically suggests weakness of the diaphragm. The maximal inspiratory pressure (MIP) (also known as the negative inspiratory force (NIF)) and maximal expiratory pressure (MEP) can further assess the strength of respiratory muscles. These measurements depend on maximal effort from the patient and the seal of the mask on the patient's face. A high maximal inspiratory pressure (normal 80–100 cm H_2O) makes neuromuscular respiratory failure unlikely, especially in conjunction with a normal FVC.

Overall, the following features suggest the need for ventilatory support in patients with neuromuscular failure (and in particular GBS) [18, 19]:

- Symptom onset to admission less than 7 days
- Rapidly progressive symptoms
- Bulbar weakness
- Bifacial weakness
- Neck flexion weakness
- Dysautonomia
- FVC < 20 mL/kg
- MIP < 30 cm H_2O
- MEP < 40 cm H_2O
- Declining FVC, MIP, and MEP by 30%
- Demyelinating features on neurophysiological testing

Given the physiological mechanism of respiratory distress in these patients, ventilatory support (and not supplemental oxygen) should be considered. Physicians should be very cautious with oxygen administration in patients with neuromuscular weakness since prolonged O_2 administration may lead to hypercapnic coma and respiratory arrest [20, 21].

In patients with MG who do not have significant bulbar weakness and pooling of secretions, noninvasive ventilation with bilevel positive airway pressure is the first step in the management of respiratory symptoms [22]. Noninvasive ventilation reduces the work of breathing and reverses mild hypercapnia and atelectasis in these patients. In contrast, GBS patients can decline rapidly and have a prolonged need for respiratory support. These patients can also develop severe dysautonomia with rapid swings in blood pressure and heart rate. Thus, GBS patients should be intubated promptly before they reach their nadir as emergent intubation can have catastrophic cardiocirculatory complications in the setting of dysautonomia [7].

Diagnosis

A combination of clinical, serologic, CSF, and electrophysiologic testing is used to diagnose patients with neuromuscular disease. GBS classically presents with progressive, generally symmetric muscle weakness and decreased or absent deep tendon reflexes with CSF typically demonstrating albuminocytologic dissociation (elevated protein and normal white blood cell count). Clinically, MG patients usually present with ocular, bulbar, respiratory, and/or limb weakness, with positive autoantibodies to the acetylcholine receptor, muscle-specific tyrosine kinase, or low-density lipoprotein receptor-related protein 4 though in some cases no autoantibody is found. Neurophysiologic testing may include a nerve conduction study (NCS), needle electromyogram (EMG), and neuromuscular junction testing.

In GBS, an EMG, which provides information on muscle activity at rest and with mild or maximal voluntary contraction, may not be particularly useful especially in the

first 3 weeks after symptom onset as patients may not yet have developed the classic features of an abnormal needle study. Increased insertional activity, spontaneous activity, fibrillation potentials, and large multiphasic motor unit potentials can eventually be seen in the denervated muscles of patients with GBS. However, a NCS (consisting of peripheral motor nerve compound muscle action potential (CMAP) and sensory nerve action potential (SNAP)) can be helpful early in the course of the disease. In patients with GBS, decreased conduction velocities, prolonged distal latencies, conduction block, and temporal dispersion suggest a demyelinating pathology, whereas reduced nerve conduction amplitude indicates an axonal process.

On the other hand, NCS assessment is within the normal range for patients with MG. A routine EMG study is typically normal in MG patients, but single fiber EMG reveals abnormal "jitter" and is the most sensitive test for MG. In addition, slow repetitive stimulation causes a decrement in CMAP amplitude, which is the most specific test in this condition.

Recently, there has been increased interest in critical illness polyneuropathy (CIP) and critical illness myopathy (CIM) as more patients spend longer amounts of time in the ICU. The incidence of CIP and CIM has been found to be 25–33% in patients requiring mechanical ventilation for 4–7 days and 24–77% in those in the ICU for >1 week. [23, 24] NCS reveals an axonal sensorimotor polyneuropathy in CIP with decreased amplitudes of both sensory and motor action potentials. In contrast, NCS in CIM patients is nonspecific with preserved SNAPs and small CMAPs. EMG in both patient populations is remarkable for fibrillation potentials and positive sharp waves. In patients who cannot activate muscles, direct muscle stimulation can be used to differentiate between CIP and CIM. When there is only neuropathy, muscle stimulation produces normal CMAPs, whereas nerve stimulation leads to low amplitude CMAPs. In patients with myopathy, both muscle and nerve stimulation produce low amplitude CMAPs, and thus the ratio of nerve-evoked CMAPs to muscle-evoked CMAPs can be used to differentiate between the two conditions (CIM > 0.5 vs. CIP < 0.5) [25].

Management

Patients with neuromuscular failure can deteriorate rapidly. Once the FVC is less than 10–15 mL/kg and/or NIF is less than −20 cm H_2O, the patient should be intubated. Treatment involves short-term, symptomatic, and maintenance therapies. Plasmapheresis and intravenous immune globulin (IVIG) remain the cornerstones of acute treatments in MG and GBS [26, 27]. In myasthenic patients treatment of the underlying etiology is equally important. Corticosteroid treatment also offers short-term benefit in MG [28]. Pyridostigmine should be used for symptomatic management. Management of CIP/CIM comprises treatment of the underlying condition such as sepsis, physical therapy, and limiting the use of corticosteroids and neuromuscular-blocking agents.

Plasmapheresis is given over five to seven sessions every other day for a total volume of 250 mL/kg. The onset of effect is within 1–7 days with the maximal effect between the first and third week after treatment. Plasmapheresis directly removes antibodies from the circulation and has a faster onset of action than IVIG. Seventy-five percent of patients show signs of improvement after two to three exchanges. Like any other treatment modality, plasmapheresis has adverse effects. It requires invasive line placement and can lead to hypocalcemia, hypofibrinogenemia, dysautonomia, hypotension, hypothermia, thrombocytopenia, and thromboembolism.

IVIG is administered as 400 mg/kg/day for 5 days and does not require central access. IVIG also has complications. IgA level should be checked prior to treatment, as patients with IgA deficiency develop a hypersensitivity reaction. Due to high sucrose load, IVIG is associated with acute tubular necrosis, especially in patients with underlying kidney disease. Aseptic meningitis, headache, fluid overload, and hyperviscosity syndromes are other potential adverse effects of IVIG.

In myasthenic patients, chronic immunotherapy is essential to prevent recurrence of disease. Prednisone (0.75–1 mg/kg/day) may prevent rebound in acetylcholine antibody surge. Onset of action is within 2–3 weeks and peak effect is seen in 6 months. Prednisone side effects include early worsening of symptoms, hyperglycemia, psychosis, gastric ulcer, osteoporosis, infection, weight gain, and glaucoma. Azathioprine, mycophenolate mofetil, and cyclosporine are used as steroid-sparing agents for immunosuppression. Rituximab (administered as 375 mg/m^2 weekly for 4 weeks in most studies) can be beneficial in the treatment of refractory cases of MG, especially in patients with anti-muscle-specific kinase (MuSK) antibodies [29].

One of the most challenging aspects of managing patients with neuromuscular weakness is ventilator weaning. Need for mechanical ventilation can be prolonged in GBS and short-term in MG. Strategies to expedite weaning from ventilation have two major components: daily sedation vacation and daily assessment for readiness to wean. Daily sedation interruption reduces the duration of mechanical ventilation and ICU stay [30]. Spontaneous breathing trials on a daily basis such as pressure support trials have also been shown to shorten the duration of mechanical ventilation [31]. Both pressure support and T-piece modes are similarly efficacious in time to wean from ventilation, whereas synchronized intermittent mandatory ventilation (SIMV) appears to be the worst weaning method [32]. Whether patients should be liberated from the ventilator should be guided by improvement in respiratory muscle strength, which can be gauged by serial pulmonary function tests. Weaning trials can be initiated

when FVC exceeds 15 mL/kg, MIP is more than 30 cm H_2O, and FiO_2 is 40% or less. It is important to note that in GBS patients, recovery of diaphragm strength can precede recovery of extremity strength and thus extremity muscle strength is not a reliable predictor of timing of ventilator weaning. Pyridostigmine should be reinstated and optimized prior to weaning in MG patients. Satisfactory management of secretions is necessary for these patients. MEP is associated with strength of the abdominal musculature and reflects the ability to cough up secretions. As such, it might be a good predictor of successful weaning in MG patients. Any major pulmonary problems such as atelectasis or pleural effusions should be managed prior to extubation.

Mean duration of mechanical ventilation in myasthenic crisis is 2 weeks. Predictors of prolonged intubation in MG include pre-intubation serum bicarbonate 30 mg/dL, peak FVC <25 mL/kg on days 1–6 post-intubation, and age >50 years [33]. In GBS, once the patient is mechanically ventilated, a prolonged ICU stay is anticipated with a high number of patients in need of a tracheostomy despite early administration of plasmapheresis or IVIG. One study found that 80% of GBS patients who were still requiring ventilatory support after 1 week required prolonged ventilation and that this longer period of ventilation was increased in those with severe deltoid weakness and axonal or unresponsive polyneuropathy on NCS; these patients are thus likely candidates for tracheostomy [34]. Predictors of poor recovery in GBS are older age, preceding diarrheal illness or cytomegalovirus infection, rapid onset, mechanical ventilation, and distal CMAP amplitude of less than 20% [35]. Notably, about 20% of GBS patients cannot walk unaided 6 months after onset, and many patients with GBS have to change their daily activities and have residual pain and fatigue [36].

Patients with CIP/CIM may be more challenging to liberate from the ventilator and require prolonged physical therapy and rehabilitation. Approximately 20% of patients with CIP, CIM, or critical illness polyneuromyopathy (combined CIP and CIM) still have sensory changes or weakness at discharge [37]. Patients who survive the underlying disease process may regain some strength within weeks to months with recovery even up to 24 months; however, many CIP/CIM patients are left with residual deficits and, in particular, it should be noted that CIM typically recovers more quickly and completely than CIP [37].

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Part V

Neurocritical Care Unit Organization and Triage

Training, Certification, and Continuing Education of Fellows and Attendings in the Neurocritical Care Unit

19

Michael Robert Halstead and Paul A. Nyquist

Introduction

History of Neurocritical Care, the Formalization of Training

The development of units focused on postsurgical management of neurosurgical patients is attributed to Walter Dandy in the 1930s at The Johns Hopkins Hospital [1, 2]. And patients with poliomyelitis around the turn of the twentieth century were typically cared for by neurologists [1]. Here among the iron lungs, airway management and surgical procedures were the neurologist's purview, until Salk and colleagues successfully sequestered polio [1, 2]. In the post-polio United States, the neurologist's interest in primary management of critically ill patients waned [2]. Management of neurologic emergencies fell largely to those from the fields of neurosurgery and anesthesiology, until Plum and Posner renewed interest in coma during the late 1960s [3] and inspired neurologists to re-engage with the field [2]. This led to a renaissance in neurocritical care during the 1980s with the development of formalized neurocritical care training programs, which was a collaborative effort, drawing on experience from neurology, neurosurgery, anesthesiology, and internal medicine. In 1988 the American Academy of Neurology formally recognized a section for Critical Care & Emergency Neurology; however, the discipline relied heavily on internal medicine and surgical critical care for the management of the neurologically critically ill. The broader community of critical care welcomed neurocritical care with a permanent section in the journal *Critical Care Medicine* in 1993. The 1990s led to refinement of our field with the development of best practices and large-scale clinical trials [2]. This set the stage for the inception of the Neurocritical Care Society (NCS) in the early 2000s, which was quickly followed by formal fellowship curricula and training requirments [1, 2]. The United Council of Neurologic Subspecialties (UCNS) formally recognized neurocritical care in 2005 [4], providing the first examination for subspecialty certification [1] and aiming to emulate the American College of Graduate Medical Education (ACGME)-based medical and surgical intensive care training programs [4]. UCNS-certified fellowships are available to trainees from neurology, neurosurgery, anesthesiology, internal medicine, pediatrics, surgery, and emergency medicine [5]. In 2013, The Society of Neurological Surgeons Committee on Advanced Subspecialty Training (CAST) further expanded focused clinical training for neurosurgeons by accrediting enfolded and postgraduate fellowships in neurocritical care, which was eventually recognized by the UCNS-accredited neurocritical care fellowship [4]. At present, neurocritical care has a foothold at most major medical centers, demonstrating improved outcomes for neurologically ill patients by our specially trained staff [6].

Demand for Certified Neurointensivists

Neurocritical care subspecialization has led to improved patient outcomes: decreased mortality, fewer complications, decreased length of stay, improved patient satisfaction, and increased discharges home [7–11]. Improvement in these metrics appears to be a function of neurointensivist-led teams in dedicated units [12], calling for the creation of additional dedicated neurocritical care units (NCCUs) staffed by formally trained neurointensivists. At present there are greater than 1200 UCNS-certified neurointensivists [4, 13]

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serving over 100 dedicated NCCUs [14]. Yet a survey of academic neurology programs suggested that >30% of centers lacked a dedicated NCCU, and among programs where dedicated units were available, 25% did not have a UCNS board eligible provider on staff [14]. Even in light of evidence suggesting subspecialized training has led to accelerated board certification in neurocritical care [15], a survey of intensivists and neurologists suggested that the majority agree that the demand for neurocritical care services exceeds the supply [16]. With consensus guidelines for acute stroke management and other neurologic emergencies calling for initial management in dedicated ICUs [17] and the ideal ratio of one neurointensivist to every four beds [18], there continues to be a strong need for a robust trainee pipeline.

Trainee Qualifications and Current Landscape

As of 2016, there are 60 UCNS neurocritical care fellowship programs [13] and 22 CAST-certified programs [4]. The vast majority of UCNS-certified neurocritical care fellowship programs recruit trainees through the San Francisco Match[1]; however, more than half offer spots outside the match [13]. Accredited programs require candidates to complete an ACGME- or Royal College of Physician and Surgeons of Canada (RCPSC)-accredited residency [19] prior to matriculation into fellowship. All programs accept trainees from neurology residencies, with fewer fellows selected from internal medicine, emergency medicine, anesthesiology, and neurosurgery [13], similar in distribution to those fields perceived to be most suitable for neurointensivist training [16]. Only two programs reported accepting pediatrics- or child neurology-trained applicants [13].

For the purposes of uniformity, the specifics of fellow training requirements reviewed in this chapter will focus on the UCNS-approved training process.

Fellow Training and Fellowship Requirements

Programmatic Requirements

Since 2005, guidelines for UCNS-recognized fellowship training in neurocritical care have been established. Sponsoring institutions are required to provide around-the-clock comprehensive ICU coverage to neurologically critically ill patients in dedicated units or within the context of larger critical care units [19]. The fellow capacity of each program is determined by the fellowship director and subject to approval by the UCNS. A minimum faculty to fellow ratio of 1:1 is required, with each eligible faculty member board-certified or possessing appropriate qualifications [13] and at least 25% of the faculty member's clinical practice dedicated to neurocritical care [19]. Additionally, one faculty member must serve as program director, responsible for programmatic oversight, organization, mentorship, and educational development [19].

UCNS neurocritical care fellowships must be completed within 2 years or, in circumstances of neurosurgical candidates or those from alternative critical care specialties, 12 months [4]. For those completing the 24-month fellowship, 12 are required to be "on service" in critical care units with primary patient care responsibilities, with greater than 50% of this service dedicated to caring for neurologic or neurosurgical patients [19].

Educational components for accredited fellowships focus on integrating general critical care, clinical practice, and scholarship [4, 5, 19]. Overarching goals are patient-focused, with training in neurologic emergencies and their medical complications as well as technical aspects of related procedures.

Since inception, core curricular requirements were put forth to facilitate trainee preparation for independent neurocritical care practice; these are composed of both a cognitive skills toolkit focused on neurologic disease, general medical disease, and general critical care as well as a procedural competencies toolkit composed of skills defined as general critical care- and neurocritical care-focused [5].

Core Cognitive Toolkit

The core cognitive skills deemed necessary by the UCNS for fellowship training in neurocritical care are broadly broken into those related to general neurologic disease states, general medicine disease states, and general aspects of critical care [5]. For a complete list of these cognitive domains, please see Table 19.1. These skills may be disseminated via direct patient care, formalized didactic sessions, journal clubs, or literature reviews.

Core Procedural Toolkit

The core procedural toolkit deemed necessary by the UCNS for fellowship training in neurocritical care is broadly divided into general critical care and those related specifically to neurocritical care [5]. This includes those standards related to general critical care and identified as essential for neurocritical care trainees (including central venous access, arterial access, enteral access, management of both invasive

[1]San Francisco Match, Neurocritical Care Fellowship, https://www.sfmatch.org/SpecialtyInsideAll.aspx?id=17&typ=1&name=Neurocritical%20Care

Table 19.1 Cognitive domains identified by the UCNS as necessary for fellow training

Neurologic specific disease states	General medical disorders: physiology, pathology, pathophysiology, and therapy	General aspects of critical care
I. Cerebrovascular diseases	I. Cardiovascular	I. Monitoring
II. Neurotrauma	II. Respiratory	II. Administrative and management
III. Seizures and epilepsy	III. Renal	III. Ethical and legal considerations
IV. Neuromuscular diseases	IV. Metabolic and endocrine	IV. Research in critical care
V. Infections	V. Infectious disease	
VI. Neuro-oncology	VI. Acute hematologic disorders	
VII. Toxic-metabolic disorders	VII. Acute gastrointestinal disorders	
VIII. Inflammatory or demyelinating diseases	VIII. Acute genitourinary disorders	
IX. Encephalopathies	IX. Immunology and transplantation	
X. Neuroendocrine disorders	X. General trauma and burns	
XI. Movement disorders		
XII. Common neurologic clinical syndromes observed in the neurocritical care unit		
XIII. Perioperative neurosurgical care		
XIV. Neurorehabilitation		
XV. Pharmacotherapeutics		

Adapted from Mayer et al. [5] (With permission from Springer Nature)

Table 19.2a General and advanced critical care procedural domains identified by the UCNS as essential or optional for fellow training

General critical care	
Essential for the neurointensivist	1. Peripheral venous access
	2. Arterial puncture
	3. Arterial catheter placement
	4. Naso-/orogastric/duodenal tube insertion
	5. Central venous catheter placement
	6. Pulmonary artery catheterization
	7. Management of mechanical ventilation (invasive and noninvasive)
	8. Administration of vasoactive medications
	9. Cardiopulmonary resuscitation and advanced cardiac life support
	10. Maintenance of airway and ventilation in non-intubated, unconscious patients
	11. Interpretation and performance of bedside pulmonary function tests
	12. Endotracheal intubation
Advanced general critical care	
Optional for the neurointensivist	1. Administration of nitric oxide or prostacyclin
	2. Hemodialysis, peritoneal dialysis, continuous venovenous hemofiltration, and hemodialysis
	3. Fiber-optic bronchoscopy
	4. Echocardiography
	5. Tracheostomy
	6. Percutaneous gastrostomy
	7. Diagnostic pleurocentesis, chest tubes/drainage systems
	8. Vascath/dialysis catheter placement
	9. Abdominal paracentesis
	10. Extracorporeal membrane oxygenation, ancillary circulatory support systems

Adapted from Mayer et al. [5] (With permission from Springer Nature)

and noninvasive ventilatory support, etc.) as well as those identified as advanced general critical care and considered "optional" for the neurointensivist (including hemodialysis, bronchoscopy, echocardiography, tracheostomy, etc.). The procedural components are further classified as those procedures related specifically to neurocritical care and essential for the neurointensivist (including lumbar punctures, interpretation of electroencephalography (EEG), management of external ventricular drains, management of plasmapheresis, etc.) and advanced neurocritical care procedures considered "optional" (including interpretation of cerebral multimodality monitoring, insertion of ventricular drainage and parenchymal pressure monitors, etc.). Details of these procedural proficiencies are detailed in Tables 19.2a and 19.2b. Competency includes demonstration of knowledge regarding indications and contraindications for procedures, complications, and management of those complications. Technical proficiency is only accomplished under direct visual supervision by qualified personnel until "competency is established." All advanced techniques may be included if there are qualified personnel to provide instruction [5].

Demonstrating Overarching Competency

In addition to these procedural and cognitive domains, six ACGME core competencies were identified, emulating the milestone approach in ACGME-accredited fellowships [13, 20]. Among these, patient care, medical knowledge, practice-based learning and improvement, interpersonal and communication skills, professionalism, and system-based practice [19] were identified as pertinent to the independent neurointensivist. Broadly speaking, these competencies demonstrate a trainee's ability to transition to independent practice. Each of the six competencies includes four subgroups on which to focus curricular development [5] (Fig. 19.1).

Table 19.2b General and advanced neurocritical care procedural domains identified by the UCNS as essential or optional for fellow training

I. General neurocritical care	
Essential for the neurointensivist	1. Lumbar puncture
	2. Shunt and ventricular drain tap for CSF sampling
	3. Performance and interpretation of transcranial Doppler
	4. Administration of conscious sedation and barbiturate sedation
	5. Interpretation of continuous EEG monitoring
	6. Interpretation and management of ICP and cerebral perfusion data
	7. Jugular venous bulb catheterization
	8. Interpretation of jugular venous and brain tissue oxygenation data
	9. Management of external ventricular drains
	10. Management of plasmapheresis and intravenous immunoglobulin
	11. Administration of intravenous and intraventricular thrombolysis
	12. Interpretation of CT and MRI imaging data
	13. Neurosurgical and interventional radiology perioperative and postoperative clinical evaluation
	14. Application of hypothermia for neuroprotection
II. Advanced neurocritical care[1]	
Optional for the neurointensivist	1. Performance and interpretation of multimodality monitoring
	2. Intrathecal administration of chemotherapy and radiographic agents
	3. Endovascular neurosurgical training
	4. Two-dimensional duplex ultrasonography
	5. Interpretation of PET imaging
	6. Insertion of ventricular drainage and parenchymal ICP monitors
	7. Lumbar drain insertion

Adapted from Mayer et al. [5] (With permission from Springer Nature). *CSF* cerebrospinal fluid, *EEG* electroencephalography, *ICP* intracranial pressure, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET* positron emission tomography

Trainee Expectations and Assessment of Trainee Proficiency

UCNS has included educational didactic components for trainees, requiring regular attendance at seminars and conferences in the disciplines of neurology, neurosurgery, critical care, and neuroradiology [5]. Insofar as is needed to achieve the cognitive proficiencies determined by UCNS, additional exposure to neuropathology, neurophysiology, and rehabilitation may be included [5].

Independent research opportunities must be offered, and trainees should actively participate in scholarly activities. Regularly scheduled research conferences are encouraged as well, including journal clubs, discussions of basic science, and local/regional/national society meetings [5].

Trainee success is required to be evaluated by members of the neurocritical care faculty at a "regular interval" with records maintained to ensure improvement is demonstrated [19]. Additionally, during training, fellow progress is established via demonstration of scientific and research productivity (presentations, abstracts, publications), with all records maintained by the fellowship director [5]. In addition to trainee evaluations, faculty must be evaluated by the program director on a periodic basis to ensure that "teaching abilities, commitment to the educational program, clinical knowledge, and scholarly activities" are maintained [19]. Included in the faculty review are written confidential evaluations by trainees [19]. The language used by the UCNS for trainees to demonstrate procedural proficiencies is imprecise. The critical care procedures required are listed; however, what is defined by the UCNS as meeting proficiency is not clear or uniform, other than "ability to perform, to attain independence or to have exposure and understanding of each procedure" [4].

Program Evaluation, Certification, and Maintenance

Annual program evaluation is mandated by the UCNS, for which written documentation must be made available. Tabulation of applicants, successful matriculants, scientific and academic productivity of trainees, post-fellowship employment, UCNS neurocritical care certification, and fellow performance on examinations are all metrics that may be included. Programs are evaluated at least annually by the program director for compliance and more frequently on an as-needed basis [5, 19]. If an issue is brought to the program director's attention, potential improvements should be discussed with fellowship faculty, with reasonable efforts to incorporate changes in a constructive fashion [21]. In a recent review of UCNS neurocritical care fellowship programs, all programs reported semi-annual fellow evaluations; however, fewer than 75% of programs described annual reporting of improvement action plans, clinical competency committees, or program evaluation committees [13].

Initial certification of new programs is completed via an online portal, known as the UCNS Accreditation Interface[2] on the UCNS website. This portal is not only utilized for accreditation of new programs but also for recertifying programs. Required information includes the primary institution, program director information, and all sponsoring

[2] "Accreditation Interface" UCNS, 2018. http://tools.ucns.org/ai/Home/Authentication; Accessed in 2/2018

Fig. 19.1 Six competencies identified by UCNS to expect from independent neurocritical care practitioners. (Adapted from Mayer et al. [5]. With permission from Springer Nature)

institutions, if different from the primary institution. Once this initial information is submitted, within 2 business days an official login is provided to the recorded program director. Programs must then submit detailed information including overseeing departments, fellow enrollment, and didactics to justify that they meet criteria set by the UCNS[2].

Key Differences Between UCNS Neurocritical Care Fellowships and Other Critical Care Fellowships in the United States

Unlike critical care medicine training in internal medicine, surgery, and anesthesiology, neurocritical care is not ACGME-accredited. The core didactic curriculum in critical care medicine is similar among all critical care training programs, with primary components focused on resuscitation, patient stabilization, and quality care. There are, however, two large key differences between the ACGME and UCNS programs. The ACGME has a mechanism to enact site visits, and while there has been a slow transition away from completing such evaluations of training programs, the UCNS lacks a mechanism for such visits. Furthermore, neurocritical care training does not utilize the milestone approach to evaluate trainees. ACGME milestones, implemented 2013, assess trainees' skills in all training-specific core competencies deemed necessary for independent practice within their field [22, 23]. While the use of milestones to assess trainees is not without limitation [22], this method of assessing medical education is now the gold standard within graduate medical education. Neurocritical care training through UCNS further differs from the ACGME-accredited critical care training programs in that neurocritical care does not utilize the ACGME duty hour guidelines and lacks formal requirements to expose trainees to multi-organ system failure and obstetric emergencies [4]. Otherwise, additional subtle differences exist, mostly focused around didactic and procedural components specific to each specialty (Tables 19.2a and 19.2b).

Future of Fellowship Training in Neurocritical Care

At the time of this publication, there has been growing discussion within the neurocritical care community regarding the transition from a UCNS to an ACGME-American Board of Medical Specialties (ABMS) pathway for accreditation. The NCS established the Program Accreditation, Physician Certification, and Fellowship Training (PACT) committee to support this process. The PACT found that nearly a quarter of neurocritical care program directors felt that the lack of an accredited ACGME-ABMS route adversely affected fellow recruitment and more than one third felt it affected graduating fellow employment prospects [13]. The vast majority of program directors believe that an ACGME-ABMS certification will best secure the future growth of neurocritical care [13]. Furthermore, a milestone-based curriculum, required by the ACGME, should be applied to neurocritical care training to ensure that future neurocritical care graduatese meet competency and universal minimum requirements [4]. At the present time, the ABPN has agreed on the need for ABMS certification and ACGME management of fellowship training with inclusion of other specialties in a manner virtually identical to the UCNS system. The application has been submitted to ABMS and is presently being evaluated, and an ACGME-ABMS-based fellowship program through the ABPN seems a very real possibility.

Practitioner Board Certification and Maintenance Certification

Historically, there have been four pathways of eligibility to sit for the UCNS certification examination in neurocritical care. These pathways include the UCNS-accredited fellowship, recertification, faculty diplomate, and practice track [24]. Regardless of the pathways, all applicants must be members in good standing with ABMS or RCPSC in at least one of the following specialties: neurology, neurologic surgery, internal medicine, anesthesiology, surgery, emergency medicine, or pediatrics [24]. Those who have not yet been certified by the ABMS or RCPSC but are eligible may sit for the UCNS examination but will not be notified of certification results until the UCNS receives confirmation of good standing with the ABMS or RCPSC. Additionally, applicants must maintain an active medical license within their jurisdiction of practice.

All initial applications for examination must be submitted online to the UCNS, and there are pre-specified calendar dates on which the examination must be completed [24].

Reexamination can be pursued for those who sit for initial examination under the accredited fellowship pathway and fail. It is possible to take the certification examination a total of three times (two additional examinations after the initial evaluation), with application for reexamination occurring within 6 years of the initial examination [24].

Contingencies of Certification

Certification is voluntary and does not substitute for the applicant's primary specialty. Applicants are required to maintain primary certification in their primary specialty, and if primary certification lapses, subspecialty certification is no longer valid. UCNS has the authority to revoke certification in neurocritical care subspecialization, placing the certificate holder on probation. Such probation may be considered due to falsification of credentials, legal action against the certificate holder, cheating, or other reasons determined by the UCNS. If such action is taken, appeal is accepted in writing. Additionally, third parties related to the clinical practice of the certificate holder (i.e., American Medical Association, state medical boards, etc.) may be notified.

UCNS-Accredited Fellowship

Trainees who have completed a UCNS-accredited fellowship in neurocritical care may apply for the certifying examination once fellowship is completed but no later than 36 months post-completion.

Recertification

As of January 2011, the UCNS board's policy for recertification states that to maintain good standing, applicants must sit for the examination every 10 years. During the decade of practice, the diplomate must maintain an active and valid medical license and be a member in good standing throughout the duration with the ABMS or RCPSC. In addition to retaking the certification examination, all must complete 300 ACGME- or RCPSC-approved category 1 continuing medical education hours, with 20% of these hours pertaining directly to neurocritical care. If for any reason the examinee is unsuccessful in passing the examination, it is possible to sit up to two additional times for the test.

Faculty Diplomate

Faculty diplomates are those who maintain an active full-time appointment as a faculty member in an UCNS-accredited neurocritical care training program. To demonstrate good standing, chairpersons of employing departments must provide a letter documenting good standing with the appoint-

ment date. Additionally, the letter must state that the faculty member's position is contingent upon the passing the certification examination and that their recruitment and retention are integral to the quality of the fellowship program [24, 25].

Practice Track: Reexamination

At present, the practice track has been closed to new applications since 2013. However, for those who were certified via this method prior to 2013, they must submit for recertification within 6 years of approval via one of three mechanisms: satisfactory completion of 24 months of formal training, 100 h of *AMA PRA Category 1 Credit*™ related to neurocritical care over the 60 months prior, or an active full-time academic position. Additionally, there are clinical requirements that must be met and confirmed by two independent physicians who can attest to his/her clinical acumen [25].

Examination

At present, the UCNS neurocritical care examination broadly covers two content areas carrying equal weights: neurology disease states and general medical critical care. The examination is a total of 200 written questions. Candidates must obtain a passing score on both subsections in order to obtain an overall passing score [26].

Education and Evaluation Specific to the Adult Learner and Neurocritical Care

A Brief History of the Intersection of Intensive Care and Medical Education

Published just over a century ago, the Carnegie Foundation's *Medical Education in the United States and Canada, Bulletin Number Four* [27], more commonly known as the "Flexner Report," marked the beginning of a "revised model of education" in medicine [28]. While this report defined undergraduate medical education, postgraduate medical training was still in its infancy and largely omitted from this appraisal. In fact, recognition of "critical care medicine," focused specifically on resuscitation, emergency care, and intensive care of life-threatening conditions, was not recognized until nearly 50 years later [29]. In 1977, while at the University of Pittsburgh, Peter Safar and Ake Grenvik authored one of the early papers on "educational philosophy" for critical care medicine, calling for formalized curricula and requirements for critical care training programs across the country [29]. Safar and Grenvik attempted to formalize training, not only through pre-defined didactics but also by suggesting techniques to deliver this material effectively to trainees (such as daily teaching rounds, radiology review, weekly conferences, and journal clubs) [29]. Many of these didactic requirements are very similar to those outlined today for neurocritical care [4]. While Safar and Grenvik clearly stated the need for "specified competencies," which were "defined in measurable terms" [29], how to effectively assess success remained elusive. Fortunately, to address these questions, the field of medical education began to mature less than 4 h north in Buffalo, New York. In 1955, George Miller and Robert Fisk conceived one of the first projects to understand fundamentals of content delivery, curricula, and assessment as related to physicians and medical students [30]. Out of this, the foundation for the formalized study of instruction, curricula, and evaluation for clinicians began [30]. Now in a medical culture influenced by mounting pressure on training programs and by expanding use of technology along with an augmented emphasis on quality metrics, patient safety, and patient preference, understanding how to effectively train and assess clinical providers has never been more important [31]. This section aims to review the foundational concepts of medical education, current research as it relates to critical care, and how to apply these concepts to neurocritical care.

Foundational Concepts in Medical Education

Traditionally, teaching and curricular development in critical care have focused heavily on seminar series consisting of protected time where trainees can dedicate cognitive energy to learning free of clinical duties [32]. It was inherently thought that faculty who were considered content experts could translate their clinical and research skills into teaching expertise [33]. However, starting in the 1990s, teaching strategies to increase teaching proficiency began to emerge [33], as did a growing interest in novel curricular designs; these included those that are team-based, problem-based, and technology-enabled to adapt to the modern trainee [34]. Integrating these novel educational designs effectively into modern graduate medical education requires teaching faculty to be familiar with modern education theory at a minimum to ensure successful learning by trainees [33, 34].

Key Principles for Medical Educators

The complexities of education theory cannot be encapsulated within the scope of this chapter, let alone this section; however, a few key concepts can be considered. We will consider principles of adult learning and aspects of effective clinical teachers as both are important when considering delivery of educational content and curricular development. First, foundational principles of effective clinical teachers

emphasize learner engagement, centeredness, adaptability, and self-reflection [35]. Focusing on these aspects, clinical educators must first demonstrate the importance of the material to the trainee [33, 36]. Engaging the learner should be done explicitly, explaining but further demonstrating why curricular components are included [36]. This not only engages the learner but also allows the learner time for self-reflection and incorporation of past experiences, maximizing the effectiveness of curricular delivery [37]. Learner-centered education embodies the main principles of adult learning, encapsulated by the following: goal-oriented learning, autonomy, self-directed learning, self-actualization, a safe and respectful learning environment, and relevance [37–39]. Recognizing these components helps instructors understand students' motivations, setting the stage for successful lifelong learning.

Educational Strategies

Classical lecture-based approaches to content delivery are less effective than alternative methods of content delivery, which are interactive and engage the audience [40]. We will not only review methods on improving lectures to maximize retention but additionally discuss alternative educational strategies that can be applied to critical care including problem-based learning, technology-enhanced learning, e-learning, and simulation. These techniques are not an exhaustive description of educational strategies; however, these techniques are a selection of some of the more common methods for medical instruction. We will further describe briefly the pros and cons of each method and any available literature demonstrating its use in critical care medicine.

Problem-Based Learning

Problem-based learning (PBL) is an educational strategy that is student - or trainee-centered and contextualizes basic or clinical knowledge questions in a clinical framework [41]. Initially conceived as a method to instruct medical students within a clinical context, PBL techniques have gradually evolved to include postgraduate and continuing medical education endeavors as well [42]. When applied broadly to graduate medical education, there appears to be evidence to suggest similar effectiveness for undergraduates [41, 42]. PBL draws on a large array of educational methods to deliver materials effectively to trainees [43].

PBL tutorials are time intensive to develop and administer [42]. Ideally, clinical prompts should present information that emulates clinical practice. An effective PBL requires a patient-centered problem that is organized and clearly defined. Furthermore, this prompt must be reviewed and vetted thoroughly by experts. The PBL process requires dedicated time away from clinical responsibilities; trainees are then divided into groups, ideally between five and seven (depending on medical practice). Trainees are divided into group roles, including a reader, team leader, and recorder. In addition to group members, there is an "expert" facilitator, whose role is to direct the trainees through discussion of the case. This discussion is intended to define and clarify the problem presented, analyze the problem in order to obtain a systematic approach to the solution, formulate an action plan, and then collect supporting evidence to finally synthesize a response [44]. This process is meant to draw on prior knowledge, with discussion and collaboration facilitating new knowledge encoding and refinement [44].

Cons of PBL include the demand for significant dedicated personnel (including faculty to facilitate it and experts for programmatic development), time for facilitation, and infrastructure (there needs to be dedicated areas for PBL teams to discuss cases). Additional criticism includes the limited evidence that PBL education demonstrates any enhanced long-term competency over traditional curricula [45, 46]. Proponents argue that students who engage in PBL-based curricula are more likely to have more collaborations and to continue with self-directed learning throughout their careers [45]. And they potentially have improved competencies in interprofessional and cognitive domains that portend long-term success [47]. As PBL implementation relates to graduate critical care education, the literature is sparse. However, in the ICU, PBL has led to improved critical thinking, clinical reasoning, and self-directed learning [43] but has failed to demonstrate better competency in technical skills over alternative techniques [48].

Technology-Enhanced Learning and E-Learning

Technology is ever more pervasive in our society. Broadly speaking, technology-enhanced learning and e-learning refer to any and all online or web-based portals, e-books, mobile devices, apps, and even simulation (simulation will be addressed below) [49, 50]. The true effect of technology-enhanced learning and e-learning on long-term retention for trainees is not clear, as evaluation metrics are still in development [51]. That being said, it is important for the educator to be aware of these limitations and understand the principles behind these educational methods' applications to trainees.

While applying and implementing a curriculum heavily based online or requiring the use of technology, it is important to not assume that all trainees have equal understanding and comprehension of how to access materials online or electronically [52]. Further, it is important that concrete training objectives are outlined [49], as is a learner's timeline. Adult learners value independence in learning [37], an

aspect that is leveraged in the implementation of online and electronic resources. However, the concept of persistent accessibility has raised concerns about "superficial" learning and an overreliance on devices for access and interpretation of clinical material as compared to true synthesis and integration of material organically [53–55]. Regardless, technology-enhanced learning and e-learning are here to stay. A recent consensus statement from Canadian educators proposed ten quality criteria for online continuing medical education modules and suggests further investigation to understand how this impacts practitioner competence [56].

Simulation

Simulation use in medical education has expanded, near exponentially, in recent years given changes in healthcare delivery and expectations of patient safety [57]. Simulators are designed to emulate reality and can range from a simple model of the lower back or arm for simulated lumbar or venipuncture puncture, respectively, to full-scale simulated environments and persons [58]. As pertaining the neurocritical care, education simulators have been used for the instruction of the brain death examination [59, 60]. Simulation provides many advantages, particularly in critical care education. First, for the controlled reproduction of specific technical aspects (central line placement, intubation, resuscitation, etc.), simulation provides a safe environment for development and practice of the technical aspects of these skills. Additionally, simulation allows demonstration of these techniques, providing trainees the opportunity to ask questions and clarify concepts prior to practice [57, 58, 61]. In order to be effective, however, there needs to be objective aims and directed feedback provided to ensure the practice effect afforded by simulation is sustained [62]. Given the importance of feedback in the success of simulation-based training, instructors should be prepared to give their assesssment, respect that the learner is in a "role" during simulation, and then provide discrete constructive feedback [57].

The evidence for simulation in critical care education is strong, suggesting that repeated practice of skills improves retention [48, 61, 63]. Yet it is important to recognize that simulation cannot replace practical experience [64]. Some have raised concern that the controlled environment of simulation does not transfer well to the chaos of medical practice [65], particularly in the ICU. This raises important points when implementing a simulation-based program. First, the proximity of clinical sites and simulation centers should be close, to allow for rapid interplay between the two so that simulated experiences can rapidly be translated to clinical practice. And second, the concept of staged acquisition in the setting of successful observed simulation, supervision, and feedback is still necessary when procedural skills are implemented in the clinical setting [57].

Lectures

Lectures remain one of the most common ways to deliver material to trainees. Cognitive load theory suggests that learners are only able to process a limited amount of knowledge over a distinct period of time [66] with evidence from the literature supporting this [67]. Additionally, there is a fallacy of understanding that occurs during lecturing; trainees perceive well-presented material that is fluent as having been mastered but when assessed are unable to apply this material effectively [66]. Furthermore, attention for learners is highest within the first 20 min of a lecture [68]. And even under ideal circumstances, evidence suggests that only 20% of material is retained at 1 week [69]. While there is a movement within the medical education community to decrease reliance on lectures [66], this is unlikely to happen in the near future. With this in mind, a few take-home points should be considered when creating lectures. Engaging the learner is key. The use of simple questioning, frequently considered threatening, can be useful when employed tactfully. The use of discussion formats, humor, or "show of hands" can help engage learners during lectures or presentations when simple questioning is not effective in engaging your audience. Successful implementation of these techniques can be limited in larger group settings, however. Student engagement in large groups can be overcome with "buzz groups," which are punctuated rapid discussions among trainees throughout the lecture. This requires the lecturer to be focused on re-engaging with students to ensure the discussion does not stray. Brainstorming and snowballing are two similar methods that leverage group participation and discussion. All aforementioned techniques strive to engage with trainees throughout the duration of the lecture to maintain enthusiasm and engagement and to increase retention [69].

Evaluation

Evaluation of trainees, educators, curricula, and educational tools are all essential components of any educational endeavor. Continual assessment and evaluation promote learning and ensure learning outcomes are obtained and curricula are acceptable [70]. Evaluation metrics take various forms, from clinical performance-based assessments such as standardized patient experiences or simulated cases to written examinations and direct bedside observations [38]. The only universal evaluation model in neurocritical care is the UCNS certification examination. However, throughout training, UCNS mandates trainees to both evaluate faculty and receive evaluations themselves. This is most frequently completed using rating scales that evaluate all-encompassing categories of a trainee's experience: patient care, knowledge, interpersonal, and communication skills. While well-meaning, these evaluations are

typically presented in summative fashion at the end of a curriculum in retrospect, exposing them to recall bias and subjectivity and potentially influencing their validity [38]. The technical aspects of the neurocritical care curricula are possibly best evaluated. The use of checklists in standardized patient or simulation cases has demonstrated high reliability [71]; however, the question of transferability to the bedside again lingers. With the advent of competency-based medical education, which is slowly entering the realm of neurocritical care education, a new cadre of evaluation techniques still require validation [72].

Providing Feedback

As mentioned earlier in this section, self-reflection by the instructor and trainee is paramount to the educational mission. Effective clinical educators must leverage feedback as a mechanism to enhance learning. However not all feedback is the same. Effective feedback must be provided to trainees in a timely fashion and be specific with regards to an observed action. Comments and critiques should focus on concrete behaviors observed [38]. Feedback is only successful if the trainee attempts to address the knowledge gap [73]. Overall trainees want feedback [38]. The psychology of feedback focuses on a few key techniques in education and medicine that should be kept in mind by all clinical evaluators. First, feedback provided to the trainee should be based on observation, be nonjudgmental but specific, focus on behaviors, and provide suggestions for improvement [74]. However, this does not imply that all feedback should be positive; negative feedback is important and should be balanced with positive feedback [75]. Feedback should additionally be dynamic, evaluating trainees based on where they currently practice, how far they have advanced based on past feedback, and how they have addressed specific deficiencies discussed in previous assessments [75]. Educators must be aware of possible barriers to effective feedback, including inconsistent evaluations; feedback that is too general, defensive, or critical; and assessments that attack personal attributes of the trainee [76]. While straightforward, keeping these key points in mind will ensure effective feedback and trainee improvement.

Conclusion

This chapter sets out to briefly introduce the history of neurocritical care training in the United States and its evolution to its current state through formalization by the UCNS. By reviewing objectives of the training pathways and comparisons with other ACGME-accredited critical care fellowships, an understanding of how trainee objectives are achieved was provided. Lastly, we aimed to describe a basic introduction to medical education theory and how this relates directly to the history of critical care education in the United States. Furthermore, we reviewed key aspects of how to structure didactics, assess curricula, and provide feedback to trainees. This chapter aims to serve as a framework on how to develop and implement the most effective neurocritical care training program possible.

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Telemedicine and Telestroke

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Historical Perspective

Telemedicine involves the use of technology to provide clinical care remotely, typically via video connection. When used for the provision of stroke care, this is commonly referred to as telestroke, as introduced by Levine and Gorman in 1999 [1]. Telestroke is defined as a network of audiovisual communication and computer systems that make up a collaborative, interprofessional care network for the clinical care and treatment of patients with acute stroke [2]. Telestroke is intended to augment local care delivery by connecting patients with providers who have remote expertise and can facilitate access to additional resources.

Upon its inception in the late 1990s, the value of telestroke was recognized as a mechanism to connect patients in remote settings to centralized expertise and resources that they would not otherwise be able to access in a timely manner, particularly with the aim of increasing thrombolytic utilization among eligible patients [2]. Many patients with acute stroke present to hospitals that lack access to the resources necessary for their care, and many emergency departments (EDs) lack coverage by neurologists and neurosurgeons [3–5]. Given the established benefit of intravenous thrombolytics for reducing poststroke disability [6] as well as the substantial hospital-level variation in tPA (i.e., alteplase) administration, telestroke was identified as a tool to bring resources and stroke expertise to patients presenting to EDs without stroke specialist coverage. Telestroke can enable remote evaluation by vascular neurologists, provide decision support for thrombolytic administration, and aid in identifying patients who may benefit from being transferred to a higher level of care. The advantages of telestroke are evident particularly in underserved and geographically remote settings.

Since its initiation, telestroke has become commonplace in US EDs [7, 8]. It continues to be utilized as a tool for improving utilization of intravenous thrombolytic administration among eligible patients. However, its applications have substantially broadened: Telestroke is now used in the prehospital setting, its use in the ED setting has expanded to include the identification of candidates for mechanical thrombectomy and patients eligible for clinical trial enrollment [9, 10], and it is used in the inpatient setting to enable hospitals to continue to provide the highest level of care to stroke patients after admission [11].

State of the Evidence for Telestroke

Telestroke for Care Delivery

There is a growing body of literature supporting the efficacy of telestroke in providing high-quality acute stroke care. This exists in the acute setting (i.e., ED), in the inpatient setting, and in the prehospital setting.

