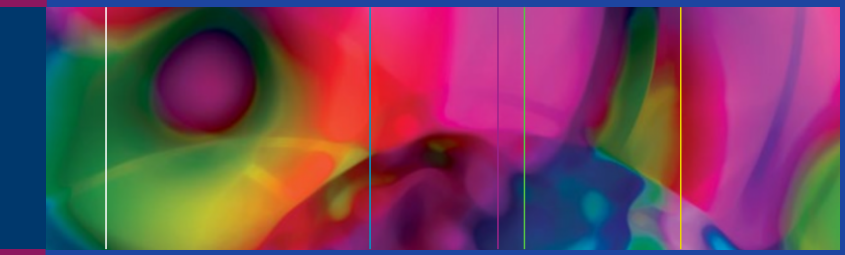
Jessica L. White
Kevin N. Sheth *Editors*



Neurocritical Care for the Advanced Practice Clinician

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Dedicated to our colleagues in the Neuro ICU – the nurses, physicians, and advanced practice clinicians who commit themselves to providing compassionate care for the neurologically ill.

And to our patients and their families – the practice and art of critical care neurology is our service to them.

Acknowledgment

This project strives to highlight the professional collaboration between advanced practice clinicians and physicians as part of a multidisciplinary team. We are grateful to our contributors for exemplifying this collaboration by generously sharing their expertise and experience in the field of neurocritical care.

We would like to thank the Yale University Neurocritical Care faculty and APC staff for their encouragement and feedback through this process. And special thanks to Guido Falcone for his editorial assistance. We are privileged to work everyday with such a phenomenal team.

Contents

Chapter 1
The Role of Advanced Practice Clinicians in the Neuroscience ICU

Jessica L. White and Kevin N. Sheth

The field of neurocritical care encompasses a broad range of neurological pathology and requires a multidisciplinary approach to provide best patient care. At institutions across the country, physicians work alongside physician assistants and nurse practitioners to care for neurologically ill patients. This collaborative relationship serves to provide an ideal complement of specialized medical knowledge and experienced bedside care. Stemming from a historical genesis in primary care practice, the fundamental education of nurse practitioners and physician assistants is general by design, including basic principles of medical science and clinical management. This educational foundation offers the benefit of professional flexibility and the ability to adapt to a myriad of subspecialties; however, such adaptation requires continued focused learning when entering a subspecialty to acquire advanced understanding of patient care. Recognizing this challenge, we embarked on a

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project to meet the knowledge needs of physician assistants and nurse practitioners that have selected neurocritical care as their field of practice.

Many terms have been used to describe the collective role of physician assistants and nurse practitioners—midlevel provider, nonphysician provider, and advanced practice provider among them. For the purposes of this project, the term advanced practice clinician (APC) is used to encompass both professions. The role of APCs has evolved considerably over the past several decades. Both professions were developed in the 1960s to adjunct a shortage of primary care providers in the United States. The implementation of restrictions on house staff work hours in the 1990s set the stage for the rapid expansion of the APC role into the hospital setting [1, 2]. This role of APCs working in inpatient medicine has grown substantially since that shift. In 1995 the acute care nurse practitioner certification was developed for the purpose of focusing training on caring for critically ill patients. This certification now represents the fifth most common area of practice for nurse practitioners [3]. Similarly, a hospital medicine specialty certification is available for physician assistants and ~25% of these professionals now work in hospital settings [4]. As the medical community is faced with continued projections of physician shortages across the board, the role of APCs in the inpatient realm is projected to increase [1, 2, 5]. The field of neurocritical care has experienced significant growth in recent years, outpacing the growth of residency and fellowship training programs. Across the country, this rapid expansion has provided a considerable opportunity for APCs to enter the field of neurocritical care and work in a dynamically evolving area.

Given this shift in scope of practice, it has been imperative to provide APCs with the training and experience necessary to provide exemplary care to the critically ill. In intensive care units across the country, it has been shown that nurse practitioners and physician assistants provide appropriate medical care to ICU patients, as measured in rates of morbidity and mortality [6, 7]. Beyond these measurements, there are also established

benefits of integrating APCs into intensive care units. APCs offer a unique level of experience and continuity of care that can result in improved compliance with clinical guidelines [8], decreased length of stay, and overall cost savings [9–11].

Intensive care units have integrated APCs in a variety of ways—some by developing units staffed by APCs alone, others by creating multidisciplinary teams of APCs and physicians. Regardless of the chosen structure, APC staffing can aid in providing sustained clinical expertise to bedside care, particularly in settings where house staff work on rotating schedules. In the challenging environment of the intensive care unit, the presence of seasoned clinicians to give support to physicians-in-training provides significant benefits. Survey data from academic institutions indicate that APCs are perceived as an effective complement to physicians-in-training, enhancing patient care through improved communication and continuity of care [12]. Furthermore, APCs contribute to the training of residents by reducing their workload, reducing patient-to-provider ratios, and increasing didactic educational time [13].