When a patient with a neurological complaint suggestive of a stroke arrives at the hospital, assessment of the patient's deficits with the National Institutes of Health Stroke Scale (NIHSS) is a critical component of the evaluation. Completion of the NIHSS via telemedicine has been shown to take only a few additional minutes compared to an in-person evaluation and to have high interrater reliability with an exam performed by a clinician at the patient's bedside [12–14]. Follow-up work has shown this to be true even among examiners without telemedicine training or experience

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[15]. The American Heart Association/American Stroke Association (AHA/ASA) has assigned high level of evidence to the use of telestroke for remote assessment of NIHSS (class I recommendation, level A evidence) [16]. Furthermore, evidence suggests that the reliability of remote evaluation of NIHSS by video may hold true for other portable devices such as handheld devices or phones as well, with high levels of ease and provider satisfaction [17–19].

In addition to the NIHSS, review of radiological imaging is another important component of the acute stroke patient evaluation. Viewing imaging remotely enables rapid and effective evaluation by stroke specialists in order to support decision-making for thrombolytic administration. Misinterpretation of imaging via telestroke is rare [20]. Furthermore, when reviewing imaging for the explicit purpose of identifying thrombolytic contraindications, there is a high level of agreement between telestroke consultants and neuroradiologists [21]. Remote review of computed tomography (CT) scans via Food and Drug Administration (FDA)-approved telemedicine systems has been assigned high level of evidence by the AHA/ASA (class I recommendation, level B evidence) [16].

Of course, the purpose of remotely evaluating NIHSS and radiological imaging is to guide thrombolytic administration via telestroke. A number of studies have confirmed that telestroke is effective for the remote recommendation and guidance of thrombolytic administration. Telestroke has been found to be superior to phone consultation for treatment decisions [22, 23]. In fact, care delivery, complication rates, and patient outcomes have been shown to be similar to those of in-person treatment at a comprehensive stroke center [24–31]. This is true even in settings where tPA had not previously been used [27]. Over time, and with increased experience, systems become more efficient as well, with telestroke enabling improvements in onset-to-treatment and door-to-needle times for tPA delivery [26, 32, 33]. Importantly, physicians express a high degree of confidence in the telestroke evaluation [24]. The AHA/ASA recommend the use of telestroke for guiding thrombolytic administration remotely in the absence of on-site stroke expertise (class I recommendation, level of evidence B) [16].

Many stroke patients require transfer between hospitals in order to access appropriate resources for their care. The use of telemedicine in patient evaluations enables effective identification of patients who will require or benefit from transfer between hospitals [34, 35]. In one analysis of patients with moderate to severe stroke, transfer to a telestroke-providing hub hospital from a spoke hospital after telestroke evaluation was associated with improved post-tPA 3-month outcomes [36]. Another study examined patients transferred for endovascular intervention after a telestroke evaluation and found that these patients had similar rates of reperfusion and functional outcomes to patients who were directly admitted [34]. By providing access to a stroke neurologist, telemedicine enables accurate identification of patients in need of a higher level of care.

Telestroke is also frequently used in the inpatient setting. Among patients who are not transferred but who stay at the hospital at which they initially presented, repeated evaluations via telemedicine may be conducted in order to review diagnostic studies and provide guidance to on-site clinicians. An even more involved application of telestroke in the inpatient setting has developed in the form of a virtual stroke unit: telestroke rounds may be conducted via a mobile telemedicine workstation, vital signs data may be transmitted, and telerehabilitation may be involved [7].

Applications of telestroke are also being explored in the prehospital setting. This is primarily for the remote evaluation of patients with potential stroke, as a means of reducing delays to treatment for eligible patients [37]. Early attempts at using telestroke in ambulances were limited by insufficient bandwidth and poor-quality videoconferencing [38]. However, as mobile technology advances, telestroke is becoming more feasible in the prehospital setting. One study using standardized patients found that a simplified NIHSS could be performed by remotely located physicians assisted by emergency medical technicians using a real-time cellular video phone connection with high reliability between in-person and remote evaluations and minimal additional time for the assessment [17]. Formalized telemedicine equipment has begun to appear on ambulances as well, particularly with the growing presence of mobile stroke units [39]. In a study of a mobile stroke unit with an onboard vascular neurologist versus a telemedicine-based vascular neurologist, researchers found a high level of agreement in patient evaluation and tPA eligibility [40] and that this could be achieved without a delay in treatment [41]. Results from the Cleveland mobile stroke unit have shown a very low rate of technical failure, and patients treated on the telemedicine-enabled mobile stroke unit had significantly faster times to CT completion and to intravenous thrombolysis relative to patients in the control group (i.e., those brought to the hospital using traditional ambulances) [42, 43].

Telestroke and Patient Outcomes

While the majority of the evidence for telestroke thus far has focused on its feasibility, safety, and its impact on care delivery, there is also support for its effect on patient outcomes. Results from the Telemedical Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria showed that 3- and 6-month mortality rates and functional outcomes at telemedicine-linked community hospitals were similar to those of patients in large stroke randomized trials (e.g., National Institute of Neurological Disorders and Stroke tPA

trial from 1995) [44]. Another TEMPiS analysis compared outcomes of stroke patients treated at telemedicine-linked community hospitals with five matched control hospitals in Bavaria. In this analysis, 3-month outcomes were significantly better among patients treated at telestroke hospitals, and after controlling for demographics, stroke subtype, stroke severity, and comorbidities, treatment at a telestroke hospital was independently associated with improved patient outcomes [45]. Though these studies were nonrandomized and nonblinded, in combination with the strong evidence for telestroke's role in improving stroke care delivery, these results suggest that telemedicine may significantly improve patient outcomes.

Telestroke Care Processes and Administration

The Telestroke Triage Process

Telestroke requests and triage typically occur either through telephone operators or through software or internet applications. Telephone operator systems may utilize hospital operators or outsourced operators who are available to page the providers on call or to triage calls accordingly. Robust systems are able to understand the complexities associated with different types of cases (e.g., acute stroke versus subacute stroke) or requests for remote consultations versus requests for transfers or referrals. If unexpected events occur during the telestroke triage process, tracking mechanisms will aid incident resolution efforts. Contingency protocols can also be developed for delayed responses to acute situations. For example, telestroke consult requestors can be educated to repeat their requests in the event of a delay, and resources can be deployed to ensure that multiple parties are notified of the ongoing delay on the provider organization's side. In all cases, clear service expectations and parameters will increase the likelihood of success: some programs thrive on early activation from emergency medical services (EMS) even if these activations are frequently related to non-acute stroke cases, whereas other programs limit activation to cases that have been evaluated by the community hospital emergency physician and for which a CT scan has already been pushed to the telestroke provider organization. Whatever the case may be, protocols should be in place so that these expectations are established and clear. It may be useful to consider the telestroke service provider in a manner similar to that of a software-as-a-service vendor in terms of service-level agreements and expectations for support as well as for predictable downtime and failsafe procedures.

When the telestroke provider is an academic center, an additional layer of triage may be provided by clinical stroke fellows. Fellow participation in a telestroke program entails particular challenges. One example is the requirement for telestroke providers to be credentialed at the covered facilities and licensed in those respective states, which often takes months and additional costs to complete. Such a time frame and expense may be prohibitive for many year-long vascular neurology training programs. However, many organizations have been able to incorporate fellows' participation under the close supervision of an attending stroke neurologist who is fully credentialed at the facility and licensed to practice medicine in the state where the facility is located, thus providing great value to both the fellows' training and to the telestroke program. The supervising attending must participate in neurological evaluations and sign off on all clinical decisions made. In this way, fellows learn skills involved in remote patient evaluation and also evaluate more potential thrombolytic candidates.

Telestroke programs may also play an important role in the triage of interventional and neurosurgical cases given that they can enable stroke specialists to review relevant studies and then to facilitate transfer to their tertiary or quaternary level centers. Structured processes may also allow expedited direct access to the interventional suite or the operating room.

The Telestroke Program Clinical Operations and Support

Different models of telestroke services may require different levels of clinical operations and support and peripheral services. Peripheral services include virtual and on-site professional education, quality reviews, certification support, and stroke service consulting or advising. In the case of a telestroke model in which the key objective is to provide decision support for thrombolytic therapy, administrative and peripheral services may be less involved. In contrast, a telestroke network designed to enhance stroke systems of care will require substantially more in the way of administrative and peripheral services [16]. Networks designed to follow best telestroke practices [2, 46] typically require robust quality monitoring, education, and care coordination processes and services. In these cases, regular quality reviews help ensure the telestroke effort is being leveraged to its full extent in terms of its potential clinical impact. These reviews may assess utilization barriers and delays, rates of thrombolytic treatment and thrombectomy candidacy, rates of patient transfer and retention, and types of diagnoses encountered. Educational sessions may also be coordinated and provided, both virtually and on-site. These efforts help to ensure an ongoing, well-coordinated local infrastructure that provides the highest level of care. Other quality improvement efforts may also contribute to data gathering and feedback, such as the AHA's Get with the Guidelines program or the Centers

for Disease Control and Prevention Paul Coverdell Acute Stroke Program. In addition, some US hospitals may use telestroke in order to meet criteria for Joint Commission Stroke Center Certification. These programs and certification processes may lead to additional demands on supporting administrative services. Program support within a telestroke program must also ensure well-established and streamlined processes for interhospital transfer of patients, with particular attention to complex cases (e.g., patients potentially eligible for mechanical thrombectomy).

Financial Oversight and Sustainability

Telestroke has been found to be cost-effective from the perspective of both providing and receiving organizations [47] as well as from public health and societal perspectives [48]. Financial models for funding telestroke programs vary. Many are developed with the support of grants, whereas others use contracted services in a stand-alone model. Even in the absence of payer reimbursement for telestroke consultations, telestroke programs tend to be financially sustainable as they enhance patient retention for hospitals receiving telestroke services. By retaining stroke patients who may have otherwise been transferred, hospitals generate additional revenue that enables the hospital to pay a fee for telestroke physician coverage and services. Thus, telestroke coverage becomes a financially self-sustaining operation for both the providing and receiving organization. Providing organizations may be additionally incentivized to provide telestroke services because they allow the development of streamlined processes for receiving transferred patients, such as pre-arrival evaluation and preparation for patient arrival (including activating the interventional radiology team, when applicable).

Physician compensation is an important component of telestroke financial models. Mechanisms for compensation will vary. For example, in some networks, salaried physicians provide telestroke services as part of their salaries. In other networks, participation in telestroke series is incentivized, which may be in the form of moonlighting hours, on a per-consult basis, or as a bonus. Integration of telestroke activities into the compensation framework of physicians is critical for program sustainability.

Telestroke networks are often developed in the absence of payer reimbursement. Particularly in densely populated areas such as the Northeast United States or the Pacific coast, patients receiving telestroke consultations may not be located in rural settings (a nonmetropolitan statistical area as designated by the US Chamber of Commerce) and therefore would not be eligible for reimbursement by the Centers for Medicare and Medicaid Services (CMS). However, new legislation such as the CHRONIC CARE Act may enable reimbursement regardless of whether the patient is in a rural setting. In addition, many states have telemedicine parity laws that aim for equal reimbursement rates for both on-site and telemedicine services. Nevertheless, there are often loopholes through which insurance companies are able to restrict reimbursement for telestroke consultations, such as by capping the reimbursable complexity and associated dollars at lower levels than those consistent with acute stroke care.

Additional Regulatory Barriers

Expansion of telestroke networks is also often limited by requirements for physician licensure in different states and for obtaining privileges at all facilities where services are delivered. Different regulatory bodies have taken steps to streamline these processes and facilitate access to medical expertise via telemedicine. In 2012, CMS approved a revision to telemedicine standards for the Joint Commission. This revision enables a site receiving contracted telemedicine services to make certain that the providers at the providing facility meet the minimum Medicare requirements of participation, which enables the receiving site to choose to use the credentialing and privileging decisions of the provider facility if it is also consistent with its bylaws. Additionally, certain states have waived the requirement for a medical license if the provider is licensed in their home state and meets other requirements for the waiver (e.g., not having an office in their state or only providing care through a locally licensed physician).

Telestroke Technology

Telestroke requires the availability of a videoconference platform to enable the remote neurologic assessment of the patient. Frequently, platforms adapted to this clinical use enable high-definition, two-way or multiparty communication as well as the remote control of the camera in the patient's room for pan, tilt, and zoom. More sophisticated systems may allow the neurologist to remotely navigate the videoconferencing device into the patient room or may integrate additional digital peripherals that support other clinical uses (e.g., digital stethoscope), though there is no consensus as to whether these technical features are essential. Radiology image exchange capabilities are essential in order to allow neurologists to assess for thrombolytic administration eligibility and for alternative diagnoses.

Another important technological component is a mechanism by which the neurologist documents the encounter and makes this information available directly or indirectly in the patient's medical record. Telestroke models vary in terms of

the remote neurologist's involvement in writing medication orders: some neurologists only provide medical advice to the local provider, while others remotely write the order directly into the medical record.

The lack of true interoperability between electronic health record systems remains a significant challenge. As most electronic health record systems operate in information silos, with limited information exchange services and demanding and expensive integration requirements, many telestroke services struggle to identify a scalable approach to enable their providers to document the care they render on the various record systems used by the many facilities they cover. Recent advancements may enable better integration of services (e.g., the Fast Healthcare Interoperability Resources standard within Health Level 7 and various file data formats and structures that are well suited to interoperability such as JavaScript Object Notation). Much of the challenge of electronic health record interoperability in telemedicine is that information exchange is not typically limited to documentation of the encounter but also extends to interinstitutional workflows and the need for incident monitoring and program oversight.

In all cases, the current standard is to create information exchange mechanisms via Internet Protocol technology. Furthermore, the momentum of the telemedicine industry is directed toward making the technologies lighter and more easily available, minimizing the need for dedicated hardware and—more recently—software, while leveraging native applications such as the available Internet browser.

Guidelines

2018 AHA/ASA Guidelines

The 2018 AHA/ASA Guidelines for the Early Management of Patients with Acute Ischemic Stroke include a section on telemedicine. These guidelines recommend the use of FDA-approved teleradiology systems for imaging interpretation when in-house expertise is not available (class I recommendation, level of evidence A; see Fig. 20.1) and for supporting decision-making for thrombolysis administration (class I recommendation, level of evidence A) [49].

The guidelines also state that telemedicine systems should be used in order to ensure 24 h a day/7 days a week coverage for acute stroke patients (class IIa recommendation, level of evidence C-EO) and for guidance in thrombolytic decision-making (class IIa recommendation, level of evidence B-R) [49]. Telestroke networks are also recognized in the guidelines as a mechanism for identifying patients potentially eligible for mechanical thrombectomy (class IIb recommendation, level of evidence B-NR) [49].

American Telemedicine Association Telestroke Guidelines

The American Telemedicine Association developed guidelines specifically focused on telestroke [2]. These guidelines were developed to assist clinicians in the assessment, diagnosis, management, and remote support for patients with acute stroke and focus on the acute phase of stroke care. The guidelines include recommendations for operations, management, administration, and economics. They highlight the importance of strong leadership and outline critical roles for a telestroke program, including physician directors at both the hub and spoke sites, a program manager, and an ED stroke champion. The guidelines recommend the development of policies and procedures that integrate telestroke into EMS, the ED, and the inpatient and intensive care unit settings. Policies should also include telestroke in quality assurance processes and sentinel event reviews.

The guidelines state that telestroke programs must include training and orientation for all involved providers, including EMS, ED and hospital staff, and radiology technicians [2]. Training should aim to build trust and develop integrated team workflows, and ongoing training may be necessary.

The guidelines also affirm that telestroke professionals should be fully licensed, registered, and credentialed and must be aware of all relevant requirements [2]. Providers in the United States must abide by the Health Insurance Portability and Accountability Act (HIPAA) and the Health Information for Economics and Critical Health Act (HITECH) as well as any additional state privacy and confidentiality regulations. Privacy and security issues must also be addressed from a technological perspective, including policies and procedures for clinical documentation and the management of patient health records.

Fiscal management is also included in the guidelines, with recommendations that budgets incorporate costs of hardware, software, data lines, licensing fees, credentialing fees, call reimbursement, marketing and communication costs, personnel, supplies, real estate, and ongoing maintenance expenses [2]. Budgets may also take into account revenue for telestroke services, such as payer reimbursements, grants, healthcare system support, and private contributions.

The guidelines stress that telestroke services should also have systematic quality improvement and performance management processes in place [2]. Ideally, a procedure should exist for reporting and disseminating quality metrics and outcomes within a telestroke network for both administrative and operational analyses.

Finally, the guidelines include considerations for physical layout and spatial design to facilitate telestroke use. They review program and operational goals, staffing models, telestroke workflows, technical equipment recommendations, and data policy and procedure recommendations [2].

Fig. 20.1 American College of Cardiology/American Heart Association classes of recommendation and levels of evidence for clinical strategies, interventions, treatments, and diagnostic testing in patient care. (Updated August 2015; with permission) [49]

Quality Metrics

Quality measures for telestroke systems have been proposed by the AHA/ASA [46]. These include both process and outcome measures. Process measures suggested include standardized time metrics for the consult process as well as for imaging and tPA delivery that should be consistent with non-telestroke measures. Measures related to the quality of audio/video encounters and related to the transfer process and timing of transfers are also suggested [46].

Proposed outcome measures include changes in stroke severity (NIHSS) over the course of the initial evaluation

and transfer, consistency of initial telestroke diagnosis and final discharge diagnosis, hospital-related outcomes such as length of stay and in-hospital complications, and patients' functional status at discharge [46]. Networks are encouraged to follow patients' functional status in the longer term (e.g., 90-day modified Rankin Scale) by telephone, video, or in person [46]. Suggested safety measures include symptomatic intracranial hemorrhage and mortality rates [46].

Finally, recommendations for measuring patient and provider satisfaction as well as technological quality are important [46].

Looking Forward

Though much progress has been made in the last decade, major challenges remain for telestroke to reach its potential. Reimbursement and regulatory frameworks must continue to adapt to this innovative but increasingly ubiquitous modality of acute stroke care delivery. Telestroke programs themselves must continue to grow and evolve in response to updates in clinical knowledge, such as the evidence for expanded time windows for treatment and new approaches to wake-up strokes and mechanical thrombectomy.

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Outcome Prediction and Shared Decision-Making in Neurocritical Care

21

Matthew F. Sharrock and Robert D. Stevens

Introduction

Prediction of neurological outcome is a fundamental yet complicated task for the neurointensive care physician [1]. Before a course of action is chosen, the treatment team is often called upon to provide an estimate of the patient's potential for recovery (or lack thereof), which is based on knowledge of the natural history of the disease as well as published regression models linking features present in the acute phase with specific short- or long-term recovery phenotypes. In many cases, however, such models do not integrate critical outcome determinants such as the effects of treatments. Moreover, neurologic prognostication can only be effective if practiced within a framework that considers a range of contextual features specific to the patient, his or her next of kin, and variables determined by the medical team and the health system where the patient is being treated [2]. In many instances, expectations and assumptions, even when not explicitly stated, may exert a significant influence on the care that a patient receives. Discussion may center on achieving a meaningful functional recovery and on quality of life, yet these may vary considerably depending upon the values and wishes of the patient and/or next of kin.

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Limitations of Prognostic Models

The value of prognostication in neurointensive care is challenged by the difficulty in making accurate predictions for individual patients. The kind of detailed quality-of-life information that patients and families commonly ask for is not well captured in population-based studies, which typically evaluate mortality and gross functional outcome using scales such as the modified Rankin Scale (mRS) or the Glasgow Outcome Scale (GOS). Functional outcome also may not capture the complexity of post-intensive care unit recovery, especially when cognitive impairment dominates long-term function or if multiple organ systems are involved [3].

One significant problem is the internal validity of prognostic models [2, 4–7]. Withholding or withdrawing treatment and then recording a poor outcome may constitute a confirmation bias or so-called self-fulfilling prophecy leading to overconfidence in a model's specificity and negative predictive value [8–10]. It should be recalled that withdrawal of life-sustaining treatment is the most common proximate factor leading to death in neurocritical care [11, 12].

Another problem is external validation and generalization of prediction models. Many models developed from population data are created in single centers at a specific point in time with data acquisition protocols and treatment strategies that may not be generalizable. Moreover, outcome scales validated in years past may not reflect the current standard of care. For example, in a study of intracerebral hemorrhage (ICH) patients, those treated with aggressive new guideline-based therapy had better outcomes than point estimates predicted by the widely implemented ICH score [5, 13]. In another report, clinical judgment-based estimates of outcome were more accurate than point estimates from the ICH score [14].

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Model Performance

In this review, we summarize existing prognostic factors and models for major disease types seen in neurointensive care. Whenever possible, we refer to multivariable models, and we discuss a model's performance in terms of its discrimination and calibration [15]. *Discrimination* is generally expressed as the area under the receiver operator characteristic curve (AUC). The receiver operator characteristic curve plots the true-positive rate against the false-positive rate (Fig. 21.1). The dashed line at 45 degrees signifies an AUC of 0.5, meaning the model operates no better than chance. A perfectly discriminating model would pass through the top left corner creating a unit square with an AUC of 1.0. The AUC can be interpreted as the probability that a test will correctly discriminate between two alternative outcomes. By convention, models that operate with an AUC of less than 0.6 are considered a "failure," those with an AUC of 0.6–0.7 are considered "poor," while those from 0.7 to 0.8 are considered "fair." When the AUC exceeds 0.8, models are thought to have potential clinical utility; models with an AUC of 0.8–0.9 are "good," and those above 0.9 are regarded as having "excellent" discrimination (Fig. 21.1). The AUC approach is validated for studies with large sample sizes but is noisy and potentially unreliable for smaller studies [16].

Calibration (goodness of fit) is the degree to which the predicted probability generated by a model agrees with the actual event rate observed in a population. While many published reports focus on discrimination as a model performance indicator, calibration could be viewed as the most important property of a model. Calibration is generally represented graphically by plotting the relationship between predicted and observed events or event rates (Fig. 21.2). Goodness of fit can be expressed quantitatively using the Hosmer-Lemeshow test and *p*-value, with smaller *p*-values (usually <0.05) indicating the model is not a good fit [17].

Prognostication in Traumatic Brain Injury

Commonly reported predictors of outcome after severe traumatic brain injury (TBI) include age, level of consciousness measured using the Glasgow Coma Scale (GCS), pupillary reactivity to light, presence of intracranial bleeding [18–20], and concurrence of significant physiologic disturbances such as hypotension [21] and hypoxia [22].

The two best-known and most widely validated outcome prediction models for patients with TBI are the International Mission on Prognosis and Analysis of Clinical Trials (IMPACT) and the Corticoid Randomization After Significant Head Injury (CRASH) models [23–25]. These models were both established using data from clinical trials (IMPACT (n = 8509) and CRASH (n = 10,008)) and focus on covariates extracted from clinical assessment, head computed tomography (CT), and discrete laboratory assessments. Both scores have shown fair to good performance characteristics for both mortality and dichotomized GOS at 6 months, without significant differences between the two in AUC or in calibration [23]. These studies confirmed that the vast majority of prognostic information is contained within the core predictors of age, GCS, and pupillary responses. In the case of IMPACT, modest improvements in predictive accuracy were obtained by adding data from head CT, presence or absence of hypoxia and/or hypotension, and admission serum glucose and hemoglobin values [25]. In the case of CRASH, model performance was improved slightly depending on whether major extracranial injuries were present [24]; however, abnormalities detected on CT (petechial hemorrhages, obliteration of the third ventricle or basal cisterns, subarachnoid hemorrhage, midline shift, or non-evacuated hematoma) added little to model performance on external validation [23].

When deciding which model is more appropriate, it is helpful to consider the case mix of the original studies: IMPACT was developed using data from patients with mod-

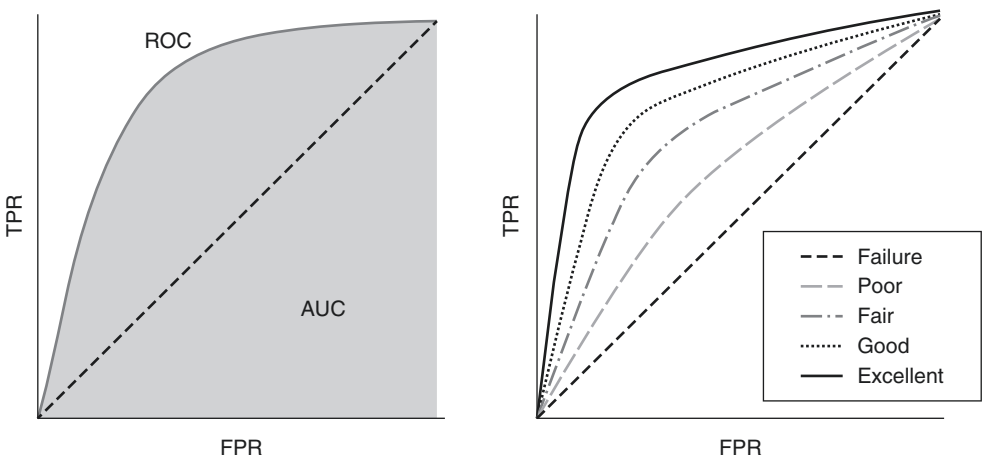

Fig. 21.1 The receiver operator characteristic (ROC) curve (left) showing the true-positive rate (TPR) as a function of the false-positive rate (FPR), where the area under the curve (AUC) in gray corresponds to the likelihood of correct discrimination. Varying curves (right) showing an increasing AUC from 0.5 to 0.9

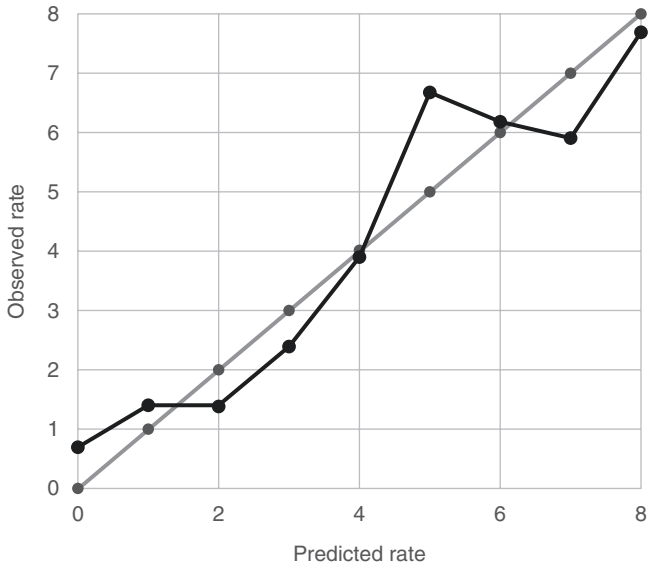

Fig. 21.2 A calibration curve plots predicted (gray) vs. observed (black) event rates in a given population. A perfectly calibrated model would fall along the gray line

erate to severe TBI recruited mostly in developed nations, while CRASH was developed utilizing data from patients with mild, moderate, and severe TBI many of whom were enrolled in lower- or middle-income countries. The timing of the predicted outcome was also different in the two studies: the CRASH model was designed to predict 14-day mortality and unfavorable outcome at 6 months, whereas IMPACT was focused on 6-month mortality and unfavorable outcome [23].

Given the frequent coexistence of multisystem injury with severe TBI, general intensive care severity scores including the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II have fair to good discrimination (AUC of 0.79 and 0.80, respectively) in predicting 6-month mortality in this population [26]. A model combining variables from both the APACHE II score and IMPACT had an AUC of 0.84 for predicting 6-month mortality in both a development cohort (n = 445) and validation cohort (n = 445) [27].

Prognostication After Cardiac Arrest

Major predictors of cardiac arrest survival and neurological outcome include the location of arrest (out of hospital vs. in-hospital), presence of a shockable initial rhythm (ventricular fibrillation and tachycardia vs. asystole and pulseless electrical activity), time to return of spontaneous circulation, age, and comorbidities [28]. A small number of studies have employed multivariable prognostic modeling in this population. In a post-hoc analysis of 933 patients enrolled in the Target Temperature Management trial, 10 independent predictors of poor outcome were identified: older age, cardiac arrest occurring at home, non-shockable rhythm, longer duration of no flow (defined as time from start of cardiac arrest to start of cardiopulmonary resuscitation), longer duration of low flow (defined as time from start of cardiopulmonary resuscitation to return of spontaneous circulation), administration of epinephrine, bilateral absence of corneal and pupillary reflexes, GCS motor subscore of 1, lower pH, and a $PaCO_2$ value lower than 34 mmHg at hospital admission [29]. The out-of-hospital cardiac arrest (OHCA) score was found to predict survival with good neurological outcome at hospital discharge (Cerebral Performance Category [CPC] score of 1 or 2) and includes the following variables: initial rhythm ventricular fibrillation or tachycardia, lower no-flow interval, lower low-flow interval, lower serum lactate, and lower creatinine [30]. AUC of this model was 0.82 in the development cohort (n = 130) and 0.88 in a validation group (n = 210) [30], with subsequent studies suggesting variable performance in the fair to good range for AUC [31–34]. The Cardiac Arrest Hospital Prognosis (CAHP) score identified seven independent predictors of poor neurological outcome at hospital discharge (CPC 3, 4, or 5): increasing age, initial non-shockable rhythm, time from collapse to basic life support, time from basic life support to return of spontaneous circulation, cardiac arrest at home, increasing epinephrine doses, and decreasing arterial pH [35]. Discrimination of this model was good to excellent in both development (n = 819, AUC 0.93) and in two validation datasets (n = 367, AUC 0.85 and n = 1129, AUC 0.91) [35]. Simplified versions of the OHCA and CAHP scores were recently tested in an independent cohort from Taiwan, with AUCs of 0.82 and 0.84, respectively [36].

Research has shown that in cardiac arrest patients managed with targeted temperature management, characteristics of the neurological examination may have reduced predictive accuracy [37]. This has spurred interest in neurophysiologic testing and neuroimaging for prognostication, the so-called "multi-modality" paradigm. In a recent report on 150 cardiac arrest patients, a model combining clinical assessment, electroencephalogram classification, and whole-brain white matter fractional anisotropy (measured using diffusion tensor MRI) yielded an AUC of 0.99 for predicting 1-year CPC [38].

Prognostication in Acute Ischemic Stroke

The caveat about advances in therapeutic management and the accuracy of prognosis is particularly relevant in the field of acute ischemic stroke, where most prediction models were developed after the widespread introduction of intravenous thrombolytic therapy but *prior* to mechanical thrombectomy

becoming a prevalent intervention. Historically, factors most consistently associated with prognosis are stroke severity and patient age [39–48]. Advanced age is a strong predictor of increased stroke morbidity and mortality and is used in numerous predictive models [39, 49]. Stroke severity can be measured clinically or radiographically. The best known and most widely validated clinical severity score is the National Institutes of Health Stroke Scale (NIHSS) [50]. When used to predict mRS at 3 months, a baseline NIHSS of ≤6 is associated with good recovery and NIHSS ≥16 is associated with high probabilities of death and severe disability [40]. The size of cerebral infarction on neuroimaging is an additional severity indicator that has been associated with outcome [51]. It should be noted that the association of outcome and infarcts is more complex in the posterior circulation, where effects are highly dependent on lesion location.

Medical comorbidities can have a profound effect on stroke outcome, for example, in patients with dementia [42], heart failure [52], severe kidney disease, and dialysis [53]. Validated scoring systems that incorporate comorbidities are the Get with the Guidelines (GWTG) Score [54], the Ischemic Stroke Predictive Risk Score (IScore) [42], and the PLAN score [52].

The GWTG Score, based on a registry of over 274,988 patients, was developed to predict in-hospital mortality after ischemic stroke. The strongest predictors found were stroke severity as measured by NIHSS, atrial fibrillation, and a history of coronary artery disease. The AUC for in-hospital mortality was 0.84 in the internal validation set. An external validation study reported an AUC of 0.87 indicating it has an 87% chance of being able to distinguish patients who will not survive to hospital discharge. When extended to 1-year mortality, the AUC was 0.78 [55].

The IScore estimates the risk of death (at 30 days or 1 year), disability (mRS ≥ 3), and institutionalization [42]. The most important contributors to the prediction of mortality in this model are stroke severity, stroke subtype, and renal dialysis as a comorbidity. The AUC for 30-day and 1-year mortality were 0.79 and 0.78, respectively, in their external validation set. An independent external validation study found AUCs of 0.80 and 0.79 for 30-day and 1-year mortality, respectively [55].

The PLAN score, which utilizes clinical data available on admission, integrates preadmission comorbidities, level of consciousness, age, and neurological deficits. In the internal validation cohort, the score achieved an AUC of 0.87 for 30-day mortality, 0.84 for 1-year mortality, and 0.80 for favorable outcome at discharge (mRS 0–2). Independent external validation found an AUC of 0.77 for 30-day mortality and 0.79 for 1-year mortality [55].

In patients who have undergone mechanical thrombectomy for an anterior circulation stroke, the Pittsburgh Outcomes after Stroke Thrombectomy (POST) score combines final infarct volume on neuroimaging, age, and the development of parenchymal hematoma to predict good outcome (mRS 0–2) [56]. The AUC was 0.85 in the derivation cohort and 0.76–0.86 in validation cohorts. However, the sample sizes in both the derivation and validation cohorts were relatively small (n = 247 and n = 803, respectively) [56].

Overall, existing models for 30-day and 1-year mortality are just at the threshold of clinical utility, with the possible exception of the GWTG Score for in-hospital mortality: it performs at a level where it can be given some consideration when discussing prognosis in patients who did not receive mechanical thrombectomy. At this time, therefore, there is a significant unmet need for effective predictive modeling that would be relevant to the increasing proportion of acute ischemic stroke patients who undergo mechanical thrombectomy.

Prognostication in Spontaneous Intracerebral Hemorrhage

Current ICH prediction models are based on relatively small samples from single site studies and have limited external validation. Advanced age, level of consciousness, hematoma volume, and location are the most consistent outcome predictors after ICH [57–59]. Several multivariable scoring systems have been developed, the most widely used being the ICH score [13], along with other similar scores such as the modified ICH score (mICH) [60] and the ICH Grading Scale (ICH-GS) [61]. The max-ICH score [62] was designed to model the effect of "maximal" treatment and to reduce the effects of confirmation bias or "self-fulfilling prophecy."

The original ICH score, published in 2001, was based on data from 152 patients at a single institution. This model predated published trials of intensive blood pressure lowering [63, 64] and the introduction of new oral anticoagulants and their reversal agents [65]. Predictors of 30-day mortality are age, ICH volume, infratentorial location, GCS score, and intraventricular extension of blood [57–59]. The original score has been externally validated [66, 67] and has been shown to also predict 1-year mortality [68].

The mICH score predicts 3-month mortality and was also developed on a single institutional dataset (n = 226) where 50% of patients had surgical endoscopic intervention for basal ganglia hemorrhage, the most common form of ICH and the most likely to produce intraventricular hemorrhage (IVH) extension [60]. The mICH stratifies GCS (3–4, 5–12, 13–15) and ICH volume (<21, 21–50, >50cc) then adds IVH or hydrocephalus. The original study reported an AUC of 0.90 in an internal validation cohort [60].

The ICH-GS, developed on another independent single site dataset (n = 378), similarly generates new stratifications within the original ICH scale but instead has different thresh-

olds for age (<45, 45–64, >64 years), GCS (3–8, 9–12, 13–15) and ICH volume (divided into either infratentorial hemorrhage (<10, 10–20, > 20cc) or supratentorial hemorrhage (>40, 40–70, >70cc)) [61]. Internal validation showed an AUC of 0.86 for in-hospital mortality, 0.88 for 30-day mortality, and 0.86 for 30-day favorable outcome (GOS of 4 or 5).

A study consisting of 1175 unselected ICH cases at a single institution in the United Kingdom was used to compare the ICH score, mICH, and ICH-GS [69]. For 30-day mortality, these authors found AUCs of 0.86, 0.82, and 0.87, respectively. Interestingly, in this cohort, these multivariable scores did not perform any better than GCS alone, which had an AUC of 0.87.

The max-ICH score was developed from a cohort of 583 patients at a single institution, where 112 had early withdrawal (<24 h) of life-sustaining support. Independent predictors of 12-month favorable outcome (mRS 0–3) were NIHSS, age, intraventricular hemorrhage, anticoagulation use, and ICH volume [62]; internal validation showed an improved AUC of 0.81 compared to 0.67 for the original ICH score. However, a recent external comparison of the ICH score and max-ICH score showed no added benefit (AUC of 0.81 vs 0.80) when predicting 3-month mortality in a single institutional cohort of 301 maximally treated patients [67].

Prognostication in Aneurysmal Subarachnoid Hemorrhage

Factors consistently identified to be important with regard to predicting outcome after aneurysmal subarachnoid hemorrhage (aSAH) have been age, radiographic and clinical severity at presentation, and delayed cerebral ischemia (DCI) [70–76]. The Hunt and Hess (HH) grading system for the clinical neurological exam was developed in 1968 to grade surgical risk in aSAH. It has subsequently been validated with regard to mortality but is limited due to moderate interobserver reliability [77]. The World Federation of Neurological Surgeons (WFNS) clinical scale incorporates GCS and has similarly been validated for predicting mortality but also is challenged by moderate interobserver variability [78].

The SAH score was developed to try to improve prediction of mortality as compared to HH and WFNS and includes admission GCS as a clinical component, along with age and number of concurrent comorbidities [79]. The model was built with data from a cohort study of 1134 patients at two institutions, and internal validation showed an AUC for in-hospital mortality (0.82) that outperformed the WFNS and HH scales (0.78 and 0.77, respectively). However, this score has yet to be externally validated.

In another report on 1620 aSAH patients, a slightly adapted WFNS was recorded not on admission but after initial neurological resuscitation (rWFNS) [80]. A multivariable model including age, rWFNS, modified Fisher grade, aneurysm size, and presence of intracerebral hematoma had an AUC of 0.87 for predicting 2-month mRS [80]. This report independently confirmed results obtained in another smaller cohort [81], suggesting that the timing of assessment weighs significantly in aSAH prognostic models.

The SAH International Trialists' (SAHIT) predictive model derives from a pooled dataset of clinical trials and observational studies consisting of 10,936 patients [82]. Independent predictors of 3-month functional outcome (GOS) included age, hypertension, and WFNS grade with an AUC of 0.80. Inclusion of information about aneurysm size/location and Fisher radiographic score (AUC 0.81) as well as treatment modality (surgical clipping vs. endovascular coiling; AUC 0.81) did not significantly increase model discrimination [82].

Several studies have focused on predicting mortality or poor outcome in patients who present with poor grade aSAH. These studies have shown that clinical neurological severity as measured by HH, WFNS, or GCS along with age are predictive of mortality [83, 84]. However, it should be noted that these studies all have small sample sizes ($n < 250$) and lack external validation. When considering advances in treatment primarily via endovascular approaches and the lack of externally validated models, it can be concluded that there is a large unmet need for more robust approaches to prognostication in aSAH.

Shared Decision-Making

Families of patients often report that they are insufficiently or poorly informed when making decisions about clinical care [85]. Since the care of patients with acute brain injury frequently engages several teams (e.g., intensive care medicine, neurology, neurosurgery, nursing), there is considerable potential for differences to exist in the content and style of communication delivered to families. In two independently conducted surveys regarding the care of severe TBI patients, patients and families reported significant dissatisfaction when variability in communicated prognosis existed between different teams [86, 87].

Shared decision-making refers to a collaborative process whereby clinicians, patients, and families work collaboratively to increase understanding of the underlying disease, evaluate the risks and benefits of different courses of action, and explore whether these possibilities align with the patient's wishes regarding an acceptable quality of life [88, 89]. Prognostic models can be used in this setting to examine possible outcomes while highlighting the uncertainty in these models and the applicability to the specific patient. Acknowledging this approach, the Neurocritical Care Society recommends that decisions about goals of care be

delayed at least 72 h after neurologic injury has occurred to allow observation of the clinical course and for trust to be fostered with the treatment team [90]. While shared decision-making is widely viewed in a positive light, additional research is needed to evaluate its efficacy and impact in a neurocritical care setting [89].

Conclusions

A number of different multivariable models have been developed to predict outcomes in patients with ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, and those who have been resuscitated after cardiac arrest. These models can be used to support discussions with patients and families regarding outcomes. Limitations in many of these models are that they have not been externally validated, represent observations made in a single center, and often do not integrate treatment variables as predictive features. Studies suggest that modeling approaches integrating disease-specific neurologic scores may increase the ability to predict mortality and functional outcome. In the case of high-resolution datasets, greater efficacy in prediction may be achieved using advanced statistical and machine learning algorithms [91].

Delivering prognosis in neurocritical care may benefit from the paradigm of shared decision-making among the patient, his or her family, and the different members of the treating teams. The impact of this approach requires validation in rigorously designed prospective studies.

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Part VI

Special Issues in the Neurocritical Care Unit

Multimodality Neuromonitoring

22

Lucia A. Rivera Lara and Jose I. Suarez

Introduction

Medicine has experienced tremendous growth in the past few decades. Such progress is due in large part to the advent of technological breakthroughs, which have allowed for the use and development of algorithms and devices that promise to improve patient care. In neurology, the neurologic examination has long been the mainstay of monitoring and management for the brain-injured patient. However, in neurocritical care, we struggle to make decisions based on this examination alone, as many patients are comatose or exhibit only very subtle changes that warrant further attention. Thus there is a need for information from supplementary and complementary sources. In this chapter, we describe the ongoing development of innovative neuromonitoring devices that could improve current patient management. Despite the fact that some of the devices presented here are not widely used in medical practice (either because they are costly or lack evidence-based studies to demonstrate benefit), we will discuss their potential utility and pitfalls. In addition, we will emphasize the current recommendations for their use in clinical practice according to the recently published guidelines of the International Multidisciplinary Consensus Conference on Multimodal Monitoring in Neurocritical Care in 2014 (Table 22.1). To understand neuromonitoring, we must understand neurophysiology. Therefore, each section will begin with a brief introduction on the importance of monitoring specific neurophysiologic changes.

Monitoring Brain Oxygen Delivery

The impetus for monitoring brain oxygen delivery stems from the fact that brain oxygen stores are very low (0.2 mL/100 g) and that they can support normal oxygen consumption for only a few seconds [1]. The corollary to this is that a lack of oxygen supply translates into a reduction in high-energy metabolites such as adenosine triphosphate (ATP) and phosphocreatine. The depletion of ATP causes loss of the cellular sodium gradient, normally maintained by the Na^+/K^+ membrane pump [1]. Subsequently, this energy failure causes influxes of calcium that further depolarize the membrane and trigger the release of glutamate into the extracellular space [2]. Glutamate is neurotoxic to ischemic cells because it induces further neuronal depolarization and mitochondrial dysfunction that eventually leads to cell death.

Brain oxygen can be measured continuously by an invasive device known as the brain tissue oxygen tension ($PbtO_2$) sensor supplied independently via the Licox™ system (Integra LifeSciences, Plainsboro, NJ) or in combination with solid-state pressure and temperature sensors via the Neurovent-PTO™ system (Raumedic, Inc., Mills River, NC). Alternatively, brain oxygenation can be measured by noninvasive near-infrared spectroscopy (NIRS) systems. Three commercial NIRS systems have been approved by the U.S. Food and Drug Administration: (1) FORE-SIGHT™ (CAS Medical Systems, Branford, CT); (2) EQUANOX™ (Nonin Medical, Plymouth, MN), and (3) INVOS™ (Covidien, Boulder, CO). NIRO is the cerebral oximeter approved in Europe (Hamamatsu Photonics, Hamamatsu City, Japan; CE-marked). In addition, oxygen venous saturation can be measured by inserting a catheter into the jugular bulb, but this is no longer used in many centers because it is invasive and lacks any proven benefit.