The neurocritical care community has experienced this shift in staffing along with the rest of the critical care realm. In keeping with broader trends, APCs working in neurocritical care are seen as promoting effective communication, a team environment, and, most importantly, timely identification of patients with neurological deterioration [14]. However, this impact does not come without dedicated learning and experience. The field of neurocritical care includes a unique spectrum of neurological disease and much of the expertise required to skillfully care for neuroscience ICU patients is not addressed in the general education of the APCs. The purpose of this book is to bridge the gap between the foundational medical education of APCs and the fundamentals of the neurocritical care subspecialty. By discussing common neurocritical topics as presented by a multidisciplinary collection of leaders in the field, we hope to engage and empower the continued expansion of the role of advanced practice clinicians in neurocritical care.

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Chapter 2
Neuroanatomy

Laura A. Lambiase, Elizabeth M. DiBella, and Bradford B. Thompson

2.1 Skull, Fossae, and Meninges

The cranium is composed of multiple bones that act as a protective container for the brain (Figs. 2.1 and 2.2). It is composed of the *frontal bone*, which articulates with the two *parietal bones* at the coronal suture. The parietal bones meet at the midline and are joined by the sagittal suture. The *temporal bones* lie inferior to the parietal bones and posterior to the greater wing of the *sphenoid bone*. The *occipital bone* meets the parietal bones at the lambdoid suture and protects the posterior surface of the brain. At the base of the occipital bone, there is a large opening, the *foramen magnum*, through which the spinal cord connects to the brainstem. A series of smaller bones including the *zygomatic, ethmoid, maxilla, mandible, nasal, vomer* and *lacrimal bones* comprise the complex facial surface of the skull [6, 7].

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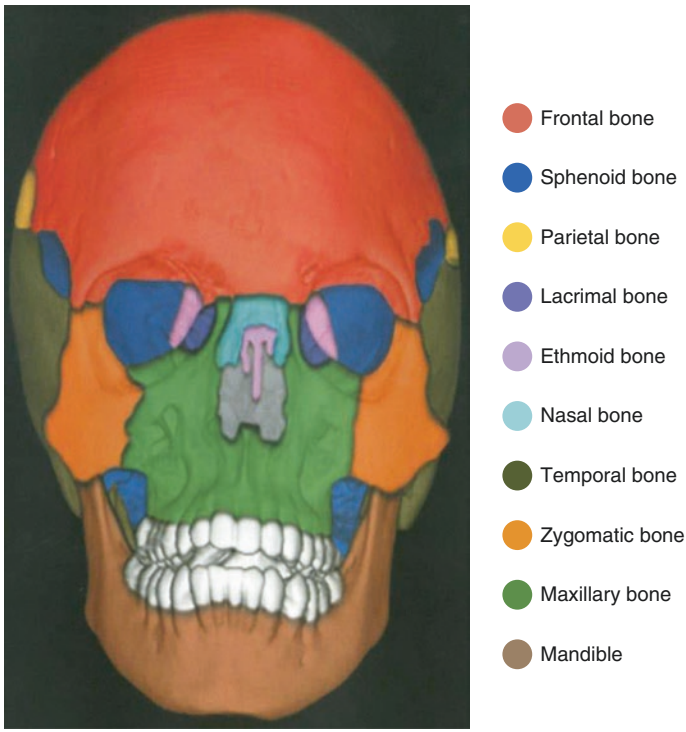

Fig. 2.1 Bones of the cranium (Used with permissions from Gallici et al. [2])

The bones of the skull articulate to form three distinct fossae: anterior, middle, and posterior (Fig. 2.3). The *anterior fossa* is formed by the frontal, ethmoid, and sphenoid bones and contains the anterior and inferior aspects of the frontal lobes. The *middle fossa* is formed by the sphenoid and temporal bones and contains the temporal lobes. Additionally, the *sella turcica* of the sphenoid bone provides a protective seat for the pituitary gland within the hypophysial fossa. The *posterior fossa* is

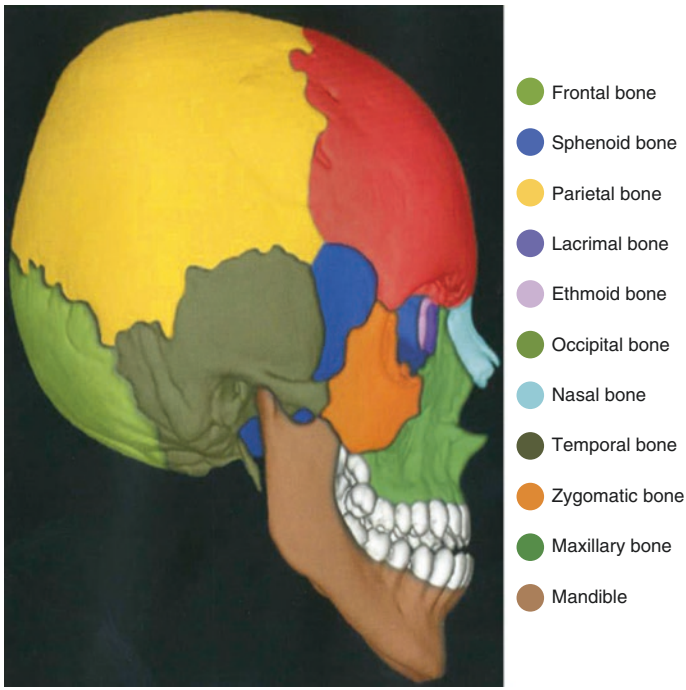

Fig. 2.2 Bones of the cranium (Used with permissions from Gallici et al. [2])

predominantly formed by the occipital bone with small contributions from the sphenoid and temporal bones—it contains the brainstem and the cerebellum.