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Table 22.1 Advantages and disadvantages of multimodality monitoring

Type of monitoring	Device	Advantages	Disadvantages	Recommendations for use[a]
Monitoring brain oxygen delivery	$PbtO_2$ sensor	Reflects the product of CBF and arteriovenous oxygen pressure difference	It is invasive; complication rate up to 3% (intracranial bleeding)	Should be used in patients with or at risk for cerebral ischemia or hypoxia (strong recommendation, low-quality evidence)
		Low $PbtO_2$ (10–20 mm Hg) is associated with worse functional outcomes in patients TBI and SAH	Regional measurements depending on where the probe is placed	
		Can be used as a surrogate of CBF to measure CA	Depends on $CMRO_2$, local oxygen diffusion gradients, and CPP	
			Depends on systemic factors such as CO, Hb levels, PaO_2, and PCO_2	
	NIRS	Measures the mean regional oxygen saturation (ScO_2) across a mixed vascular bed dominated by gas-exchanging vessels	ScO_2 values are affected by hemoglobin concentration, skull thickness, hair follicle density, skin tone, and underlying area of cerebrospinal fluid (CSF) layer	NIRS should be used to answer research questions but not to guide clinical management of patients
		Can be used as a surrogate of CBF to measure CA	Measurements are regional (most commonly frontal lobes)	
			Depends on systemic factors such as CO, Hb levels, PaO_2, and PCO_2	
	Jugular bulb catheter	It provides global venous oximetry	It is invasive and can cause blood infections and jugular venous thrombosis	If used, it should be part of a multimodal monitoring approach or at least used in combination with an ICP monitor (low-quality evidence)
		The recognized threshold for ischemia is <55%	No proven benefit	
Monitoring CBF	TCD	It has a high PPV and NPV for cerebral vasospasm detection	It measures the CBF velocity, not the flow	It should definitely be used to predict cerebral vasospasm after aneurysmal SAH (strong recommendation, high-quality evidence)
		It can measured CA	Variability of measurements between technicians	
	TDF	It has shown great correlation when compared to Xe-CT–derived CBF measurements	It is invasive with infection rates up to 5%	It can be used to identify patients with focal risk within the vascular territory of the probe
		A minimum threshold of 15–18 cc/100 g/s can be assumed	It is not reliable in patient with fever	
			It provides a local measurement of CBF	
Monitoring cerebral metabolism	Cerebral microdialysis	It can provide hourly sampling of the extracellular fluid	It is invasive	It should be used only when combined with clinical indicators and other monitoring modalities for prognostication and in patients at risk of cerebral ischemia, hypoxia, energy failure, and glucose deprivation (strong recommendation with low-quality evidence)
		Extracellular metabolic markers are independently associated with outcome after TBI	It provides only local measurements of the extracellular fluid	

Table 22.1 (continued)

Type of monitoring	Device	Advantages	Disadvantages	Recommendations for use[a]
Monitoring ICP	ICP monitor	A sustained elevation in ICP to above 22 mm Hg has been associated with poor functional outcomes	It is invasive with high rates of infection (up to 22%) and intracranial hemorrhage (up to 41%)	It should be used in patients at risk for intracranial hypertension (strong recommendation, moderate-quality evidence)
		A ventriculostomy can be therapeutic and allow for CSF drainage	Provides only a compartmental measurement of the intracranial pressure	
		It can measure cerebrovascular reactivity		
Electrophysiology	EEG	It can identify epileptiform activity	It is expensive	It should be used in patients with acute brain injury and unexplained and persistent altered consciousness (strong recommendation, low quality of evidence)
		It can also detect delayed cerebral ischemia in comatose patients with aneurysmal SAH	It requires a technician to place the leads	It may be used to detect delayed cerebral ischemia in SAH patients (weak recommendation, low quality of evidence)
			Variability between EEG readers	

CA cerebral autoregulation, *CO* cardiac output, *CBF* cerebral blood flow, *$CMRO_2$* cerebral metabolic rate of oxygen, *CSF* cerebrospinal fluid, *CPP* cerebral perfusion pressure, *EEG* electroencephalogram, *Hb* hemoglobin, *ICP* intracranial pressure, *NIRS* near-infrared spectroscopy, *NPV* negative predictive value, *PaO_2* arterial pressure of oxygen, *PCO_2* arterial pressure of carbon dioxide, *$PbtO_2$* brain tissue oxygen tension, *PPV* positive predictive value, *SAH* subarachnoid hemorrhage, *TBI* traumatic brain injury, *TCD* transcranial Doppler, *TDF* thermal diffusion flowmeter

[a]Recommendations from the guidelines of the International Multidisciplinary Consensus Conference on Multimodal Monitoring in Neurocritical Care in 2014 [6]

Regional Brain Tissue Oxygen Tension ($PbtO_2$) Monitoring

$PbtO_2$ best reflects the product of cerebral blood flow (CBF) and arteriovenous oxygen pressure difference and is influenced by the oxygen diffusion gradient [3]. Therefore, impaired local tissue extraction of oxygen (e.g., cerebral edema) can also lower $PbtO_2$ despite normal CBF. The normal values are 25–35 mm Hg, and any recording <20 mm Hg is considered abnormal (cerebral ischemia and energy dysfunction). It is important to bear in mind that $PbtO_2$ can be modified by several factors, including cerebral perfusion pressure (CPP), local CBF, cerebral metabolic rate of oxygen ($CMRO_2$), and systemic factors such as cardiac output, hemoglobin levels, PaO_2, and PCO_2. Although $PbtO_2$ monitoring is invasive, surprisingly, the reported complication rate is low: 0–3% local bleeding around the catheter with no catheter-related infections. It is also magnetic resonance imaging (MRI) 1.5 Tesla compatible [3].

Many observational studies have shown that low $PbtO_2$ (10–20 mm Hg) is associated with worse outcomes (lower Glasgow Outcome Scale, increased neuropsychological deficits), mainly in patients with traumatic brain injury (TBI) and some with subarachnoid hemorrhage (SAH). An ongoing randomized multicenter study (BOOST 2, NCT00974259) is currently comparing protocols in which therapy for TBI patients is guided with only intracranial pressure (ICP)/CPP to those that use ICP/CPP and $PbtO_2$.

One recent application of $PbtO_2$ is the measurement of cerebral autoregulation using multimodality monitoring. In this case, $PbtO_2$ serves as a surrogate for CBF, and different brands of commercial software [4] are used to measure a continuous correlation of $PbtO_2$ and mean arterial pressure (MAP) (dynamic cerebral autoregulation). The index of cerebral autoregulation derived from $PbtO_2$ (tissue oxygen index or TOx) has been validated against the pressure reactivity index (PRx) and transcranial Doppler ultrasonography (TCD)-derived index (mean flow velocity index) and has shown moderate correlation with each ($r = 0.4$, $p = 0.04$ and $r = 0.61$, $p = 0.004$, respectively) [5].

The International Multidisciplinary Consensus Conference on Multimodal Monitoring in Neurocritical Care [6] strongly recommends the use of $PbtO_2$ for patients with or at risk for cerebral ischemia or hypoxia. However, the quality of evidence and the prevalence in clinical practice are low.

Near-Infrared Spectroscopy (NIRS)

NIRS is a noninvasive optical technique used to measure regional cerebral oxygen saturation (ScO_2). It relies on the relative transparency of the skull to near-infrared light (700–900 nm), where the spectroscopically observed color changes are due to the proteins that deliver (hemoglobin) and consume (mitochondrial cytochrome c oxidase) oxygen. Hemoglobin

changes color when it binds oxygen. The changes in cytochrome c oxidase are due to the electron occupancy (reduction) of a particular copper metal center in the enzyme [7].

Measuring near-infrared light absorption by hemoglobin (oxygenated and deoxygenated) allows the calculation of ScO_2 [8]. Cerebral oximetry provides a percent measurement of mean oxygen saturation across a mixed vascular bed dominated by gas-exchanging vessels, especially venules (arterial/venous ratio 16:84) in the tissue of interest [8]. ScO_2 is calculated as follows [9]: $ScO_2 = [O_2Hb/Hb] \times 100\%$, where O_2Hb = oxyhemoglobin, Hb = total hemoglobin = O_2Hb + HHb, where HHb = deoxyhemoglobin.

NIRS signals indeed encode information regarding tissue oxygen levels and blood flow. NIRS has been validated against computed tomography (CT) perfusion for use as a CBF surrogate ($p < 0.0001$) [10]. However, it has been challenging to understand and integrate ScO_2 into patient care not only because of the technological limitations described below but also because ScO_2 values are also affected by $CMRO_2$, hemoglobin concentration, skull thickness, hair follicle density, skin tone, underlying area of cerebrospinal fluid (CSF) layer, [7, 11, 12] and the same systemic factors that affect $PbtO_2$.

One of the pitfalls of NIRS is extracranial contamination. In a study of 12 healthy volunteers, changes in cerebral oximetry caused by extracranial flow in the forehead measured by 3 commercial cerebral oximeters varied from a mean of 6.8% to 16.6% (the lower difference was from EQUANOX NIRS) [13]. Another limitation is that it is unclear how the state of cytochrome c oxidase changes ScO_2 in various situations (e.g., hypoxemia) [7, 14].

Most of the NIRS studies in neurocritical care have been small and with several limitations [12, 15]. However, NIRS is also used with multimodality neuromonitoring to measure cerebral autoregulation. The NIRS-derived index of autoregulation, the cerebral oximetry index or COx, has been validated against the TCD-derived index, Mx, in patients with coma from acute brain injury, and a moderate correlation has been identified ($r = 0.4$, $p = 0.005$) [16].

The current recommendation from the International Multidisciplinary Consensus Conference on Multimodal Monitoring in Neurocritical Care [6] is to use NIRS to answer research questions but not to guide routine management of patients (low-quality evidence), as the data are insufficient and conflicting. When used, NIRS should be integrated into a multimodal neuromonitoring concept (low quality of evidence).

Monitoring CBF

The brain requires 15–20% of the cardiac output during healthy and resting conditions. However, this amount is often altered by brain injury, differs in women and men, decreases across the adult lifespan, and is inversely associated with body mass index [17]. Although it is critical to ensure normal CBF delivery to the brain, developing a device that can monitor CBF has been challenging. Currently, three devices are commercially available, but each has disadvantages. (1) TCD is a noninvasive device that measures CBF velocity within the large vessels. (2) c-FLOW™ (Ornim, Inc., Israel) is a noninvasive device that combines NIRS signals with low-powered ultrasound to calculate the cerebral flow index or CFI (the CFI is the output of this device and its algorithm is proprietary). (3) QFlow 500™ (Hemedex, Inc., Cambridge MA) is an invasive implantable thermal diffusion flowmeter (TDF).

TCD

The TCD probe emits high-frequency (2 MHz) acoustic energy that can penetrate biologic tissue and delineate anatomic morphology. Detection of changes in the frequency of sound waves reflecting from intravascular erythrocytes indicates the presence, absence, velocity, and direction of CBF [18]. The most common clinical application of TCD is detecting cerebral vasospasm after aneurysmal SAH. The sensitivity and specificity of TCD velocity >120 cm/s to detect cerebral vasospasm confirmed with angiography vary from 45% to 80% and 77% to 84%, respectively, in the anterior circulation [19]. The positive predictive value of TCD velocities >200 cm/s for vasospasm is 87%, while the negative predictive value for middle cerebral artery velocities <120 cm/s is 95% [20].

One pitfall of TCD is that it measures the velocity but not the flow itself. Therefore, other causes of elevated CBF velocity (e.g., anemia or increases in blood volume delivered from the heart) can alter the measurements. A second pitfall is the variability seen between technicians in the measurements, as the insonated velocity is sensitive to changes in angle insonation or location. Typically, most centers use one or two technicians and monitor daily trends to minimize sampling errors. The Multidisciplinary Consensus Conference on Multimodal Monitoring in Neurocritical Care [6] recommends that TCD be used to predict angiographic vasospasm after aneurysmal SAH (strong recommendation, high-quality evidence).

Ultrasound-Tagged NIRS (UT-NIRS)

UT-NIRS is a hybrid technology based on NIRS that uses a localized low-power ultrasound wave (1 MHz) via the acousto-optic effect. The UTLight™ technology aims brief, focused pulses of ultrasound into the tissue over the volume of interest (roughly 1 cm) through which near-infrared light passes. The higher the blood flow, the broader the Doppler shift of the scat-

tered light. The UTLight™ algorithm analyzes the Doppler shift of the tagged light signal to render the CFI.

The Cerox™ (Ornim, Inc., Israel) monitor was the first-generation UT-NIRS. c-FLOW, the second generation, has a similar but superior base algorithm with an improved tagging system and near-zero flow detection. Cerox™-derived CFI was validated against ^{133}Xenon single photon emission CT (^{133}Xe-SPECT) CBF in ten healthy volunteers who had received an intravenous bolus of acetazolamide. The authors found a significant correlation between CFI and ^{133}Xe-SPECT CBF values ($r = 0.67$, $p < 0.033$) at 15 minutes, but not at 60 minutes ($p = 0.777$) [21]. UT-NIRS–derived cerebral autoregulation indices (cerebral blood flow velocity index, CFx) based on Cerox™ have also been validated against the TCD-derived index (Mx) with a moderate correlation ($r = 0.39$, $p < 0.001$). The pitfall of UT-NIRS is that it renders an index instead of flow measurements. Therefore, UT-NIRS is unitless and the normal values are still unknown.

Thermal Diffusion Flowmeter (TDF)

The TDF utilizes a probe equipped with two thermistors. The distal thermistor is intermittently heated, while the proximal thermistor assesses blood flow by applying mathematical models to the conductive and convective dissipation of heat from the distal thermistor [18]. Researchers have shown good correlation between TDF-derived CBF values and Xe-CT–derived measurements in animal studies ($r = 0.89$, $p < 0.0001$), with a mean difference between the two techniques of 1.1 ± 5.2 mL/100 g/min [22]. Monitor values are expressed in cc/100 g/s and, given the high correlation with other CBF standards, it is reasonable to assume minimum thresholds for cerebral ischemia of 15–18 cc/100 g/s. One pitfall of this device is that the probe must be implanted in the brain parenchyma, and the reported infectious complication rate is up to 5% with minimal hemorrhagic complications. Another limitation is that it is unreliable in patients with fever (>39°C), when tissue contact is lost, and when positioned near large vessels.

The recommendation from the International Multidisciplinary Consensus Conference on Multimodal Monitoring in Neurocritical Care [6] is that the TFD probe be used to identify patients with focal ischemic risk within the vascular territory of the probe (weak recommendation, very low-quality evidence).

Monitoring Cerebral Metabolism

Glucose is the main metabolic substrate for the adult brain. Oxidation of 1 mol of glucose supplies ~35 mol of ATP. The high metabolic rate in the brain is largely necessary for active ion transport and counteracting dissipative ion fluxes across cell membranes [1]. Just seconds of cerebral ischemia causes activation of compensatory glycolysis, which leads to increased levels of inorganic phosphate, lactate, and H_1 formation that results in cellular acidification. The main technique available at the bedside for monitoring cerebral metabolism is microdialysis.

Cerebral Microdialysis

Cerebral microdialysis allows hourly bedside invasive sampling of the extracellular fluid. The main metabolites sampled are lactate and pyruvate (in order to calculate the lactate/pyruvate (L/P) ratio) and glucose. One of the most important considerations when interpreting microdialysis is to understand the probe location and whether it is in a normal environment or around injured tissue.

An elevated L/P ratio may indicate ischemia or hypoxemia. However, this abnormality can also be seen in patients with increased glycolysis or mitochondrial dysfunction. Pyruvate may help differentiate these two entities. Pyruvate (the output of glycolysis; one molecule of glucose gives rise to two molecules of pyruvate) is low during ischemia or hypoxemia and normal or elevated during cellular dysfunction (e.g., mitochondrial dysfunction, cortical spreading depression) with normal oxygen and blood flow delivery. An L/P ratio >25 indicates abnormal tissue oxidative metabolism and >40 is indicative of brain energy crisis. Elevated glutamate (>10 mmol/L) and low glucose (<1 mmol/L) are indicators of ischemia or energy crisis in patients with acute brain injury. An important concept to remember is that lactate also acts as an energy substrate via the astrocyte-neuron lactate shuttle when hypoxemia is not present. This nonhypoxic brain lactate is produced when glucose utilization increases to sustain neuronal activity under stressful conditions and can be an adaptive response to increased energy requirements [23].

One of the largest observational studies included 223 patients with TBI who were monitored with microdialysis beginning on day 1 (1–2) [median (interquartile range)] after injury for a duration of 4 (2–7) days. Results showed that glucose, L/P ratio, ICP, cerebrovascular pressure reactivity index, age, and pyruvate were significant independent predictors of mortality. These results suggest that extracellular metabolic markers are independently associated with outcome after TBI. Whether treatment-related improvement in biochemistry translates into better outcomes remains to be established [24].

The recommendation from the International Multidisciplinary Consensus Conference on Multimodal Monitoring in Neurocritical Care [6] for the use of microdialysis is strong only when combined with clinical indicators and other monitoring modalities for prognostication and in patients at risk of cerebral ischemia, hypoxia, energy failure,

and glucose deprivation. Nevertheless, the quality of evidence and prevalence in clinical practice is low.

Monitoring ICP

The importance of measuring ICP was first articulated in 1783 when Alexander Monro described the skull as a fixed structure containing an incompressible brain. He stated that the volume of blood must remain constant unless "water or other matter is effused or secreted from the blood-vessels" in which case "a quantity of blood, equal in bulk to the effused matter will be pressed out of the cranium." [25] In 1824, his student, George Kellie, confirmed in human and animal autopsies that cerebral blood volume was similar no matter what the cause of death (e.g., hanging or exsanguination) [26]. The concept of intracranial compliance was then understood to mean that an increase in volume may be accommodated by changes in the blood, CSF, and/or brain. But once the system runs out of compensatory mechanisms (decrease in CSF, decrease in cerebral blood volume), an exponential rise in ICP occurs that is very detrimental and can result in brain herniation and brain death if untreated.

We know now that the Monro-Kellie doctrine is not that simple. Each volume component may not deserve the equal weighting that this static concept implies. The slow production of CSF (0.35 mL/min) is dwarfed by the dynamic inflow and outflow of blood (~700 mL/min) [27]. More important, besides focusing on ICP alone, we may interrogate its main drivers, such as the arterial inflow and venous outflow as well as other influences, such as altitude and microgravity.

Intracranial hypertension is defined as a sustained (>5 minutes) elevation in ICP to above 22 mm Hg [28]. There are several types of invasive ICP monitors named after their placement location: intraventricular catheter (IVC), intraparenchymal catheters, and the less commonly used epidural, subdural, and subarachnoid bolts. The IVC (or external ventricular drain (EVD)) is the gold standard because it can be re-zeroed after placement. It also can be used therapeutically by allowing CSF drainage.

The use of ICP monitors became standard of care before evidence-based trials established their value. The only randomized controlled trial assessing ICP monitors in TBI patients was published in the *New England Journal of Medicine* in 2012. This study showed no significant benefit of the ICP monitor-driven protocol compared to a protocol based on imaging and clinical exam without monitoring [29]. Notably, this trial suffered from the same problem that plagues all studies of neuromonitoring devices: the benefit depends on how effectively changes seen on the monitor are managed.

As with other invasive devices, pitfalls include infection (0–22%) and intracranial hemorrhage (0.7–41%) [30]. However, with the implementation of institutional protocols, infection rates have decreased to 1–3% [31]. Probe location is one of the most important variables to consider, as the brain is compartmentalized and probes placed in the supratentorial compartment may not reflect pressures in the infratentorial compartment. Moreover, the pressure measured in a non-lesion site with midline shift toward the non-lesion site may differ from that in the lesion site. Many noninvasive ICP monitors are being developed that will probably replace the invasive ones once they are shown to be accurate. However, none has yet received FDA approval.

ICP monitoring can be used to measure cerebrovascular reactivity. The pressure reactivity index (PRx) is the most commonly used index of cerebral autoregulation. PRx is derived from a moving Pearson correlation between ICP and MAP using 30 consecutive 10-s windows [32]. The advantage is that it can be measured continuously as long as the ICP monitor is in place. It is one of the cerebral autoregulatory indices that best predicts functional outcome in patients with TBI [33].

ICP monitoring is recommended for patients with acute brain injury who are at risk of elevated ICP based on clinical and/or imaging features (strong recommendation, moderate quality of evidence from the Neurocritical Care Multimodal Monitoring Consensus Guidelines 2014) [6].

Electrophysiology

Electroencephalography (EEG) has been one of the longstanding monitoring tools in neurology. Currently, it has multiple clinical applications besides the detection of epileptiform activity. The Neurocritical Care Multimodal Monitoring Consensus Guidelines [6] recommend EEG in the following situations: (1) all patients with acute brain injury and unexplained and persistent altered consciousness (strong recommendation, low quality of evidence); (2) urgent EEG (within 60 minutes) in patients with clinical status epilepticus who do not return to functional baseline within 60 minutes after seizure medication administration or who have refractory status epilepticus (strong recommendation, low quality of evidence); (3) during therapeutic hypothermia and within 24 hours of rewarming to exclude nonconvulsive seizures in all comatose patients after cardiac arrest (strong recommendation, low quality of evidence); and (4) in comatose intensive care unit patients who do not have an acute primary brain condition but who have unexplained impairment of mental status or unexplained neurologic deficits to exclude nonconvulsive seizures, particularly those with severe sepsis or renal/hepatic failure (weak recommendation, low quality of evidence). For the latter group, continuous EEG monitoring is recommended as the preferred method over routine EEG monitoring whenever feasible (weak recommendation, low quality of evidence).

Another indication for EEG is the detection of delayed cerebral ischemia in comatose SAH patients, in whom neu-

rologic examination is unreliable (weak recommendation, low quality of evidence). A drop in the alpha/delta ratio and/or in the percent alpha variability occurs up to 3 days before any clinical or radiographic evidence of delayed cerebral ischemia [34].

The pitfalls of EEG are its high expense (much greater with continuous EEG) and the need for on-call technicians to place the EEG leads. Moreover, there is some variability in the EEG interpretation between expert readers.

Cerebral Autoregulation

Sixty years after the cerebral autoregulatory curve was first described by Lassen, it is now feasible to delineate individual cerebral autoregulatory curves at the bedside with multimodality monitoring [35]. The importance of monitoring cerebral autoregulation is predicated under the assumption that it protects the brain against hypoperfusion caused by hypotension as well as against hypertension-induced hyperemia [36].

Measuring cerebral autoregulation at the bedside requires two inputs: a device that measures CBF and an arterial line that allows for continuous measurement of MAP or CPP. Devices that measure CBF directly (TCD, UT-NIRS, TDF) can be used for cerebral autoregulation measurements. ICP can measure cerebrovascular reactivity. Additionally, many of the devices that are used to measure cerebral oxygenation ($PbtO_2$, NIRS) are used as surrogates of CBF to determine cerebral autoregulation.

More than 21 cerebral autoregulation indices have been described. Some measure cerebral autoregulation (cerebral oximetry index [COx], tissue oxygen index [TOx], cerebral blood flow velocity index [CFx], systolic flow velocity index [Sx], mean flow velocity index [Mx], and brain tissue oxygen pressure reactivity index [ORx]), whereas others measure cerebrovascular reactivity (pressure reactivity index [PRx], hemoglobin volume index [HVx], tissue hemoglobin index [THI], and dynamic autoregulatory index [ARI]). Generally, when cerebral autoregulation is lost, the cerebral autoregulation indices approximate to 1, indicating pressure passivity; a negative index or one that approaches 0 indicates intact pressure reactivity [32].

In a meta-analysis of 33 studies published from 1990 to 2015 that compared the cerebral autoregulation indices as predictors of patient outcome and their dependence on duration of monitoring, three cerebral autoregulation indices (pressure reactivity index, mean flow velocity index, and autoregulation reactivity index (also known as dynamic autoregulatory index)) were found to be the best outcome predictors for patients with TBI. For patients with SAH, autoregulation reactivity index was the only predictor of Glasgow Outcome Scale. Continuous assessment of cerebral autoregulation predicted outcome better than intermittent monitoring [33].

Advanced software that measures a continuous Pearson correlation between the surrogate of CBF and MAP or CPP, such as ICM+ software, can use cerebral autoregulation indices to calculate optimal MAP or optimal CPP [4]. More than 13 observational studies, mostly small and in TBI, have shown that the calculation of optimal CPP and MAP is feasible and may help to improve patient outcomes. The largest published study was retrospective with prospectively collected data from 327 patients in whom the pressure reactivity index was used to define optimal CPP. CPP below the optimal level increased the incidence of fatal outcome, whereas excessively high CPP was associated with an increased proportion of severe disability [37].

The Neurocritical Care Multimodal Monitoring Consensus Guidelines suggest that (1) monitoring and assessment of autoregulation may be useful in broad targeting of cerebral perfusion management goals and prognostication in acute brain injury (weak recommendation, moderate quality of evidence); (2) continuous bedside monitoring of autoregulation is now feasible and should be considered as a part of multimodality monitoring; and (3) measurement of pressure reactivity has been commonly used for this purpose, but many different approaches may be equally valid (weak recommendation, moderate quality of evidence) [6].

Conclusion

The goal of multimodal neuromonitoring is to optimize CPP, oxygen delivery, metabolic control (ensure glucose delivery), and ICP control to prevent secondary injury. As stated in each section, every neuromonitoring device has its limitations (Table 22.1). Some just monitor a small area of the brain (1 cm), and others reflect a compartmental state (ICP monitors). Some monitor brain oxygenation, others brain metabolism and blood flow, and the rest ICP. The state of the art in neuromonitoring culminates by combining the data derived by these multimodal technologies to find the true problem and then develop the right protocols to resolve it. It is the integration of all the available data, laboratory analyses, imaging data, medical record documentation, and neuromonitoring data that will translate into better patient care. As technology continues to evolve, specialized software will be developed that can accept multiple monitor outputs and integrate them for storage and review, such as the CNS Monitor™ (Moberg ICU Solutions, Ambler, PA). This system comes with a portable computer that is able to monitor only one patient and requires cable connections in order to begin data processing. The Neurocritical Care Multimodal Monitoring Consensus Guidelines recommend the use of ergonomic data displays that present clinical information in a sensible uncomplicated manner to reduce cognitive load and improve judgments of clinicians [6]. The development of new tools that integrate all available data from bedside monitors as well as electronic

health records and brain imaging will enhance our ability to develop predictive algorithms to prevent secondary brain injury and estimate successful therapeutic interventions.

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Continuous EEG Monitoring: Systems of Care

23

Sahar F. Zafar, Shravan Sivakumar, and Eric S. Rosenthal

Introduction

Electrographic seizures and periodic and rhythmic patterns can be seen in up to 40% of critically ill patients on continuous electroencephalogram (cEEG) recording and are shown to be associated with worse outcomes [1–4]. Diseases most frequently associated with electrographic seizures include traumatic brain injury, ischemic and hemorrhagic strokes, subarachnoid hemorrhage (SAH), and hypoxic-ischemic encephalopathy [5]. With the publication of consensus recommendations and increased application of cEEG monitoring in critically ill patients, the diagnosis of electrographic seizures is increasing [6]. Here we review the indications and practical aspects of cEEG monitoring in the intensive care unit (ICU).

Indications for Continuous EEG Monitoring

The American Clinical Neurophysiology Society (ACNS) published a consensus statement on indications for cEEG monitoring in critically ill adults and children [5]. cEEG monitoring can be performed for diagnostic, prognostic, and therapeutic indications.

Diagnostic Indications

Diagnosis of non-convulsive seizures (NCS) and non-convulsive status epilepticus (NCSE) NCS can be seen in up to 40% of patients after generalized convulsive status epilepticus (GCSE) in the first 24 hours [7, 8]. Clinical improvement post GCSE typically occurs within the first 30 minutes [5], and cEEG should be initiated within an hour of continued altered sensorium after GCSE [9].

Providers should also consider cEEG for detection of NCS and NCSE in patients with altered sensorium and acute brain injuries such as ischemic and hemorrhagic stroke, traumatic brain injuries, and central nervous system infections, particularly when altered mental status cannot be explained by the degree of injury. Finally, cEEG can be used to detect NCS and NCSE in patients with altered mental status in the absence of an acute brain injury, such as in cases of sepsis-related and toxic-metabolic encephalopathy [1]. In fact, NCS and NCSE can be seen in up to 10% of patients with toxic and metabolic encephalopathies [1]. Common neurological and non-neurological disorders frequently associated with NCS and NCSE are listed in Table 23.1.

Diagnosis and monitoring of periodic and rhythmic patterns In addition to electrographic seizures, critically ill patients frequently have other seizure-like periodic and rhythmic patterns that have come to be called the ictal-interictal continuum (IIC; Fig. 23.1) [10].

Diagnosis and characterization of paroxysmal events Critically ill patients can have a range of paroxysmal events such as abnormal motor movements, episodes of altered mental status,

Table 23.1 Common neurological and non-neurological disorders associated with electrographic seizures [5]

Epilepsy and post generalized convulsive status epilepticus
Traumatic brain injury
Intracerebral hemorrhage
Subarachnoid hemorrhage
Central nervous system infections
Post-neurosurgery
Brain tumors
Anoxic brain injury
Sepsis-related encephalopathy

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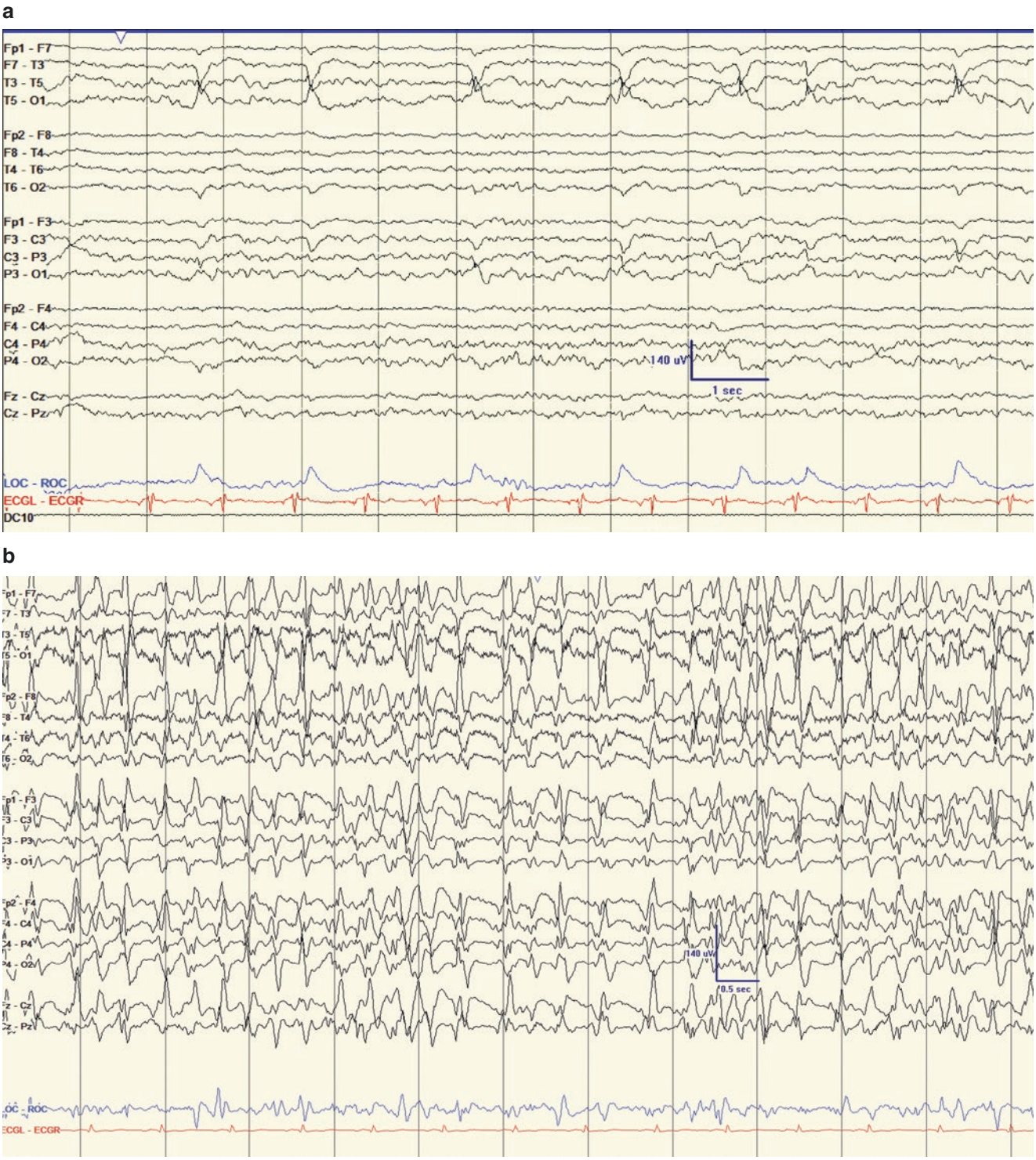
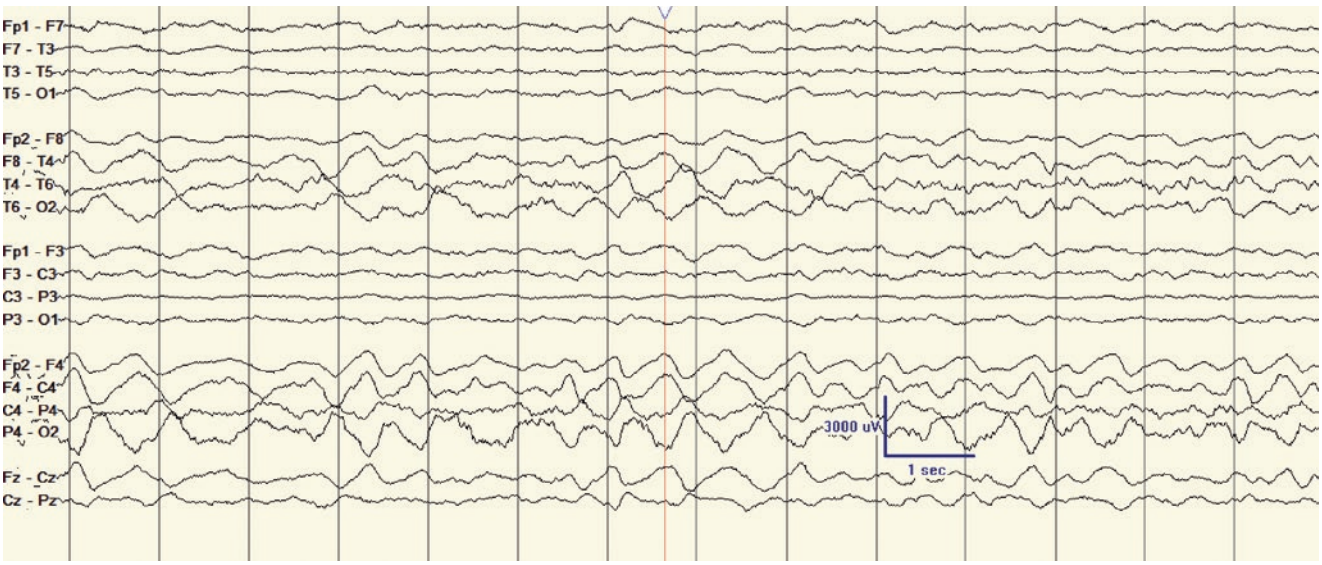


Fig. 23.1 The American Clinical Neurophysiology Society nomenclature has defined main terms for patterns on the ictal-interictal continuum including (**a**) lateralized periodic discharges (LPDs), (**b**) generalized periodic discharges (GPDs), (**c**) lateralized rhythmic delta activity (LRDA), and (**d**) generalized rhythmic delta activity (GRDA) as well as specific instances of these patterns denoted by main terms with modifiers, including examples such as (**e**) GRDA+S when sharp waves are embedded within rhythmic delta or (**f**) LPD+F when embedded fast activity occurs within periodic discharges

c



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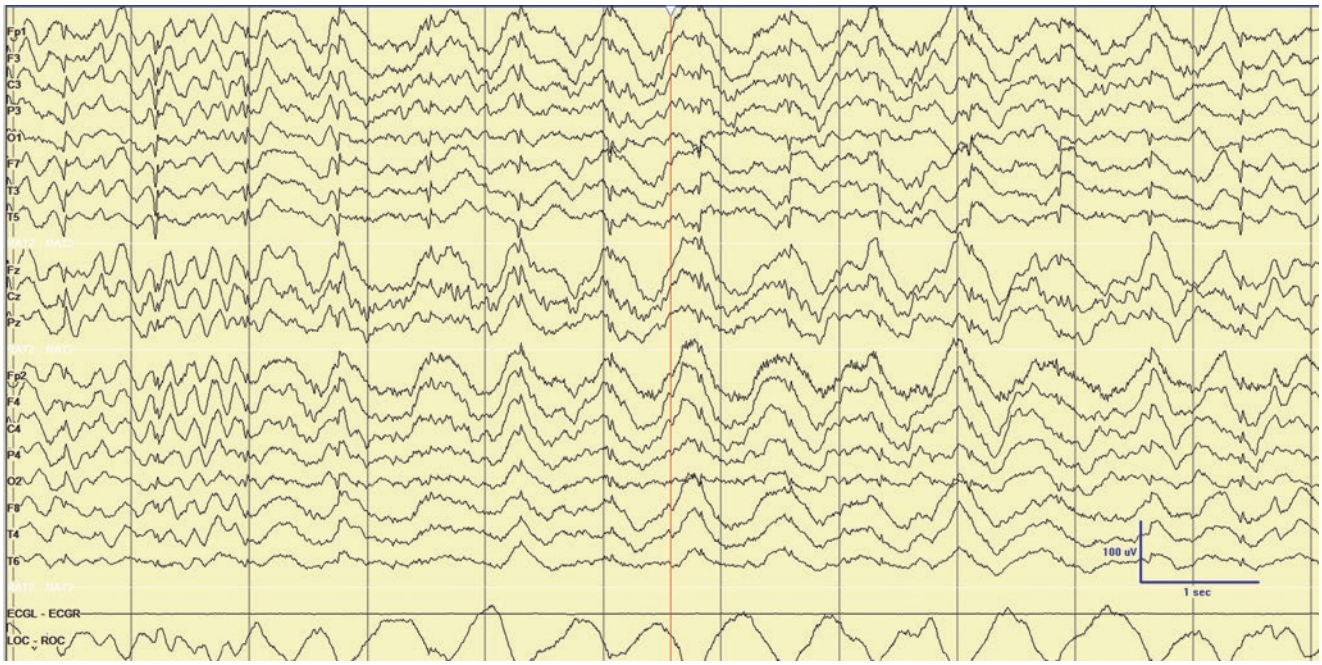

Fig. 23.1 (continued)

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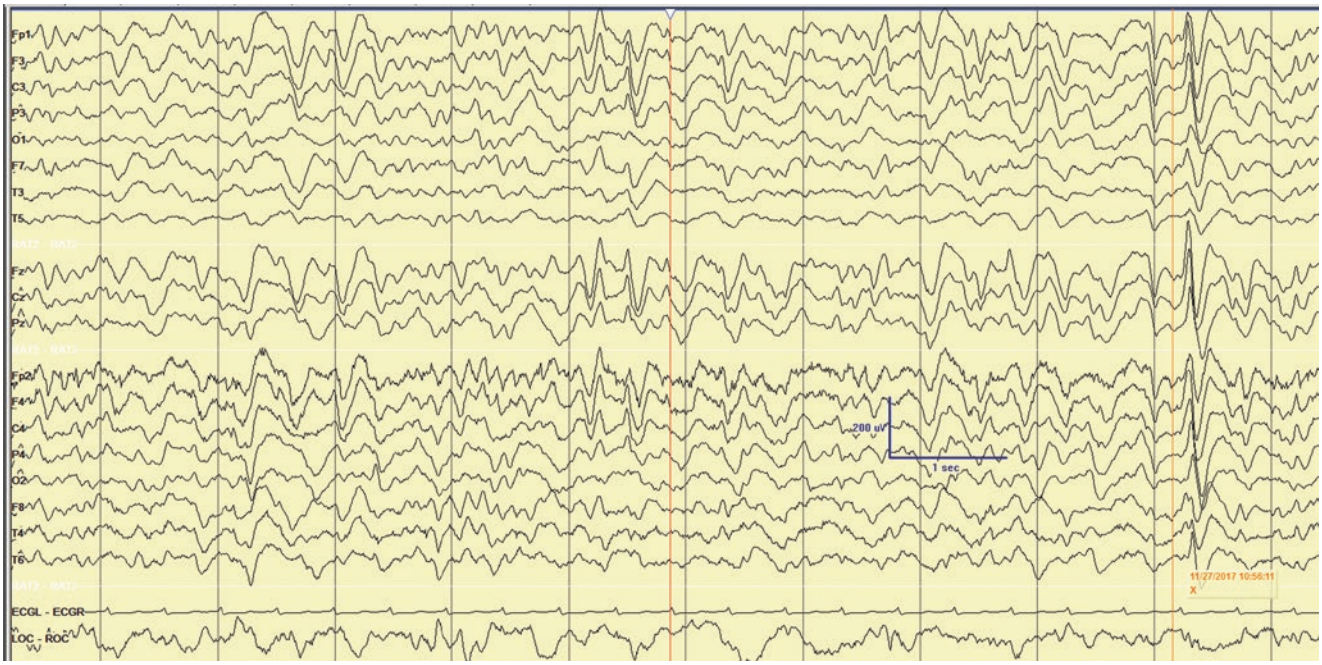

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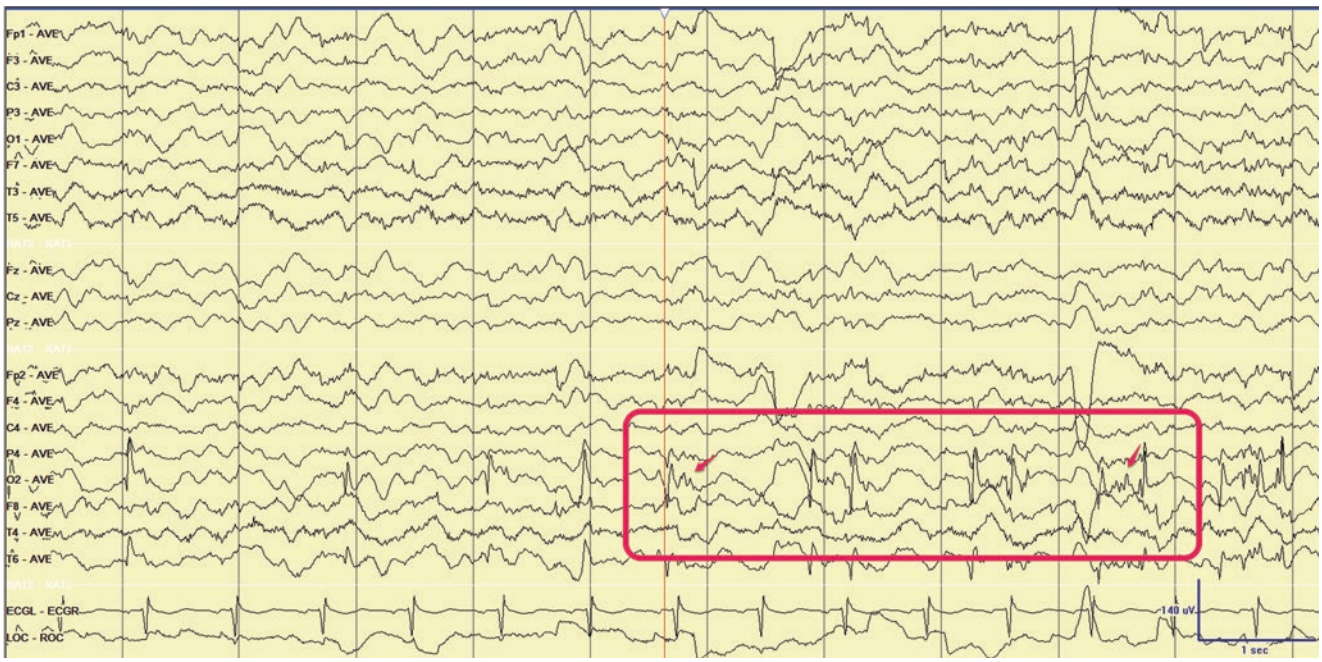

Fig. 23.1 (continued)

and autonomic paroxysmal events that often raise suspicion for seizures [5]. cEEG monitoring can help further characterize these events and guide appropriate management.

Detection of cerebral ischemia Reduction in cerebral blood flow results in loss of fast EEG activity and eventually an increase in slower frequencies. Cell infarction and death occur when cerebral blood flow decreases to a threshold of approximately 10–12 ml/100 g/min [11]. cEEG and quantitative EEG techniques can be utilized for ischemia detection in critically ill patients, with the largest body of evidence for patients with aneurysmal SAH [11–14].

Several retrospective studies and a recent prospective study have shown that cEEG and quantitative EEG trends can accurately predict delayed cerebral ischemia after aneurysmal SAH [12–14]. cEEG can be considered for ischemia monitoring in patients with high grade (≥Hunt and Hess grade 3 and ≥Fisher grade 3) aneurysmal SAH [5].

Determination of electrocerebral silence In the appropriate clinical setting, electrocerebral inactivity (ECI) (also known as or electrocerebral silence (ECS)) on EEG monitoring can serve as ancillary evidence in the evaluation of brain death [15]. ECI is defined as no EEG activity over 2 uV when recording from scalp electrode pairs 10 or more centimeters apart with inter-electrode impedances under 10,000 Ohms (10 kOhms) but over 100 Ohms. The EEG must be recorded by a registered EEG technologist, the electrical circuit of each electrode must be interrogated, and tracings should be read at such a sensitivity (usually 2 uV/mm or less) that voltage excursions can be visualized despite pixel size.

Therapeutic Indications

Management of seizures and NCS As reviewed above, cEEG is indicated for the detection of NCS in patients with altered mental status and concern for subclinical seizures. cEEG can also be used for continued anti-epileptic drug (AED) management in these patients [5]. Since many of these patients do not have a clear or discrete clinical correlate, the number and frequency of seizures on cEEG can be used to guide AED titration. Because the diagnosis of NCS may include periodic and rhythmic activity on the IIC that responds to treatment intensification, cEEG may also be utilized to manage medications in this setting [16, 17].

Management of refractory and super-refractory status epilepticus Status epilepticus that does not respond to initial first- and second-line agents is referred to as refractory status epilepticus (RSE) [18]. RSE resistant to treatment after 24 hours of additional third-line AEDs (including anesthetic agents) is referred to as super-refractory status epilepticus [18]. RSE and super-refractory status epilepticus are typically nonconvulsive and require intravenous (IV) AEDs and anesthetic agents [18]. cEEG is indicated to guide management of electrographic seizures, allowing titration of these treatments. IV anesthetic agents can be titrated to seizure suppression or burst suppression if desired [5, 9].

Monitoring depth of sedation Therapeutic coma with anesthetic agents such as barbiturates and propofol is often used in the management of refractory intracranial hypertension [19]. Close monitoring and titration of the anesthetic drugs are needed to ensure a sufficient level of sedation is achieved in order to lower intracranial pressure (ICP) and at the same time balance the adverse effects of high levels of anesthetic agents. In addition to monitoring drug levels, cEEG can be utilized to monitor the level of sedation.

Patients with severe cardiac and respiratory insufficiency (e.g., acute respiratory distress syndrome and post-cardiac arrest patients) often require pharmacological neuromuscular blockade to assist with mechanical ventilation strategies and oxygen delivery [5]. Anesthetic agents and cEEG monitoring are indicated to maintain adequate levels of sedation in patients requiring neuromuscular blockade, avoiding under- and oversedation. In addition, cEEG can be used for detection of seizures in high-risk patients requiring neuromuscular blockade [5].

Prognostic Indications

Following neurologic injury, cEEG can be used to help predict outcomes, particularly in patients with anoxic brain injury [5, 20]. Although there is debate over whether cEEG is superior to shorter recordings, there is data to support cEEG use for prognostication in patients with traumatic brain injury and SAH in addition to anoxic brain injury [5]. Poor prognostic indicators include an isoelectric pattern, burst suppression, periodic patterns, and electrographic seizures [20–22] (Fig. 23.2). Favorable prognostic indicators include background continuity, reactivity to stimuli, spontaneous variability, and presence of normal sleep architecture [20–22].