The brain is covered in three layers of protective meninges, which work with the skull and cerebrospinal fluid (CSF) to blunt the effects of insults to the brain. The *dura mater* is the thickest fibrous external layer, which adheres to the internal surface of the cranium. The dura can be dissected into two distinct layers: the periosteal layer, which connects the dura to the skull, and the meningeal layer, which lies more medially. The

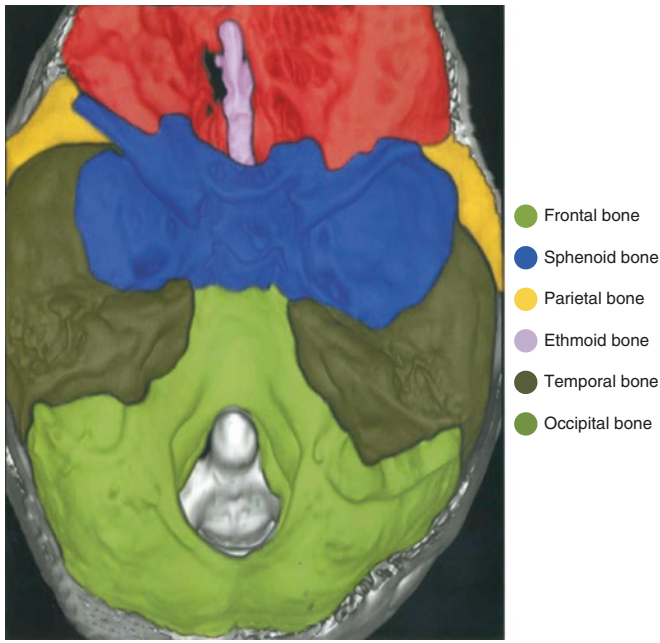

Fig. 2.3 Cranial fossa (Used with permissions from Gallici et al. [3])

dura mater folds in on itself in the interhemispheric fissure to create the *falx cerebri*. An additional dural fold creates the *tentorium cerebelli*, separating the cerebral hemispheres from the cerebellum. While these dural folds provide structure to the brain, they constitute sites of potential herniation in the setting of space occupying lesions or cerebral edema.

The *arachnoid mater* lies medial to the dura mater. The subarachnoid space separates the arachnoid and pia mater. Small fibrous strands called trabeculae tether the arachnoid and pia to one another. The CSF in this space serves as another protective buffer for the brain. The *pia mater* is the thinnest meningeal

layer and is adherent to the brain. This layer is highly vascular and provides oxygen and nutrients to the brain [6, 7, 15].

Clinical Correlate

- With traumatic injury, there is potential for bleeding between the skull and dura (epidural hematoma), between the dura and arachnoid meninges (subdural hematoma), or within the subarachnoid space (subarachnoid hemorrhage). (See Chap. 10 for further clinical information).
- An epidural hematoma occurs most commonly when a temporal bone fracture severs the middle meningeal artery, although venous bleeding can also be a cause.
- A subdural hematoma is most often caused by tearing of the bridging veins in the subdural space.
- Subarachnoid hemorrhage can occur in a number of conditions, including rupture of a cerebral aneurysm and trauma.

2.2 Cerebrum

The *cerebrum* constitutes the bulk of the brain and is the area responsible for intellectual thought and function. The *cerebral cortex* is the circumferential gray matter on the surface of the brain that covers the white matter and the deeper gray matter structures. The cortex folds to create raised *gyri* and sunken grooves called *sulci*.

The cerebrum is separated into two hemispheres by the interhemispheric fissure and connected by a bundle of nerves called the *corpus callosum*. Each hemisphere contains a frontal, parietal, temporal, and occipital lobe (Fig. 2.4). The *frontal lobe*

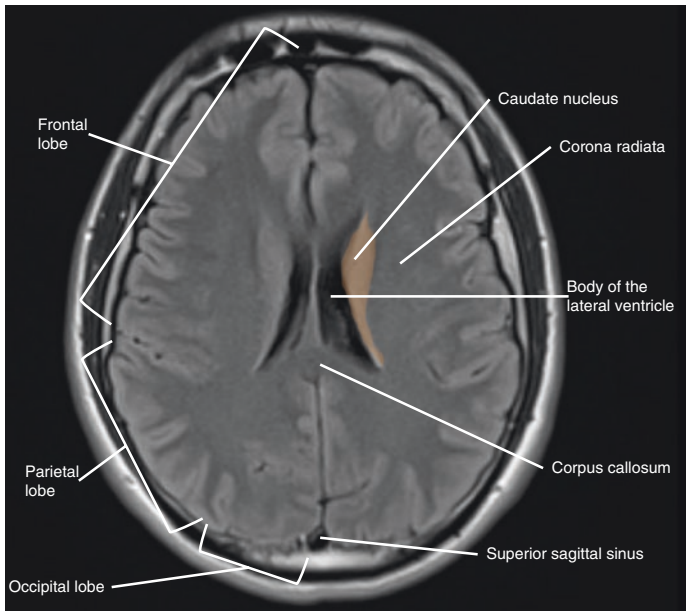

Fig. 2.4 Cerebrum (Flair sequence MRI brain)