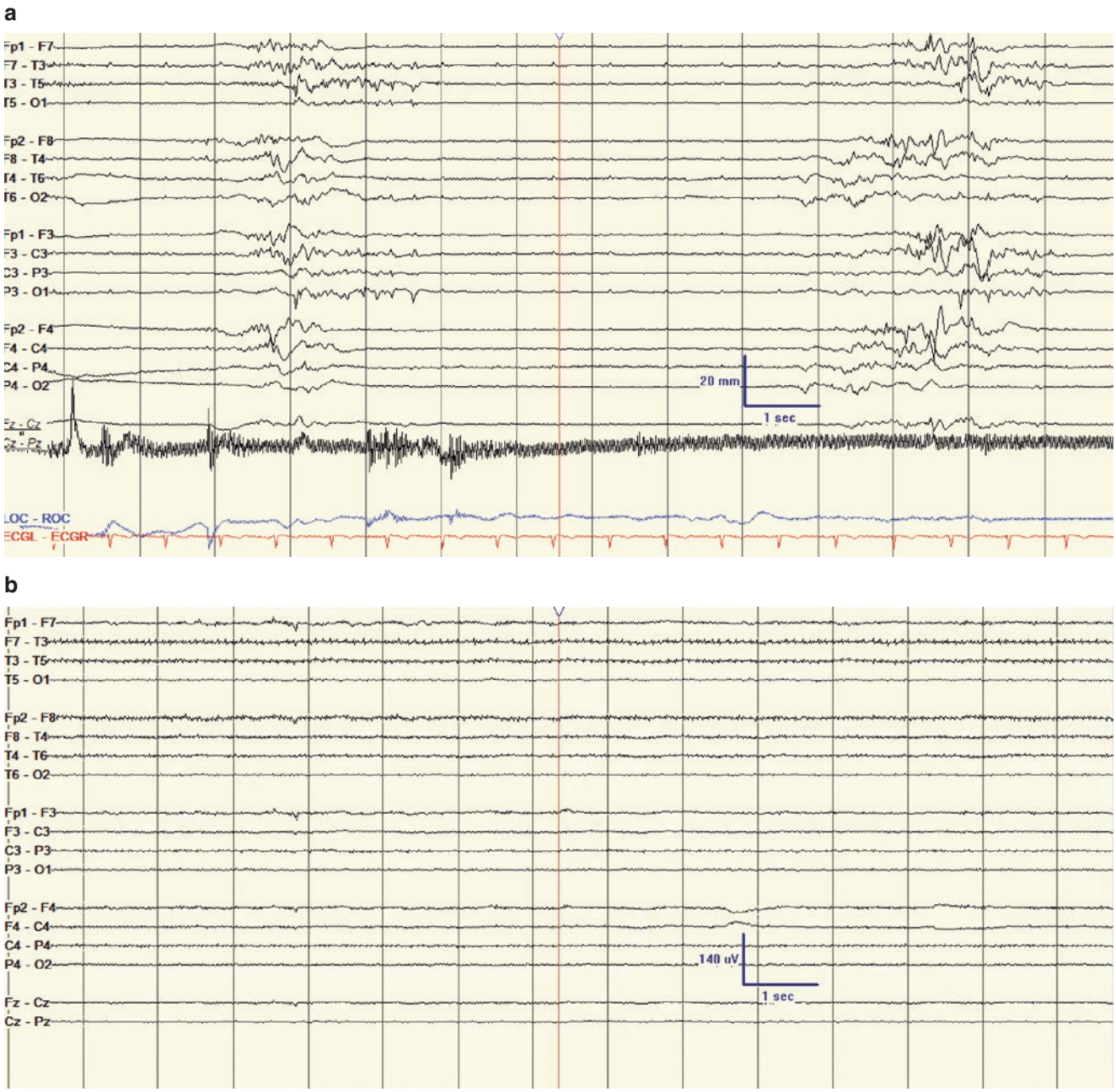

Fig. 23.2 Continuous EEG features associated with poor prognosis after cardiac arrest include (**a**) burst-suppression or suppression-burst patterns and (**b**) isoelectric patterns

Workflow, Methodology, and Maintenance

Technologist Availability

The successful implementation of cEEG monitoring in a NCCU and other units in which neurocritical care is provided will require both daytime and off-hours support for recording and review. As described above, the ACNS specifically recommends that a certified registered EEG technologist (REEGT) perform EEG studies intended to diagnose ECS when aiding clinicians in determining clinical brain death [23].

A variety of models exist for EEG technologist staffing. From a web-based survey [24] of cEEG practices assessing indications and procedures conducted in October 2012 in 151 institutions in the United States, 86% of institutions were found

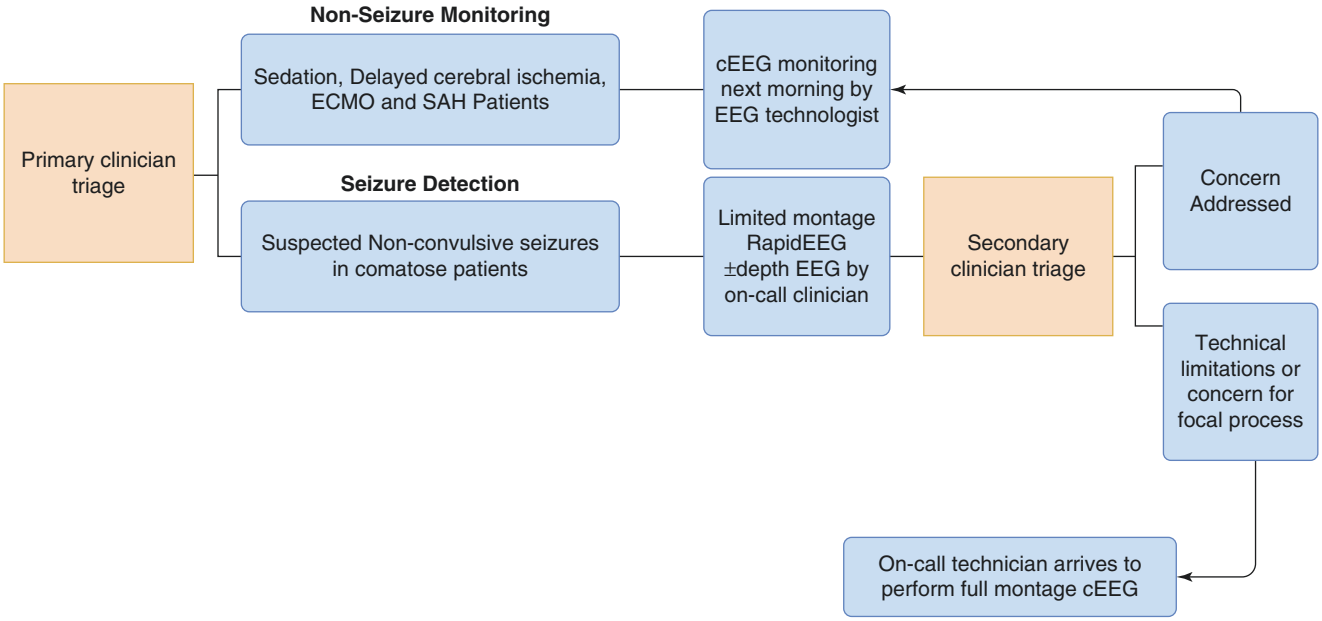

Fig. 23.3 On-call technologist triage systems should be defined as appropriate to the local environment. In the setting in which an on-call technologist is not continuously available, one approach is to perform a primary clinician triage. When monitoring is for detection of a suspected seizure, a limited montage or rapid EEG system can be performed by an on-call physician. If the interpretation yields sufficient information to answer the initial question, then referral for a full-montage EEG can occur the following morning, similar to when recording for sedation optimization or subarachnoid hemorrhage ischemia monitoring. Alternatively, if there is residual concern based on technical or regional factors, then an on-call technologist may be called in for a full-montage EEG. Abbreviations: ECMO extracorporeal membrane oxygenation, SAH subarachnoid hemorrhage, cEEG continuous electroencephalogram

to have an on-call EEG technologist available around the clock for new patient hookups, but only 26% had technologists available in-house at all hours. If around-the-clock technologist coverage is elected, then overnight technologist roles can often shift to repairing electrodes, reducing artifact, and initating emergency setups, decompressing daytime technologists to perform new studies that may be ordered in the morning.

Lack of around-the-clock coverage requires triaging on-call studies to determine which clinical situations should trigger a technologist to come into the hospital, which can be deferred until the subsequent morning, and which can be managed with a short-term limited montage or rapid EEG solution until the next morning. For example, our hospital's current triage system calls for deferring cEEG for ischemia monitoring and sedation optimization in SAH and extracorporeal membrane oxygenation (ECMO) until the morning and instead utilizes an acute, limited-montage, rapid EEG overnight for patients in whom NCS are suspected. For the latter indication, an on-call technologist may be called in to the hospital to start cEEG if the rapid EEG study has insufficient coverage or technical problems (Fig. 23.3).

There is currently no standardized guideline for selecting which patients with suspected NCSE should undergo urgent cEEG monitoring, and many tertiary centers do not have after-hour technologist availability for urgent acquisition of cEEG. Some risk stratification criteria [25] have been proposed to identify which patients with initial EEG need long-term cEEG monitoring, but criteria defining which patients benefit from the initial EEG hookup are less well-validated. Factors denoting high risk for NCS and NCSE include a recent onset generalized tonic-clonic seizure, a known history of epilepsy, female gender, and known brain injury [26].

A variety of alternative staffing models have been explored for off-hours triage and acquisition, including a hybrid training model, a limited staffing model, an outsourcing model, and a technology bridging model. The hybrid training model involves staff with informal training in cEEG performance or interpretation sharing responsibilities with trained staff and initiating EEG recordings during evening and weekend periods. This strategy has been found to increase the availability of EEG with minimal impact on the quality of short-term recordings. A limited staffing model may entail minimal coverage during off-hours and weekends such that critical patients requiring urgent cEEG should be considered for transfer to a center where urgent cEEG monitoring and interpretation are available [27]. The outsourcing model involves contracting the acquisition of cEEG to mobile technologists, the interpretation to remote clinical neurophysiologists, or both to external providers. A technology bridging solution consists of using alternative equipment for emergency EEG to provide an acute but limited recording that can bridge the patient until a more full-

coverage recording is possible (see section below on "Emergency Placement").

Hospitals commonly select the model appropriate to their population, volume, expertise, and budget. For example, scaling to around-the-clock technologist coverage would likely require a patient volume to sustain the service, including a high fraction of patients not undergoing transfer to a secondary facility. Technology bridging models may be useful when the reason for acute EEG is to rapidly make a diagnosis in the short-term rather than needing continued management over a longer weekend period, for example.

Data Acquisition, Storage, and Remote Monitoring

Continuous monitoring of quantitative EEG trends not only may aid the speed of interpreting cEEG, but also may provide additional analytic tools that improve diagnostic yield or increase the conspicuity for intensivists and nurses. However, it is often impractical to perform post-processing for quantitative trends on recordings performed on a large volume of patients. Accordingly, quantitative EEG tools are often implemented on the acquisition machine to minimize processing delays.

All cEEG amplifiers, converters, central processing units (CPU), and monitors should meet ACNS-recommended specifications [28]. The cEEG acquisition computers used should have both sufficient processing capability and storage capacity to run EEG and video acquisition and perform quantitative EEG analysis. File sizes for cEEG recorded using a standard 21 channel montage sampled at 500 Hz over 24 hours range from 4 to 12 GB. The number of electrodes and the sample speed have proportionate impacts on file size.

A concurrent and synchronized video recording is recommended alongside cEEG monitoring as it enables correlation of clinical features and helps in artifact detection. High-resolution video formats with a resolution size of 320 × 240 or 640 × 480 pixels are commonly used. The use of video recording in an uncompressed format can accrue over 100 GB of data per hour, but digital compression can reduce file sizes to 5–20 GB per 24 hours with high-definition quality video generating file sizes at the higher end of that range. As a result of storage limitations, video files are often pruned after a patient is discharged to preserve clinically relevant events documented on video.

Various strategies are employed to remotely review cEEG data. One approach is to use a virtual private network (VPN), which functions as a tunnel through the internet, allowing a remote computer to appear to be a part of the hospital's network complete with access to resources normally not available beyond the hospital's firewall. Other approaches include the use of a remote desktop system to which keystroke markers and screen images are sent. These methods, however, may entail significant latencies in reviewing studies opened on a hospital system.

Alternatively, virtualized server environments may be configured (e.g., Citrix Workspace, Citrix, Inc., Fort Lauderdale, FL) to run EEG review software. In this setting, multiple different client operating systems may be utilized with a single central configuration with the advantages of faster browsing speed.

The maintenance of software involved in EEG analysis and remote monitoring requires significant information technology support for networking, server maintenance, software updates, and the configuration and management of storage.

Duration and Timing

Several aspects influence the duration of cEEG monitoring in critically ill patients. For one, the presence or absence of abnormalities (e.g., NCS/ NCSE, rhythmic and periodic patterns) and the need for additional monitoring to increase the sensitivity for these EEG findings may require longer recordings. Related considerations include the following:

1. The time course during which providers plan to evaluate a response to treatment
2. The patient's condition (e.g., if NCSE/NCS were treated and the patient recovered, cEEG monitoring can be discontinued; if not, cEEG monitoring will be continued) [29]

The occurrence and time course of NCS, NCSE, lateralized periodic discharges (LPDs), and other specific EEG patterns are highly variable and disease/pathology-specific. Duration of cEEG monitoring should be individualized depending on the clinical scenario.

cEEG monitoring should be initiated within an hour of suspected status epilepticus and should be continued for 24 hours after cessation of electrographic seizures [9]. AED withdrawal may increase the frequency of seizures and shorten the total cEEG recording time and duration of hospitalization [30, 31].

NCS can occur in 10–30% of hospitalized critically ill patients, and 80–95% of these patients can be identified within 24–48 hours of cEEG initiation regardless of AED prophylaxis. A longer duration of recording is associated with higher detection of NCSE, prompting many clinicians to extend the recording longer than 24 hours when there is a high suspicion for NCSE [32]. Twenty-four hours and 48 hours have been documented to optimize the detection of NCS to sensitivities of 88% and 93%, respectively [8].

Although lack of epileptiform activity during the initial 4 hours of cEEG monitoring may be associated with lower detection rates [33], certain patient populations are known to

have a longer latency to first seizure detection even when the early cEEG recording is bland. Among comatose patients, 20% had their first seizure after more than 24 hours of monitoring, and 13% required more than 48 hours of monitoring to detect the initial seizure [34, 35]. Among patients with SAH of high clinical or radiologic grade, the median time to first detected seizure was 6.5 days, possibly due to the dynamic course of this illness and high potential for secondary brain injury during which seizure activity may ensue [36].

When EEG is used to detect ischemia, particularly delayed cerebral ischemia (DCI) after aneurysmal SAH, monitoring is started before the highest risk window for vasospasm, which is approximately post-hemorrhage day 3, and continued the entire period of DCI risk (on average 7 days) [37]. Over 90% of clinical neurologic deterioration events occur when a 10-day cEEG monitoring period is used with a median 7-day monitoring duration [38].

Optimal duration of monitoring for ischemia detection in patients with transient ischemic attacks and acute ischemic strokes has not been established. cEEG of 24–48 hours duration would cover the high-risk window [5].

Emergency Placement

Emergency EEG (EmEEG) is performed to rapidly exclude NCS and NCSE [39] and to influence acute management [40]; for instance, EmEEG can be used to aid in the evaluation of altered mental status. Even in tertiary care centers with accredited EEG laboratories and 80% coverage for emergency EEG, there is typically a delay in response time of a few hours from the time of request to initiation of EEG monitoring and interpretation [41]. Problems with availability of full-montage EEG devices for long-term use in the ICU have led to the development of alternative methods for monitoring cerebral activity. Given their rapid setup, EmEEG solutions can be used for early initiation of EEG monitoring and bridge the gap until technologist arrival and setup of a full montage.

EEG Template System

EEG template systems are alternative means by which healthcare providers not specifically trained in conventional electrode placement can quickly assemble EEG electrodes and initiate EEG recordings. The use of these templates can reduce the average time to obtain EEG data by 3 hours [42].

One example is the BraiNet system (Jordan NeuroScience, Inc., Redlands, CA), a modified 15 electrode placement template made of a non-latex-containing elastic cap that is entirely disposable. The template has color-coded holes, which facilitate easy placement of EEG leads and the connection of the patient to the EEG recording equipment. It can be used with either disc, subdermal needle, or subdermal wire electrodes. Minimal scalp preparation is needed for subdermal electrode leads making them easier and faster to apply.

StatNet

StatNet (HydroDot, Westford, MA) is a simplified single-use disposable EEG headpiece system. It is a peel-and-stick device that can be rapidly applied without prior scalp preparation by a non-EEG technologist after minimal training. It has an average setup time of 9 minutes. The StatNet EEG montage consists of a longitudinal and transverse bipolar montage without F3, F4, P3, P4, and Pz electrodes. In a feasibility study, it was found that StatNet significantly decreased mean delay time from EEG order to acquisition with no difference noted in the quality of the recordings or duration of artifacts between the StatNet EEG and the conventional EEG groups [43].

Rapid Response EEG

The rapid response EEG system is one that can be easily set up within a few minutes by new users. It consists of a portable EEG recording device with a built-in display to view the EEG recordings (e.g., Ceribell Model C100, Ceribell Inc., Mountain View, CA). It uses a disposable headband with an integrated ten electrode assembly (Ag-Cl Cup electrodes) with four electrode pairs on each hemisphere that record eight channels of EEG data. In a study, rapid response EEG and conventional EEG recordings were visually equivalent with all waveforms being distinguishable in the recordings of both systems [44]. An EEG detecting system was introduced to enable users with limited EEG knowledge to easily identify seizures; a novel feature of the system is the option to convert electrical frequencies to sound, which may aid seizure detection [45].

Channels, Montages, and References

Long-term EEG recordings are generally performed to distinguish between spells that are epileptic or nonepileptic in nature, to determine the frequency of seizure activity, and to localize an epileptogenic source. Montage selection is usually guided by individual patient event characteristics and prior interictal abnormalities [46]. While there is a large set of montages to choose from, the regular use of a small set of montages improves the familiarity and efficiency of readers in a given laboratory. A minimum of at least one longitudinal, transverse, and referential montage incorporating the 10–20 international system of electrode placement is used for routine recordings [46, 47]. This system uses 21 electrodes with 9 electrodes for each hemisphere and 3 midline electrodes. Placement of electrodes is guided by measuring the distance between anatomical landmarks, which are bony

points in the skull: the nasion, the inion, and the two preauricular locations.

Bipolar and referential montages are commonly used for EEG interpretation. Bipolar montages subtract out noise due to proximity of electrode pairs. They can consist of either anteroposterior electrode chains running from the front to the back of the head or transverse electrode chains that run from left to right across the head.

Referential montages typically increase the distance between active and reference electrodes, thus resulting in a greater ability to distinguish and detect epileptiform activity and demonstrate a topographic map of voltage. Other commonly used physical reference points are earlobes or mastoid areas, the nose, the CS2 location that represents the skin overlying the spinous process of the seventh cervical vertebra, or most rarely the Cz electrode. However, it is difficult to find an ideal reference electrode point that is completely neutral; for example, a cervical spine reference may have in-phase cancellation with respect to occipital electrodes, while a vertex electrode may have in-phase cancellation with nearby central or other midline electrodes. Average references incorporating all electrodes may be used, but when a large voltage is evident in one region, it may appear as a negative voltage in otherwise silent regions when it is subtracted.

Choice of reference point should be individualized as no such ideal point exists. For example, at our institution, a vertex reference is often used in the NCCU because it is often free of artifact, which can be encountered with a posterior cervical spine reference in recumbent patients.

Limited Montages

A few studies have found that limited montages using fewer electrodes structured in a referential and bipolar configuration may be of value [48–50]. For example, Labar et al. successfully used five electrodes and two channels to analyze trends in compressed spectral arrays in SAH patients [51]. A limitation is that reducing the number of electrodes limits spatial resolution and coverage.

One of the most commonly used limited montages is the subhairline or hairline, a montage in which stick-on electrodes are applied, usually by nurses or by house staff, below the hairline [52]. The recording can be carried out at the bedside using modular EEG technology with the help of nine electrodes that are placed symmetrically on the forehead, anterior to the ear, and immediately posterior to the ear with one electrode in the center. Placement is based on anatomical landmarks. It consists of four channels (left and right frontal and temporal). Continuous subhairline EEG monitoring detects about 70% of NCS when compared to formal EEG with a 98% specificity for seizure detection [48].

Karakis et al. used a seven electrode montage akin to that of the subhairline montage. They found it quick and easy to use with minimal technical support and demonstrated its usefulness in a cohort of obtunded ICU patients [53]. The average sensitivity and specificity of the study montage for seizure detection were 92.5% and 93.5%, respectively [50].

Kolls and Husain mimicked the subhairline EEG using eight electrodes, which were FP1–2, F7–8, T3–4, and T5–6 [54]. Three montages were designed to maximize the sensitivity for detecting seizures, among which the longitudinal bipolar montage was based on the original montage used by Bridgers and Ebersole [52]. They demonstrated a 72% sensitivity and a 95% specificity for seizure detection.

Scalp Electrodes

Disc or cup electrodes have conventionally been used, and these often come with a central hole that allows for easy refilling with an electrode conductive gel. Subdermal needle electrodes can be rapidly positioned beneath the skin and secured with the help of an adhesive paste. They do not require abrasive skin preparation and are useful for short-term recordings.

Metal disc and subdermal needle electrodes may produce computed tomography (CT) artifact and may not be considered magnetic resonance imaging (MRI) safe or are MRI conditional. Silver epoxy coating can provide EEG recording quality characteristics equivalent to metal electrodes [55]. Each individual lead terminates at a similar ten contact mass connector. The mass connector and harness permit quick, accurate, and easy disconnection/reconnection of the patient by nursing staff. Conductive plastic electrodes (CPE) are affixed to the scalp by applying small amount of collodion around their rim. CPE can be individually and easily replaced because they can be removed from the mass connector and exchanged for a spare without removing the entire set. Plastic electrodes from Ives EEG Solutions (Newburyport, MA), Rhythmlink (Columbia, SC), and others are composed of silver-silver chloride-impregnated plastic. They are cost-effective, are easy to apply, and are widely used due to their imaging compatibility [56]. Some of these varieties are disposable and appropriate for certain populations in which reuse is prohibitive.

Subdermal wire electrodes are silver chloride-tipped thin wires that are guided beneath the skin using a 25G or 27G needle. On the skin, some fixation with patches or glue is usually required. They have low impedance and good stability for many days. They produce fewer artifacts when compared to subdermal needle electrodes [57].

Intracranial Electrodes

Implanted electrodes that record directly from the surface of the brain such as subdural electrodes and intraparenchymal

electrodes can help in localizing the region of seizure onset with greater precision.

Subdural electrodes are usually made from stainless steel or platinum (usually platinum-iridium). They can be placed in a variety of locations such as temporal, subtemporal, frontal, subfrontal, within the interhemispheric fissures, and posterior. They come in a variety of shapes and sizes that can be customized individually. Strips of electrodes consisting of a line of 2–10 electrodes are usually used, and these are typically configured as arrays. A large number of such arrays can be placed. When placed in arrays, subdural electrodes can help determine the extent of the epileptogenic region [58].

Subdural electrodes have some disadvantages. They are usually fixed in position and can miss epileptogenic activity arising from more than one foci. There is some concern for mass effect, and cerebrospinal fluid leakage caused during placement of the electrodes can act as a nidus for infection.

Intraparenchymal electrodes are used to record within the deep brain structures. They usually consist of eight electrode contacts (Ad-Tech, Racine, WI, USA) with a length of 2.2 mm and diameter of 1.1 mm. They are probed through a cranial burr hole and tunneled out through the scalp. The points of deep contacts are usually the subfrontal region, cingulate gyrus, amygdala, and hippocampus. As they directly record electrical activity within the deep brain structures, they can overcome certain disturbances found on scalp EEG such as poor signal-to-noise ratio and electrical and myogenic artifacts. They are useful in delineating foci of seizure onset in epileptic patients. They also can detect cortical spreading depressions as well as seizure activity that may be equivocal on scalp EEG recordings [59, 60].

Patient Event Button Use

Push-button events can be initiated by the clinician or bystanders of the patient and can focus the analysis of EEG data at specific points that are synchronized with events. They can be a valuable tool in differentiating between artifacts and seizure activity in the absence of video recordings.

Staff can designate the patient event as one of the following:

1. A recent clinical event suspicious for seizures
2. Events before and after patient examinations useful for evaluating reactivity

In either setting, events should be specified for consistency. Often, given seizures are predominantly nonconvulsive in the ICU, clinical events suspicious for seizure may be rare and better designated by indicating the type of event in the record.

Stimulation and Reactivity

EEG analysis involves evaluating the background activity for continuity and reactivity in response to stimuli and events. EEG reactivity is tested by application of external (e.g., auditory and nociceptive) stimuli [61]. Eye opening and intermittent photic stimulation are other techniques used in the evaluation of EEG reactivity. Changes in amplitude and frequency of background activity in response to stimuli are required for documentation of EEG reactivity. The variety of changes in EEG reactivity in response to stimulation has been shown to have prognostic significance in post-cardiac arrest and in comatose patients [62].

Stimulation techniques such as hyperventilation, sleep deprivation, and intermittent photic stimulation have been routinely used in evaluating patients for reactivity during EEG monitoring. These help by unmasking hidden electrical activity, thereby resulting in an increased likelihood of seizure detection.

One example of an institutionalized stimulation technique is the ACYSTE protocol. Perform the stimulation protocol as follows:

- *A* = already *A*wake and alert
- *C* = aroused by *C*alling name
- *Y* = aroused by *Y*elling name and clapping
- *S* = aroused by gentle *S*haking
- *T1* = reaction to nostril *T*ickling
- *T2* = reaction to *T*rapezius squeezing
- *T3* = reaction to *T*racheal suction
- *E* = passive *E*ye opening

Document stimulation in the EEG recording, for example, as "STIM: grade A." If the patient is grade A, there is no need to proceed with further stimulation. The stimulation grade reported is the minimum grade at which there is reproducible reactivity in the EEG. If the complete protocol is completed and no reactivity is observed, document as "STIM: grade: no reactivity."

Skin Breakdown Prevention

Imaging compatible electrodes, by remaining in place, can reduce the skin breakdown caused due to repeated electrode removal and reapplication [63]. An increased incidence of skin/scalp abrasions is noted when metal electrode application is used and left on patients for 24 hours or more. In a large sample of over 1500 patients, pressure ulcers related to electrodes occurred in 8% of patients, but 92.3% were mild and consisted of hyperemia without skin breakdown. Risk factors included duration of monitoring, older age, ICU location, lack of a head wrap, use of vasopressors, enteral feeding,

and fever. Only 6 per 1000 monitored patients had a pressure ulcer consisting of more than a hyperemic response [64].

At Texas Children's Hospital, a team consisting of epileptologists, epilepsy monitoring unit (EMU) technologists, wound care specialists, and registered nurses was formed in order to determine ways to reduce skin breakdown in the EMU. A standardized procedure for the care and placement of electrodes was implemented to minimize skin breakdown. These involved steps such as changing skin preparation solutions to less abrasive products, switching to disposable leads, education regarding application techniques, and performing focused skin assessments. These changes decreased the incidence rate of pressure ulcers by 90% [65]. Maintenance of electrode impedance up to 10 kOhm in long-term EEG recordings has been suggested to maintain skin integrity [66].

The utilization of collodion with Ten20™ paste has been documented to have long-lasting adhesive effects and the lowest incidence of skin breakdown [67]. Using a disposable electrode/skin saver such as HydroDot® SkinSavers (HydroDot®, Westford, MA, USA) can reduce skin abrasions and bruising.

Continuous EEG Evaluation and Review

EEG Nomenclature

The ACNS has proposed a standardized nomenclature for patterns commonly encountered in cEEG monitoring [68]. A detailed description of these patterns is beyond the scope of this chapter. Here we provide a brief overview. Each pattern is defined by their location (main term 1) and chief rhythmic pattern (main term 2):

1. *Region*
   - G: generalized
   - L: lateralized
   - BI: bilateral independent
   - Mf: multifocal
2. *Chief rhythmic pattern* (requires 6 cycles)
   - PD: periodic discharges
   - RDA: rhythmic delta activity
   - SW: spike-wave and polyspike-wave

Examples of each pattern are shown in Fig. 23.1. Higher-frequency (>2 Hz) periodic and rhythmic patterns are associated with increased risk for seizures [10]. These patterns are also associated with increased cerebral blood flow and metabolic crises [69, 70]. Higher-frequency (>2 Hz) periodic discharges on depth EEG are further correlated with decreased brain tissue oxygenation [71]. Although optimal treatment of these patterns remains to be determined, given their association with seizures and worse outcomes, it is reasonable to consider prolonged cEEG monitoring in patients found to have periodic and rhythmic patterns on routine EEG or early cEEG.

Screening Methods

Spectrogram Screening

Color density spectral array is a quantitative EEG technique that can display several hours of cEEG data in a single color map, enabling interpreters an overview of raw EEG data and possibly shortening review time in the ICU, while maintaining a high sensitivity of detection for the majority of seizure patterns [72, 73]. Compressed spectral arrays (CSAs, spectrograms) display time on the x-axis and frequency on the y-axis and use a variety of colors to represent amplitude of the power spectrum. Power is calculated as a function of the amplitude and frequency using fast Fourier transformation. Seizure activity involves an increase in frequency and amplitude compared to baseline; these increases can be represented as an upward shift with varying color changes (denoting changes in amplitude) in the spectrogram, respectively. A drawback of the time-compressed array is that brief changes in frequency and power may be missed unless the timescale is adjusted by the reviewer. Spectrograms are also routinely used in the long-term monitoring of comatose patients [74].

Amplitude-Integrated EEG in Children

Amplitude-integrated electroencephalography (aEEG) uses a limited set of channels to record EEG that are transformed and displayed with time compression as the x-axis and amplitude on a logarithmic scale as the y-axis. aEEG helps in trending long-term changes in background electrical activity. aEEG has been extensively used in European centers for the past two decades and is now increasingly used in North America [75, 76]. In neonates with hypoxemic-ischemic encephalopathy, aEEG has primarily been used to evaluate for seizures, to detect changes in sleep-wake cycles, and to evaluate background activity [77]. It has also been found to be effective in the detection of subclinical seizure activity in neonates [78]. Continuous quantitative trending of aEEG with simultaneous display of raw EEG data and video of the patient is now available for more complete detection of seizures and artifacts.

Limitations of aEEG include lack of seizure localization and potential reduction in sensitivity for seizures originating from distant points due to a limited and fixed position of the electrodes [79]. Additionally, in the absence of conventional cEEG tracings and video, aEEG may yield false alarms due to high-amplitude artifacts [80].

Quantitative EEG and Trending

Several quantitative EEG (qEEG) analyses have been implemented for use in cEEG monitoring to help with interpreta-

tions of large volumes of data. These involve the use of computerized mathematical algorithms (e.g., fast Fourier transformation) to transform raw EEG data in real time into meaningful information in the form of trend panels that are subsequently displayed in a compressed form on a timescale. With the help of trend panels, hours of raw EEG recordings over several days can be reduced to a single screen of time-frequency values with a variety of variables to choose from. The trends are commonly presented in windows of 30–120 minutes. The use of graphical displays enables a rapid and real-time review of EEG that can be performed at the bedside by both neurophysiologists and non-neurophysiologists [11, 13]. These can be used to detect specific events such as seizures, changes in background activity, ischemia, and burst suppressions in coma.

Analysis can be based on envelope trends, which provide the median amplitude of background activity over a specified time period. Examples of these are (a) the ratio of the alpha-to-delta power frequency spectra (ADR), (b) the asymmetry index (ASI), and (c) the alpha variability (AVR) of the relative alpha frequency power band.

Seizure Detection

The panel of frequently used qEEG trends such as frequency spectrograms, rhythmicity spectrograms, asymmetry indices, and aEEG has demonstrated high sensitivity for seizure detection [81, 82]. Due to their ability to trigger false alarms due to high false positives and failure to quantify the number of seizures, they should be used in conjunction with conventional cEEG recordings. While they cannot yet replace conventional interpretations performed by expert electroencephalographers, they are proving to be valuable bedside tools that will likely be optimized over time for detecting seizures.

Ischemia Detection

In settings such as cerebrovascular disease, which may have high lateralization, a brain symmetry index (pdBSI) was able to discriminate between stroke and transient ischemic attack and correlate with clinical status [83].

In conditions such as SAH, DCI prediction is facilitated by using a combination of raw and quantitative trends such as alpha-to-delta power ratio (ADR) and relative alpha variability (RAV) [11]. Specifically, a set of pre-specified criteria such as focal slowing on raw EEG and decreasing RAV or ADR have been used to predict DCI following SAH [12, 14]. ADR is calculated using a moving average (2-minute window) of the ratio of 8–13 Hz power divided by 1–4 Hz band power. Power is calculated by the squared magnitude of the EEG signal Fourier transform. An ADR decrease of 10% lasting 6 hours or when at least 50% decrements in the ADR are observed for 2 hours or more can be defined as ADR decrements that predict DCI [14, 38]. For decreasing RAV, an alarm criterion of a "clear and persistent worsening or new emergence" is defined as worsening by $\geq$1 grade versus the preceding 8–12-hour epoch (e.g., from 3, "good," to 2, "fair").

Coma and Depth of Sedation

qEEG software algorithms can be used to automatically segment burst-suppression patterns in critically ill patients [84]. These trends usually define EEG suppression as background amplitude less than 5 μV for greater than 0.5 seconds, although this threshold may be customized. Some qEEG-based trends such as bispectral index [85], patient state index [86], and Narcotrend [87] have been used in operating rooms and ICUs to monitor level of sedation in critically ill patients.

Context and Correlation

Cerebral perfusion pressure (CPP) is the pressure gradient that drives cerebral blood flow (CBF). CPP is defined as the difference between mean arterial pressure (MAP) and ICP. Cerebral autoregulation is the process that regulates and maintains constant CBF across a range of blood pressures. As patients with brain injury have deranged cerebral autoregulation that can last up to 2 weeks [88], EEG findings may in some cases reflect the impact of real-time changes in CBF and ICP on cortical physiology. Thus, cEEG monitoring can reflect real-time changes in CBF and CPP and enable continuous monitoring of cerebral autoregulation; therefore, it can help guide management of critically ill patients.

The sensitivity of cEEG monitoring in ischemia detection with the help of trend panels to detect changes in CBF has previously been described [11–14]. These cEEG changes may then be utilized in patients at risk for ischemia to direct treatment approaches to optimize CPP [89]. Increased ICP is associated with a loss of fast frequencies on EEG recordings, which has been shown to appear up to 24 hours before a clinical change is seen [90].

NCS are also associated with a rise in ICP that can often be delayed [91]. Treating NCS identified through cEEG monitoring should be considered in patients with otherwise unexplained episodes of elevated ICP.

Hemodynamic Integration

The use of integrated displays (CNS Monitor, Moberg Research Inc, Ambler, PA, USA) at the bedside helps in integrating neuro-monitoring parameters such as ICP, cerebral tissue oxygenation, and cEEG recordings (both scalp and

intracranial EEG) along with physiological hemodynamic parameters routinely measured in ICUs. These displays can provide immediate feedback and individualize treatment approaches and responses to therapies.

Reporting

The ACNS has published guidelines for EEG reporting in an attempt to standardize reporting across institutions and guide clinical neurophysiologists and neurologists in efficiently providing reports [92]. While the actual frequency of reporting cEEG is variable across different institutions [93], the majority of institutions report EEG on a twice-daily basis.

An ideal structured EEG report should follow the ACNS guidelines [92] but may vary by indication. A standard format for cEEG reporting may include five sections: history, technical description, cEEG description, impression, and clinical correlation. The structure used at our center, which incorporates these elements for cEEG, is shown in Table 23.2.

When monitoring SAH patients, clinical electroencephalographers at our institution report on the following for each monitoring epoch: (1) cEEG background activity and reactivity including the development of any new focal slowing; (2) changes in ADR trends; (3) grading of RAV; (4) development of new epileptiform waveforms, periodic or rhythmic patterns, or seizures; or (5) an overall impression of whether the combined findings are concerning for ischemia. For cardiac arrest patients, however, attention to the background and its trend over time, the minimum stimulation necessary for reactivity, seizure and IIC patterns, response to treatment, and intensity of sedation are most relevant. Monitoring for status epilepticus requires attention to background rhythms, changes in IIC and seizure frequency, and whether such activity stabilizes after anesthetic weaning.

Table 23.2 Sample continuous EEG report

Clinical history:
Impression/summary of relevant findings:
Technical performance:
Individual epochs: *(repeats for every 12 hours; may be helpful to list in reverse chronological order)*
Relevant medications/doses:
Background:
Ischemia monitoring trends:
Alpha-delta ratio, by region
Relative alpha variability (RAV), by region
Sporadic epileptiform discharges:
Periodic and rhythmic patterns:
Seizures:
Clinical and contextual events:
Patient events/button presses:
Response to new treatment or individual dose:
Changes compared to prior epoch:
Per-epoch clinical correlation:

Collaborative and Team-Based Approaches to Integrating Continuous EEG into Care

A successful cEEG monitoring service requires a multidisciplinary collaborative approach comprised of the primary ICU team, nursing staff, consulting neurologists, neurophysiologists, EEG technicians, and pharmacists.

Role of the Primary Team and Bedside Providers

Accurate and detailed communication between the primary team and neurophysiologists regarding indications for cEEG monitoring along with relevant clinical questions and concerns is essential for the success of a cEEG monitoring service. Bedside providers can also enhance the quality of cEEG interpretation by, for example, marking times when clinical examinations are being performed, when any paroxysmal events concerning for seizures occur, and when medications are being administered. Bedside providers can also mark the EEG when they identify a source of artifact (e.g., when the patient is receiving chest percussion treatment).

Role of EEG Technologists

Appropriate setup of the monitoring equipment requires a collaborative approach by bedside providers and EEG technologists. Together, they can ensure appropriate positioning of patients, identify and address any artifacts on the EEG, and test reactivity at the beginning of the recording. This is vital information for neurophysiologists [94].

In addition, there should be daily communication between the EEG technologists and bedside providers about any clinical updates and regarding cEEG equipment operation [28]. EEG technologists should check the quality of the cEEG recording on a daily basis along with assessing impedance and for artifact [28]. The primary team, bedside providers, and EEG technologists should also perform a daily assessment of the patient's scalp to assess for skin breakdown [28].

Similarly, a collaborative approach is needed for EEG takedowns. Once electrodes have been removed, the patient's hair and scalp should be thoroughly cleaned and inspected again for any signs of skin breakdown or infection. Bedside providers and nursing staff should have training in the removal of cEEG leads in case EEG technologists are not immediately available, particularly in cases of emergency such as urgent imaging [28].

Role of the Clinical Neurophysiologists

The frequency of cEEG review and reporting has been detailed above. The clinical neurophysiologists and primary team should communicate daily regarding the patient's clinical sta-

tus, any medication changes, new diagnostic information including imaging (e.g., head CT, MRI, transcranial Doppler), and findings on additional multimodal methods such as ICP monitoring. In addition to written reports, verbal communication with the primary team including multidisciplinary rounds can improve the quality of care provided to patients.

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Cerebral Angiography

24

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Principles of Neuroangiography

Digital subtraction angiography (DSA) is currently the gold standard in vascular imaging of the brain and spine. The number of indications for purely diagnostic cerebral DSA has greatly decreased in recent years due to the increase in accuracy of noninvasive cross-sectional modalities such as CT angiography (CTA) and magnetic resonance (MR) angiography (MRA). As a diagnostic tool, DSA is presently indicated in some very specific clinical contexts due to its still unparalleled spatial and temporal resolution. On the other hand, minimally invasive endovascular neuroangiographic techniques have evolved to such an extent in the last 30 years that they are now the established and routinely performed treatment of a multitude of neurovascular conditions such as aneurysms, arteriovenous malformations (AVMs), and arteriovenous fistulas (AVFs) that were previously treated with open neurosurgical approaches or were deemed untreatable [1–3]. Most recently, the development of clot-retrieving stents (stentrievers) and large-bore intracranial aspiration catheters has made it possible to safely and effectively treat strokes resulting from large intracranial vessel occlusions with previously unthinkable patient outcomes [4, 5]. Regardless of the purpose, be it diagnostic or therapeutic, angiographic techniques share the same basic concepts and most pre- and postoperative management measures. The first part of this chapter will describe general radiological and management concepts of neuroangiography, while its second and third parts will approach technical and management aspects of specific therapeutic neuroendovascular procedures.

Radiological Concepts of DSA and Clinical Rationale of Diagnostic Procedures

DSA is a technique based on the acquisition of serial two-dimensional X-ray images immediately before and during a catheter injection of nonionic, iso-osmolar contrast media in the lumen of a vessel, typically an artery, in order to assess the anatomy and hemodynamic pattern of a particular vascular territory. The images obtained before contrast injection (the "mask") are digitally subtracted from those obtained during its injection in order to eliminate bony structures or abdominal gas from the obtained pictures, eventually showing only the contrast within the injected vessel. The contrast creates a high-resolution anatomical "silhouette" of the vessel lumen and at the same time mixes with flowing blood and follows its arterial, parenchymal, and eventually venous distribution, thus showing the circulation pattern in the territory of interest. Thus, DSA is a lumen-based technique that exclusively gives information about the inner lumen of a vessel and about blood flow patterns within the injected territories; with the exception of newer applications such as 3D DSA and cone beam computed tomography (CBCT), standard acquisitions do not clearly show parenchymal structures, though it may approximate the structure with capillary blush. These additional applications allow the operator to obtain angio-tomographic CT images of an injected vessel and of the surrounding structures as part of dedicated neuroangiographic examinations and provide additional, three-

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dimensional information on the morphology of an aneurysm, AVM, AVF, or whichever structure is filling with contrast. DSA thus only supplies specific types of information, and its use should be balanced against inherent risks, even in centers with high volumes and experience.

With a spatial resolution of 0.2 mm and a temporal resolution 6 frames per second or higher, DSA has the highest accuracy of any vascular diagnostic modality and is therefore considered the gold standard for vascular imaging of cerebral and spinal neurovascular structures [6]. This accuracy comes at a price: DSA is a lengthy, invasive, and expensive procedure that requires pre- and postoperative patient care and an experienced neuroangiography team and, despite enormous technical advancements in the last decades, still has a complication rate between 1% and 2% [7–11]. Currently, CTA and MRA allow excellent anatomical neurovascular imaging with a submillimetric spatial resolution of 0.4–0.5 mm [6, 12]. Time-resolved CTA and MRA techniques, in addition, allow radiologists to obtain hemodynamic information on blood flow within cerebral blood vessels and hence characterize the hemodynamic patterns of vascular malformations to some extent, although these are not yet widely available or used in clinical practice [1, 13, 14]. These cross-sectional modalities are noninvasive, faster, and less expensive than DSA, and the risk rate is essentially that of contrast media administration. Therefore, it is important to remark that noninvasive imaging should always be the first-line examination in the setting of a suspected cerebrovascular pathology and that angiographic and cross-sectional imaging are never mutually exclusive but complement each other in the diagnosis, preoperative planning, and postoperative follow-up of neurovascular diseases.

A DSA should be ordered in two instances: (1) as a second-line test when the clinical question requires superior vascular anatomical detail and/or high temporal resolution, and (2) when planning an endovascular or microsurgical intervention. Focused cerebral angiograms are also sometimes performed intraoperatively to immediately assess an open neurosurgical treatment of an aneurysm or AVM. Although indications may vary according to clinical practice and institutional guidelines, the following is a list of reasonable indications for a DSA:

- To clarify the anatomy of a known or suspected cerebral aneurysm, either electively or in the setting of a subarachnoid hemorrhage (SAH)
- To clarify the angioarchitecture and shunting pattern of a vascular malformation such as an AVM or AVF, including carotid-cavernous fistulae
- In cases of intracerebral (ICH) or extra-axial hemorrhages without clear causes
- To assess the degree of post-SAH vasospasm
- To better define the anatomy and degree of carotid or vertebral artery stenoses or dissections in cases of inconclusive cross-sectional imaging. In particular, slow flow in a stenosed or partially occluded vessel can falsely indicate complete thrombosis on non-dynamic cross-sectional imaging, thus overestimating clot burden
- To precisely define anatomy and degree of intracranial stenoses
- To confirm the suspicion for cerebral vasculitis
- As part of the surgical planning for extracranial-intracranial carotid bypass procedures (e.g., for treating diseases like moyamoya) or for complex aneurysmal lesions
- To assess patency of the deep or superficial venous system of the brain, eye, or neck once a diagnosis of thrombosis is made or suspected by CT or MR venography
- To follow up treated aneurysms or AVMs, although this depends on different institutional practices, as aneurysms have recently been followed via noninvasive imaging such as MRA [15].

Although less commonly performed due to the relative rarity of spinovascular pathology, spinal DSA is the undisputed best modality to assess spinal vascular anatomy and lesions. Spinal vessels are among the smallest in the body, and cross-sectional modalities still do not have sufficient spatial resolution to accurately define their anatomy and pathology and appear to have low sensitivity [16]. For reference, the artery of Adamkiewicz, the largest radiculomedullary feeder to the anterior spinal artery, has a mean diameter of 1.8 mm [17]. The procedure has a complication rate similar to that of cerebral angiography of approximately 1%, with spinal ischemic complications being extremely rare, if not only anecdotal [18]. Reasonable indications for spinal DSA include the following:

- To define anatomy and angioarchitecture of a spinal AVM or AVF detected by cross-sectional imaging
- In cases of high suspicion for a spinal vascular malformation with negative cross-sectional imaging
- In the setting of an acute spinal cord stroke
- To define a spinal arterial aneurysm

Procedural Concepts of Diagnostic Neuroangiography

Angiographic images are obtained by injecting contrast in a particular vessel through a catheter. All angiographic procedures therefore start by obtaining access to the arterial or (less commonly) venous systems, usually through the common femoral vessels. This access point is ideal because these vessels are large, superficial, and easily found by palpation or ultrasound and allow effective hemostasis by manually compressing the artery against the femoral head. In particular

instances, such as bilaterally thrombosed iliac arteries or extremely tortuous aortas or supra-aortic trunks, the operator can decide to obtain access through the brachial or radial artery or, even more rarely, through direct common carotid artery puncture [19–21]. Access to the desired vessel is obtained through the following steps of the Seldinger technique: (1) after local analgesia is obtained, usually with bicarbonate buffered lidocaine, a hollow needle is used to puncture the desired vessel, and intravascular localization of the tip is confirmed by arterial or venous blood return; (2) a wire is then passed through the needle and pushed until its tip is fluoroscopically confirmed to be within the arterial or venous vascular system; (3) the needle is removed and the wire left in place, while manual pressure is applied to the puncture site in order to avoid formation of a hematoma; (4) a sheath to accommodate a 5 French catheter is inserted over the wire, which is then removed. Once the sheath is in place, operators can exchange wires and catheters as technically required by the procedure without losing access. Correctly obtained safe access is a key component to the success of the procedure and is of paramount importance to minimize post-procedural complications. In common femoral artery access, the puncture site should overlie the femoral head for two reasons: (1) the site lies below the inguinal ligament, therefore guaranteeing an extra-retroperitoneal location of the arteriotomy and (2) in order to allow efficient manual compression in the closure phase.

Catheterization is carried out by selecting the desired vessels with a wire and then by advancing a catheter over it in a coaxial fashion. The wire is then removed and a contrast dispenser such as a syringe or injector is connected to the catheter hub in order to inject dye and obtain the DSA images. Acquisitions will show the injected artery, the capillary phase of the parenchyma nourished by that vessel, and the venous drainage pattern. This operation is then repeated for all desired vessels.

In order to obtain images of diagnostic quality, it is important that the patient remains as still as possible, following the operator's breathing instructions at the time of DSA acquisition. The exam is therefore most often carried out with minimal sedation (usually starting with 0.5 mg of midazolam and 25 mcg of fentanyl, mostly for patient comfort) or without any sedation at all, depending on institutional and operator preferences. If the patient is unable to follow the physician's instructions due to illness or mental status or in cases of obstructive sleep apnea in which procedural sedation might risk loss of airway patency or further worsen cooperation, the exam can be carried out under general anesthesia or with anesthesia assistance.

Unless the specific clinical question requires an exam focused on one particular vessel, a complete cerebral angiogram should include imaging of both the anterior and posterior circulations.

Depending on the operator's preferences and on patient characteristics, the DSA can start with an ascending aortic injection to determine the anatomy of the supra-aortic trunks. This is particularly useful in elderly individuals with very tortuous and atherosclerotic vessels; an aortic arch acquisition can prevent multiple attempts at catheterization of the great vessels of the neck with potentially long fluoroscopy times and an increased risk of embolization from the movement of catheters and wires against atherosclerotic plaques.

Imaging of the cervical portions of the carotid and vertebral arteries is not routinely obtained at most centers unless the exam is performed to assess atherosclerotic disease or dissections of these vessels.

The anterior circulation can be evaluated through injections in the common or internal carotid artery (Fig. 24.1). These injections demonstrate the distal cervical and intracranial carotid arteries and the anterior and middle cerebral artery and their branches. They also give important informa-

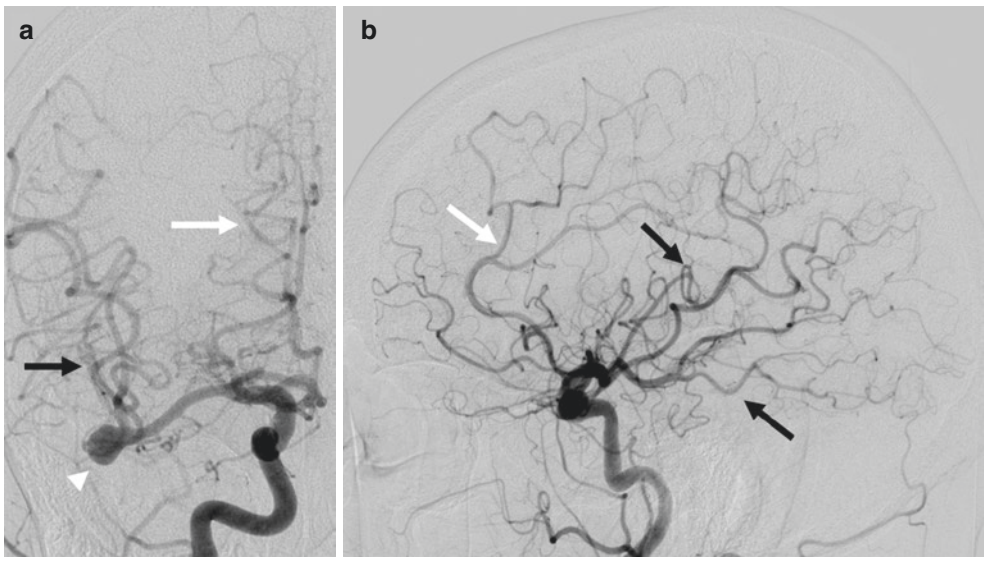

Fig. 24.1 Anteroposterior (**a**) and lateral (**b**) views of a right common carotid artery injection depicting the anterior cerebral artery (white arrow) and the middle cerebral artery (black arrows). The patient underwent the procedure for pre-treatment planning of a right middle cerebral artery aneurysm (white arrowhead)

tion about the anterior and posterior communicating arteries, which can be particularly relevant compensation mechanisms in cases of ischemic disease. At a minimum, the operator should obtain anteroposterior and lateral views, with 45-degree ipsilateral oblique views in case imaging findings warrant further investigation.

The posterior circulation is evaluated through injections obtained from the proximal vertebral artery. Images should include an anteroposterior and lateral view and should demonstrate the ipsilateral intracranial vertebral artery and its branches (posterior inferior, anterior inferior, and superior cerebellar arteries), the basilar artery, and the posterior cerebral arteries and their branches (Fig. 24.2).

The external carotid artery and its branches are studied when there is the suspicion for a DAVF, a facial vascular malformation, or as part of surgical planning for intracranial-extracranial bypass procedures.

Spinal angiography includes selective catheterization of all intersegmental arteries and, depending on the clinical question, of the vertebral arteries, thyrocervical and costocervical trunks, and internal and external iliac arteries. The exam is not complete until at least the artery of Adamkiewicz has been demonstrated.

In selected cases, DSA tomographic acquisitions can be added to provide further anatomical details. In particular, aneurysms should be imaged with 3D rotational angiography to show the three-dimensional shape of the lesion and guide choice of the embolic device and help determine the correct sizing (Fig. 24.3). In cases of AVMs or cavernous malformations, DSA CT acquisitions such as Dyna CT or Vaso CT help clarify the features that assign the malformation a grade on the Spetzler-Martin scale (Fig. 24.4). This score is determined by the lesion's location (in an eloquent or non-eloquent area), size (<3 cm, between 3 and 6 cm, and >6 cm), and venous drainage (superficial versus deep) and is used to decide the most appropriate treatment strategy.

Once the desired information has been obtained and no further imaging is needed, catheters and wires are withdrawn, and vascular access is closed either via manual compression or with a closure device. This step is particularly important because complications at the access site are relatively common. Manual pressure has historically been considered the gold standard closing modality and is performed by compressing the artery between the operator's fingers and the femoral head in cases of groin access, or the radius or humerus in cases of upper extremity approaches [22]. The duration of compression varies depending on the coagulation status of the patient and on the bore of the utilized sheath and can vary from 10 minutes to more than an hour. Hemostasis is usually followed by a variable period of immobilization and periodic vascular checks (described in detail below). The last few decades have seen an increase in utilization of multiple closure devices in order to obtain a fast and reliable closure with decreased immobilization times, hence reducing the time to discharge and increasing patient comfort. These devices, initially dedicated to patients on anticoagulation or those who have undergone procedures with large-bore catheters, are now widely used even for diagnostic procedures. Multiple randomized controlled trials have demonstrated closure devices to be non-inferior to manual compression in terms of complication rates and hemostasis success, while granting increased patient comfort and shortened time for hemostasis, ambulation, and hospital discharge [23–25].

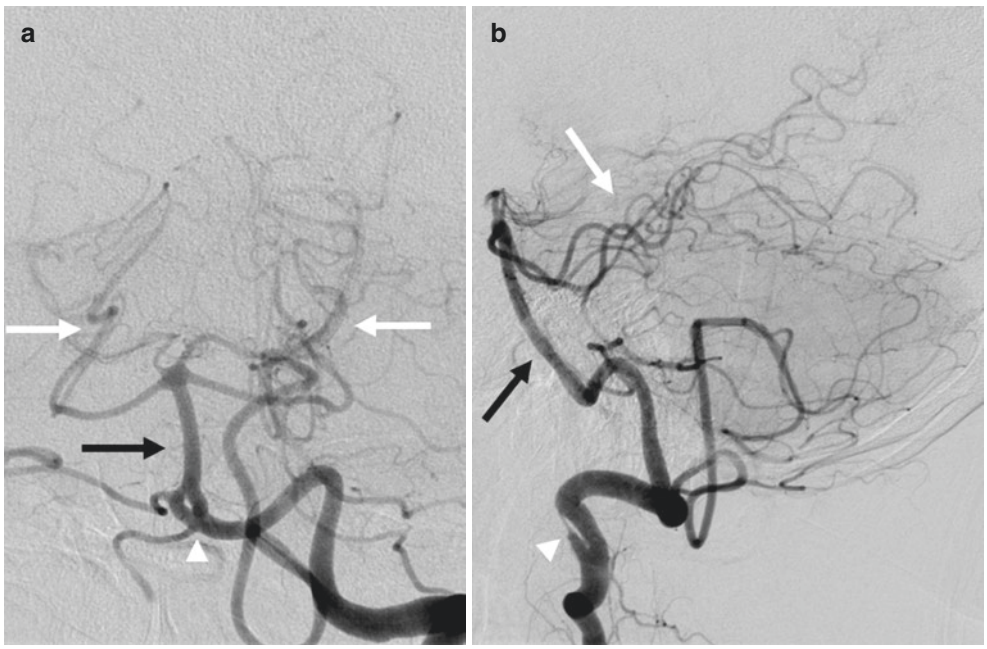

Fig. 24.2 Anteroposterior (**a**) and lateral (**b**) views of a left vertebral artery injection depicting the basilar artery (black arrow) and both posterior cerebral arteries (white arrows). Note is made of an incidentally found basilar artery fenestration (white arrowhead), with a morphology suggestive of a post-dissective origin

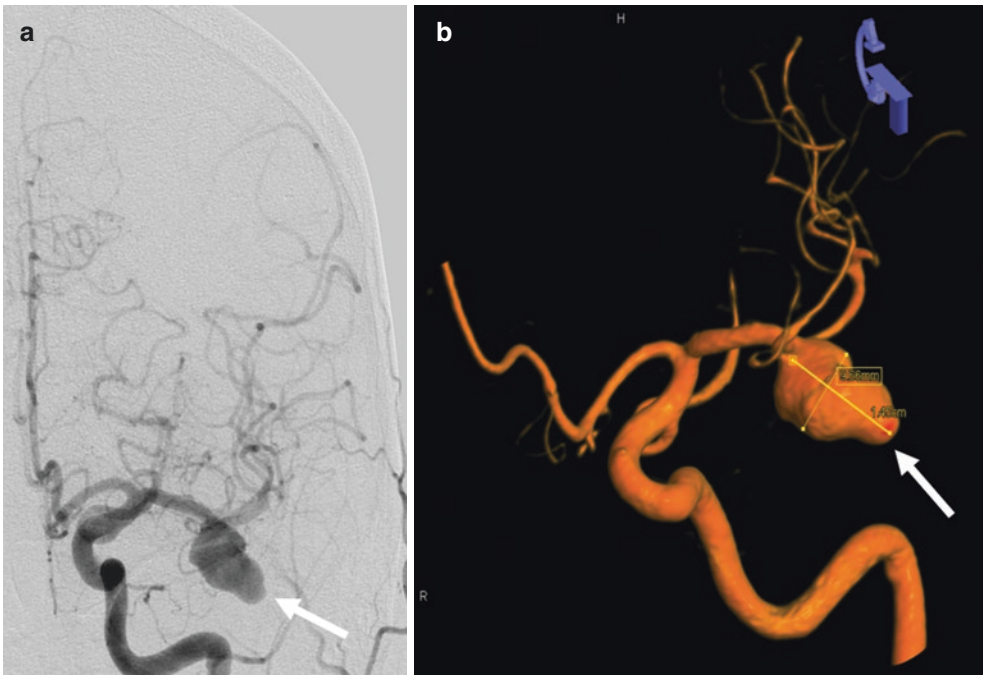

Fig. 24.3 Left common carotid artery DSA (**a**) and 3D rotational angiography (**b**) obtained for preoperative planning for a left middle cerebral artery bifurcation aneurysm (white arrow). The 3D acquisition allows visualization of the lesion in multiple planes and accurate measurements in all 3 axes

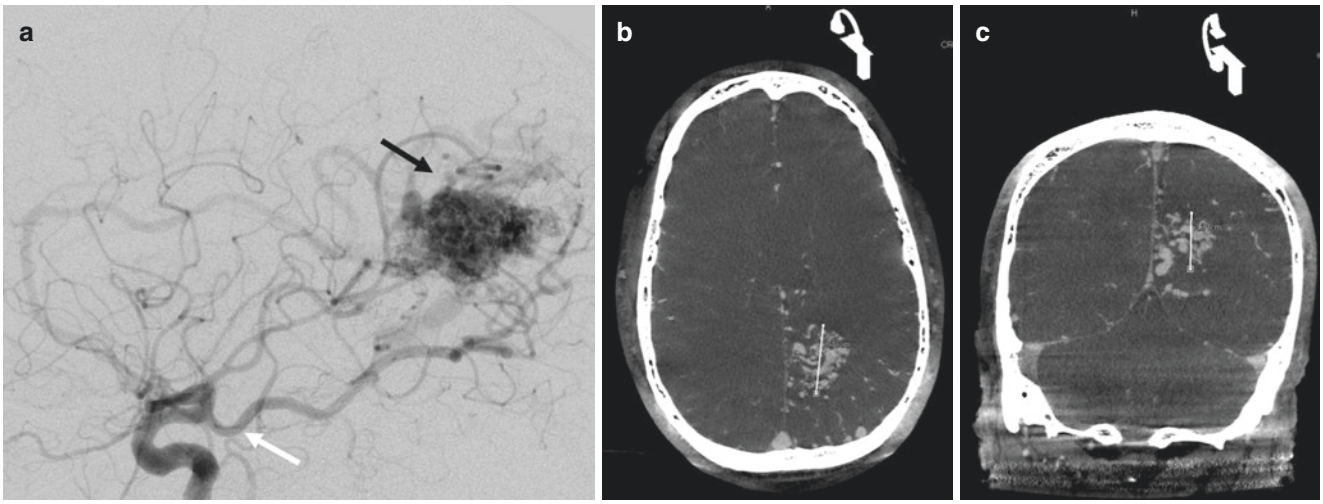

Fig. 24.4 Left common carotid artery DSA (**a**) and axial and coronal Dyna CT reconstructions (**b**, **c**) in a patient with a left parietal AVM (black arrow) fed by branches of the left middle cerebral artery. Note how the lesion can be characterized in all planes, allowing an accurate measurement of the nidus. Note is made of a prominent posterior communicating artery giving way to the left posterior cerebral artery (fetal configuration) (white arrow)

Preoperative Management

Diagnostic angiographic procedures do not usually require complicated patient preparation, but a careful preoperative assessment is instrumental in avoiding delays and potentially serious complications. The same general concepts apply to patients undergoing interventions. A focused history and a few laboratories to determine the likelihood of contrast-related adverse reactions should always be obtained first. Allergic reactions to intravenous (IV) iodinated contrast are rare (aggregate 0.6%, severe 0.04%) since the introduction of nonionic, low osmolality contrast agents and can vary in severity from urticarial-like reactions to potentially life-threatening conditions such as anaphylactic shock or glottis edema [26]. A history of a prior allergic-like reaction to a same-class contrast media increases the likelihood of an adverse event by approximately five orders of magnitude, although this does not guarantee that the reaction will take

place again after a second administration [27]. Unrelated allergies, including shellfish and povidone-iodine, increase occurrence of contrast reactions 2–3 times [28, 29]. A prior allergic reaction to MRI contrast does not increase the likelihood of an iodinated contrast reaction since there is no cross-reactivity between these compounds.

Premedication strategies are recommended by the American College of Radiology (ACR) in the case of prior allergic-like or unknown-type contrast reactions to the same class of contrast medium [30]. These regimens vary depending on the urgency of the exam and are carried out with steroidal medications. There is no demonstrated efficacy of steroids given less than 4–5 hours before contrast injection.

Elective premedication can be carried out with two protocols:

- 50 mg of oral prednisone at 13, 7, and 1 hour(s) before the examination, with 50 mg diphenhydramine IV, intramuscular, or by mouth 1 hour also before the procedure. If the patient cannot tolerate oral administration, 200 mg of hydrocortisone IV can be substituted for each dose of oral prednisone [31, 32]
- 32 mg of methylprednisolone by mouth 12 and 2 hours before contrast administration with 50 mg diphenhydramine added as above [33]

Emergent premedication is less well-defined and can be carried out with 40 mg of methylprednisolone sodium succinate IV or 200 mg of hydrocortisone sodium succinate IV immediately and then every 4 hours until the exam, plus diphenhydramine 50 mg IV 1 hour before contrast administration. This regimen should last at least 4–5 hours in duration. In patients who are allergic to methylprednisolone, 7.5 mg dexamethasone sodium sulfate IV can be used instead [32].

Intravascular iodinated contrast can cause or aggravate renal insufficiency leading to so-called contrast-induced nephropathy [34]. Etiology of such damage is not well understood, and there are no universally accepted guidelines in terms of patient preparation or preoperative examinations. The accepted consensus is that the most important risk factor is preexisting severe renal insufficiency; therefore contrast administration should be avoided in these patients if possible [35, 36]. The latest edition of the Contrast Media Manual of the ACR states that, if a risk threshold should be used at all, the use of IV contrast should be avoided in patients whose estimated glomerular filtration rate (eGFR), estimated via creatinine values, is equal to or lower than 30 mL/min/1.73m^2 [30]. It is important to stress the fact that IV contrast administration, as for any other drug, always implies an analysis of the risk-benefit ratio tailored to the individual patient's clinical scenario. If a patient with severe renal insufficiency needs a life-saving procedure, such as endovascular thrombectomy for acute ischemic stroke, contrast should be administered. Depending on the patient's hemodynamic status, after the procedure, the patient can then undergo dialysis. Patients in end-stage renal disease without functioning kidneys can receive IV contrast without risk for additional damage. There is so far no specific evidence that demonstrates that contrast doses should be administered at least 24 hours apart, and the timing between two injections should not deter repeat use of contrast if needed in urgent clinical situations. The most widely accepted preparation strategy in patients at risk for renal damage is volume expansion with isotonic fluids such as lactate Ringer's or 0.9% normal saline. The ACR manual suggests a possible protocol using 0.9% saline at 100 mL/hour, beginning 6–12 hours before and continuing 4–12 hours after contrast administration [30]. Metformin itself is not a risk factor for renal damage, but, in patients with renal disease, it could theoretically lead to lactic acidosis in case of contrast-mediated kidney damage. It should therefore be held for 24 hours before and for 48 hours after the procedure in patients with renal insufficiency.

Coagulation studies should be obtained for every critical care patient undergoing an angiographic procedure in order to minimize risk of bleeding, especially at the access site. Institutional guidelines vary greatly among different centers, but a pre-procedural international normalized ratio (INR) of 1.5 or lower and a platelet count higher than 20,000 platelets per microliter can be considered reasonable cutoff values. Coagulation values should be adjusted in order to reach acceptable thresholds with IV platelets and frozen fresh plasma, depending on the patient's particular needs. In general, an INR higher than 3 is a contraindication to every invasive procedure. A patient on aspirin and/or clopidogrel does not need to hold these medications before undergoing a procedure.

Ultimately, as noted above, it should be determined if the patient can undergo the procedure with sedation or if there is a need for general anesthesia. Cerebral angiography under sedation has classically been performed with the patient having nothing by mouth (nil per os or NPO) for at least 6 hours before the procedure, theoretically to reduce the risk of aspiration in case of intra-procedural nausea or vomiting. The incidence of nausea and vomiting during and within 1 hour after angiography was found to be 1.05%, and no cases of aspiration were recorded in a large population study, regardless of diet or fasting [37]. It is therefore possible that fasting is not strictly necessary before a cerebral DSA, and the patient not being NPO should not delay a needed angiographic procedure.

Post-procedural Care and Possible Complications

As mentioned above, cerebral DSA has a non-negligible overall complication rate that varies greatly depending on the reviewed literature, with rates ranging from 0.3% to 4%

but averaging at least 1–2% [7–11]. Postoperative care aims to promptly recognize complications that have occurred during the angiogram and to avoid the occurrence of adverse events after the patient's return to the unit. Complications can be divided into access-related, neurological, and systemic.

The largest study conducted so far on the subject analyzed complications occurring in a total of 19,826 cerebral DSAs. Complications at the access site were present in 4.2% of cases, systemic complications in 2.5% of patients, and neurologic complications attributable to the angiography in 2.6% of patients [10].

Local access complications include hematomas (most commonly), pseudoaneurysms, or arteriovenous fistulas, as well as complications that are unique to closure devices.

The degree of severity of and treatment options for a post-procedural groin complication vary greatly depending on the needle entry site chosen at the time of femoral access. If the point of entry was correctly chosen overlying the femoral head, the hematoma will be outside the retroperitoneum and will be manageable in most cases by direct compression, rarely requiring surgical repair of the artery, transfusion, or evacuation. On the other hand, if the puncture site was inadvertently located too high, above the inguinal ligament, the hematoma will be in the retroperitoneal space, which will make it more cumbersome to compress, not having a stable compression surface. The retroperitoneal space will also accommodate more blood than the fascial planes of the thigh, potentially resulting in a more severe hemorrhage requiring blood transfusions. Retroperitoneal hematomas are rare (0.4% of patients in interventional cardiology literature series) but require surgery in as high as 8% and are associated with increased mortality [38]. Pseudoaneurysms can potentially complicate any hematoma and in some series have rates as high as 0.8–2.2% of patients. Theoretically, small pseudoaneurysms (<2 cm) might spontaneously thrombose and can simply be followed by serial ultrasound. Larger aneurysms should be actively treated with either ultrasound-guided probe compression or thrombin injection or by angiographic positioning of a covered stent. Surgical repair should be employed in cases refractory to these percutaneous treatments [39].

Arteriovenous fistulae are rare and occur when the femoral vessel is accessed lower than the femoral head. At this level, the femoral vein courses immediately underneath the femoral artery and can therefore be punctured if the needle passes the artery in a biparietal fashion. Once both adjacent vessels are damaged by the needle, a fistula can develop, with various degrees of arteriovenous shunting. About 40% of these lesions close spontaneously, while the rest might require compression, angiographic repair, or rarely surgical treatment [40]. Occlusive complications are rare and can be the result of a vascular dissection during the access phase, the distal embolization of an atherosclerotic plaque along the wall of the punctured femoral vessel, or the dislodgement of a portion of a closure device. This is more common with those closure devices that have an intravascular component. Infection at the puncture site is nowadays extremely rare and would manifest with signs of local inflammation, rather than signs of vascular compromise.

Access site post-procedural care should include groin inspection and palpation as well as peripheral pulse checks every 15 minutes for the first hour, every 30 minutes for the second, and every hour until ambulation after the third hour. Although institutional practices vary greatly, patients should observe a monitored bed rest of at least 2 hours in case of usage of a closure device and of 4 hours in case of manual compression after an angiogram performed with a 5 French sheath. If the sheath is larger and the access site was closed with manual compression, bed rest should be increased by approximately 1 hour for each French above 5. Ideally, a pre-procedural baseline pulse check should have been obtained before the procedure: this could avoid useless workup in case, for example, of an absent dorsalis pedis pulse after a femoral access, if the condition was present before. While some degree of skin discoloration from subcutaneous blood is extremely common, any enlarging or pulsating mass arising at the puncture site as well as disappearance of a distal pulse or a cold foot or limb should be considered suspicious and promptly evaluated by ultrasound or abdominal CTA.

Access site complications assume particular significance in the cohort of patients who are admitted to the NCCU after an intracranial stenting procedure. These patients have usually been treated preoperatively with double antiplatelet therapy for 1 week and have received large intra-procedural amounts of heparin. If the intracranial stenting was performed in an emergent fashion, for example, in cases of ruptured supraclinoid carotid artery aneurysms treated with flow diversion, these patients arrive to the unit having had a dose load of both aspirin and clopidogrel. Furthermore, many operators prefer to post-procedurally treat these patients with heparin to a goal activated partial thromboplastin time (aPTT) between 60 and 80 seconds. Femoral vascular complications in these patients would hence be more severe and difficult to treat than normal due to these patients' profoundly anticoagulated status. Hematomas or pseudoaneurysms for which surgical repair is deemed necessary as well as rapid exsanguination might force the treating team to suspend administration of heparin and of at least one antiplatelet agent, potentially exposing the patient to the risk of thrombosis of a freshly deployed stent and of a consequently devastating cerebral infarction.

Post-angiographic systemic complications are relatively common. In particular, postoperative headache has been reported in different series in as many as 55% of patients. This headache is usually transient and can be easily treated with pain medications [41]. It is important to differentiate

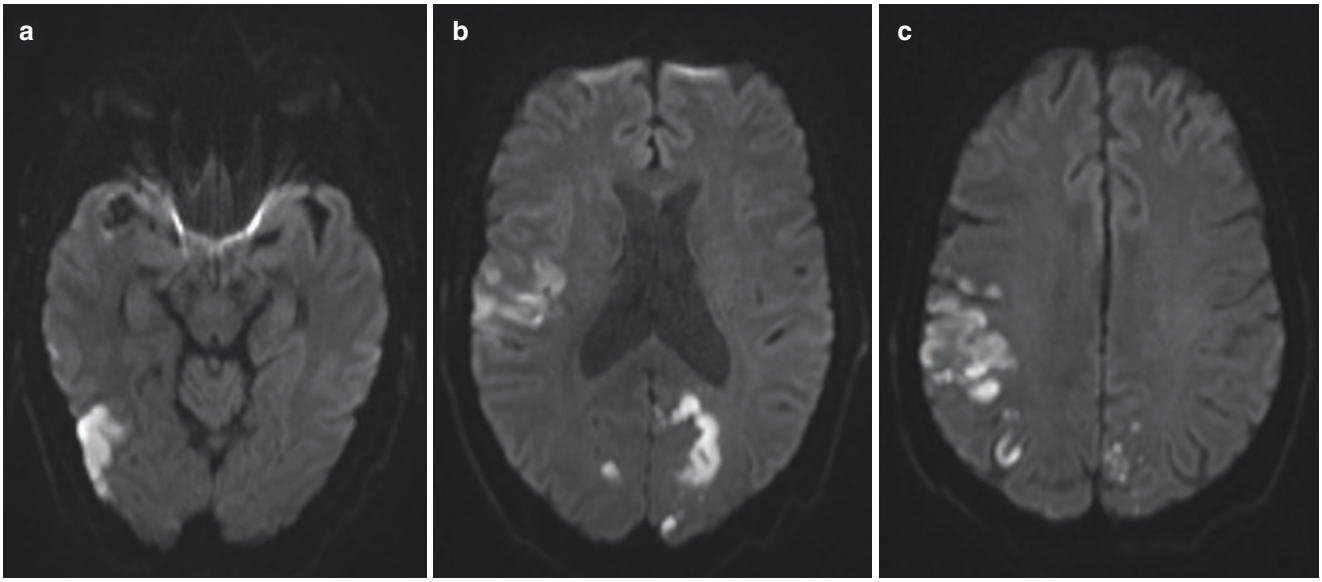

Fig. 24.5 Diffusion-weighted MRI sequences showing multiple, bilateral areas of cytotoxic edema in the right temporal lobe (**a**), left occipital lobe (**b**), and right parietal lobe (**c**) compatible with acute embolic infarctions following a diagnostic DSA performed in a 70-year-old male for preoperative planning of a right middle cerebral artery aneurysm. The patient had multiple vascular risk factors and complex aortic arch anatomy

this headache from that of a subarachnoid hemorrhage or of a ruptured AVM, especially in posttreatment patients. If the clinical suspicion for an adverse event is high, a non-contrast CT of the head should be ordered. Contrast-induced nephropathy and delayed contrast allergic-like reactions are overall rare, with rates of 0.02% and 0.1%, respectively, in the largest series available for review [10].

The most feared complication of a neuroangiographic procedure is a cerebral ischemic event. The movement of catheters and wires as well as intravascular injections pose an intrinsic risk of creating emboli directed to the brain vasculature, either from disruption of an atherosclerotic plaque or from injection of small quantities of air or blood clots that have formed within the catheters or the syringes (Fig. 24.5). To minimize these occurrences, operators normally continuously flush the catheter with heparinized saline and administer a bolus of 2000 IU of saline at the beginning of the procedure. In case of intraoperative large vessel occlusion, aspiration or mechanical thrombectomy techniques can be used to remove the iatrogenic embolus in the same fashion as in a stroke case. If the emboli are lodged in branches that are too distal to be safely catheterized, GpIIb/IIIa inhibitors can be infused intra-arterially. It is likely that the overwhelming majority of intra-procedural embolisms are subclinical and only incidentally noticed with imaging modalities obtained for other reasons. Studies that analyzed MRI findings in patients who underwent angiographic procedures found that 9–25% of patients had evidence of foci of hyperintensity on diffusion-weighted imaging, representative of cytotoxic edema from small infarctions, in a distribution compatible with an embolic etiology [42–45]. The etiology of these microemboli is unclear and, if not associated with clinical symptoms, they should not be considered a complication of the procedure even when seen on MR imaging (Fig. 24.6).

When they are clinically evident, neurologic complications are usually transient and self-resolving (0.4–2.3%; mean, 1.3%). Very rarely, ischemic complications can result in permanent neurological deficits (0.1–0.5%; mean, 0.3%) and, even more rarely, in death (0.06%). Neurologic complications have been found to be associated with patient age greater than 55 years, prior history of stroke, atherosclerotic disease, and hypertension [7, 10, 46]. Postoperative care should include rigorous neurological checks every 15 minutes in the first hour after the procedure, every 30 minutes in the second hour, and then following the neurointensive care team recommendations based on the patient's clinical scenario.

Overview and Management of Non-emergent Conditions

Unruptured Cerebral Aneurysms

The choice between endovascular and surgical treatment of an unruptured cerebral aneurysm depends on multiple parameters including its location, morphology, neck-to-dome and aspect ratio, parent vessel tortuosity, possible vessels originating from the aneurysm itself, comorbidities, and ultimately the patient's treatment preference if multiple appropriate choices are available. Current endovascular

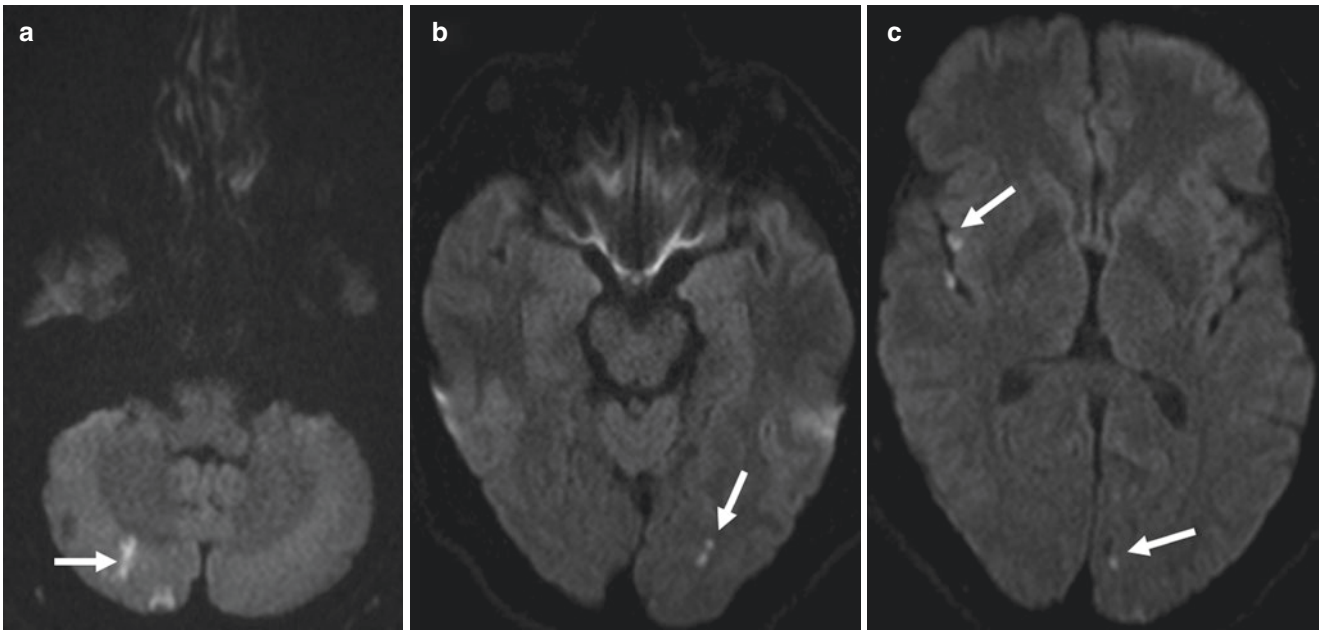

Fig. 24.6 Diffusion-weighted MRI sequences showing multiple, bilateral punctate areas of cytotoxic edema at the gray-white junction (white arrows) in the cerebellum (**a**), left occipital lobe (**b**), and right insula (**c**) compatible with microemboli in a 65-year-old patient imaged for treatment planning for multiple small AVMs (not shown). The MRI was obtained a day after the diagnostic DSA for preoperative purposes. The patient was completely asymptomatic

approaches include simple coiling, stent- or balloon-assisted coiling, flow diversion, and endosaccular flow disruption.

Coiling involves packing the aneurysmal sac with detachable platinum coils in order to induce rapid intrasaccular thrombus formation. This technique alone is usually sufficient for aneurysms with a narrow neck but, if the aneurysmal neck is wide, poses the risk for coil herniation into the parent vessel. This issue has been resolved with the introduction of coiling-assisting devices such as balloons or stents, whose aim is basically to hold coils in place within the aneurysmal sac. Balloon-assisted coiling involves the temporary inflation of a balloon to block the aneurysmal neck until the coil mass is dense enough to avoid migration or prolapse into the parent vessel. Stenting can be carried out with various types of devices that can be deployed to cover the aneurysmal neck before or, rarely, after coil deployment. Stenting in these cases serves the double purpose of assisting the coiling and acting as a "scaffold" for endothelialization of the parent vessel, eventually resulting in a wall reconstruction with higher occlusion rates [47]. More recently, stents with a denser metal mesh called flow diverters have become indicated in the treatment of supraclinoid aneurysms, many of which were previously considered untreatable. These devices aim to divert the physiologic blood flow away from the aneurysm, thereby causing intrasaccular thrombosis and at the same time promote vessel wall reconstruction over time. Off-label usage of these devices has been extensively reported for giant, fusiform, and blood blister aneurysms [48]. Other devices such as intrasaccular flow disruptors or complex scaffolding stents are available and under study but are beyond the scope of this chapter.

Postoperative Care

Post-procedural care aims to treat the sequelae of possible intra-procedural complications and to strictly monitor the occurrence of post-procedural ones.

The most feared intra-procedural complication of endovascular treatment is aneurysmal rupture, which can be spontaneous but is most commonly iatrogenic, being caused by movements of the microcatheter and guidewire or from using oversized coils. A patient who suffers an intra-procedural aneurysmal rupture has essentially suffered a SAH and should be treated accordingly, with the added layer of complexity of possible ischemia resulting from hemorrhage tamponade maneuvers such as emergent coiling, gluing, or vessel sacrifice.

Thromboembolic complications can occur during or after the procedure secondary to coil migration into the parent vessel or emboli detachment from clots formed on a prolapsed coil or in the coil pack or as a result of acute in-stent stenosis/occlusion when such devices are used. Rarely, ischemia can be secondary to intracranial vascular dissection from a balloon [49].

Neurocritical care should include the routine postoperative care described above for a cerebral angiography.

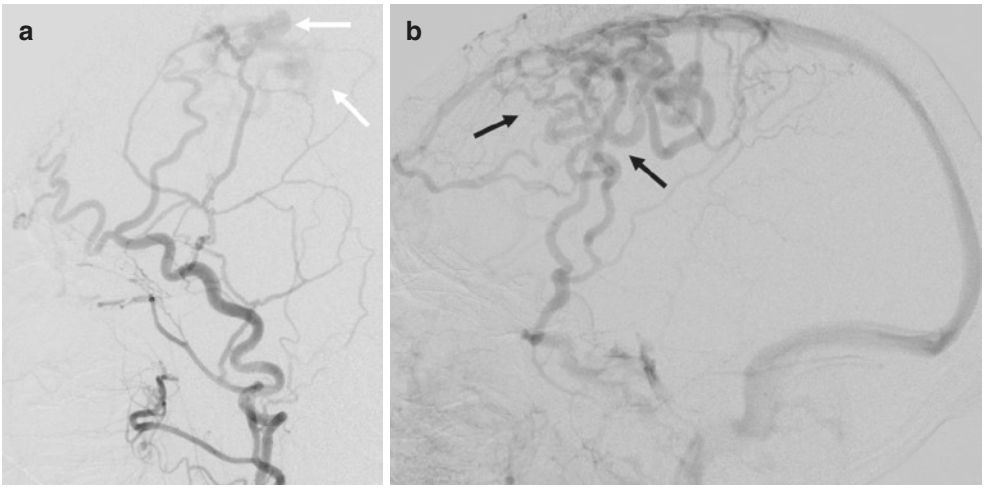

Fig. 24.7 Lateral views of a left external carotid artery injection in a patient with a high-grade dural AVF. The arterial phase (**a**) shows a hypertrophic superficial temporal artery feeding a dural AVF, identified by opacification of early draining veins (white arrows). The venous phase (**b**) shows retrograde drainage into multiple dilated cortical veins (black arrows) and reflux into the superior sagittal sinus

Neurological checks should be performed for at least 12–24 hours after the procedure, and the onset of headache or of neurological deficits should prompt imaging with CT or MRI to investigate ischemia or rupture of incompletely protected lesions. The arterial line – if present– should be maintained for continuous blood pressure monitoring for at least 12 hours.

As described above, patients who undergo stent-assisted coiling or flow diversion need particularly thorough observation of the puncture site in order to avoid hemorrhages that could potentially require anti-aggregation/coagulation reversal and hence put the patient at risk for in-stent thrombosis. These patients should have been tested for clopidogrel sensitivity before the procedure in order to detect hypo- or nonresponders who would be at increased risk for thromboembolic complications if not pre-treated with a different antiplatelet agent [50].

Abnormal Arteriovenous Shunting

High-flow cerebral vascular malformations can be broadly classified into two types: AVMs and AVFs. These entities are characterized by an abnormal arterial to venous shunt with bypassing of the capillary bed, the main difference between the two being the presence at the shunting point of either an abnormal tangle of dysplastic vessels called the nidus in AVMs or of a direct communication between an artery and a draining vein in AVFs. In both pathologies, the absence of the physiologic pressure decrease associated with capillary blood distribution creates high-pressure stress on the draining veins, which can become hypertrophic and tortuous and eventually prone to rupture, causing a hemorrhage. Increased venous pressure can also lead to hypertensive encephalopathy to varying degrees. In the case of AVMs, continuous arterial pressure on the dysplastic nidal vessels can promote the formation of aneurysms that can lead to SAH and/or ICH. In the adult population, AVMs are primarily seen within the brain parenchyma and are considered congenital lesions, while AVFs more commonly involve the meningeal arteries and the dural venous sinuses and/or cortical (leptomeningeal) veins and are often acquired lesions (Fig. 24.7). The treatment of both pathologies is the occlusion of the abnormal communication between the artery and the vein, which nowadays is almost exclusively achieved via liquid embolic agents, mostly consisting of acrylic glues such as N-butyl cyanoacrylate (NBCA) and/or Onyx. Glue is an effective and durable agent traditionally used in AVMs [51], while Onyx is currently preferred by many for treatment of AVFs, since it allows for prolonged and controllable embolization and more complete penetration of a fistulous shunt with extension into and obliteration of the venous side of the fistula [52, 53]. While AVFs can often be cured by the endovascular approach alone, AVMs usually require an adjunct surgical resection and/or stereotactic radiosurgery. Both diseases may need a staged approach with multiple embolizations, depending on their degree of complexity.

Postoperative Care

Postoperative care of AVMs or AVFs does not differ from that of a DSA, with the exception of the duration of the neurological checks, which should be performed for at least 12–24 hours.

Intra-procedural complications include nidal ruptures, often requiring immediate neurosurgical intervention with placement of a drain or decompressive craniectomy, and unwanted embolizations of normal arterial vessels by the embolic agents, resulting in arterial ischemia.

In the acute post-procedural period, the most severe complication is acute post-embolization hemorrhage, most commonly a sequela of excessive venous thrombosis. Decrease in alertness, headaches, or appearance of a new neurological deficit should prompt CT imaging. Extension of embolysate distally into adjacent normal veins or propagating venous

thrombosis due to sluggish flow may cause venous congestion and ultimately be further complicated by venous infarctions with or without hemorrhage [53, 54]. Hemorrhage, especially in AVMs, can also be secondary to restoration of normal blood flow to a previously hypoperfused brain parenchyma following the shunt closure. Therefore, in addition to the routine post-angiography management, post-procedural monitoring should include strict blood pressure control, especially in hypertensive patients.

Vessel Sacrifice

Vessel sacrifice is an occlusive therapeutic option for a variety of cerebrovascular conditions including blunt, penetrating, or iatrogenic carotid or vertebral artery injuries, carotid involvement in head and neck malignancies, dissecting aneurysms, fistulous arteriovenous shunting, and selected aneurysms, usually giant [55–57]. The rationale of the procedure is to halt or avoid acute bleeding or prevent thromboembolic sequelae from injured vessels not amenable to vascular reconstruction. The procedure is most commonly performed on the internal carotid artery and is usually completed with coils and in selected cases with vascular plugs [58, 59]. The risk of ischemic stroke after internal carotid artery occlusion can be as high as 30% – therefore, unless performed in an emergent setting such as that of the iatrogenic rupture of a vessel with uncontrolled bleeding, a balloon test occlusion is usually performed before the embolization to assess the patient's collateral circulation and response to the occlusion of the targeted vessel. The test involves the inflation of a balloon in the desired artery in order to simulate the planned embolization, followed by serial neurological and angiographic checks over the following 30 minutes. Patients who fail the test may need surgical bypass prior to vessel sacrifice [60, 61]. Unilateral vertebral artery sacrifice is generally safe even without preprocedural test occlusion, as long as flow to the ipsilateral posterior inferior cerebellar artery territory and the vascular contribution to the spinal cord are preserved [62].

Postoperative Care

Despite favorable occlusion test results, post-sacrifice ischemia can still occur, either due to hemodynamic problems or to thromboembolisms from the coil pack [63]. Frequent neurological checks in the early post-procedural period are required to monitor for delayed ischemic events due to hypoperfusion, typically presenting as waxing and waning neurological symptoms that show a positive feedback to changes in blood pressure. Close maintenance of an adequate systolic blood pressure with appropriate medical therapy and volume expansion is required to preserve cerebral perfusion and avoid hypotensive infarctions [64, 65]. In addition, dual antiplatelet therapy is usually started post-procedure to minimize unintended distal embolizations from the coil pack [60, 66].

Spinal Embolizations

Endovascular interventions on spinal vessels are performed to treat spinal vascular malformations or for preoperative tumor embolization. Spinal vascular malformations conceptually resemble their cerebral counterparts and are similarly classified into AVMs and AVFs. AVMs are very rare and almost exclusively located in the spinal parenchyma. Complete obliteration of the nidus is required for cure, which harbors a significant risk of neurological morbidity. AVFs are less rare and are subclassified according to their draining pattern into dural, extradural, and perimedullary, with dural ones being the most common lesions and usually located along the nerve root. The endovascular approach is the treatment of choice for AVFs and primarily involves liquid embolization with NBCA to occlude the fistulous connection with penetration into the proximal dural or perimedullary draining vein [67–70].

Preoperative embolization of spinal tumors, most commonly metastases from hypervascular cancers such as renal cell, thyroid, breast, and melanoma, is commonly performed prior to surgical resection or fixation to avoid excessive intraoperative blood loss during surgical resection. Particles, coils, and liquid embolic agents have all been successfully used with good outcomes [71, 72].

Postoperative Care

Spinal endovascular embolization, irrespective of the indication, carries the risk of occluding normal anterior or posterior spinal arterial supply, causing spinal infarction and para- or tetraparesis/plegia, depending on the treated level [70]. Excessive embolization of dural AVFs may result in distal venous occlusion, exacerbating venous hypertension and potentially causing hemorrhage [67]. Post-embolization swelling of a neoplastic lesion might cause cord compression, and it is reasonable to post-treat the patient with IV steroids to avoid this occurrence. Post-procedural care is essentially the same used for a diagnostic DSA, with more protracted neurological checks needed to monitor for symptoms of cord infarction or compression, which should be promptly investigated with a spine MRI. Additionally, when treating cervical arteriovenous shunts, there is a risk of unintended intracranial embolization via the vertebral artery or the many carotid anastomoses in the cervical region. These concerns should be investigated with head CT or MRI.