is anterior to the central sulcus that separates the frontal and parietal lobes. The frontal lobe is the site of abstract reasoning, judgment, behavior, creativity, and initiative. The *parietal lobe* is involved in language, maintaining attention, memory, spatial awareness, and integrating sensory information including tactile, visual, and auditory senses [8]. The lateral (or Sylvian) fissure separates the parietal and frontal lobes from the temporal lobe. The *temporal lobe* processes sensory input such as language, visual input, and emotions. Tucked deep within the lateral fissure lays the *insula*, which is involved with emotion and consciousness. The *occipital lobe* is the most posterior lobe of the cerebrum and is separated from the parietal and temporal lobes by the parieto-occipital fissure. The occipital lobe con-

tains the primary visual cortex and is involved in sight and interpretation of visual stimuli. On the medial surface of each cerebral hemisphere, the *limbic cortex* modulates emotion, behavior, and long-term memory [5].

Clinical Correlate

- In a majority of people, the left hemisphere is dominant, being responsible for language production and comprehension. This is true for both right-handed (90% left dominance) and left-handed individuals (70% left dominance).
- In the dominant hemisphere, Broca's area in the frontal lobe is responsible for fluent speech. Damage to this region causes expressive aphasia. Wernicke's area, located in the temporal lobe of the dominant hemisphere, is responsible for comprehension. Damage to Wernicke's area causes receptive aphasia.
- Damage to the nondominant hemisphere can cause unilateral neglect of the contralateral side and apraxia, which can impact activities of daily living and lead to spatial disorientation.

2.3 Diencephalon

The diencephalon is composed of the thalamus and hypothalamus. The *thalami* are bilateral relay stations for sensory information located medial to the internal capsule and lateral to the third ventricle. They initiate reflexes in response to visual and auditory stimuli. Sensory fibers ascend from the brainstem to the thalamus and then their signals are relayed to the cortex.

The *hypothalamus* is connected inferiorly to the *pituitary gland*; together, these structures regulate many hormonal activities within the body. The anterior lobe of the pituitary gland (adenohypophysis) secretes hormones including adrenocorticotrophic hormone, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, prolactin, and melanocyte-stimulating hormone in response to signals from the hypothalamus. The posterior lobe (neurohypophysis) contains axons extending from the hypothalamus that secrete oxytocin and vasopressin [11].

Clinical Correlate

- After pituitary surgery, central diabetes insipidus can develop due to reduced secretion of antidiuretic hormone (vasopressin). Patients develop excessive urine output with resultant hypovolemia and hypernatremia.

2.4 Basal Ganglia

The *basal ganglia* are the deep gray matter structures consisting of the caudate nucleus, globus pallidus, and putamen (Fig. 2.5). The basal ganglia relay information from the cortex and work with the cerebellum to coordinate movement. They are responsible for the initiation and termination of movements, prevention of unnecessary movement, and modulation of muscle tone.

2.5 Brainstem

The *brainstem* consists of three components: midbrain, pons, and medulla. It contains critical structures, such as the cranial nerve nuclei, regulates several autonomic functions and basic reflexes, and determines the level of consciousness (Figs. 2.6–2.9).

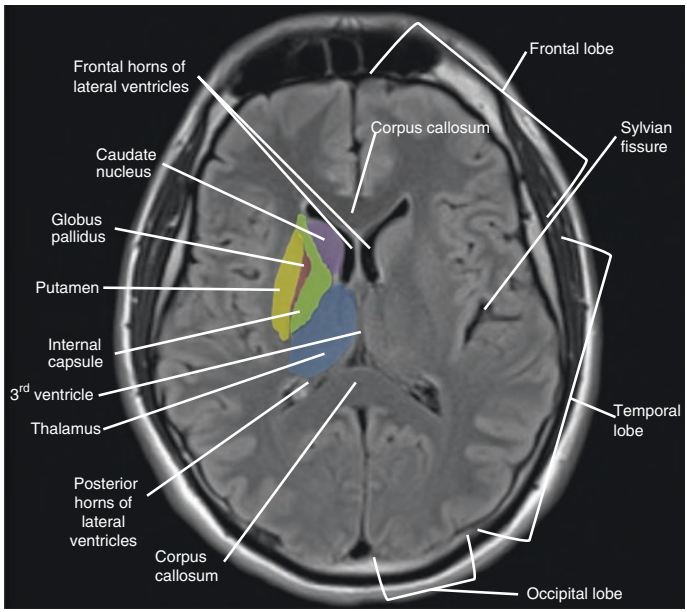

Fig. 2.5 Basal ganglia (Flair sequence MRI brain)

The descending motor and ascending sensory pathways pass through the brainstem. The reticular activating system resides in the rostral brainstem and projects to the thalami and then the cortex to maintain wakefulness. Damage to this structure results in decreased level of arousal or coma.