Overview and Management of Emergent Conditions

Subarachnoid Hemorrhage

Early trials including the Kuopio study, the International Subarachnoid Aneurysm Trial (ISAT), and the Barrow Ruptured Aneurysm Trial (BRAT) showed superior outcomes for coil embolization over surgical clipping in aneurysms amenable to either strategy, and recent data further support the long-term durability of the endovascular approach [73–76].

Non-contrast CT of the head should be the first imaging study obtained for a suspected SAH. Following the diagnosis, a CTA of the head and neck is usually performed as a first step to identify a ruptured aneurysm, which causes up to 85% of spontaneous SAH [77]. If the patient cannot receive IV contrast, time-of-flight MRA can be considered, although its lower spatial resolution and the need for the patient to stay still during the scan make it a less desirable option. DSA most often follows noninvasive imaging, either to assess for very small or dissective lesions below resolution limits of CTA or to further aid the decision for an endovascular versus surgical approach for treatment. Per American Heart Association/American Stroke Association (AHA/ASA) and the European Stroke Organization guidelines, endovascular coiling should be considered for treating ruptured aneurysms that are equally amenable to coiling or surgical clipping [78, 79].

Regardless of the chosen approach, treatment of a ruptured aneurysm is aimed at preventing rebleeding, which is fatal in most cases, and is performed emergently or as early as logistically possible. The available endovascular techniques are the same as described for the treatment of unruptured aneurysms. In general, due to the lack of dual antiplatelet premedication, simple and balloon-assisted coiling are preferred to techniques requiring deployment of a stent; this is especially true for patients with external ventricular drains, who might be at increased risk of bleeding once antiplatelet therapy is in full effect. On the other hand, if antiplatelet therapy is not promptly started upon stent deployment, the stent might thrombose or acutely stenose, putting the patient at risk for developing ischemic stroke. When intracranial stenting is deemed necessary, the patient is usually prepared intra-procedurally with a bolus dose of aspirin per rectum and with crushed clopidogrel through a nasogastric tube. Emergent flow diversion has proven to be effective in the treatment of uncoilable aneurysms in multiple series [80]. However, given the fact that the device usually does not exclude the lesion from the circulation immediately after deployment, the patient might be at increased risk of rebleeding especially given the necessary antiplatelet therapy [81]. Conversely, in cases of stent-assisted coiling, once the aneurysm is excluded from the circulation, the risks are essentially those of intracranial stenting discussed before.

In approximately 15–30% of patients with nontraumatic SAH, a vascular etiology may not be identified on initial DSA (also called SAH sine materia). An angiogram can be repeated at 1 and then at 2–6 weeks to identify vascular abnormalities that may have been previously masked by thrombosis, vasospasm, or rupture of the aneurysm with vessel wall damage obscuring the original lesion, although the yield of this approach is low and imaging beyond 6 weeks may have little utility [75, 82].

In approximately 5% of SAH patients, CT imaging reveals a characteristic symmetric SAH pattern confined to the prepontine and perimesencephalic areas, without extension into the upper fissures or sulci. This constellation of imaging findings is classic for non-aneurysmal perimesencephalic subarachnoid hemorrhage, a benign condition, and diagnosis can be confirmed after one negative angiographic evaluation to rule out posterior circulation aneurysms that may present similarly [83]. Repeat imaging studies or further interventions are not necessary in these cases, and the majority of these patients have a good prognosis with low risk of vasospasm, rebleeding, or neurologic sequelae.

Postoperative Care

If the aneurysm has been incompletely embolized, the patient is at risk for re-hemorrhage, an event which is most often fatal. If the aneurysm has been fully excluded from the circulation, the patient's main risk is that of ischemic events that can be secondary either to thromboemboli from the coil pack and/or intracranial stent or to a SAH-specific entity termed delayed cerebral ischemia. This kind of ischemia is a major contributor to morbidity and mortality in SAHs, typically occurring 3–14 days following the hemorrhage, with peak incidence at 7 days. The phenomenon likely results from multiple mechanisms including macro- and microvascular spastic stenosis, platelet activation, and distal microthrombosis. The occurrence of vasospasm of major intracranial vessels should be monitored by means of serial neurological checks and of transcranial Doppler ultrasounds. A decrease in alertness, the new onset or worsening of neurological symptoms, a fever higher than 38°C, or an increase in transcranial Doppler mean velocities of the intracranial vasculature should prompt more advanced imaging with MRA, CTA, or DSA. Current guidelines recommend administering 60 mg of oral nimodipine every 4 hours for 21 days after SAH and the maintenance of euvolemia in order to avoid delayed cerebral ischemia. Symptomatic vasospasm prompts induction of controlled hypertension and of further endovascular therapy in selected cases, carried out by balloon angioplasty and/or intra-arterial infusion of vasodilating agents such as nicardipine, verapamil, or milrinone [78].

Interventional therapy should be considered in patients who (1) do not improve despite maximum medical management, or (2) experience adverse effects or cannot tolerate prolonged medical management. Large infarct size precludes aggressive therapy due to risk of reperfusion hemorrhage. Balloon angioplasty of vasospastic vessels demonstrates more durable effects and is the preferred method for proximal vasospasm but should be performed by experienced operators, since it harbors potentially devastating complications such as vessel dissection or rupture. Intra-arterial infusion of vasodilators is technically simple and can help dilate small distal vessels that would be inaccessible to a balloon, but its effects are less well-established.

Serial groin checks are particularly important in patient who received intracranial stenting since, as explained before, a groin complication may necessitate reversal of anticoagulation, leading to a significant increase in risk for thromboembolic complications.

Intracerebral Hemorrhage

ICH is the nonspecific manifestation of a multitude of diseases and is diagnosed by non-contrast CT of the head. Approximately 80% of all spontaneous ICHs are due to rupture of perforating vessels damaged by chronic hypertension; for a well-circumscribed hematoma of the basal ganglia or thalamus in a hypertensive patient above 65 years of age, it is reasonable not to proceed with further imaging [84]. When the etiology is not clear, workup should include CTA and/or MRI and MRA. If these exams are suspicious for an underlying vascular abnormality such as an AVM or AVF or if no cause is identified, a DSA can be indicated. Features that are suspicious for an underlying vascular malformation include (1) normotensive patients younger than 45 years, (2) patients with SAH associated with ICH, (3) patients with recurrent hemorrhages, and (4) unusual locations such as near the cortex or in the ventricle. A negative DSA in the setting of high clinical suspicion does not completely rule out a vascular malformation, since the hemorrhage could be compressing a small AVM or fistula. In such cases, it is reasonable to repeat the exam at 4–6 weeks once the hemorrhage volume has decreased.

AVMs with intra-nidal aneurysms have a 9.8% annual hemorrhage risk, compared to 2–4% for those that do not have this feature [85]. When identified in patients with ICH, targeted embolization of the aneurysm should be performed emergently in order to lower the risk of early rebleeding. In cases of AVFs of high grade with prominent cortical venous drainage, endovascular treatment is usually pursued as soon as possible, given the high risk of early rebleeding, which is estimated at up to 35% [86].

Cavernous venous malformations are angiographically occult and best visualized on MRI. Endovascular techniques do not play a role in treatment; symptomatic cavernous malformations are surgically resected.

Postoperative Care

Post-procedural care for patients with ICH status post endovascular interventions involves the typical precautions described in earlier sections of this chapter, with a focus on access site complications and monitoring for neurological symptoms that may indicate new ischemia/hemorrhage.

Stroke from Large Vessel Occlusion

Endovascular management has recently become the mainstay for acute ischemia secondary to anterior circulation large vessel occlusions. The blockage is usually the result of embolic phenomena arising from a carotid plaque or an intra-atrial thrombus in patients with atrial fibrillation or, more rarely, due to a paradoxical embolus from the deep venous system which passed through a patent foramen ovale. The basic concept behind endovascular stroke therapy is to mechanically remove the embolus in order to re-establish flow in the occluded territory as fast as possible. This is accomplished using stentrievers, large-bore aspiration catheters, or a combination of these modalities (Fig. 24.8). The aim of restoring blood flow is to save those parenchymal areas that were in the territory of the occluded vessel but still kept viable by collateral circulation, the so-called penumbra. Several recent multicenter randomized clinical trials have demonstrated superiority of endovascular approaches over medical management with IV tissue plasminogen activator (tPA) in anterior circulation occlusions. While this benefit of endovascular treatment was initially shown for just the first 6 hours or so after the ischemic event, newer trials are now proposing to expand this therapeutic window based on perfusion imaging findings to up to 24 hours after stroke onset. Current AHA/ASA guidelines recommend mechanical thrombectomy in patients with acute anterior circulation large vessel occlusions within 6 hours of symptom onset and, in selected patients, in the 6–24-hour window [4].

Stroke imaging workflow should include at a minimum a non-contrast CT head primarily to exclude hemorrhage and to evaluate the extent of cytotoxic edema, if present, and a CTA of the head and neck to identify intracranial vessel occlusion and cervical vascular anatomy relevant to catheter access. Guidelines on MRI or perfusion imaging vary greatly between institutions but, regardless of the employed modality, have the common purpose of differentiating areas of infarction from possibly salvageable areas of penumbra.

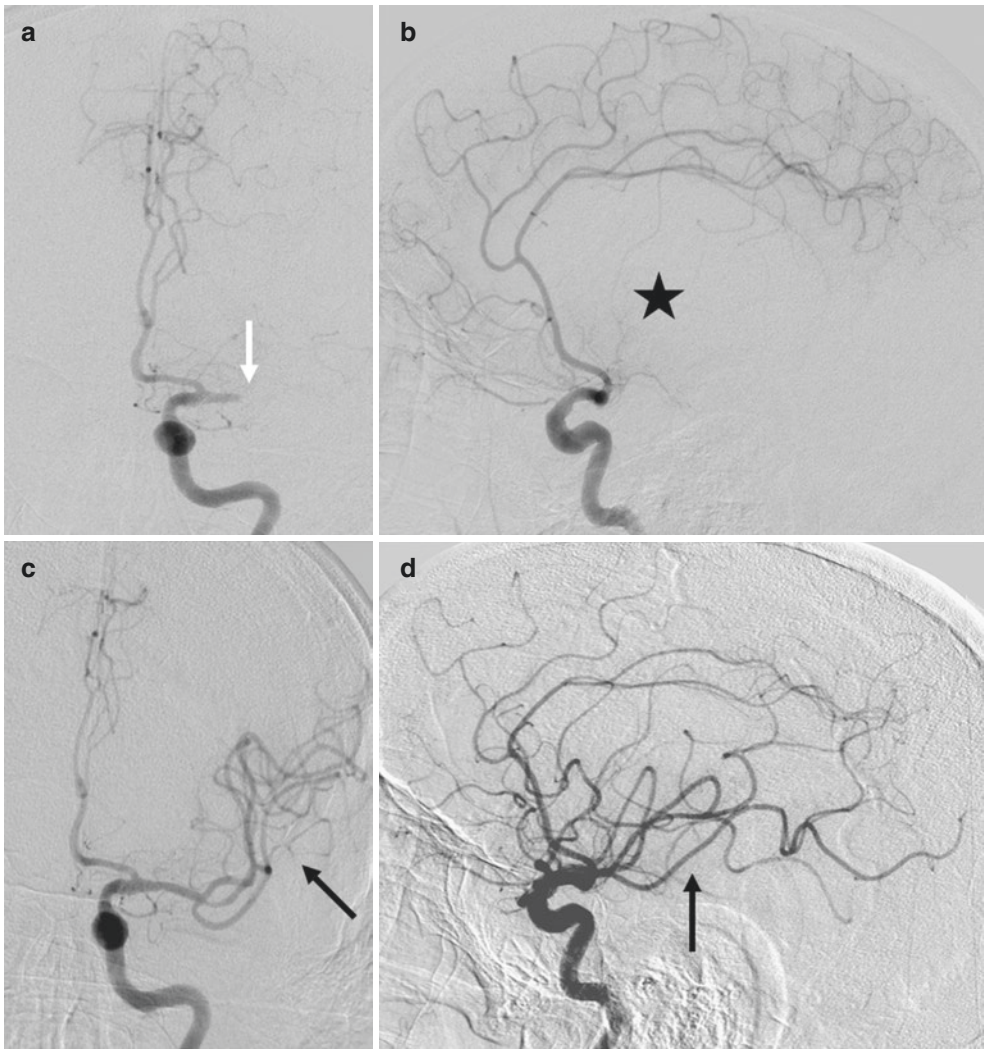

Fig. 24.8 Anteroposterior (**a**) and lateral (**b**) views of a left internal carotid artery injection in a patient with acute right hemiplegia. There is occlusion of the left middle cerebral artery (white arrow), with no visualization of its branches in the lateral view (star). After aspiration of the clot with a large-bore catheter, there has been restoration of flow in the left middle cerebral artery and its branches (black arrows in **c**, **d**)

Basilar artery occlusions usually undergo interventional revascularization regardless of the time of onset since the condition has an extremely high mortality if left untreated.

Postoperative Care

Following mechanical thrombectomy, patients are kept in the critical care unit for at least 18–24 hours for neurological monitoring and blood pressure control. Patients post-mechanical thrombectomy and often concurrent IV tPA are at significant risk for hemorrhagic transformation of the infarct and should receive frequent neurological checks. Avoiding hypertension lowers the risk of reperfusion injury after successful clot removal but, on the other hand, relatively elevated blood pressures are beneficial in maintaining collateral flow and perfusion pressure to the still viable penumbra, especially following failed or incomplete recanalization [87]. There are currently no guidelines for blood pressure management following mechanical thrombectomy; common practice is for conservative but permissive hypertension, with a lower blood pressure goal after successful revascularization. It has been demonstrated that elevated blood pressures and extreme blood pressure variations in the immediate post-procedure period lead to worse outcomes [88–92]. At least one head CT is usually obtained 24 hours after recanalization to assess for hemorrhagic transformation and edema. Hyperdense material is commonly seen in the intraparenchymal or subarachnoid space immediately following intra-arterial interventions, likely representing contrast extravasation and/or a small amount of blood. This does not represent hemorrhagic transformation, and its relevance should be correlated with the clinical status of the patient since it has not been shown to be correlated with negative outcomes [93, 94].

Frequent groin checks are recommended since a large 8 French sheath is commonly used and patients who received IV tPA are at increased risk of hemorrhagic complications.

Other Causes of Stroke

Intracranial Stenosis

Intracranial atherosclerotic stenosis causes only 8–10% of strokes in the United States, but is one of the most common causes of stroke worldwide and is much more prevalent in Asian, African, and Hispanic populations [95]. Recurrent strokes are common in patients with severe symptomatic intracranial stenosis despite medical management. Currently, there is no definitive guideline regarding intracranial stenting with or without angioplasty, and indications for this intervention vary greatly according to institutional policies and preferences and operator experience [96, 97]. The condition can be diagnosed with CT and MR angiography but requires definite assessment with a cerebral DSA. Intracranial stenting is rarely performed in the acute setting since it is ideal to prepare patients with dual antiplatelet therapy. Postoperative care is the same as described above for other types of intracranial stentings.

Cerebral Venous Thrombosis

Cerebral venous thrombosis is responsible for 0.5–1% of strokes in the United States. More common in women and in individuals with prothrombotic conditions, it usually has a nonspecific clinical presentation that includes headaches and other symptoms of increased intracranial pressure, focal neurological symptoms, seizures, or encephalopathy. Once the condition is suspected, workup should be based on CT or MR venography (ideally with contrast), which are more sensitive and specific than DSA [98]. The standard of care is systemic anticoagulation, even in the setting of intracranial hemorrhage. Endovascular interventions can be employed for patients who fail conventional anticoagulation therapy but should be considered a last-resort therapy and never be pursued as a first option. Techniques used include direct IV thrombolysis or mechanical thrombectomy with clot stent retrieval or aspiration [99, 100]. It is important to understand that currently available catheters only allow recanalization of major dural sinuses and not of cortical veins, hence the superiority of systemic anticoagulation as a first-line therapy. Post-procedural care does not differ from that of a conventional angiogram.

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Neurocritical Care Ultrasound

25

Faheem G. Sheriff, Sakina Sheriff, Shyam S. Rao, and David Y. Chung

Introduction

The first documented diagnostic medical use of sonography was in 1942, incidentally, by a neurologist named Karl Dussik, who transmitted an ultrasound beam through the human skull in an attempt to diagnose brain tumors [1]. Since then ultrasound has improved considerably, and its applications have expanded to involve every major medical subspecialty. Ultrasound including transcranial Doppler (TCD) is inexpensive, noninvasive, and does not require the use of ionizing radiation. It has good temporal and spatial resolution and is therefore ideal for continuous bedside monitoring in complicated neurophysiologic and critical care disease states [2, 3]. This chapter will focus on the application of ultrasound in specific neurocritical care conditions including subarachnoid hemorrhage (SAH), ischemic stroke, intracranial hemorrhage (ICH), traumatic brain injury (TBI), brain death as well as its use in bedside procedures. Images from clinical cases collected at our institution will be used to highlight important concepts. Finally, we will discuss important future potential applications of ultrasound in neurocritical care.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH), with its multisystem involvement, best exemplifies the spectrum of uses of ultrasound in the neurocritical care unit.

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Cerebral Vasospasm/Delayed Cerebral Ischemia (DCI)

The diagnosis of large vessel vasospasm is the best known application of TCD [4]. TCD is an indirect measure of cerebral blood flow (CBF), given assumptions about vessel diameter and CBF [3]. The velocity of blood flow is inversely proportional to the area of the vessel lumen [4]. Therefore, during vasospasm velocities on TCD increase as the vessel lumen area decreases.

TCD is a valuable tool for the detection of vasospasm prior to onset of neurologic deficits and in patients without a reliable neurologic exam. In patients with an intact neurological exam, there is evidence that it can predict neurological deficits an average of 2.5 days prior to onset of symptoms [5]. Furthermore, TCD can be used to guide treatment of vasospasm in combination with the clinical exam and ancillary imaging such as cerebral angiography (Fig. 25.1) [6].

Daily TCDs are recommended in all cases of SAH, where it is available, and is most valuable between 3 and 10 days after ictus; serial measurements are typically discontinued after this time point except in the case of active vasospasm in which case measurements are continued until resolution of vasospasm [7]. In normal subjects, mean flow velocity (MFV) is approximately 80 cm/s for the middle cerebral artery (MCA), 70 cm/s for the anterior cerebral artery (ACA), 60 cm/s for the posterior cerebral artery (PCA), 40 cm/s for the terminal internal carotid artery (ICA) and basilar artery (BA)/vertebral artery (VA), and 20 cm/s for the ophthalmic artery (OA) [4, 8]. It should be noted that TCD criteria are most useful for the detection of vasospasm in the MCA and BA and are less sensitive and specific for ACA and PCA vasospasm (Table 25.1) [9].

In addition to velocity measurements, it is also important to follow the Lindegaard ratio (LR), which is useful in distinguishing hyperdynamic flow from intracranial vasospasm. The LR is defined as the ratio of MCA mean flow velocity (MFV) to extracranial ICA MFV. An LR less than 3 indicates hyperdynamic flow (or hyperemic flow in the setting of

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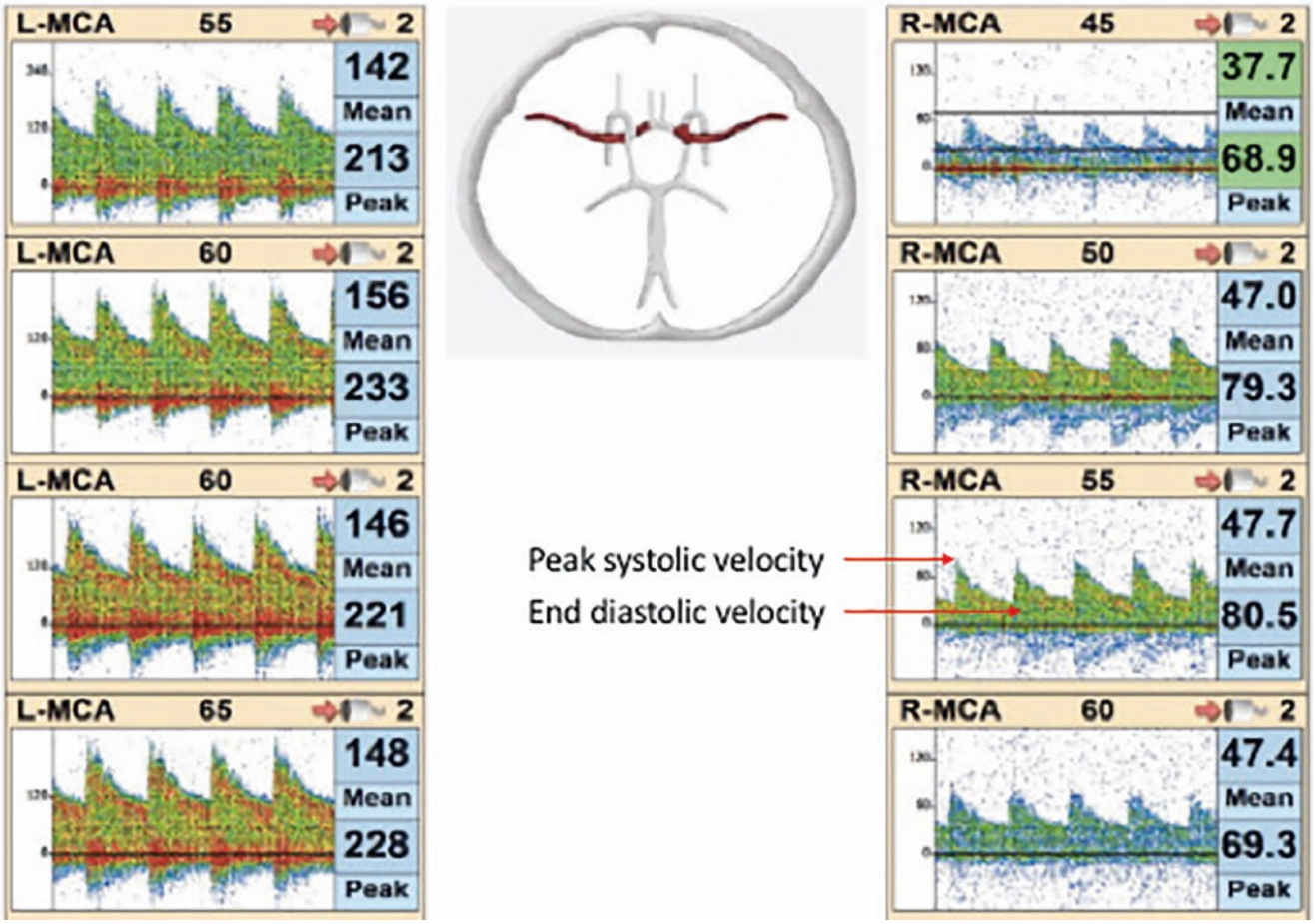

Fig. 25.1 See *Clinical case 1*

Table 25.1 Grading of severity of the vasospasm in the MCA and BA in SAH

Degree of vasospasm in MCA	*MFV*	*A N D*	*LR*
Mild (<25%)	120–149 cm/s		3–6
Moderate (25–50%)	150–199 cm/s		3–6
Severe (>50%)	>200 cm/s		>6
Degree of vasospasm in BA	*MFV*		*LR*
Mild (may represent vasospasm)	70–85 cm/s		2.00–2.49
Moderate (25–50%)	>85 cm/s		2.50–2.99
Severe (>50%)	>85 cm/s		≥3

Modified with permission from John Wiley and Sons [7]
MFV mean flow velocity, *LR* Lindegaard ratio, *MCA* middle cerebral artery, *BA* basilar artery

elevated intracranial velocities) and an LR greater than 3 indicates vasospasm [10]. Although less commonly used, the equivalent of the LR for the ACA is called the Sloan ratio (i.e., ACA to extracranial ICA MFV) [11]. Similarly there is the Soustiel or Sviri ratio for the BA, which is the ratio of BA to extracranial VA MFV [12]. A Soustiel ratio greater than 3 with BA velocities higher than 85 cm/s has been associated with a 92% sensitivity and 97% specificity for BA narrowing >50% [13].

It should be emphasized that TCD evidence of vasospasm is not always predictive of the syndrome of delayed cerebral ischemia (DCI). In one retrospective study, the sensitivity of MFV >120 cm/s in any vessel for subsequent DCI was 63%, with a positive predictive value of 22% among patients with low Hunt and Hess grades (I to III) and 36% in patients with higher Hunt and Hess grades (IV and V) [14]. With the advent of dynamic measures of cerebral autoregulation (see below), the capability to detect vasospasm can be signifi-

cantly enhanced albeit these techniques are still considered experimental and require further validation [15]. A recent study showed early impaired autoregulatory capacity within SAH patients as measured by TCD; in addition, those who developed DCI had a distinct autoregulatory profile, and this supports the idea that large artery vasospasm combined with early worsening of autoregulation correlates with subsequent DCI [16].

The spectral waveform is another feature of TCD to consider and can help distinguish normal vascular resistance from high resistance patterns that are seen in vasospasm even before an increase in velocity. Gosling's pulsatility index (PI) and the Pourcelot's resistive index (RI) are quantitative measures of vascular resistance patterns that take advantage of the spectral waveform (Eqs. 25.1 and 25.2); also see Fig. 25.1 for features of the spectral waveform.

$$\text{Gosling's PI} = \frac{\text{PSV}(\text{peak systolic velocity}) - \text{EDV}(\text{end diastolic velocity})}{\text{MFV}(\text{mean flow velocity})} \tag{25.1}$$

$$\text{Pourcelot's RI} = \frac{\text{PSV}(\text{peak systolic velocity}) - \text{EDV}(\text{end diastolic velocity})}{\text{PSV}(\text{peak systolic velocity})} \tag{25.2}$$

PI is normally between 0.5 and 1.19 while an RI greater than 0.8 is abnormal. An elevation of either index is reflective of vasospasm [17]. One important limitation of these approaches, however, is that other processes such as increased intracranial pressure (ICP) can also increase the PI and RI; therefore, these indices should be interpreted with caution.

The potential for inter-operator variability is cited as a major limitation of TCD but can be addressed by rigorous training and by limiting the number of operators performing studies during a given time period (i.e., having the same operator perform serial studies). Absence of bone windows is another limitation, particularly in older patients, women, and certain ethnic groups (e.g., descendants of Asian or African-American heritage). These technical limitations can be overcome in some by simultaneous use of echo contrast or use of transorbital windows (i.e., insonating the ICA terminus and proximal MCA and ACA via the orbit anteriorly with gel applied to the closed eyelid).

Volume Assessment

While "triple H" therapy has largely fallen out of favor in the management of vasospasm post-SAH (with the exception of induced hypertension), most practitioners agree on the importance of maintaining a euvolemic state. Both hyper- and hypovolemia are detrimental to neurologic outcomes after SAH [18]. Bedside ultrasound is used to determine volume status by assessing inferior vena cava (IVC) diameter variability with respiration and left ventricular contractility on transthoracic echocardiography (TTE). Ultrasound is also used to assess lung parenchyma for pulmonary edema. IVC parameters are a well-validated measure of volume status in the critical care setting; this holds true for SAH as well: the distensibility (i.e., difference in diameter between inspiration and expiration of the IVC; DV_{IVC}) has been demonstrated to be a reliable predictor of cardiac response to volume loading and in one study showed a better predictive value than central venous pressure (CVP) [19]. In controlled mode ventilation, the absence of DV_{IVC} or variability suggests that the patient will not be fluid responsive [20]. One study suggested that $DV_{IVC} > 12\%$ can identify patients who will respond to fluid [21].

IVC distensibility (DV_{IVC}) is calculated as follows:

$$DV_{IVC} = \frac{100 \times (D_{max} - D_{min})}{D_{mean}} \tag{25.3}$$

Where

D_{max} = Maximum diameter
D_{min} = Minimum diameter
D_{mean} = Mean diameter over respiratory cycle

In terms of the absolute IVC diameter, a value >2 cm implies a right atrial pressure >10 mm Hg and suggests a lower likelihood of volume responsiveness in the absence of right heart disease. Conversely, a right atrial pressure of <10 mm Hg can be assumed if IVC diameter is <1.2 cm in diameter and suggests a higher likelihood of volume responsiveness. However, the absolute IVC diameter in isolation should be interpreted with caution, especially in spontaneously breathing patients [22]. Of note, IVC parameters are measured just distal to the entry of the hepatic vein in 2D B-mode (Fig. 25.2a) [23].

A complementary technique for assessing volume status is the use of bedside TTE to assess the size of the left ventricle. A very small left ventricular size resulting in papillary

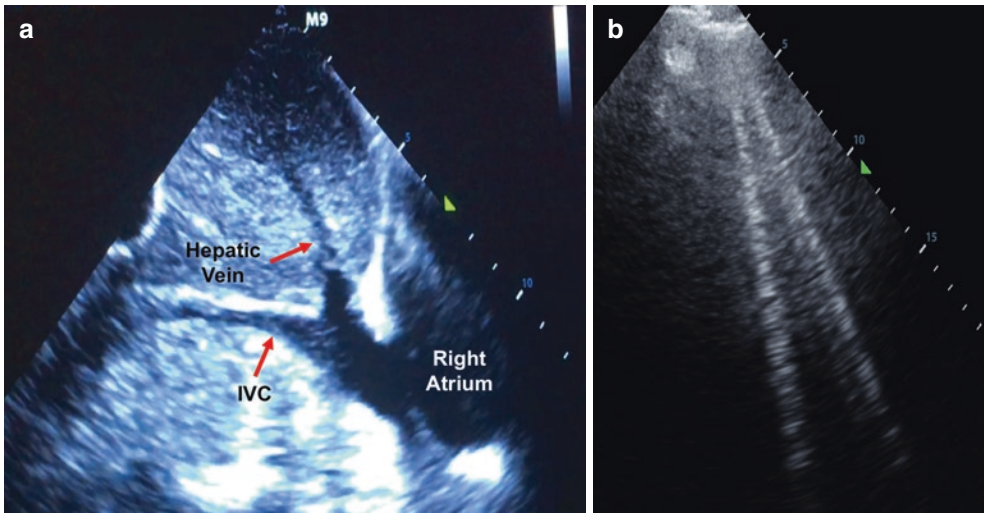

Fig. 25.2 See *Clinical case 2*

apposition (or "kissing ventricles") has been strongly associated with hypovolemia and fluid responsiveness [24], especially in conjunction with a small, collapsible IVC. Dynamic indices of fluid responsiveness are particularly helpful in the absence of overt hypovolemia. Dynamic measures involve calculating the velocity time integral (VTI) or stroke volume (SV) on TTE before and immediately following a small fluid bolus (usually 250 mL) or passive leg raise [23]. However, these parameters need to be frequently reassessed and may need a higher level of proficiency in ultrasound technique to be clinically useful in fluid titration.

Detection of fluid overload and pulmonary edema—either iatrogenic or due to excessive sympathetic activity (neurogenic pulmonary edema)—is also key in the management of SAH patients. Bedside ultrasound of the lung parenchyma can detect specific ultrasound artifacts called B-lines [25] (Fig. 25.2b), which appear as well-defined linear hyperechoic artifacts arising from the pleural line and which move with lung sliding. A study involving 59 SAH patients who underwent bilateral lung ultrasound for five consecutive days showed that the presence of three or more B-lines on lung ultrasound had a sensitivity of 90% and a specificity of 82% for acute respiratory failure due to pulmonary edema [26]. Interestingly, the emergence of three or more B-lines predated the onset of acute respiratory failure by a median of 1 day.

Neurogenic Stunned Myocardium (or Takotsubo Cardiomyopathy)

The classic cardiac complication following SAH is neurogenic stunned myocardium (also known as Takotsubo cardiomyopathy) and is variably characterized by hypokinesis involving the apex [27], an apex-sparing pattern involving mid-basal walls [28], or global hypokinesis. The condition is usually reversible. One of the cardinal features favoring SAH-induced cardiac dysfunction as opposed to acute myocardial infarction is the presence of severely reduced ejection

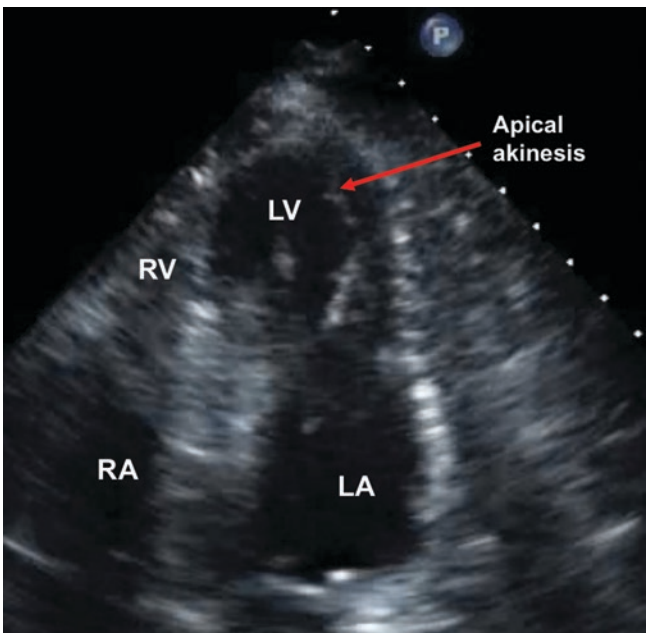

Fig. 25.3 See *Clinical case 3*

fraction (EF) associated with broad regions of hypokinesis and only a relatively modest troponin elevation [29]. The putative mechanism is catecholamine excess. Of note, Takotsubo cardiomyopathy can be seen in other neurocritical care conditions including TBI, seizures, and ischemic stroke (Fig. 25.3).

While a detailed examination requires echocardiographic expertise and formal training, a focused "point of care" bedside TTE even by trainees with brief dedicated training can provide important information that can guide further diagnostic testing and initiation of specific therapies such as inotropes [30]. The use of simplified algorithms such as the "FATE" (Focus Assessed Transthoracic Echocardiography) protocol further standardizes training of non-cardiologist intensivists in the performance of bed-

side TTE and potentially increases ease of implementation and accuracy of results [31].

In addition to assessing reduced EF and wall motion abnormalities, a more sensitive (albeit currently less commonly used) echocardiographic method to identify impaired LV function utilizes an acoustic thumb-print in reflected sound waves from each myocardial segment. The resulting "speckle pattern" enables tracking that segment through 2-D space and is referred to as "speckle strain" [32]. This technique has been well-validated in a spectrum of non-neurological diseases and has recently been described in the setting of SAH. The assessment of speckle strain (as compared to left ventricular EF) was more sensitive for detecting impaired LV function in a cohort of SAH patients: up to 37% of SAH patients with neurogenic stunned myocardium and a normal EF showed impairments using a speckle strain approach [33]. Therefore, speckle strain echocardiography may have a role in the future care of patients with acute brain injury.

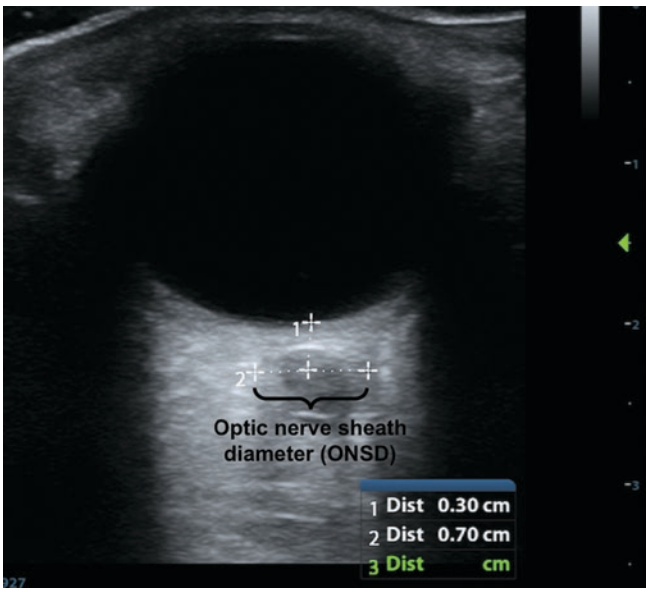

Fig. 25.4 See *Clinical case 4*

Dynamic Cerebral Autoregulation

The ability to assess dynamic cerebral autoregulation, while currently primarily a research tool, has had a major impact on our understanding of the pathophysiology of SAH. For instance, there are distinct autoregulatory profiles for patients who develop vasospasm alone, DCI alone, or a combination of both [16]. Therefore, measures of dynamic cerebral autoregulation have the potential to guide the development of specific therapeutic targets for these unique subgroups. Finally, cerebral dysregulation detected on TCD has been linked to long-term poor outcomes, the likelihood of being admitted to rehabilitation facilities (as opposed to being discharged home), and worse mortality [34].

Traumatic Brain Injury

Like SAH, TBI is a multi-systemic disease process and benefits greatly from a multimodal approach to monitoring with the ultimate goal of ameliorating secondary brain injury. In addition to the use of IVC ultrasound for volume assessment, there are other ultrasound indications such as noninvasive ICP estimation for CPP optimization, diagnosis of posttraumatic vasospasm, and assessment of cerebral compliance that are particularly useful in the management of TBI patients, especially when more invasive options are limited [3]. These indications are outlined below.

Noninvasive ICP and CPP Measurements

The best studied approaches to noninvasive ICP assessment include optic nerve sheath diameter (ONSD), straight sinus flow velocity (FV_{SV}), MCA PI, and MCA diastolic flow velocity (FV_d). Of these, nerve sheath diameter (ONSD) and straight sinus flow velocity FVsv measurements on TCD have the strongest correlations with invasive ICP measures [35, 36]; the combination of ONSD and FV_{SV} has an even stronger correlation with elevated ICP [35]. ONSD is the cross-sectional diameter of the optic nerve sheath measured 3 mm behind the retina with the optic lens imaged in the same plane. The upper limit of normal ranges between 4.5 and 5 mm for pediatric age groups and young adults [37, 38], while older adults have cutoffs as high as 5.7–5.9 mm [35, 36, 39]. ONSD is the best validated measure of noninvasive ICP assessment; however, it is to be used primarily as a screening tool to identify patients requiring further invasive monitoring and emergent therapies for raised ICP (Fig. 25.4). There is less robust data for FV_{SV} alone; a cutoff value of >38.5 cm/s for detection of intracranial hypertension (ICP > 20 mm Hg) has been proposed [35]. Other less-specific TCD findings in patients with intracranial hypertension include decreased MCA diastolic flow velocity and increased MCA PI [40, 41].

Assessing ICP and CPP early and frequently are key to maintaining perfusion to the injured brain; this is not always possible due to logistic issues that delay insertion of invasive ICP monitors as well as medical comorbidities such as coagulopathies that may contraindicate their insertion. This is where noninvasive ICP estimation may be quite helpful in triaging patients and deciding whether to initiate hyperosmolar therapies early.

Posttraumatic Vasospasm

Similar to SAH, CBF post-TBI undergoes three distinct phases: oligemia, hyperemia, and vasospasm [42]. Based on TCD studies, the incidence of posttraumatic vasospasm ranges

from 26.7% to 40% and can occur from day 0 to 13, most commonly peaking at days 2 and 3 [43–45]. It can also occur in the absence of traumatic SAH [46] and tends to be shorter in duration than vasospasm from aneurysmal SAH, usually resolving within 5 days [47]. Notably, patients with blast-related (i.e., in the setting of explosive devices) traumatic vasospasm may have neurologic improvement if subjected to open surgical treatment (decompression) and improved MCA and basilar flow velocities with micro-balloon angioplasty, although this has not yet been verified in randomized clinical trials [48].

Goal-Directed Therapy

Goal-directed therapy using TCD parameters for the purpose of optimizing CPP is promising. One study proposed cutoffs to identify patients at risk for cerebral hypoperfusion: MCA MFV (<30 cm/s), MCA mean diastolic velocity (<20 cm/s), and PI (>1.4) [49]. Although this study was underpowered to demonstrate differences in clinical outcomes, it did demonstrate the feasibility of noninvasive goal-directed therapy. It remains to be replicated in large-scale trials with a comprehensive, standardized protocol for optimizing cerebral perfusion. In addition, TCD indices of cerebral autoregulation have been used to calculate the optimal CPP, which would allow tailoring of hemodynamic management to the individual patient and to disease-specific altered cerebrovascular hemodynamic states [50]. This is yet to see widespread clinical use and will need further validation.

Ischemic Stroke

TCD and carotid ultrasound are complementary examinations in the diagnostic workup of stroke patients. Together with echocardiography they play an essential role in distinguishing between various stroke etiologies. In addition, there are important therapeutic applications such as in the management of sickle cell disease patients and high-grade carotid stenosis that are outlined below. Prognostic applications are still in the preclinical or early clinical stages but will be discussed briefly.

Extracranial Carotid Disease

Carotid and vertebral ultrasound (using B-mode and duplex modes) has an important role in screening for extracranial vascular pathologies ranging from atherosclerosis and dissection to less common processes such as fibromuscular dysplasia. Like TCD, the advantages of carotid ultrasound include low-cost and portability, which allow for serial monitoring of hemodynamic changes. Limitations include operator dependence and anatomy that limits the exam to the region of the ICA that can be assessed using the neck and interosseous vertebral artery segments. Therefore, ultrasound is less valuable for assessment of the posterior circulation [51]. This necessitates other imaging modalities such as TCD, computed tomography angiography (CTA), and magnetic resonance angiography (MRA), which complements this study especially with regard to understanding the hemodynamic effects of intracranial carotid and vertebral disease.

Table 25.2 Ultrasound grading criteria for severity of carotid stenosis by NASCET criteria

The Society of Radiologists in Ultrasound consensus criteria for carotid stenosis				
Stenosis range NASCET method	ICA PSV	ICA/CCA PSV ratio	ICA EDV	Plaque
Normal	<125 cm/s	<2.0	<40 cm/s	None
<50%	<125 cm/s	<2.0	<40 cm/s	<50% diameter reduction
50–69%	125–230 cm/s	2.0–4.0	40–100 cm/s	>50% diameter reduction
70% -near occlusion	>230 cm/s	>4.0	>100 cm/s	>50% diameter reduction
Near occlusion	May be low or undetectable	Variable	Variable	Significant, detectable lumen
Occlusion	Undetectable	Not applicable	Not applicable	Significant, no detectable lumen

Modified with permission from Springer Nature [51]
EDV end-diastolic velocity, *ICA/CCA* internal carotid artery/common carotid artery, *PSV* peak systolic velocity

Regarding carotid stenosis, the current recommendation is to measure percent diameter reduction in the stenosed segment relative to ICA diameter in the disease-free ICA segment distal to the stenosis as per the North American Symptomatic Carotid Endarterectomy Trial (i.e., the NASCET method) (Table 25.2 and Fig. 25.5) [52].

Carotid ultrasound is both sensitive and specific for proximal ICA occlusions due to atherosclerosis. In the diagnosis of cervical artery dissection, however, there is variable sensitivity in the detection of a double lumen and intimal flap [53]. Therefore, if dissection is strongly suspected then CTA or MRA possibly followed by digital subtraction angiography may be necessary. Follow-up post-carotid endarterectomy (CEA) or carotid stenting is another important indication for carotid ultrasound [51].

Another technique that is useful to risk-stratify patients with carotid disease is cerebrovascular reactivity (CVR). CVR quantifies the change in CBF in response to vasodilatory or vasoconstrictive stimuli. The most common vasodilatory stimuli include inhaled CO_2, acetazolamide, and the breath-holding test. CVR has important applications in extracranial (and occasionally intracranial) carotid artery stenosis

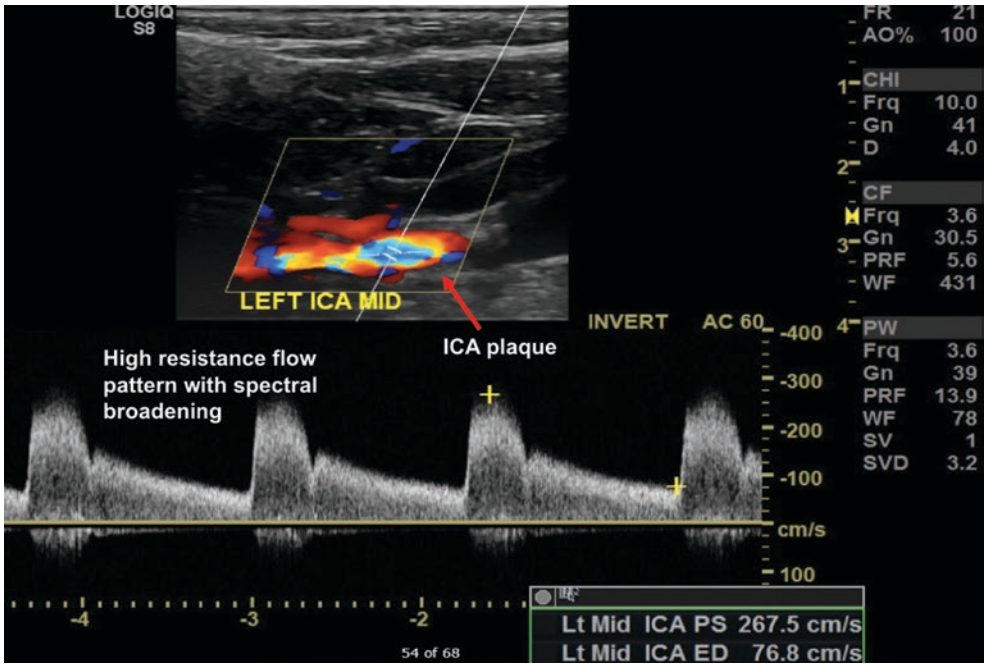

Fig. 25.5 See *Clinical case 5*

or occlusion, both in asymptomatic and newly symptomatic patients, and can help triage those who are most likely to benefit from urgent carotid revascularization [54].

Intracranial Stenosis

Both TCD and MRA can noninvasively identify intracranial large artery stenosis with substantial negative predictive values [55]. Abnormal findings on TCD (or CTA/MRA), however, require digital subtraction angiography to confirm and quantify the degree of stenosis.