2.6 Cerebellum

The *cerebellum* is located posterior to the brainstem (Figs. 2.7, 2.8 and 2.9). The cerebellum works in tandem with the basal ganglia to provide smooth coordinated movement. Damage to the cerebellum causes limb ataxia, vertigo, and gait disturbances.

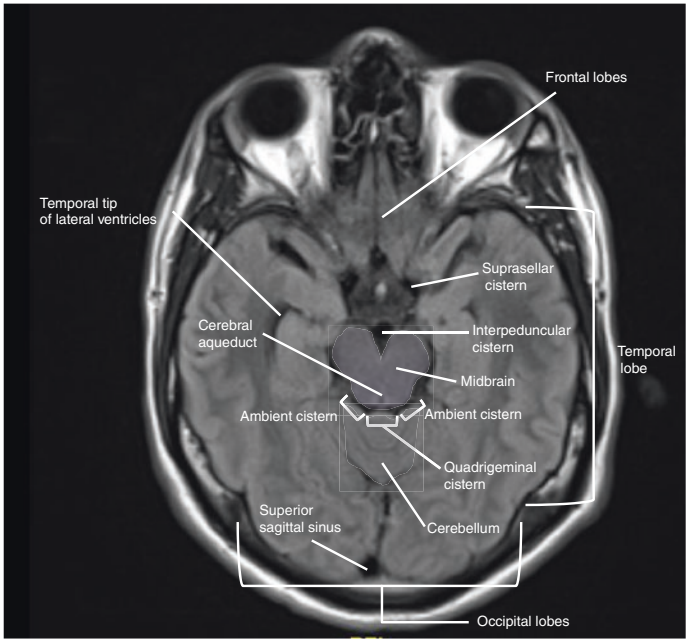

Fig. 2.6 Midbrain and cisterns (Flair sequence MRI brain)

2.7 Cerebral Vasculature

The arterial supply to the brain is divided into anterior and posterior circulations. The anterior circulation originates from bilateral *internal carotid arteries* (ICA). Each ICA travels superiorly through the neck and enters the cranium via the carotid canal within the temporal bone. The ICA then bifurcates into the *anterior cerebral artery* (ACA) and the *middle cerebral artery* (MCA). The ACA supplies the anterior medial surface of the brain, which includes the frontal and anterior parietal lobes. The

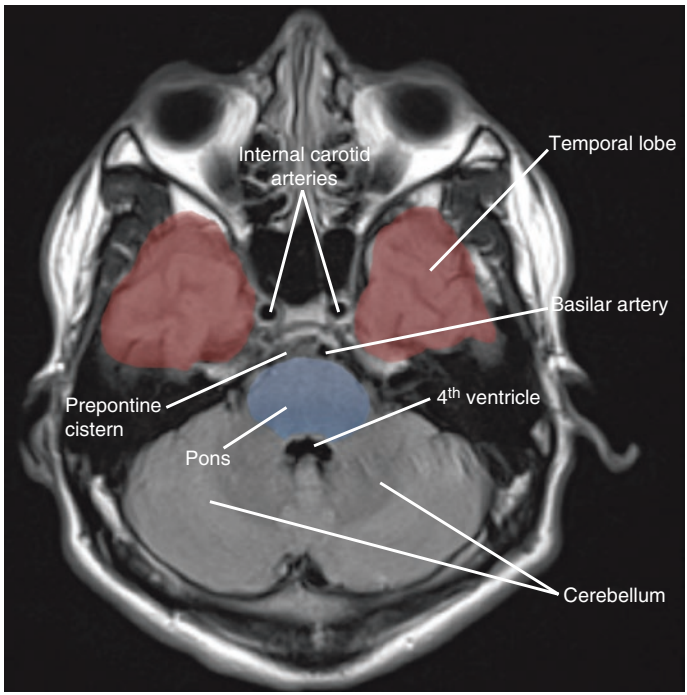

Fig. 2.7 Pons and posterior fossa (Flair sequence MRI brain)

MCA supplies the bulk of the cerebral hemisphere. It typically divides into *superior* and *inferior divisions* as it passes through the lateral fissure. These divisions supply the cortex superior and inferior to the lateral fissure, respectively. Prior to this bifurcation, several small vessels called the *lenticulostriate arteries* arise from the MCA. These vessels provide the blood supply for a majority of the basal ganglia and internal capsule.