TCD yield of intracranial stenosis is greatest soon after stroke symptom onset and has better sensitivity and specificity in the anterior compared with the posterior circulation [56]. Furthermore, the use of power mode and color-coded duplex improves diagnostic accuracy, especially for the posterior circulation [57]. MFV cutoffs are 100 cm/s and 80 cm/s for >50% stenosis (SONIA criteria) in MCA and VA/BA, respectively. Conversely, MFV of >120 cm/s and > 110 cm/s were validated in the SAMMPRIS trial for >70% stenosis of MCA and VA/BA, respectively. An increase in focal velocity as determined by the stenotic-to-prestenotic ratio (i.e., ratio of velocity through the region of maximum stenosis compared to velocity through the normal region just proximal) is another marker of intracranial stenosis. A ratio of ≥3 indicates 70% stenosis of MCA and VA/BA [55, 58]. Important patterns to recognize are: (a) a distal resistance pattern characterized by an upstream (or prestenotic) decrease in velocity and an increased PI; (b) an intrastenotic pattern manifested by a focal increase in velocity; and (c) a poststenotic pattern marked by turbulent flow, a "tardus parvus" appearance (blunted and delayed waveform), and a decrease in PI. There are also tertiary changes notable in the collateral circulation including elevated velocities, decreased PI, turbulence at branch points, and alternating or reversed flow in other territories [8, 59, 60] (Fig. 25.6).

Finally, TCD has a role in the stroke patient following administration of intravenous (IV) tPA. The Thrombolysis in Brain Ischemia (TIBI) flow grading system was developed to evaluate residual flow and monitor lysis of thrombus using TCD. It has been shown to be predictive of clinical severity, early recovery, and mortality in patients treated with IV tPA [61] (Fig. 25.7).

Embolic Stroke

Embolic etiologies of stroke can be of venous origin (paradoxical embolism associated with a right-to-left shunt) or arterial origin due to cardiac, aortic arch, or carotid/vertebral disease. TCD can be used to detect microembolic signals (MES). These are high intensity transient signals (HITS) that interrupt the normal sonographic background and have characteristic acoustic patterns that correspond with microemboli passing through large cerebral blood vessels (usually the MCA) and hence enable stratification and monitoring of ongoing embolic risk.

Right-to-Left Shunt

TCD with MES detection provides comparable sensitivity to trans-esophageal echocardiography (TEE) and TTE for the diagnosis of a right-to-left shunt [62]. In fact, TCD may be more sensitive for smaller shunts and extracardiac shunts compared with TEE [63, 64]. At a minimum, TCD is suitable as a useful screening tool prior to more invasive

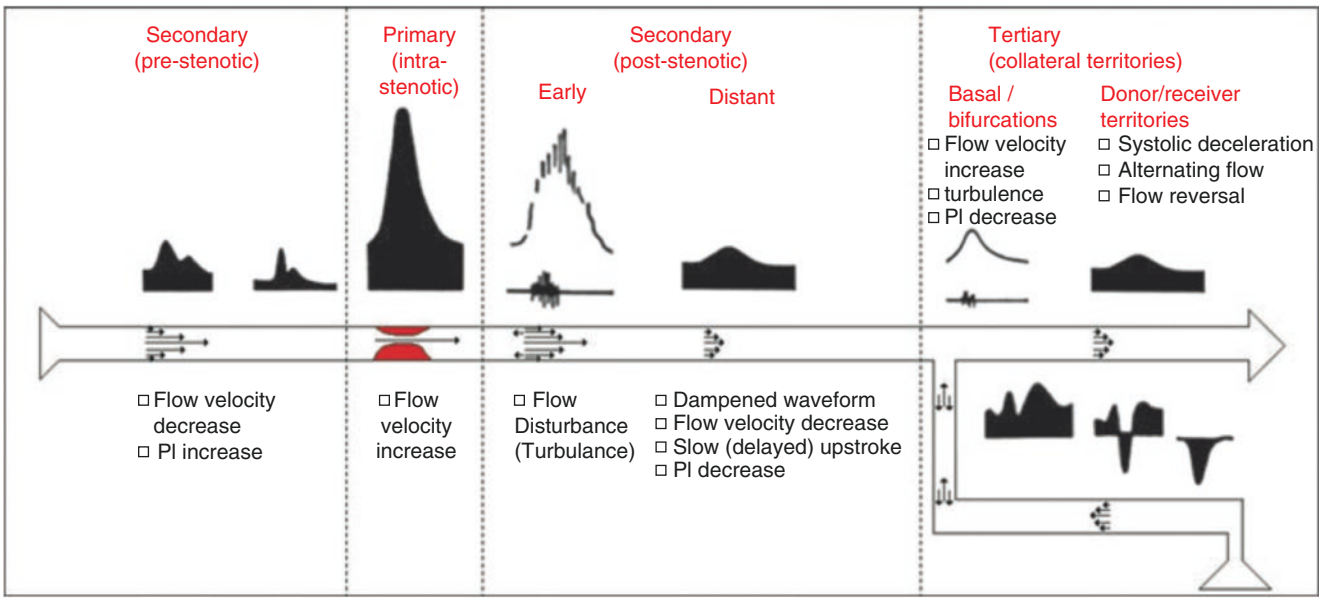

Fig. 25.6 Altered cerebrovascular hemodynamic flow state pre-, intra-, and post-intracranial stenosis as well as tertiary changes seen in collateral territories. (Reproduced with permission from John Wiley and Sons)

Category	Appearance	Description
TIBI 0 COGIF 1		**ABSENT FLOW** No flow signal
TIBI 1 COGIF 2		**MINIMAL FLOW** Systolic spikes with variable velocity and duration: zero EDV: reverberating flow
TIBI 2 COGIF 3		**BLUNTED FLOW** Systolic upstroke delayed (duration >0.20 sec); EDV>0; PI<1,2
TIBI 3 COGIF 3		DAMPENED FLOW Vmean decrease greater than 30% of contralateral value; upstroke normal; EDV>0
TIBI 4 COGIF 4c		**HYPEREMIC FLOW** Segmentally increased flow velocities (Vmean >80 cm/s and/or >30% compared to the control side, no turbulence; low PI; no harmonics; low degree spectral broadening.
TIB14 COGIF 4b		**PSEUDOSTENOTIC FLOW** Focally increased flow velocities (Vmean >30 compared to the control side; EDV>0; Significant turbulence or flow disturbance.
TIBI 5 COGIF 4a		**NORMAL FLOW** Flow velocities normal or in the range of ±%30 of the control side. **[* Bar: 50 cm/sec]**

Fig. 25.7 The TIBI (Thrombolysis in Brain Ischemia) scoring system (with comparative COGIF grading, i.e., Consensus on Grading Intracranial Flow Obstruction). V_{mean} = MFV. (Reproduced with permission from John Wiley and Sons)

workup. The sensitivity of TCD can be improved by using a higher volume of agitated saline, use of a contrast medium (such as Echovist) instead of agitated saline, and performance of the Valsalva maneuver. Testing can be repeated if initially negative [65].

Recurrent Embolic Risk Stratification

Detection of MES or HITS is useful for risk stratification in carotid stenosis, especially in patients with asymptomatic disease who may benefit from CEA [66]. MES detection is similarly helpful in patients with MCA stenosis at risk for

recurrent stroke who may benefit from optimization of antithrombotic therapy [67]. Anticoagulation tends to decrease the frequency of HITS [68]. In a study of patients with nonvalvular atrial fibrillation on warfarin, the frequency of HITS was inversely proportional to the international normalized ratio (INR) [69]. In addition, the multicenter CARESS trial showed that TCD with HITS detection was a feasible method to evaluate the efficacy of antiplatelet therapy. The trial randomized patients with recently symptomatic carotid stenosis to aspirin plus clopidogrel versus aspirin alone. The frequency of HITS was reduced by 39.8% in the dual antiplatelet group, which was also associated with fewer strokes and TIAs compared with the monotherapy group [70].

Vasculopathy

Vasculopathies can be inflammatory such as vasculitis or non-inflammatory such as reversible cerebral vasoconstriction syndrome (RCVS). In the case of RCVS, multiple intracranial cerebral arteries develop focal areas of stenosis or dilatation with symptoms resolving within days to weeks. While CTA or MRA followed by conventional angiography is the mainstay for confirming the diagnosis, TCD can be a useful adjunct in monitoring these vascular territories and predicting the risk of stroke and other complications. For instance, in one cohort of patients with RCVS, patients with mean MCA MFV >120 cm/s and LR >3 were at a significantly higher risk of a related vasculopathy—posterior reversible encephalopathy syndrome (PRES)—and ischemic stroke [71]. In the case of primary CNS vasculitis, the utility of TCD velocities in following therapeutic response and risk of complications might prove to be a helpful measure, although evidence supporting its use remains anecdotal [72, 73]. TCD can also be used to trend the course of cerebral vasoconstriction in other medical conditions that present with transient vasculopathy such as thrombotic thrombocytopenic purpura (TTP) [74].

Since proximal large caliber cerebral blood vessels are better insonated via TCD compared with the more distal vessels, vasculitides that preferentially affect proximal vessels are ideal for monitoring. This includes granulomatous meningitides including tuberculous (TB) and fungal meningitis but also acute bacterial meningitis. In one study, patients with acute bacterial and viral meningitis demonstrated initial hyperemia followed by a decrease in MFV and an increase in PI; this worsening hemodynamic pattern likely reflected ICP elevation and was associated with poor outcomes [75]. Similarly, in a cohort of adult patients with TB meningitis, one-third had elevated MCA MFVs and elevated LRs. Eighty percent of these patients with high velocities had narrowing on CTA/MRA. The abnormalities were noticed early and persisted up to 4 months [76].

Sickle Cell Disease (SCD)

Sickle cell disease (SCD) is a genetic hemoglobinopathy associated with abnormal red blood cells (RBCs) that assume a "sickle-shaped" contour under physiologic stress. It is associated with progressive narrowing of proximal cerebral arteries and an inflammatory cascade that leads to intimal hyperplasia and an increased risk of stroke. Standard of care involves regular blood transfusions, which suppress de novo erythropoiesis of native RBCs carrying sickle-prone hemoglobin S (HbS). High-quality evidence in the form of randomized controlled trials (such as the STOP trials) has demonstrated that regular blood transfusions in patients with SCD lead to a significant reduction in ischemic stroke risk [77]. Notably, these trials highlighted TCD as an important screening tool for patients with SCD at high risk for stroke. In the first STOP trial, TCD velocities were the sole predictor of clinical stroke in a multivariable analysis [78]. The second STOP trial showed that when blood transfusions were discontinued, there was a higher rate of strokes and a reversion to abnormal TCD blood flow velocities [79].

Venous Sinus Thrombosis (VST)

VST is a challenging diagnostic entity due to its wide variety of clinical manifestations. The dynamic assessment of venous collaterals using TCD provides useful information regarding patency of the venous system [80]. Its utility can be further improved with the use of sonographic contrast and transcranial color-coded duplex. While digital subtraction angiography remains the goal standard for diagnosis of VST, due to its invasiveness its utility in serial monitoring and assessing hemodynamic changes is limited. Computed tomography venography (CTV) and magnetic resonance venography (MRV) are frequently employed alternatives; however, there remains a unique role for TCD in understanding evolving hemodynamics and response to therapy. The veins that can be insonated are:

- The basal vein of Rosenthal (BVR): insonated through the posterior temporal window at a depth of 60 mm together with the P2 branch of PCA. It usually flows away from the probe [81] (Fig. 25.8).
- The deep middle cerebral vein (DMCV): through the anterior temporal window adjacent to the MCA with flow away from the probe [81].
- Veins in the anterior parasellar region: through the anterior temporal window at a depth of 50–60 mm adjacent to main inflow vessels to the cavernous sinus with flow away from probe [82].
- Inferior petrosal sinus (IPS): using a suboccipital approach at a depth of 80–90 mm adjacent to the BA with flow directed toward the probe [83].

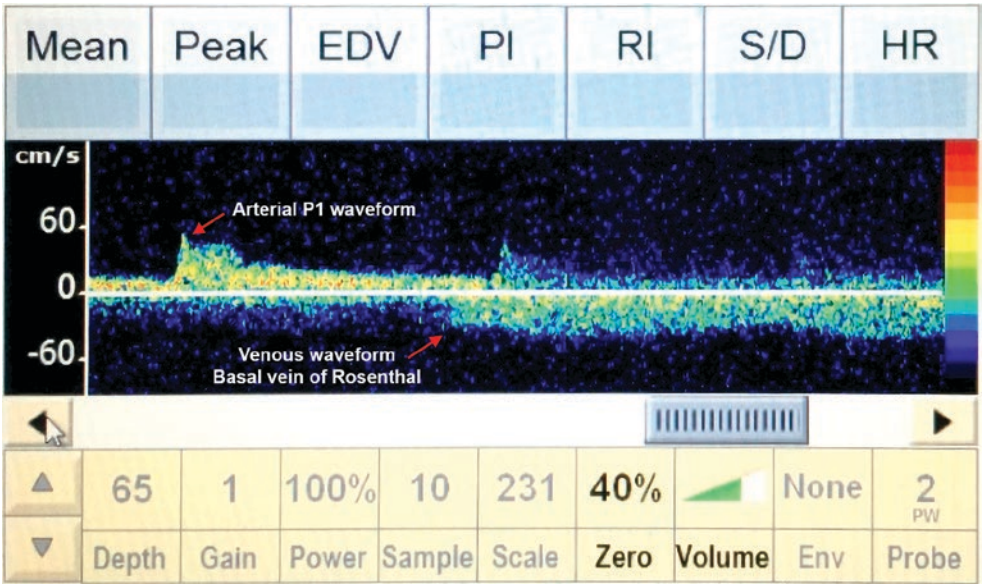

Fig. 25.8 See *Clinical case 6*

In a cohort of 18 patients with VST, elevated venous velocities were noted on TCD; these velocities decreased with time before reaching a plateau except for two patients in whom a transient increase was noted during heparin cessation. Of note, high venous velocities were significantly associated with alteration of consciousness [84]. While no major inferences can be made due to the small sample size, there may be a role for trending venous velocities in order to understand hemodynamics of disease progression and risk for complications.

A related application of TCD involves noninvasive assessment of ICP, although this is not specific to VST. The TBI section above includes a discussion of the role of TCD in the setting of elevated ICP.

Dynamic Cerebral Autoregulation

Among the various research applications of TCD in ischemic stroke, one of the most promising is the assessment of dynamic cerebral autoregulation with widespread potential applications including guiding blood pressure management goals and duration of permissive hypertension as well as predicting risk of cerebral edema, risk of hemorrhagic transformation, final infarct size, and long-term functional outcomes [85, 86].

Intracranial Hemorrhage

Bedside ultrasound is quite sensitive for the diagnosis of neonatal germinal matrix hemorrhage (especially if >5 mm in diameter) [87, 88]. In adults, the most important application of ultrasound in the management of intracranial hemorrhage (ICH) is the noninvasive assessment of ICP (see the above section on TBI). Other less known, but promising, applications of bedside ultrasound include midline shift assessment and prognostication (by assessment of cerebrovascular reactivity).

Midline Shift (MLS) Assessment

ICH can clinically manifest as a space-occupying lesion on bedside ultrasound. A promising application of ultrasound in the setting of ICH is in trending the degree of MLS if there is significant mass effect and impending risk of herniation. This may be especially helpful in patients with unreliable neurologic exams who cannot be regularly imaged with CT or MRI due to hemodynamic instability or resource limitations. Horizontal displacement of midline structures on non-contrast CT head (particularly the pineal gland) correlates well with depression of consciousness in patients with acute hemispheric masses [89]. In a prospective study of 51 patients with spontaneous supratentorial hemorrhage who underwent non-contrast CT head and transcranial color-coded sonography (TCCS) both performed within a 12-hour window of each other, there was a strong correlation between MLS by CT and TCCS. Similarly, hematoma volume and MLS by TCCS had a good linear correlation [90].

MLS was calculated by the following method:

$$\text{MLS} = \frac{(A - B)}{2} \tag{25.4}$$

where

A = distance from probe to middle of third ventricle on ipsilateral side

B = distance from probe to middle of third ventricle on contralateral side

The third ventricle is identified by its hyperechoic "double reflex" surrounded by hypoechoic thalami on either side. The hyperechoic pineal gland can sometimes be seen dorsal to the thalamus (Fig. 25.9) [91].

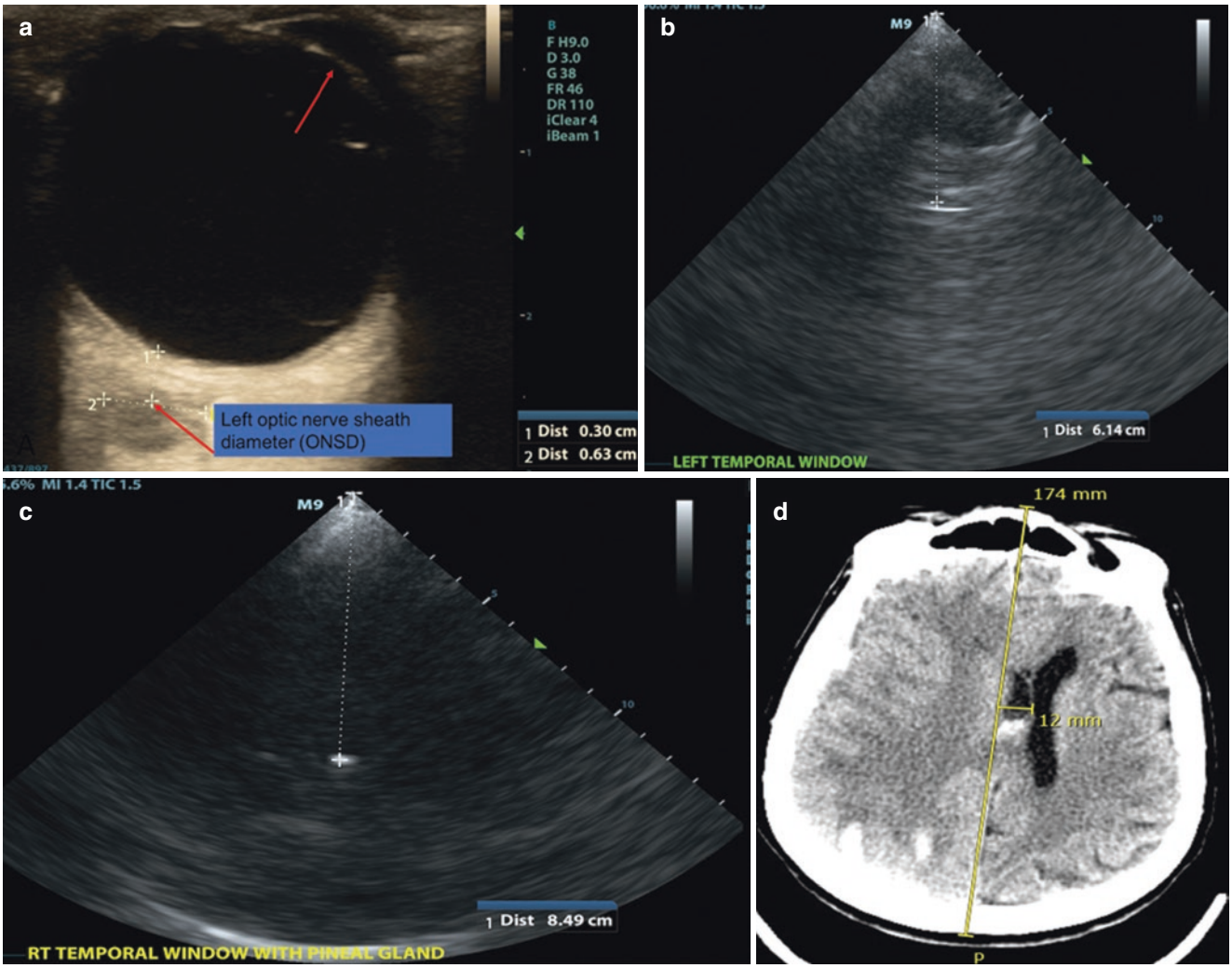

Fig. 25.9 See *Clinical case 7*

Prognostication

As in SAH and ischemic stroke, measures of cerebral autoregulation and CVR can be used for a better understanding of the altered cerebrovascular hemodynamics and reserve in patients with ICH. This may be useful for prognostication as was demonstrated in a cohort of 40 ICH patients. Those with good recovery had largely preserved reactivity not significantly different from healthy controls while patients who died had the worst CVR [92].

Brain Death

Cerebral circulatory arrest (CCA) is the sine qua non of brain death, even though the latter remains a clinical diagnosis and ancillary testing to confirm CCA is not required. In cases where the clinical exam is not reliable, however, ancillary testing may become necessary. While angiography is the gold standard for confirming CCA, it is not available everywhere. In addition, in some cases CCA and brain death can be transiently dissociated [93]. It is notable that all ancillary tests for confirmation of brain death have important limitations. Despite the known limitations of TCD such as operator dependence, the ability to conduct real-time hemodynamic monitoring with frequent serial exams is a distinct advantage and may even guide the timing of other ancillary testing when the diagnosis is challenging. The characteristic pattern of CCA seen on TCD has been described as a sharply contoured, brief anterograde systolic envelope with reversed diastolic flow also known as *reverberating* or *oscillating* or *pendular* flow. The temporal evolution of these changes is summarized as follows: as ICP increases, a high resistance profile develops first, characterized by decreasing diastolic flow and rising PI, followed by flow reversal during diastole [94]. With further decrease in cerebral perfusion pressure, the characteristic oscillating flow and small systolic spikes appear followed by absolute cessation of flow [94, 95]. Systolic spikes shorter than 200

milliseconds in duration and a PSV less than 50 cm/s with no diastolic flow is consistent with lack of cerebral circulation. These flow patterns should be present in both MCAs and the BA, and TCD should preferably be repeated at least 30 minutes apart to confirm these findings and to exclude the effect of transient increase in ICP [7]. Among 130 patients with a clinical diagnosis of brain death, TCD and angiography independently confirmed CCA in all patients except for one who had an extended skull defect; of note, this study had no false positives for CCA [93]. In a similarly designed study, there was 100% concordance between TCD and angiography among 82 brain dead patients. In this cohort, several patients had no transtemporal windows: in these patients the transorbital approach was used and CCA was confirmed in the carotid siphon (ICA). This study also looked at comprehension among relatives receiving the clinical diagnosis of brain death and found that the group with additional confirmation by TCD or angiography reported better understanding and satisfaction compared with the group receiving the clinical diagnosis without further testing. Interestingly, there was a higher number of organs donated in the group with TCD or angiography confirmation [96]. Although these findings require further validation, they highlight the unique role that studies that directly assess cerebrovascular hemodynamics can play in enhancing both caregivers and clinical providers' understanding of the disease process and in influencing patient care.

Bedside Procedures

Ultrasound has improved the success rate and safety profile of a wide range of critical care procedures ranging from routinely performed arterial lines, central venous catheters, thoracenteses, and paracenteses to less commonly performed procedures such as anatomically challenging lumbar punctures [97], chest tubes, and IVC filter placements [98]. It must be emphasized, however, that the use of ultrasound is not a substitute for proper understanding of local landmark anatomy. Learning to track the needle tip in real time and distinguishing it from the needle shaft is essential, especially in the short axis view. Tracking the needle tip in the long axis view has the advantage of visualizing an entire length of the needle but can be technically challenging to learn for novices (Fig. 25.10). A less commonly known application of ultrasound in the setting of bedside procedures is the confirmation of central venous line placement using an agitated saline flush with concomitant subcostal echocardiography. Opacification in right-sided cardiac chambers indicates appropriate venous placement of the line. This approach has been described for femoral lines but is likely also applicable to other anatomic locations [99].

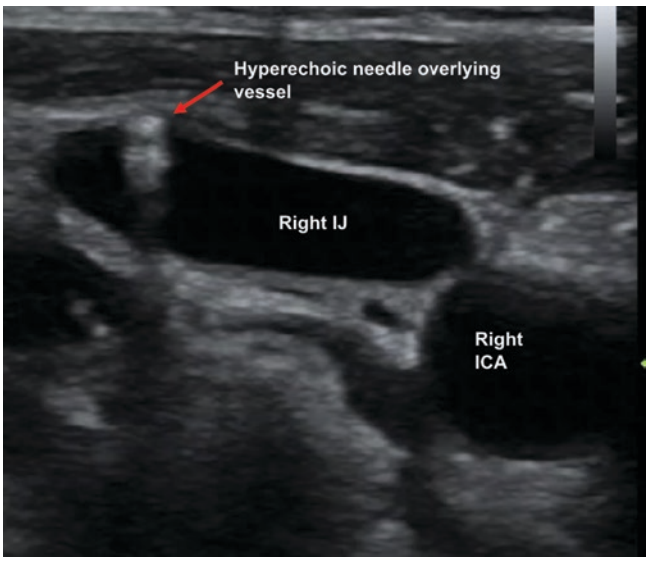

Fig. 25.10 See *Clinical case 8*

Conclusions

Since its first reported medical use by a neurologist over 75 years ago, ultrasound has revolutionized the practice of medicine and critical care. Despite certain limitations, appropriate clinical and research use of ultrasound can have a significant impact on patient care, especially in the understanding and management of complicated neurophysiologic disease states. The concept of TCD being a "stethoscope for the brain" holds true for a wide range of cerebrovascular conditions [3]; this has yet to reach its maximum potential and may be achieved with a more hands-on, "point of care" approach to address day-to-day bedside clinical questions aimed at achieving a better understanding of impaired cerebrovascular hemodynamics and at monitoring the efficacy of ongoing therapies. There are numerous gaps in our understanding of cerebrovascular and CSF flow dynamics as well as in the management of other pathophysiologic changes in various neurocritical care conditions that will benefit greatly from well-designed TCD and other ultrasound-based studies.

Clinical Case Descriptions

Clinical Case 1: A 59-year-old man presents with the worst headache of his life and is diagnosed with Hunt and Hess grade 3 and modified Fisher grade 3 SAH due to a ruptured left MCA bifurcation aneurysm. On day 8, TCD reveals elevated left MCA MFV (mean 156 cm/s) and an LR of 5.7 consistent with moderate vasospasm. Velocities continue to

increase, prompting an angiogram on day 12 that reveals mild to moderate vasospasm that is treated with intra-arterial verapamil. Velocities reach a plateau and gradually decrease thereafter. See Fig. 25.1 for key features of the spectral waveform including peak systolic velocity (PSV) and end-diastolic velocity (EDV); all other indices are calculated from these velocities.

Clinical Case 2: Volume assessment using bedside ultrasound in a patient with aneurysmal SAH. (a) A highly collapsible IVC with an absolute diameter <1 cm suggested fluid responsiveness. The IVC diameter increased and collapsibility was reduced following a bolus of IV fluids (not shown). All measurements are performed just distal to the entry point of the hepatic vein into the IVC. (b) Development of multiple B-lines after further resuscitation suggested fluid overload. Fluids were stopped to prevent the development of respiratory distress.

Clinical Case 3: A 76-year-old woman presented with severe traumatic SAH after falling down a flight of stairs. A CT head revealed diffuse subarachnoid and subdural hemorrhage. She was hypotensive on presentation and required vasopressors. The initial EKG revealed ST segment elevations in septal leads and a mild troponin elevation. Bedside TTE (apical four chamber view) in systole showed apical akinesis consistent with a diagnosis of Takotsubo cardiomyopathy. No segmental wall motion abnormalities were present to suggest myocardial ischemia. Her hypotension improved with supportive care and she was weaned off vasopressors by day 3. A follow-up TTE (not shown) showed resolution of the apical akinesis.

Clinical Case 4: A 50-year-old man was found down with a Glasgow Coma Scale of 5 and diffuse multi-compartment hemorrhage on CT head consistent with severe traumatic brain injury. ICPs >30 cm H_2O (corresponds to ~22.1 mm Hg) were noted on external ventricular drain insertion. The ONSD was 0.70 cm (upper limit normal 0.50 cm). At the time of ONSD measurement, the ICP was 23 mm Hg. There was also a poor ICP waveform with a prominent P2 wave consistent with decreased intracranial compliance. An axial image of the globe is shown with the lens anterior (top of the image) and the optic nerve posterior (bottom of the image).

Clinical Case 5: A 76-year-old woman with fibromuscular dysplasia had a routine carotid ultrasound that revealed severe (>70%) stenosis of the left ICA. The stenosis was manifested by elevated left mid-ICA flow velocities (PSV 267.5 cm/s, EDV 76.8 cm/s) and a poststenotic turbulent flow pattern in the distal ICA. The ICA to CCA ratio was 4.4. Heterogeneous plaque was seen in the same location. She was referred for and underwent successful carotid revascularization.

Clinical Case 6: A 32-year-old woman was admitted with severe headache, nausea, and vomiting. She was found to have extensive cerebral VST involving the superior sagittal and transverse venous sinuses on CTV. TCDs were performed. Insonation through the posterior temporal window demonstrated an arterial waveform from the right P1 segment of the PCA (early in the tracing and above baseline; the PCA [especially the P2 segment of the PCA] serves as a useful landmark for the deep venous system since they both tend to be adjacent to each other), followed by a venous monophasic waveform (the basal vein of Rosenthal, seen below baseline) that represents flow away from the probe. The tracing reveals elevated venous velocities (~40 cm/s). The patient was immediately started on a heparin drip, her symptoms resolved, and she was later transferred to a floor bed in stable condition.

Clinical Case 7: A 78-year-old woman presented with sudden onset headache. A non-contrast head CT revealed right frontoparietal ICH. Her neurologic exam was concerning for elevated ICP and impending uncal herniation (ipsilateral "blown pupil") but invasive monitoring was not possible. (a) B-mode ultrasound shows left ONSD measured 3 mm behind the optic disc. The lens is visualized in the same axis. Prior to IV mannitol administration, ONSD was 0.69 cm (not shown). Thirty minutes after mannitol it was 0.63 cm. (b) Calculation of MLS using Eq. 25.4 (see text). Ultrasound image via the left temporal window shows a "double reflex" (i.e., third ventricle) measuring 6.14 cm from the contralateral (left) temporal window (distance B); note the hypoechoic thalami surrounding the third ventricle. The third ventricle from the ipsilateral temporal window measured 8.54 cm (or distance A, image not shown). Using Eq. 25.4, MLS is 1.15 cm, which correlated closely to the MLS determined from CT head (see [d]). (c) The pineal gland, another midline marker, is demonstrated as a hyperechoic structure dorsal to the thalami/3rd ventricle and measures 8.49 cm from the ipsilateral temporal window. Of note this is quite similar to the position of 3rd ventricle measured ipsilaterally which was at 8.54 cm (not shown). (d) A CT head obtained within 12 hours of the ultrasound in this patient shows MLS of 1.2 cm at the septum, similar to the estimated MLS using ultrasound (see [b]).

Clinical Case 8: Right internal jugular vein (IJ) central venous catheter placement in short axis view. Following the needle point is key to correct placement. The needle shaft can masquerade as the needle point such as in this case. Tenting of the anterior wall of the vein is another clue to the actual position of the needle point.

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Reducing Clot Burden for Intracerebral Hemorrhage and Intraventricular Hemorrhage

26

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Background

Spontaneous intracerebral hemorrhage (ICH) is a devastating condition that results in mortality rates of 20–50% with only 20% of survivors achieving functional independence [1]. The majority of these cases occur in the setting of long-standing hypertension followed by amyloid angiopathy. ICH clot burden has complex interactions at the molecular level and influences neurotoxicity and inflammation. Once red blood cells are released into the parenchyma, they undergo lysis within several hours to days, releasing hemoglobin [2]. Hemoglobin is then converted to hemosiderin upon breakdown by macrophages; hemoglobin breakdown also induces oxidative damage by its generation of free radicals leading to neurotoxic effects. Additionally, edema follows ICH with the most rapid growth in the first 48 hours [3, 4].

Intraventricular hemorrhage complicates ICH in about 40–45% of cases and is associated with hydrocephalus in approximately 50% of cases [5]. Concomitant IVH and early expansion of IVH result in worse clinical outcomes [5–11]. If the ventricular system is obstructed, increased intracranial pressure (ICP) and cerebral hypoperfusion have been found to be associated with higher mortality and short-term disability [12].

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Rationale for Hematoma Volume Reduction

Following hemorrhage, perihematomal edema develops due to multiple mechanisms such as release of biological factors from activated platelets [13] and iron-mediated toxicity [14]. However, emerging evidence suggests that complex hemoglobin scavenging mechanisms mitigate toxicity on neurons and associated cells such as astrocytes and pericytes, but that these mechanisms can become overwhelmed [15]. Hemoglobin-related toxicity may be avoided through the direct removal of blood at the earliest stage of hemorrhage formation [16]. Other factors that affect enzymatic disruption of the blood-brain barrier thus permitting water and deleterious molecules to enter the parenchyma are matrix metalloproteinases (MMPs), which have been associated with worse outcomes after hemorrhage and are correlated with residual cavity volume [17]. There is a direct correlation between hematoma volume and perihematomal edema volume [18]. This edema can subsequently reduce local perfusion as well as exert mechanical forces on parenchyma and result in necrosis and trigger apoptosis of nearby neurons [15]. Single-photon emission computerized tomography (SPECT) studies show reduced cerebral blood flow in the perihematomal region [19]. As perihematomal edema is predictive of functional outcome among patients with ICH [20], many prior studies have investigated the association between hematoma volume reduction and clinical outcomes [21–26].

Diagnostic Workup Prior to Surgical Intervention

Initial Assessment

Upon admission of the patient to the emergency room or neurocritical care unit, the ICH patient should be stabilized acutely, and control of airway, breathing, and circulation

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established. Airway protection in the form of intubation and mechanical ventilation is frequently required due to ICH location, especially if in proximity to or causing mass effect on deep centers in the brainstem, which can also impair lower cranial nerves. Patients with severe functional deficits (Glasgow Coma Scale [GCS] ≤ 7) or moderate deficits (GCS 8–12) should be carefully monitored as they may lose the ability to protect their airway and therefore require intubation [27]. Altered arousal may be the first indicator of an enlarging ICH or development of hydrocephalus.

Laboratory evaluation in patients considered for surgical intervention should focus on reversal of any existing coagulopathy. Although platelet transfusion is not currently recommended for conservatively treated patients taking antiplatelet agents, targeted platelet transfusion before surgery may improve intraoperative and postoperative bleeding and reduce blood transfusion volume in ICH patients [28]. Catheter tract hemorrhage following insertion of an external ventricular drain (EVD) is also significantly associated with pre-operative use of antiplatelet agents [29]. Further study of intraoperative and postoperative effects of reversal agents for antiplatelet- and anticoagulant-associated ICH is needed.

Imaging Studies

Computed tomography (CT) head should be performed at the earliest possible time, followed by interval scans during the initial 24 hours to assess for early ICH and IVH expansion [9, 30–33]. Early hematoma expansion occurs in up to one-third of ICH patients and generally within 24 hours, although delayed expansion has been described and is frequently associated with neurological deterioration [30, 34]. Among patients with ICH in one study, 48% had IVH on initial imaging and 21% developed delayed IVH occurring at a median time interval of 8.9 hours from symptom onset [9].

Timing of Surgery for ICH

Specific ICH location and surrounding brain structures can together result in sudden clinical deterioration, for example, if the ICH is located in close proximity to the brainstem with associated mass effect near the ventricular system or is associated with midline shift or crowding of the basilar cisterns [35]. Presently no data exist demonstrating different clinical outcomes in patients treated with ultra-early clot reduction (≤7 hours) after symptom onset compared to patients who were treated early (7–24 hours) [36]. However, ultra-early craniotomy for ICH is associated with postoperative rebleeding [37]. Delayed surgery (>24 hours) has been associated with non-hemorrhagic complications such as urinary, respiratory, and gastrointestinal adverse events [36]. Other studies show a trend toward higher postoperative hemorrhage rates among patients operated on between 3 and 5 hours after ICH onset compared to those who were operated between 6 and 8 hours post ictus [38]. Given the risk of re-hemorrhage, the concept of hematoma stability prior to surgical intervention was incorporated as a clinical requirement in both the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) and MISTIE III clinical trials. In these trials, the stabilization of blood pressure as well as hematoma volumes on 2 CT scans at least 6 hours apart was required prior to trial enrollment [39, 40]. This emphasis on constancy of the hematoma has been de-emphasized in more recent surgical trials that have focused on earlier hematoma removal. The optimal approach to surgical timing is still a topic of debate.

ICH and IVH Volume Assessment for Surgical Planning

The majority of surgical trials for ICH have relied on CT assessment of clot size measured with the ABC/2 method, although a move to fully automated ICH and IVH volume determination is not far away. IVH and formal ICH volume assessment have relied on semi-automated segmentation and Hounsfield thresholds [16, 41] using software such as OsiriX (Pixmeo; Geneva, Switzerland) on DICOM images. This approach has been validated for accuracy and inter-rater reliability in many studies and is the standard method for ICH volume determination for research purposes [16, 41]. There are a number of validated IVH scoring tools including the Graeb score, modified Graeb Score, and IVH score [41–44], which can be useful for early prognostication and evaluation of therapeutic clot removal. The Graeb score ranges from 0 to 12; a score of 1–4 is assigned to each of the right and left lateral ventricles depending on how much of the ventricle is filled with blood and whether the ventricle is expanded. The third and fourth ventricles are given a score of 1–2 each depending on whether the ventricle is filled with blood and expanded. The modified Graeb score (mGS) utilized in the CLEAR III trial additionally includes scores for the occipital horns and temporal horns one each side [41]. Scores for each of the four ventricles can range from 0 (no blood) to 4 (>75–100% of blood), and scores for each horn can range from 0 (no blood) to 2 (>75–100% of blood). An additional 1 point can be given to each of the 8 sections if there is expansion of the region beyond its normal anatomic boundary, resulting in a possible maximum score of 32. Evaluation of the mGS using the Lund Stroke Register showed that a 1 point increase in mGS increased the odds for a poor 90-day functional outcome (mRS > 3) by 11%, which is similar to a 12% increase in the odds of a poor outcome for each point increase from clinical trial data [8].

Surgical Management in Reducing Clot Volume

ICH Management

Early hematoma evacuation in patients with supratentorial ICH has been assessed by three large randomized, multicenter clinical trials: the International Surgical Trial in Intracerebral Hemorrhage (STICH I) and its follow-up study STICH II, and Early Surgery versus Initial Conservative Treatment in Patients with Traumatic Intracerebral Hemorrhage (STITCH[Trauma]): The First Randomized Trial [26, 45, 46]. In STICH I and STICH II, medical treatment was compared to early surgery within 24 and 12 hours of randomization, respectively.

In the STICH I trial where 1033 patients were assessed by the Glasgow Outcome Scale at 6 months [47], there was no significant difference in clinical outcome between the early surgery and initial conservative treatment groups. However, a post-hoc analysis of STICH suggested that patients with superficial hematomas and those without IVH showed favorable outcomes following early surgery [5]. As patients with hemorrhage in deep locations or with IVH and hydrocephalus fared worse, potentially biasing the initial study to a neutral result, a second trial (STICH II) was performed, focusing on superficial supratentorial ICH (less than 1 cm from cortical surface) without IVH [45]. ICH volume was also required to be 10–100 cc, and most patients (98%) who required surgery (including patients in both the early surgery and initial conservative management groups) received craniotomy for hematoma evacuation with remaining patients undergoing craniectomy or minimally invasive surgery (MIS). At 6 months, 297 patients subjected to early surgery and 286 patients treated with initial conservative management were compared. There was no significant difference in outcome as assessed by Extended Glasgow Outcome Scale between the two groups. Other secondary measurements such as mortality, time to death, and Rankin were also similar. Volume of hematoma reduction was not assessed. In STITCH(Trauma), 82 patients with traumatic ICH were randomized to early surgery (within 12 hours of randomization) with complete follow-up as were 85 patients randomized to initial conservative treatment; there was no difference in unfavorable outcome as per the Glasgow Outcome Scale, though in the first 6 months more deaths occurred in the initial conservative treatment group (33% vs. 15%, $p = 0.006$). Nonetheless, questions remain regarding surgical treatment of traumatic ICH given that this trial was halted early due to failure to recruit a sufficient number of patients [46].

Despite these findings, a meta-analysis of 15 trials of surgery for ICH including STICH I and II reported a significant benefit for surgery with an odds ratio for unfavorable outcome of 0.74 (95% confidence interval [CI] 0.64–0.86; $p < 0.0001$) [45]. This meta-analysis, however, was limited by highly significant heterogeneity due to different types of patients and surgical procedures. Subgroup analysis of only lobar intracerebral ICH and no IVH demonstrated no significant benefit from surgery, and studies involving minimally invasive clot evacuation techniques such as endoscopic aspiration through a burr hole [24, 48, 49] or stereotactic placement of a catheter and administration of recombinant tissue plasminogen activator (alteplase or rt-PA) showed more promising results [50, 51]. These smaller studies, which comprise a variety of randomized prospective studies as well as single center observational studies, have shown good clinical outcomes, low mortality rates, and resolution of hydrocephalus and ICH volume. Based on these encouraging results, a randomized multicenter clinical trial called Minimally Invasive Surgery and rt-PA in Intracerebral Hemorrhage Evacuation Phase II (MISTIE II) was initiated, which investigated the utility of stereotactic clot evacuation and administration of rt-PA in reducing ICH volume and perihematomal edema [16]. There were significantly lower hematoma and perihematomal edema volumes in the surgical group at end of treatment (EOT). The phase III trial, MISTIE III, evaluated whether ICH reduction via the MISTIE procedure improves functional outcomes as measured by modified Rankin Score (mRS) at 365 days after the procedure in patients with large ICH (>30 mL) [40]. Modified intention-to-treat (mITT) analysis was performed on 249 eligible patients exposed to MIS and 240 patients treated conservatively. Although there was no significant difference in proportion of patients with mRS 0-3 (good outcome) at 1 year, there was a 6% increase in survival (adjusted hazard ratio 0.67, 95% CI 0.45–0.98) in the MIS group. More importantly, stereotactic removal with thrombolysis was safely adopted by a large number of surgeons. When clot size was reduced to the planned goal of less than 15 mL, MISTIE produced a significant improvement in mRS 0–3 of 10.5% compared to the standard medical care group. MISTIE III provides the first description of specific hematoma evacuation thresholds to impact functional outcome in ICH surgery trials (Fig. 26.1); reduction of ICH to ≤15 mL at EOT or ≥70% evacuation was required for good functional outcome at 1 year whereas less stringent clot evacuation (<30 mL at EOT or >53% evacuation) was sufficient for improved survival [52]. The MISTIE III trial is remarkable for several reasons. It is the first in ICH and stroke to integrate surgical interventions into a medically based treatment paradigm in a consistent fashion. Secondly, it is the first time that improved clinical outcomes have been validated by predetermined endpoints in a prospective trial. While the surgical targets identified apply specifically to the MISTIE procedure, this trial provides definitive evidence that appropriate surgical interventions can result in improved outcomes in ICH.

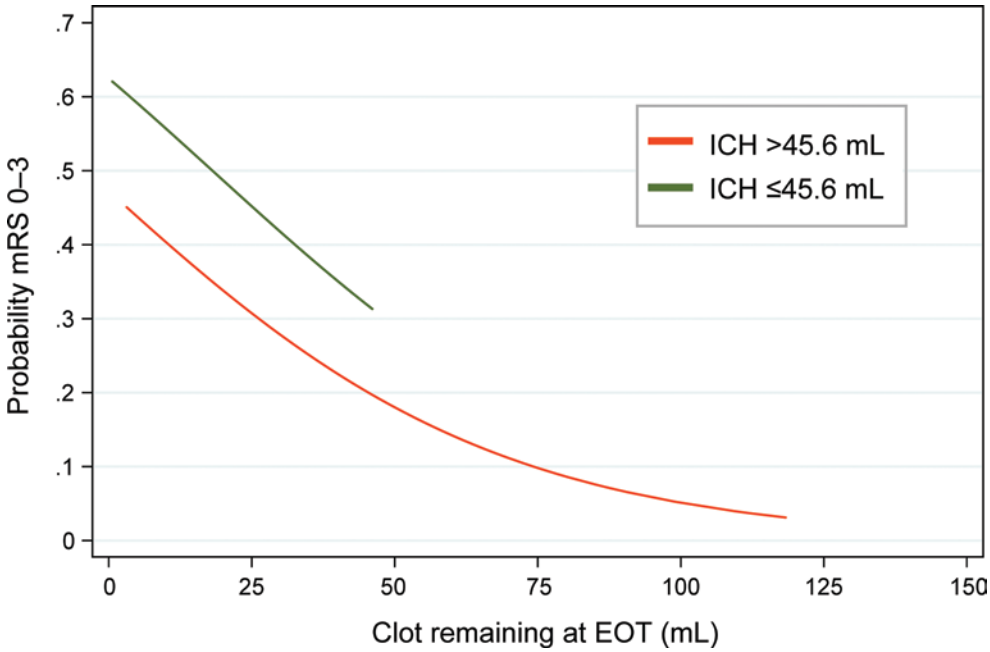

Fig. 26.1 Plot of probability of mRS 0–3 as a function of clot remaining at the end of treatment (EOT). Probabilities are given for stability ICH size ≤45.6 mL and >45.6 mL, the median stability ICH size. Probability estimates obtained from unadjusted logistic regression model of dichotomized mRS 0–3 values regressed on clot remaining at end of treatment ($p = 0.005$). There was a significant increase in probability of good outcome with removal of ICH volume for both large and small clots. The graph also shows the differences in baseline prognosis between the large and small clots

The results of MISTIE III, while not confirmatory of improved outcomes, are consistent with current knowledge from meta-analyzed MIS data for ICH evacuation. A meta-analysis of randomized controlled trials comparing MIS (stereotactic aspiration or endoscopic drainage) to other treatments included 12 trials of 1855 patients with supratentorial ICH and reported significant reduction in the endpoints of both death and dependence at end of study follow-up compared to conventional craniotomy or conservative management [53]. The patient subgroups most likely to benefit from MIS were: superficial hematomas, GCS score of ≥9, hematoma volume between 25 and 40 mL, and within 72 hours after onset of symptoms. A second larger meta-analysis reported similar results for both endoscopic surgery and stereotactic thrombolysis versus medical treatment or conventional craniotomy and for MIS versus craniotomy only [54]. At the time of the writing of this chapter, we await further results from several randomized controlled trials evaluating different MIS techniques for hematoma evacuation.