The posterior circulation is supplied by bilateral *vertebral arteries* (VA). They travel superiorly through the transverse

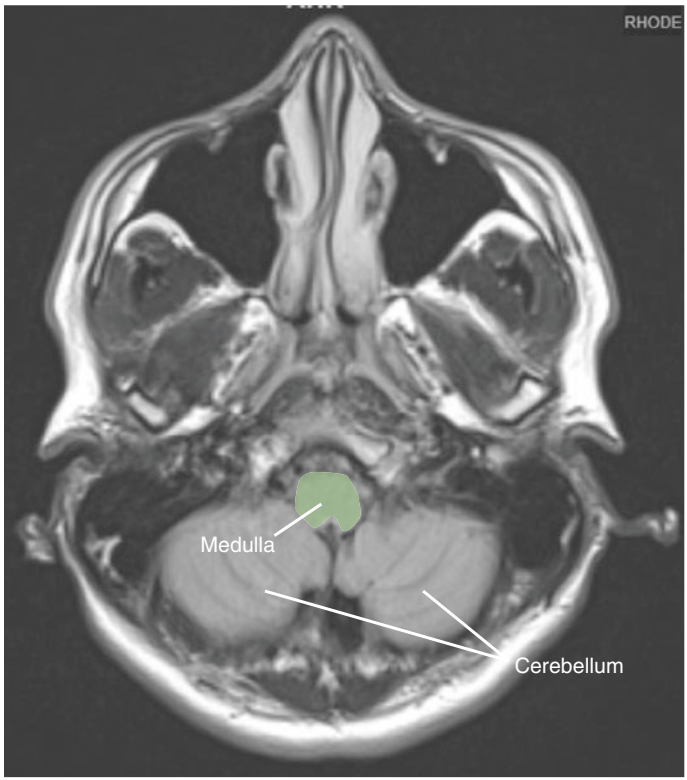

Fig. 2.8 Medulla and posterior fossa (Flair sequence MRI brain)

processes of the cervical vertebrae and then the foramen magnum to enter the skull. The VAs then merge to form the *basilar artery* (BA), which in turn branches into bilateral *posterior cerebral arteries* (PCA). The PCAs supply the inferior and medial temporal lobes as well as the occipital lobes. There are three major paired branches which arise from the posterior circulation to perfuse the brainstem and cerebellum. The *posterior inferior cerebellar artery* (PICA) arises from the VA and supplies the lateral medulla and

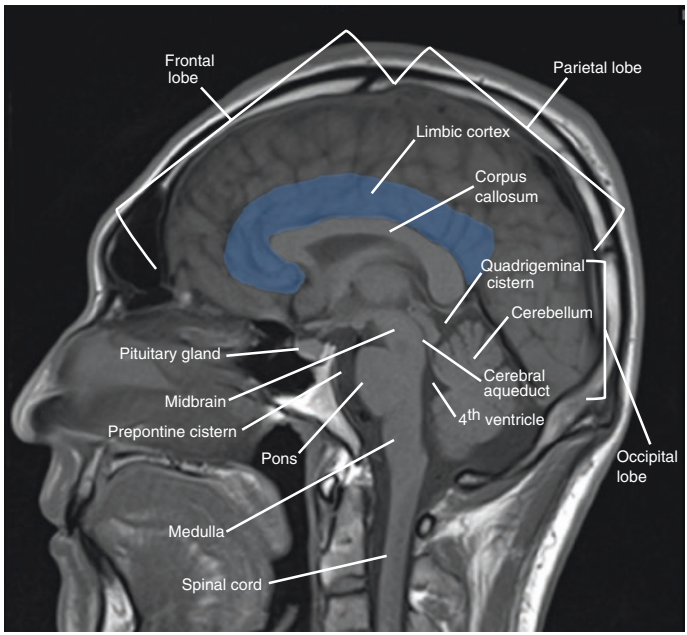

Fig. 2.9 Sagittal view (Flair sequence MRI brain)

inferior cerebellum. The *anterior inferior cerebellar artery* (AICA) arises from the lower BA and supplies part of the pons, the middle cerebellar peduncle, and an anterior strip of the cerebellum. The *superior cerebellar artery* (SCA) arises near the top of the BA and supplies the upper pons, the superior cerebellar peduncle, and the superior half of the cerebellum. The BA also supplies the brainstem directly via small perforating arteries.

The two halves of the anterior circulation are connected at the ACAs via the *anterior communicating artery*. The anterior and posterior circulations are connected via bilateral *posterior communicating arteries* which join the ICAs and the PCAs. Together, these arteries form an anastomotic ring at the base of the brain which is referred to as the *Circle of Willis*. (Fig. 2.10) [12].