IVH Management

Among IVH patients with clinical deterioration and hydrocephalus on CT, placement of an EVD should be considered [55]. An EVD allows monitoring for and a mode of treating elevated ICP. Even after IVH has cleared, persistent hydrocephalus is not uncommonly seen weeks after the initial hemorrhage due to mechanisms that could include breakdown products from blood causing inflammation in the ependymal layer of the ventricular system, prohibiting cerebrospinal fluid outflow, and dysfunction of arachnoid granulations impeding cerebrospinal fluid flow out of the subarachnoid space [56].

As patients with early presence of IVH and IVH expansion have poor outcomes, the rationale for early fibrinolytic clot removal with rt-PA or urokinase has biologic plausibility based on improved blood clot removal, hydrocephalus, inflammation, and return of consciousness in translational models [57–59]. Data from small prospective as well as retrospective studies have shown that intraventricular injection of rt-PA or urokinase induces faster IVH clot resolution and can result in good clinical outcomes [25, 60–62]. Several meta-analyses have confirmed significant reductions in mortality and poor outcomes with intraventricular fibrinolysis as compared to EVD alone or conservative management, and no significant differences in bacterial ventriculitis or re-hemorrhage rates have been noted although the impact on the need for permanent shunting is variable [63–66]. The American Stroke Association guidelines consider intraventricular fibrinolysis to be safe, although efficacy is uncertain [67].

The Clinical Trial on Treatment of Intraventricular Hemorrhage (CLEAR IVH) trials comprise a multiphase clinical trial program with the goal of determining the efficacy of intraventricular alteplase for treatment of obstructive IVH [39, 68]. The control groups used for these trials received normal saline injection via EVD. The trials focus on patients with ICH volume less than 30 cc and obstruction of the third or fourth ventricles and excluded patients with structural vascular lesions on imaging. The primary outcome of the 500 patient phase 3 clinical trial (CLEAR III) was good outcome (mRS ≤ 3) at 180 days; there was no significant difference between the alteplase and saline groups (48% vs. 45%, respectively; risk ratio [RR] 1.06, 95% CI 0.88–

1.28, $p = 0.55$) [39]. At 180 days, mortality was significantly lower in the alteplase group (18% vs. 29% in the saline group), but there was a greater proportion of patients with mRS 5 in the alteplase group (17% vs. 9% saline group) although with no difference in vegetative state (3% in both groups). Symptomatic intracranial bleeding was low (2%) in both groups. Similar to the MISTIE III trial results, a focus on clinically important clot removal found that in those patients who achieved >85% reduction in IVH volume at the end of the 3–4 day intraventricular treatment phase, the primary outcome was significant for the alteplase-treated group after adjustment for confounders (age, GCS, thalamic ICH location, and IVH volume at baseline) [39]. In addition, a planned post-hoc analysis of patients with initial IVH volume greater than 20 mL found a significant treatment effect for intraventricular fibrinolysis, again with a statistically significant increase in patients with good functional outcome (mRS 0–3) at 180 days, suggesting that smaller IVH may not benefit from this intervention [39]. Thus, the pursuit of benchmarks of success for surgical tasks involving MIS or IVH clot reduction appear to be critical for optimal management of these patients in order to achieve good functional outcome.

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Part VII

Neurocritical Care Unit Personnel

Attending Physicians in the Neurocritical Care Unit

27

J. Ricardo Carhuapoma

Introduction

Neurocritical care is a subspecialty of neurology that focuses on the optimal management of life-threatening neurological and neurosurgical emergencies or the life-threatening neurological manifestations of systemic disease. The evolution of clinical practice in neurocritical care has been intimately linked to the model that neuroscience critical care units (NCCUs) have adopted throughout the years. A substantial body of literature addresses the role of the intensivist in the medical and surgical intensive care units (ICUs), the impact that type of physician staffing has on outcome measures after critical care, and the different forms of critical care delivery in the ICU environment [1–6]. Such information is not readily available for ICUs staffed by neurointensivists who care for the neurologically injured critically ill patient. The NCCU is a relatively recent healthcare and academic construct that encompasses those ICUs that care for neurology/neurosurgery patients with critical illness. Since the early-to-mid 1980s, when the modern version of an NCCU was established across the country, such ICUs have been staffed with neurosurgeons as primary attendings, or more recently by neurologists and anesthesiologists with additional training in neurocritical care, or a combination of both [7]. With the formation of the Neurocritical Care Society (NCS) and the influence of the Leapfrog Group, both of which were founded in November 2000, a contemporary version of the NCCU has been developed in which multidisciplinary clinical collaboration is at the center of the clinical mission. In June 2015, under the direction of the NCS executive leadership, a multidisciplinary national writing group of NCS members was formed. Its primary purpose was to identify resources and standards by which to designate adult NCCUs in the United States. The result of this 2-year effort was published in 2018 in the journal *Neurocritical Care* [8]. This document is an important contribution that sets recommendations related to basic organizational aspects of NCCUs, including neurointensivist qualifications and training. Nevertheless, aspects of neurointensivist staffing and how that staffing affects the role of the NCCU attending are not included, primarily because of a lack of available literature in this field.

In this chapter, I will summarize some important concepts pertaining to the types of ICU models that directly affect the role of the intensivist in an academic ICU as well as the pertinent available literature that begins to address the issue of intensivist staffing conducive to balanced and optimal delivery of clinical care, teaching, implementation of administrative duties, and performance of non-ICU activities. The relevant information in these areas originates from research into and expert opinions of the organizational aspects of non-neuro ICUs. However, I put forth the notion that, although they are different ICU environments, NCCUs and non-neuro ICUs face similar organizational challenges in the contemporary academic medicine climate and structure.

Models of the Intensive Care Unit

Classic ICU model definitions have centered on the dichotomous concepts of "closed" versus "open" [9]. It is not a mystery that the initial concept of a full-time attending intensivist managing the ICU environment was met with skepticism and resistance during the late 1990s and early 2000s [10]. Such definitions did not seem to recognize the benefits of the primary care physician's knowledge of the patient and their family and the potential value of both parties. A main source of opposition derived from the perception that the ICU would now be closed to non-ICU medical staff, and that such staff would be excluded from the care of their patients. Additionally, non-intensivist physicians raised concerns

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regarding loss of autonomy and continuity of care. A position statement from the American Academy of Neurological Surgeons in 2009 reflected these concerns after the Leapfrog Group adopted four hospital safety standards supported by evidence-based research, one of which is ICU Physician Staffing (IPS) [11, 12].

Early research in 2002 showed that greater use of intensivists in the ICU (high-intensity ICU physician staffing) leads to significant reductions in ICU and hospital mortality and length of stay (LOS) [9]. Such findings were found consistently across a variety of populations and hospital settings with important implications for patient care. Other studies revealed that daily rounds by an ICU physician were associated with a three-fold reduction in hospital mortality among patients who underwent abdominal aortic surgery and reduced hospital LOS and postoperative complications after esophageal resection [6, 13]. There is no reason to expect a different impact of the IPS standard in the NCCU under the current standards recommended by the NCS. Early evidence for the benefits of an NCCU intensivist attending and dedicated team included improved outcomes after neurological/neurosurgical critical illness and increased rates of other types of procedures such as organ donation [14–17]. Conceivably, the positive impact of an intensivist-led ICU team may be the result of at least four important attributes of intensivists (including neurointensivists):

1. The presence in the ICU of a physician trained in critical care medicine is important. Being physically present enables early identification and interventions when problems occur and therefore helps prevent poor outcomes.
2. An intensivist's knowledge of relevant protocols and evidence-based practice will benefit patients.
3. Intensivists coordinate communication and collaboration with the patient, family members, other ICU providers, and medical specialists to provide optimum and informed care.
4. The intensivist is an ICU manager who facilitates the standardization of care processes, patient triage, timely discharges, and performance evaluations.

A more thoughtful view of such models includes not only the presence but also the involvement of the attending intensivist. Below is an operational classification of such models, provided by Pronovost and colleagues [9]:

1. Closed ICU: The intensivist is the patient's primary attending physician.
2. Mandatory critical care consultation: The intensivist is *not* the patient's primary attending physician, but *every* patient admitted to the ICU receives a critical care consultation.
3. Elective critical care consultation: The intensivist is involved in the care of the patient *only* when the attending physician requests a consultation.
4. No critical care physician: Intensivists are unavailable.

More practically, ICUs could be divided into:

1. High-intensity ICU physician staffing: Mandatory intensivist consultation or closed ICU.
2. Low-intensity ICU physician staffing: No intensivist or elective intensivist consultation.

Of similar importance to hospital safety standards, many healthcare organization experts, based on experience gathered since the adoption of the IPS standard, strongly suggest that the notion of open versus closed units is ambiguous, confrontational, and should be avoided. We should support a model of team-based care in which intensivists, along with a patient's primary physician, manage the patient's care. Such an approach acknowledges the primary physician's knowledge of the patient, his/her family, and the personal values of both parties [18].

Role of the Neurointensivist Attending in the NCCU

Determining the ICU model that provides a collaborative environment among intensivists and primary attendings and is most conducive to providing the best patient care is a very important first step. This milieu allows the ICU physician to perform best in all domains needed to ensure an optimally functioning ICU, including the NCCU. Time assigned to each of the specific roles the attending has is crucial to meet the necessary goals of any given ICU. This is particularly important in academic centers, where teaching and research are fundamental aspects of the academic mission. The following are the most commonly recognized roles of an ICU attending physician.

1. Teaching: Attending intensivists, including neurointensivists, are expected to deliver bedside medical education to different subsets of trainees. The trainees who are commonly assigned to (or request) an ICU rotation range from medical students to residents to fellows. Occasionally, visiting scholars are part of the rounding team. In NCCUs, it is almost universal that the rotating residents represent different disciplines such as anesthesiology, neurology, and neurosurgery. Each trainee has different educational needs and goals, and the attending neurointensivist must tailor the delivery of the bedside educational content appropriately.

2. Patient care: Delivery of patient care in an NCCU includes bedside rounding on all NCCU patients. Systematic bedside rounds require the active participation of specialized nursing as well as of other disciplines such as pharmacy and respiratory therapy. Extensive efforts have largely failed to determine the ICU physician to patient ratio needed to provide appropriate clinical care to patients. ICUs are ecosystems that respond to regional and institutional characteristics and needs. The composition of ICU teams also varies widely and can include non-attending physicians such as residents and fellows as well as other ICU providers such as nurse practitioners or physician assistants. All these and other variables significantly modify the ICU physician to patient ratio needed to accomplish the goals described in this section.
3. Non-direct patient care duties: Non-direct patient care can involve time-intensive activities such as regular family meetings, end-of-life family discussions, coordination of procedures and testing that require special attention to the specific needs of individual patients, and daily multidisciplinary meetings to discuss comprehensive and expeditious care for patients. Furthermore, most high-intensity ICU physician staffing units should coordinate care with the primary admitting services in a professional and collaborative manner to guarantee delivery of the best care to all NCCU patients. This extremely important duty of the attending neurointensivist can be time consuming, even when practiced efficiently.
4. Triage: The triage of patients in a busy NCCU can be a particularly dauting task. Most NCCUs care for a mixed population of neurosurgery and neurology patients. Surgical cases posted to an NCCU can challenge the census and capacity of a busy tertiary referral academic hospital. The neurointensivist should determine the ICU needs of all posted surgical patients in order to appropriately triage them. Generally, the decision to admit patients to an NCCU is clear (acute physiological derangement that requires critical care or monitoring) and the responsibility of the attending neurointensivist. The decision to discharge patients from the NCCU is also the responsibility of the attending neurointensivist. Primary services that admit patients to NCCUs are usually neurology and neurosurgery. A meeting early every day with each of these services is mandatory to discuss triage and efficiently expedite patient flow.
5. Administrative duties: ICU attending physicians such as neurointensivists also participate in many ICU-related activities such as leadership meetings, comprehensive unit-based safety programs, morbidity and mortality conferences, quality improvement activities, divisional faculty meetings, and critical care committee meetings. These commitments, depending on the complexity of the medical system, can necessitate significant time demands that can challenge the ability to fulfill other roles expected of ICU physicians.

In 2013, the Society of Critical Care Medicine (SCCM) released the results of a taskforce whose mission was to provide recommendations for physicians and hospitals regarding maximum patient workloads based on the available information at that time. The following were their recommendations [19]:

1. Appropriate staffing of ICUs with intensivists affects the quality of patient care, patient safety, education, and intensivist and staff well-being. Individual ICUs need to be aware of their current intensivist to patient ratios and monitor these ratios to guarantee staffing models that are commensurate with the institution's expectations for patient care and other duties.
2. Caseloads should allow daily rounds to conclude at an acceptable time in accordance with other valued duties, including teaching, other non-ICU duties, and administrative responsibilities.
3. Staffing policies should factor in surge capacity and non-direct patient care duties, such as family meetings, procedures, consultations, duties outside the ICU, and teaching.
4. Institutions should regularly assess the appropriateness of their ICU staffing models with objective data. Data collected should include assessments of staff satisfaction, burnout, and stress because these factors may indirectly reflect the appropriateness of the staffing model in place [20].
5. High staff turnover or decreases in quality-of-care indicators in an ICU should be viewed as potential indicators of overworked staff and should prompt ICUs to evaluate their intensivist to patient ratios.
6. Adding telemedicine, advanced practice professionals, or non-intensivist medical staff may be useful in alleviating the overburdened intensivist, but their introduction into the ICU should be predicated by a needs assessment and evaluated with rigorous assessment methods.
7. In teaching institutions, feedback from faculty and trainees should be sought to understand the effects of potential understaffing on medical training and education. The tradeoffs between patient care and education must be weighed carefully and explicitly when expanding the intensivists' clinical responsibilities. A reduction in the quality of education that accompanies increased workload may be acceptable if it is an anticipated side effect, but it is not acceptable if it is an unforeseen and unintended consequence.
8. In academic medical ICUs, evidence suggests that an intensivist to patient ratio less than 1:14 may negatively affect perceptions of teaching quality, stress, patient care, and workforce stability.

Examples of necessary adaptations made to a physician staffing model to meet the goals of an effectively run NCCU in a current medical center may illustrate the preceding discussion. The Johns Hopkins Hospital's NCCU in Baltimore, like other tertiary referral centers in urban settings, has gone through a series of changes to meet the expectations of the healthcare system locally and of modern or contemporary medicine more generally. The evolution from an 8-bed NCCU and a 6-bed neuroprogressive care unit in 1987 to a 24-bed combined NCCU in 2003 appears to reflect the changing needs of the institution. In 1987, the NCCU team consisted of an attending, two neurocritical care fellows, and two residents. The current Hopkins NCCU has three provider teams. The clinical care provided to the 24 NCCU patients is split between two teams. One is composed of an attending neurointensivist, a neurocritical care fellow, and up to three residents (from the departments of Neurology, Neurosurgery, and/or Anesthesiology and Critical Care Medicine). A second team consists of an attending neurointensivist, a neurocritical care fellow, and up to three neurocritical care nurse practitioners. A third attending handles triage, including the daily surgical case triage; coordinates transfers out of the NCCU; and facilitates admissions to the NCCU from the emergency department, rapid response team, inter-hospital transfers, and remote locations such as the post-anesthesia care unit. Additionally, the third neurointensivist attending is responsible for daily academic activities for the NCCU teams during the work week and responds to neurocritical care consults from other ICUs in the hospital. Such a system allows a neurointensivist attending staffing level of approximately 1:12 (i.e., 1 attending to 12 patients) to maintain the fragile balance of providing adequate teaching, clinical care, administrative duties, non-direct patient care activities, and triage.

It is clear that each ICU should strive to determine its needs in order to satisfy its own mission. The recommendations provided by the SCCM taskforce in 2013 are useful rules to follow when determining variables that will affect the ideal ICU physician to patient ratio. I anticipate that future iterations of the NCS Writing Group that is addressing NCCU standards will provide more granular suggestions for neurointensivist staffing to satisfy the growing needs of each institution.

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Advanced Practice Providers in Neurocritical Care

28

Lourdes Romero Carhuapoma and Mallory Trosper

Introduction

The specialty of neurocritical care by its nature involves a multidisciplinary approach to the optimal management of life-threatening neurological and neurosurgical emergencies or the acute manifestations of systemic disease [1, 2]. The establishment of a physician subspecialty in neurocritical care and the continued development of the specialty for nurses and other healthcare providers has contributed to a growing workforce of highly skilled, multidisciplinary professionals trained in the field of neurocritical care [2].

In 2018, the Neurocritical Care Society (NCS) published recommendations for the development of a successful neurocritical care program [2]. The NCS recommendations identify advanced practice providers (APPs), a term used to define nurse practitioners (NPs) and physician assistants (PAs), as playing instrumental roles in the delivery of care and critical members of the multidisciplinary care team in neurological critical care units (NCCUs) [2]. This chapter will: (a) detail the roles and responsibilities of the APP in neurocritical care; (b) discuss APP integration and opportunities within neurocritical care practice models; (c) review strategies for successful and effective implementation of a neurocritical care APP program; and (d) explore future directions for the role of APPs in neurocritical care.

Roles and Responsibilities of the APP in Neurocritical Care

In neurocritical care, APPs maintain a broad range of roles and responsibilities. APP clinical duties include obtaining histories, performing physical exams, ordering and interpreting diagnostic tests, prescribing and adjusting medications, managing mechanical ventilation, performing medical procedures, conducting family meetings, and leading multidisciplinary rounds [2–4]. In addition to clinical duties, APPs commonly spearhead or support evidence-based practice and quality improvement initiatives directed toward improving the care of patients in the NCCU, provide education in the area of neurocritical care to healthcare providers, and lead or support research aimed to advance the practice of neurocritical care [2]. Within this wide scope of responsibilities, APPs are expected to achieve competency in each task they perform and are subject to institutional standards and assessments of competency, including professional practice evaluations within the healthcare organization [3]. It should also be noted that APPs seeking to provide neurocritical care services in a hospital setting must undergo a credentials review process similar to that of physicians and other providers and be granted the privilege to practice in the hospital [5].

APP Education and Training

While NPs and PAs are commonly assumed to be one and the same, the education and training of these providers are vastly different. Education for NPs begins with receiving a bachelor's or master's degree in nursing before passing a national standardized licensing exam to become a registered nurse (RN). Graduate education for advanced practice registered nurses (APRNs), a term that encompasses the roles of NPs, clinical nurse specialists, certified nurse-midwives, and certified registered nurse anesthetists, has historically entailed master's level preparation; however, many programs nationally have transitioned to offering a doctor of nursing practice (DNP) degree for entry into advanced practice [6]. The DNP degree is designed to provide education for advanced nursing practice roles, which include those focused on practice at the population, systems, or organizational level [6].

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Currently, each state independently determines the legal scope of practice for NPs, the roles that are recognized, the criteria for entry into advanced practice, and the certification examinations accepted for entry-level competence assessments. The inconsistencies in the scope of practice legislation across states have created variations in the clinical responsibilities assumed by NPs. As a result, the Consensus Model for APRN Regulation, completed through the joint efforts of the APRN Consensus Workgroup and the National Council of State Boards of Nursing APRN Advisory Committee in 2008, provides guidance to states regarding uniformity of APRN roles [7]. The Consensus Model dictates that APRN regulation includes the essential elements of licensure, accreditation, certification, and education (LACE) [7]. The model further specifies that in order to be granted the authority to practice, NPs must have completed a comprehensive, graduate-level NP program offered by an academic institution meeting recognized standards, indicated by accreditation from a nursing or nursing-related accrediting organization recognized by the U.S. Department of Education (USDE) and/or the Council for Higher Education Accreditation (CHEA). Certification is granted once a national certification examination assessing role- and population-focused competencies has been passed. Once certified, licensure may be obtained through the state board of nursing within the state the APRN chooses to practice [7].

The adult gerontology acute care nurse practitioner (AG-ACNP) is best suited to provide neurocritical care to patients [2, 5]. NP educational curriculums offer either a primary care or acute care focus as outlined by the Consensus Model for APRN Regulation [7]. AG-ACNPs are educationally prepared to provide advanced nursing care to patients with complex acute, critical, and chronic health conditions, including the delivery of acute care services to those patients found in critical care areas throughout the hospital [5]. The scope and standard of practice for AG-ACNPs recommend that most AG-ACNPs practice in acute care and hospital-based settings, including intensive care units [5]. National certification for AG-ACNPs is provided by the American Nurses Credentialing Center (ANCC) and the American Association of Critical Care Nurses (AACN) [8].

Educational preparation for PAs begins with a bachelor's degree prior to entering an accredited PA program. Many programs consist of approximately two years of training culminating in a master's degree [8]. PA programs are a combination of classroom instruction as well as clinical rotations focusing on primary care in ambulatory clinics as well as patient management in acute and long-term care facilities [9]. Upon completion of an accredited PA program, certification is obtained by passing the Physician Assistant National Certifying Exam, which is administered by the National Commission on Certification of Physician Assistants (NCCPA). This is the only certifying body for physician assistants, and obtaining a passing score on the examination provides the credential of *PA-C* [8, 9]. State licensure for PAs varies, with some states utilizing boards of medicine and others using boards of PAs [4, 9].

APP Subspecialty Training in Neurocritical Care

APP onboarding has evolved significantly over time. Historically, the post-graduate training of APPs has occurred via an informal orientation or on-the-job training under the helm of intensivists and tenured APPs. In recent years, post-graduate residency programs in critical care have emerged in academic centers [3, 4]. Formal post-graduate residency programs offer APPs the opportunity to specialize in critical care and provide competency-based training representing the gold-standard for APP post-graduate education [3, 4]. Subspecialty training in neurocritical care continues to be provided to APPs via an informal approach.

The NCS recommends that APPs involved in direct patient care in NCCUs be provided a focused orientation to assessment, diagnosis, management, and procedures encountered in managing the care of patients with neurocritical illness states [2]. The orientation to neurocritical care concepts may be provided via a formal fellowship or informal approach [2]. Prior to providing independent, direct patient care, the APP should be assessed for competency in neurocritical care concepts [2]. APPs should be encouraged to participate in continuing professional development activities in the area of neurocritical care [2]. Certification for Emergency Neurologic Life Support (ENLS), provided by the NCS, is highly encouraged for APPs to ensure team members are adequately prepared to manage neurologic emergencies [2].

APP Integration and Opportunities Within Neurocritical Care Practice Models

The utilization and integration of APPs in critical care practice models, including neurocritical care, has become increasingly more accepted in healthcare organizations and aligns with the recommendations of the NCS and the American College of Critical Care Medicine [2, 4, 10]. There are several factors that support the incorporation of APPs within neurocritical care teams, including (a) the widespread growth and expansion of NCCUs, which require a highly skilled, multidisciplinary workforce of providers with subspecialty training in neurocritical care to staff the NCCUs; (b) the increasing need for continuous, on-site specialty-trained providers in NCCUs, particularly in tertiary, academic centers; (c) rising healthcare costs, which require a cost-effective approach to the management of patients with

neurocritical illness states; and (d) reduction in residency hours resulting in a shortage of providers in tertiary, academic centers [4, 11, 12]. The incorporation of APPs into the NCCU environment offers a safe and cost-effective solution to these complex issues.

Since the inception of the subspecialty of neurocritical care, there has been widespread growth of dedicated NCCUs specializing in the management of patients with acute neurological and neurosurgical disease states. The expansion of NCCUs has resulted in the need for a highly skilled, multidisciplinary workforce of healthcare providers with subspecialty training in neurocritical care to staff these specialty ICUs. While studies evaluating outcomes of APP-managed NCCU patients are lacking, critical care studies have demonstrated that APPs positively impact outcomes, length of stay, implementation of practice guidelines, and cost control in ICU settings [3, 4]. In 402 adult patients cared for by ACNPs using a multi-disciplinary model of care in a neuroscience ward or NCCU compared with a baseline sample of 122 adult patients who lacked ACNP management, patients managed by ACNPs had significantly shorter length of stay, lower rates of urinary tract infections and skin breakdown, and shorter time to mobilization and discontinuation of Foley catheter use. Further, the ACNP-managed group was hospitalized 2,306 fewer days than the baseline comparison group, resulting in a cost savings of $2,467,328 [13].

In addition, APPs provide a consistent presence in the NCCU and ensure a workforce of "experts" in neurocritical care, particularly in tertiary, academic centers where physician residents cycle through the unit in blocks and neurointensivists rotate coverage each week [4, 8]. The consistent presence of APPs permits improved communication and ICU culture as APP team members are commonly more familiar with members of the multi-disciplinary team. A national study of ICU culture found a positive correlation between a climate of safety and reduced length of stay, highlighting the potential clinical benefits of a positive work community [8]. With the consistency provided by APPs, improvements in patient care hand-offs may mitigate errors known to be associated with cross-coverage, thus improving the transfer of care for patients [8].

Due to the acuity of patients receiving care in the NCCU of a tertiary medical center, a neurointensivist with neurocritical care privileges or designee should provide on-site care 24 hours a day, seven days a week. When not on-site and care is delegated to other providers, the neurointensivist must be available to return calls within five minutes as well as arrange for a physician or APP to be at the NCCU bedside within five minutes [2, 4]. APP neurocritical care practice models address the need for cost-effective delivery of care by providing in-house coverage 24 hours a day, seven days a week with neurointensivist backup. In addition, while the reduction in the number of hours a resident can work per week has been a positive change for residents, it has added an additional layer of complexity in providing critical care services since this decreases the number of available on-site providers. This change is particularly evident in tertiary ICUs where the management of critically ill patients requires a continuous on-site provider [4]. Multidisciplinary professional teams, which includes APPs, therefore provide an ideal practice model for stabilizing and managing complex critically ill patients with acute neurological and neurosurgical disease states in a safe and cost-effective manner.

Lastly, APPs employed in the NCCU have chosen to be educated in the subspecialty of neurocritical care and, therefore, are much more likely to be interested and engaged in learning about the unique and specific management of critically ill patients with neurocritical illness states [8]. By being present in the NCCU continuously, APPs are repeatedly exposed to NCCU-specific interventions, offering a significant advantage in becoming proficient with performing such procedures [8].

Effective Strategies to Developing and Implementing a Neurocritical Care APP Program

As opportunities for APPs are expanding within the neurocritical care setting, it is essential to consider the potential challenges in successfully integrating APPs into existing neurocritical care practice models. We will review strategies for the successful recruitment and retainment of qualified APPs, APP provider-to-patient ratios, and the role of a lead APP for larger APP neurocritical care programs.

Seeking and retaining qualified APPs are essential components in developing and maintaining a successful APP program in the NCCU. Formal preceptorships offered by APP graduate programs and residency programs provide opportunities for rotating in the NCCU affording prospects for the recruitment of new graduate APPs. Such opportunities also allow experienced APPs to expand their educational skill-base by serving in the role of preceptor.

APP provider-to-patient ratios have been reported to range from 1:3 to 1:8 with a mean of 1:5 [14]. When developing an APP program in the NCCU, factors such as daily bed occupancy, number of daily NCCU admissions and discharges, patient acuity, hours of coverage, number of residents and/or fellows, and number of NCCU consults should be carefully considered [3, 14].

Lastly, the NCS recommends the addition of an APP lead to serve as a manager of larger APP groups [2]. The lead APP should work in concert with the unit medical director and unit nursing director to resolve issues that arise in the neurocritical care APP program, which allows for effective

management of the program using a multidisciplinary approach [2, 3].

Future Directions for Neurocritical Care APP Programs

Research is critical to advancing the understanding of neurocritical illness states, including the development of novel strategies for optimizing patient management, improving outcomes, and reducing healthcare-related costs [2]. Tailoring quality improvement initiatives for the neurological and neurosurgical patient is essential given the unique challenges faced by these patients. Clinical and quality improvement research foci may include mobility and rehabilitation, pain management, delirium management, agitation/sedation, and sleep disruption. Improving care in these areas may reduce NCCU and hospital length of stay, improve recovery and overall outcome, and reduce healthcare costs. Further, APPs may obtain additional specialization in emerging fields within neurocritical care. For example, neuropalliative care enables APPs to identify disease-specific issues related to palliation for this unique population, including disease/symptom-specific considerations, pain management, family-provider communication, patient/surrogate end-of-life decision making, health-related quality of life, and caregiver support for the purpose of integration into clinical practice.

The projected growth in the neurocritical care APP workforce should stimulate further development of research focusing on the role of the APP within the neurocritical care team and outcomes of critically ill patients with neurological and neurosurgical disease states cared for by APPs [4]. Research is also needed to measure competency outcomes concerning postgraduate APP subspecialty training in the field of neurocritical care and financial aspects of care delivery among neurocritical care APP programs.

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Residents and Fellows in Neurocritical Care

29

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Postgraduate medical education is an ever-changing science. This pertains to neurology residency programs in particular given the recent strides undertaken in vascular neurology and other neurological specialties as well as in critical care. A recent survey by the American Academy of Neurology (AAN) that intended to study the comfort level of neurology residents in various aspects of training as well as future plans revealed that most residents aspire to obtain further training in various neurologic subspecialties [1]. This might pose a concern that neurology residents do not feel ready to start a job directly after residency. Yet, in the same survey, most residents agreed that they are comfortable beginning their career immediately after residency, though some reported requiring more training in specific subspecialties and/or procedures [1].

Another survey by the AAN, now directed toward neurology residency program directors, evaluated the need for formal "hands-on" experience in neurocritical care to obtain a rounded neurology training. The majority responded that there's an increased interest in neurologic critical care experience, and now with the pending development of formal Universal Council of Neurologic Subspecialties (UCNS)/Accreditation Council for Graduate Medical Education (ACGME)-accredited fellowship programs more residents are aspiring for this training. When asked about the format by which residents are taught the critical care aspects of neurology, the overwhelming majority indicated lecture series and journal clubs with a need for designated neurocritical care rotations [2].

There is an increasing interest in unifying and standardizing resident education, and toward this goal the ACGME and the American Board of Psychiatry and Neurology mandated evaluating residents in achieving core competencies in addition to completing five clinical scenarios, one of which is the examination of a critically ill patient [3]. This emphasizes the importance of this aspect of neurological care.

The neurological critical care unit (NCCU) has shown time and time again to decrease the rate of mortality, length of stay, and cost of caring for neurocritically ill patients. Through a multidisciplinary team, intricacies in the neurological examination, physiology, and pharmacology are synthesized and a plan of care set forth [4, 5]. In addition, formal hands-on teaching and experience have been shown to lead to better goals of care and treatment plans [6, 7]. It is therefore no surprise that distinct neurocritical care fellowship programs, with the goal of unifying the knowledge base and clinical and procedural skills in this area, were developed. The UCNS accredited this fellowship in 2005 and the ACGME in 2018. Core competencies include general aspects of critical care medicine as well as the pathology, pathophysiology, and treatment of medical and neurological diseases [4, 5, 8].

To aid neurocritical care fellows in obtaining all required skills and competencies during their short (usually 2 year) training period so that they are best prepared to care for a variety of patients, high-fidelity simulation exercises have been utilized [9]. Several pilot studies testing the benefits of these simulations in teaching medical students revealed that the students acquired an improved knowledge base and procedural skills all in a safe and controlled environment. These simulated scenarios can also be extended to neurological emergencies and many types of disease states to better equip students, residents, and fellows to handle neurologic and medical emergencies [10, 11]. Airway and mechanical ventilation management remain a cornerstone in critical care, and

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mannequin-based simulations are often used [12, 13]. This also applies to neurologically ill patients who tend to require special considerations due to the brain-lung axis.

In addition to receiving simulation-based training that includes airway management, neurocritical care fellows typically spend at least half of their training rotating in the NCCU as well in other intensive care units (ICUs), including the medical ICU and surgical ICU. As a result, they gain the clinical and procedural experiences necessary to manage many types of critically ill patients and not solely neurocritical care patients. Typical neurocritical care fellowship programs also provide the opportunity for studying other disciplines relevant to neurocritical care, including optional rotations in ultrasound (which can include learning more about transcranial Doppler) and in electrophysiology (e.g., electroencephalography). Programs also generally encourage scientific exploration and thus provide time away from clinical rotations during which fellows may engage with faculty members, pursue research interests, create posters for research meetings, and write manuscripts for publication.

Neurology residents, having increasing inpatient responsibilities, must achieve required milestones in identifying and in treating the neurologically deteriorating or critically ill patient. This comes with formal education (such as regular lectures) as well as hands-on experience. The NCCU provides a milieu in which residents are able to function under controlled and highly supervised conditions. In addition, with the advent of new technologies permitting quantitative electroencephalography and multimodality monitoring (including ongoing measurements of intracranial pressure), the neurology resident can learn and have a better grasp of the physiology and the pathophysiology of neurological diseases as well as optimal management strategies in different situations [14].

The NCCU also may house residents from different backgrounds including anesthesiology, neurology, neurosurgery, and internal medicine in addition to nurses and many times nurse practitioners and/or physician assistants. As a result, residents from different subspecialities can help each other learn the nuances and intricacies of taking care of the sick patient, enhancing interdepartmental interactions and camaraderie [15].

Finally, it should be noted that trainees' neurocritical care education can take other forms as well. For example, conferences arranged by organizations such as the AAN, Neurocritical Care Society (NCS), and Society of Critical Care Medicine (SCCM) typically host many sessions that discuss neurocritical care topics. Additionally, in an attempt to disseminate knowledge regarding the neurocritically ill patient population, the NCS has developed a course called Emergency Neurological Life Support (ENLS), which helps identify and manage critically ill neurologic patients. The focus of the course, which can be taken by any healthcare provider, is to standardize management of and stabilize the neurological patient in the first hours of a neurological emergency [15].

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Nursing Training and Management in the Neurocritical Care Unit

30

Elizabeth K. Zink

Introduction

The cornerstone of neuroscience nursing is the comprehensive serial assessment of neurologic status to detect deterioration, facilitate rapid intervention, and preserve neurologic function. Neurocritical care nursing integrates the frequent and comprehensive assessment of neurologic status with monitoring and management of multiple organ systems. The neurocritical care nurse is a key member of the interprofessional care team performing frequent assessments, exercising judgment, and expertly communicating with other members of the healthcare team as well as the patient and his/her family members. Communication within the multidisciplinary team is crucial in all healthcare settings; however, due to the first-hand knowledge that the neurocritical care nurse holds in terms of neurologic status, formal and informal communication strategies for sharing information are crucial to patient care. This chapter will review recommended structure regarding the training and administration of nursing in the neurocritical care unit.

Training

Initial training in neurocritical care nursing focuses on two major themes: neurologic assessment and identification of neurologic deterioration. Patients cared for in neurocritical care units often have medical and surgical disease requiring a broad skillset from post-anesthesia care to medical care, surgical care, and trauma care. A general critical care nursing curriculum must be supplemented with additional modules on neuroanatomy, comprehensive neurologic assessment including the brain and spine, and identification and management of neurologic deterioration. Neurologic deterioration may present as increased intracranial pressure or herniation syndromes in post-operative patients after craniotomy or in patients with traumatic brain injury; respiratory failure in patients with neuromuscular disease; status epilepticus in patients with central nervous system infection; or an ascending level of motor or sensory deficit in patients with spinal cord pathology. Perturbation of other organ systems such as cardiac dysrhythmias, heart failure, hypo- or hypertension, or pulmonary edema may have unique implications for patients with central nervous system disease or injury that the neurocritical care nurse must recognize and appreciate when formulating a plan for nursing care. Table 30.1 contains a full listing of suggested topics for initial training and recommended methodology for teaching and learning. Combinations of educational approaches such as live didactic sessions with neuroscience nursing subject matter experts, e-learning modules, and simulation may be used to deliver necessary content to participants [1].

The foundation for neurocritical care nursing consists of knowledge of neuroanatomy and neurologic assessment. Neuroanatomy and neurologic assessment must be coupled in order for the nurse to begin to understand the common language that will be used by multiple disciplines to describe, assess, and treat patients. For example, one may observe a unilateral drooping of the mouth, which is localized to the seventh cranial nerve by neurologists and neurosurgeons and documented as a "central VIIth." The goal of initial education for neurocritical care nurses is to provide a foundation of knowledge whereby nurses can also translate observations to their anatomic correlates so that all disciplines are using the same nomenclature, adding precision to communication of neurologic status [2, 3].

Developing this foundation is accomplished through a combination of didactic education and hands-on training in the patient care environment. Training in the clinical arena with constant exposure to neurologic assessments performed by all members of the care team, progressing to return-demonstration with feedback is critical to skill

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Table 30.1 Topics for training and associated educational methods

Key components of education and training	Useful methods for education and training
Neuroanatomy and neurologic assessment	Didactic sessions with a clinical nursing expert E-learning modules Precepted learning experience with return-demonstration and real-time feedback on performance Didactic sessions Certifications Emergency neurologic life support Advanced cardiac life support
Identification and management of neurologic deterioration Increased intracranial pressure Herniation syndromes Intracranial pressure monitoring	Simulation, case-based instruction
Disease-specific nursing care Brain tumors Stroke, acute ischemic, intracerebral hemorrhage, and subarachnoid hemorrhage Traumatic brain injury Spinal cord injury Spinal surgery	Case scenarios Didactic sessions with a clinical nursing expert Precepted clinical assignments focusing on patients with specific disease states
Cardiac and respiratory monitoring Hemodynamic monitoring Rhythm identification Advanced cardiac life support Intubation and mechanical ventilation Non-invasive ventilation	Case scenarios Didactic sessions with a clinical nursing expert Precepted clinical assignments focusing on patients with specific disease states

mastery. Return-demonstration serves as an important evaluation tool whereby the learner is instructed in a skill and then performs the skill with or without prompts from an instructor allowing for near real-time feedback and reinforcement of good technique [4]. This teaching and evaluation technique can be used in the clinical environment or in simulation. Similar to most skills, neurologic assessment falls on a continuum of novice to expert where beginning competency aims to ensure that baseline neurologic deficits can be confirmed by a physician or mid-level provider and that deterioration from an established baseline can be detected by the nurse and reported for further evaluation and intervention [5]. Neurologic assessment is not easily simulated outside of the patient care environment; therefore, opportunities for practice need to be woven throughout the orientation process exposing the orientee to normal neurologic assessments as well as abnormal assessment features including patients with varying levels of responsiveness.

The second major focus for training in neurocritical care nursing is the identification of and interventions for neurologic deterioration. Included within this major competency is assessment, communication, and advocacy in conveying neurologic deterioration to the multidisciplinary team, knowledge of pathophysiology of deterioration and patient response, and psychomotor skills such as assisting with ventriculostomy insertion and intracranial pressure (ICP) monitoring. Development of skills and knowledge associated with neurologic deterioration, in particular increased ICP and herniation syndromes, consists of further refinement in assessing early and late signs as well as pathophysiologic concepts such the Monro-Kellie doctrine and cerebral autoregulation. The pairing of physiologic concepts and treatments facilitates understanding that assists nurses in prioritizing prescribed tasks and nursing care during neurologic emergencies. Simulation of skills such as set-up and maintenance of external ventricular drains and ICP monitoring devices can be an effective preparatory tool prior to practice in the patient care environment. Programs such as Emergency Neurologic Life Support provide learning modules and algorithms for the most common types of neurologic deterioration or emergencies during the first hour, which can enhance initial and ongoing training programs [6].

General critical care curriculum is essential in preparing the neurocritical care nurse to provide holistic care with the knowledge to assess and support all organ systems. Cardiac rhythm identification, hemodynamic monitoring, shock states, pharmacology of vasoactive medications, airway management, and mechanical ventilation are among topics that comprise general critical care core knowledge. Critical care curriculum is often delivered using one or more of the following strategies: classroom sessions, case-based simulation sessions, and online learning modules. Opportunities to reinforce didactic learning in the clinical environment are important to consider during the orientation period.

Disease-specific care is included through the design of case-based learning using common disease states cared for in the neurocritical care unit such as subarachnoid hemorrhage, intracerebral hemorrhage, acute ischemic stroke with thrombolysis and endovascular intervention, traumatic brain injury, central nervous system infection, and seizures and status epilepticus among other disease states. National guidelines such as those developed by the American Stroke Association and the Brain Trauma Foundation should be used to ensure that evidence-based standards are incorporated into teaching [7, 8].

Team Communication in Neurocritical Care

Optimal team communication can be hard-wired into unit culture during the development stages with multidisciplinary input. Successful strategies for facilitating daily input of all team members such as nurses, physicians, mid-level providers, pharmacists, and respiratory therapists include

bedside interprofessional rounds guided by a rounding script [9]. Gonzalo and colleagues found that the use of a standard rounding script and support of unit leadership were two factors associated with the incidence and sustainability of bedside interprofessional rounds [9]. An example of a standard rounding script used in a neurocritical care unit where nurses lead the rounding process is pictured in Fig. 30.1. Bedside interdisciplinary rounds are particularly important in neurocritical care due to the significance of determining a baseline for a patient's neurologic status as a team and documenting agreement against which future assessments can be compared. In fact, additional brief rounding periods particularly when team members are changing may be important in ensuring communication of current neurologic status and a patient's response to planned interventions.

Similar to the importance of interprofessional rounding, bedside nurse-to-nurse shift report is an important facilitator of continuity from shift to shift. One-to-one handoff where oncoming and off-going staff can view the neurologic assessment together enhances continuity of care and prevents potential errors or miscommunication that can occur with gaps in information-sharing during hand-off. For example, the character and strength of motor function and pupillary size and reaction is known to vary between raters at times leading to unnecessary testing to rule out an actual neurologic change versus measurement variation between clinicians. Tools similar to the rounding script in Fig. 30.1 can be used for multiple purposes including nurse-to-nurse hand-off in addition to the medical record.

At the unit level, communication and decision-making regarding unit processes such as patient-flow, interprofessional workflow, technology acquisition, and policy development or revision can be accomplished successfully with an interprofessional oversight group of leaders and peers. Oversight group members are charged with the responsibility of obtaining feedback from colleagues on issues to be presented to the group so that practice decisions are made on behalf of all health care team members. Neurocritical care is rapidly changing with advances in medical therapeutics, patient monitoring, and new evidence-based interventions

DATE: **ALLERGIES:** **NCCU ROUNDS WORKSHEET** **CODE STATUS:** **ROOM:**

NAME: Dx/OPERATION AGE ICU DAY POD (SAH) post- bleed day

Past Medical History:

DATA	ISSUES/GOALS/PLAN
NEURO Sedation: RASS Goal: RASS range: Exam: LOC: GCS: ___ CAM-ICU: _____ Pupils: CN: Motor: RUE____ LUE _____ RLE _____ LLE _____ CT/MRI (Date/Results): TCD Results: ICP monitor or LD Day: PO: ICP: CPP: 24 hr CSF: GOALS: _____ Labs: Na/K q_____ Hypertonic saline: _____ Steroids: AED: Level: ( ) Other: Pain: Scores: Rx:	
RESTRAINTS: ☐ Yes ☐ No ☐ order placed during rounds	
CARDIAC Goals: BP/MAP Range: Rx: HR Range: Rhythm: Rx: FLUID BALANCE: I:_____ O:_____ Net:_____ TF: IVF: CVP: Labs: PT/PTT q _____ H8 q _____ Lines: _____ ***Please pose these questions to providers during rounds:*** **Does patient still require a central line? ☐ Yes ☐ No ☐ NA ☐** **Does patient still rewqire an arterial line? ☐ Yes ☐ No ☐ NA ☐**	**Must have for rounds- Today's weight:** _____ (_____) yesterday
RENAL: Na: K : CO2: BUN/Creat Cl: Ica: Mg: Phos: Electrolyte Replacement: Hourly U/O:_____ **Can foley catheter be discontinued? ☐Yes ☐No** Renal replacement therapy: IHD CVVH net fluid goal mL/hr	
DATA	**ISSUES/GOALS/PLAN**
HEME: H/H: Plt: PT/PTT/INR: DVT prophylaxis: SCDs ☐ SQ heparin: _____ Platelet antagonists (e.g., ASA, Plavix) Labs: PT/PTT Q:_____ H8Q_____ Heparin infusion current rate units/hour:_____ aPPT goal:_____	

Fig. 30.1 An example of a rounding script organized by organ system and specialty focus and customized to the interdisciplinary practice of neurocritical care. (Used with permission of the Johns Hopkins Hospital, Neurosciences Critical Care Unit)

affecting care such as mitigation of hospital acquired infections and early rehabilitation interventions.

Role of Policies and Procedures in the Neurocritical Care Unit

Development of policies and procedures specific to patients and processes in the neurocritical care unit assist in standardizing care where possible and setting expectations or guidelines where the lack of evidence makes standardization suboptimal. Unit-specific policies and procedures create structure and standard expectations of the healthcare team pertaining to specific topics such as admission and ongoing monitoring of patients during their neurocritical care course, admission and discharge criteria, management of temperature in normothermic or hypothermic ranges, and management of multi-modality monitoring. A process for regular review and revision of policies is necessary to maintain relevance and ensure that best practices are identified and updated in a timely manner. Engaging nursing staff as active members of the multidisciplinary team in the development and review of policies is essential in ensuring realistic expectations that support practice at the bedside.

Summary

The practice of neurocritical care nursing is based largely in physical assessment and judgment rooted in a firm grasp of neuroanatomy and neurologic assessment. Early detection of deterioration can be life-saving particularly in patients with neurologic pathology, and neurocritical care nurses are central to the mission of identifying and intervening as early as possible to prevent or mitigate brain injury. Rapid and appropriate prioritization of care is based on knowledge of treatment rationale, which is facilitated by detailed knowledge of physiologic concepts such as increased ICP and cerebral autoregulation. Optimal team communication supported by unit processes and leadership support and exemplified by interprofessional rounds creates an environment for the neurocritical care nurse to optimally contribute as an integral team member to patient care.

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