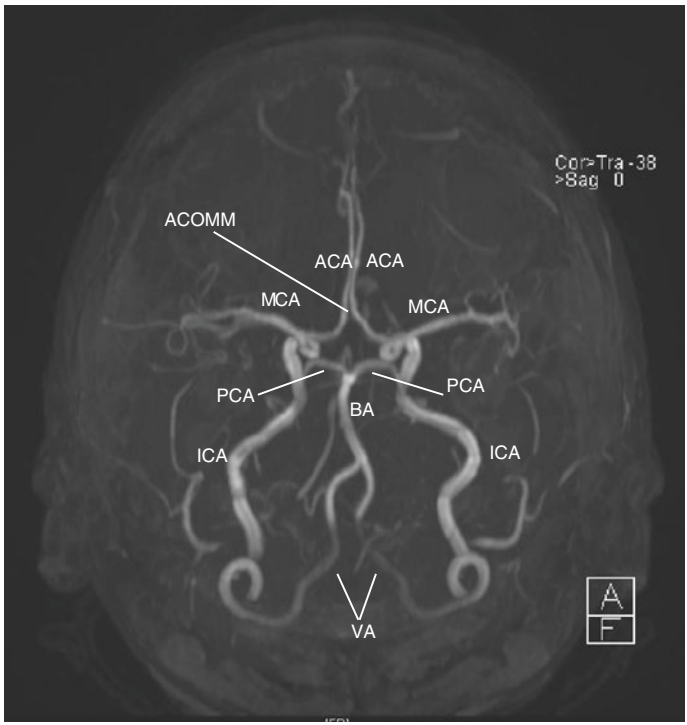

Fig. 2.10 Vascular anatomy (MRA)

Clinical Correlate

- Large-vessel occlusions, due to embolism (such as from atrial fibrillation) or in situ thrombosis, lead to specific stroke syndromes. For example, a left MCA infarction results in aphasia, right hemiparesis, and left gaze preference amongst other symptoms.
- Chronic hypertension causes damage to the lenticulostriate and pontine perforator arteries. This can lead to

a lacunar infarct or vessel rupture, resulting in intraparenchymal hemorrhage.
- The branch points of the Circle of Willis are typical sites of aneurysm formation. Aneurysmal rupture leads to subarachnoid hemorrhage.

Venous drainage is more variable than arterial supply. The anterior and superior cortical veins drain into the *superior sagittal sinus* (Fig. 2.6), which traverses posteriorly between the falx cerebri and the skull. At the level of the tentorium cerebelli it divides into two *transverse sinuses* at the *confluence of sinuses (torcula)*. Each transverse sinus receives direct drainage from more inferior and lateral cortical veins. They then each continue inferiorly to become the *sigmoid sinuses* and ultimately the *internal jugular veins*. Other superficial veins drain into the *cavernous sinuses* along either side of the sella turcica. The cavernous sinuses drain into the *superior petrosal sinus* and then the transverse sinus, or into the *inferior petrosal sinus* and then the internal jugular vein.

The deep cerebral veins drain into the *internal cerebral veins*, the *basal veins of Rosenthal*, and the *great vein of Galen*. The great vein of Galen then joins the *inferior sagittal sinus* to form the *straight sinus*, which joins the superior sagittal sinus at the confluence of sinuses.

2.8 Ventricles

The main role of the ventricular system and the CSF within it is to cushion the brain (Figs. 2.4, 2.5 and 2.7). Within the ventricles, the *choroid plexus* produces approximately 450 mL of

CSF each day, which circulates through the ventricular system and subarachnoid space before being drained into the venous system, where it is reabsorbed by the *arachnoid granulations*. At any given time, there is approximately 150 mL of CSF within the ventricular system. The two *lateral ventricles* are large, C-shaped structures that lie within the cerebral hemispheres and connect to the *third ventricle* through the *intraventricular foramina* (foramina of Monro). The third ventricle lies midline within the diencephalon and projects posteroinferiorly to the *cerebral aqueduct* in the midbrain. The cerebral aqueduct connects to the *fourth ventricle* between the brainstem and the cerebellum. CSF then drains from the fourth ventricle into the subarachnoid space through the *median aperture* (foramen of Magendi) and two *lateral apertures* (foramina of Lushka). The subarachnoid space contains a series of cisterns including the cisterna magna, premedullary cistern, prepontine cistern, cerebellopontine cistern, suprasellar cistern and the perimesencephalic cisterns (ambient, quadrigeminal and interpeduncular) [15].

Clinical Correlate

- Hydrocephalus occurs when CSF production outstrips CSF reabsorption or when CSF flow is obstructed. Hydrocephalus is categorized as communicating, when there is diffuse dysfunction of the arachnoid granulations; or noncommunicating, when there is an obstruction to CSF flow within the ventricular system. Hydrocephalus can be treated with an extraventricular drain which provides an outlet for excess CSF. For long-term CSF diversion, a ventriculoperitoneal shunt may be placed.

2.9 Cranial Nerves

There are 12 pairs of *cranial nerves* (*CN*), which arise directly from the brain and exit the skull through foramina or fissures in the cranium. (See Table 2.1 Cranial nerves) [3].

Table 2.1 Cranial nerves [3]

Cranial nerve	Name	Brainstem nucleus location	Main functions
I	Olfactory		Smell
II	Optic		Vision
III	Oculomotor	Midbrain	Eyelid retraction; eye elevation, adduction, depression, and external rotation; pupil constriction
IV	Trochlear	Midbrain	Eye depression and internal rotation
V	Trigeminal	Pons (also Midbrain and Medulla)	Sensation of face; mastication
VI	Abducens	Pons	Eye abduction
VII	Facial	Pons	Facial movement
VIII	Vestibulocochlear	Pons	Hearing; vestibular sense
IX	Glossopharyngeal	Medulla	Taste from posterior third of tongue; gag reflex
X	Vagus	Medulla	Swallowing; parasympathetic innervation of much of the body
XI	Accessory	Medulla	Shoulder shrug (trapezius muscle) and neck rotation (sternocleidomastoid muscle)
XII	Hypoglossal	Medulla	Tongue movement

Clinical Correlate

- Compression of the CN III causes a "down and out" deviation of the eye, dilated, unreactive pupils, and ptosis. Subacute and chronic conditions, like aneurysms of the posterior communicating artery, produce the full clinical syndrome. Acute and hyperacute conditions, like lateral transtentorial (uncal) herniation of the medial temporal lobe (uncus), initially compress the external parasympathetic fibers of the nerve, causing pupillary dilatation only.

2.10 Spinal Column and Spinal Cord

The *spinal column* protects the spinal cord, much like the cranium protects the brain. There are 24 vertebrae separated by intervertebral discs articulating in a long, bony column. Each vertebra has a weight-bearing body and a vertebral arch formed by two pedicles and two laminae. Two transverse processes project posterolaterally off the vertebral column at the junction of the pedicles and laminae. A single spinous process projects posteroinferiorally at the articulation of the two laminae. There are 7 cervical, 12 thoracic, and 5 lumbar vertebrae, plus the sacrum and coccyx. The *spinal cord* courses through the vertebral foramen and together they form a continuous vertebral canal. While the canal is continuous from the first cervical vertebral level (C1) to the sacrum, the spinal cord terminates at approximately the second lumbar vertebral level (L2) as the *conus medullaris*. Below this level, spinal roots continue caudally creating the *cauda equina* within a CSF-filled subarachnoid space called the *lumbar cistern*. The cord is tethered to the meninges by the *filum terminale* and bilateral *denticulate ligaments*. Within the vertebral canal, the cord is covered in protective meninges that are continuous with the meninges covering the brain.

The spinal cord is composed of gray matter surrounded by white matter. The gray matter is divided into anterior (ventral) and posterior (dorsal) horns. The *anterior horns* contain the motor neurons that relay motor signals to skeletal muscles. The *dorsal horns* receive sensory information from the peripheral nervous system via the dorsal roots.

The intervertebral foramina allow spinal nerves to leave the column to communicate with the peripheral nervous system. The spinal cord gives off ventral motor spinal roots and receives dorsal sensory spinal roots. These roots converge to form *spinal nerves*.

The blood supply for the spinal cord consists of the anterior and posterior spinal arteries, which arise from the vertebral arteries and segmental branches from the aorta. The *anterior spinal artery* supplies the anterior two-thirds of the cord. The two *posterior spinal arteries* supply the posterior one-third of the cord including the dorsal horns. The largest of the segmental arteries from the aorta is the *artery of Adamkiewicz* [13, 14].

Clinical Correlate

- The lumbar cistern is the site for spinal fluid sampling by lumbar puncture.
- Abdominal aortic aneurysm surgery can be complicated by laceration or occlusion of the artery of Adamkiewicz. This can result in a spinal cord infarction and paraparesis below the level of the lesion.

2.11 Spinal Tracts

Descending tracts transmit motor impulses from the cerebrum through the brainstem and on to the spinal cord and peripheral nervous system to initiate motor responses, while ascending tracts transmit sensory information from the peripheral nervous system through the spinal cord and brainstem to the cerebral cortex.

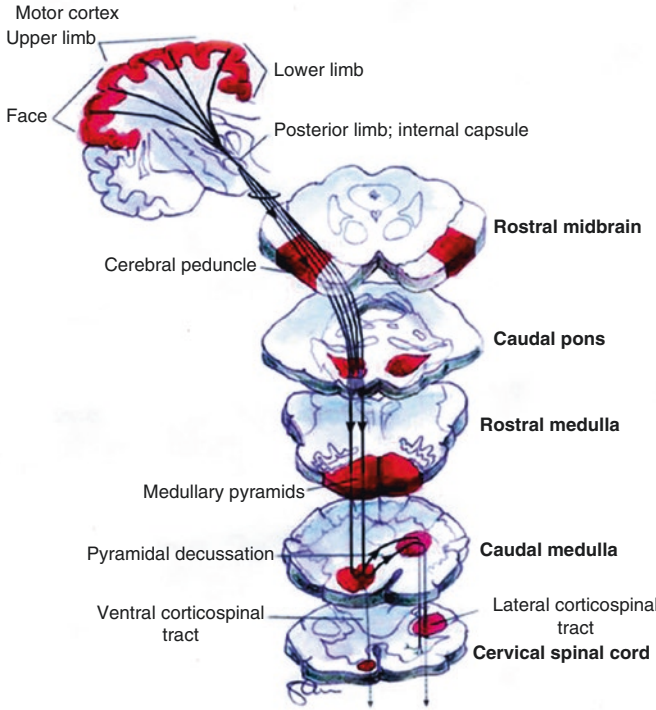

Fig. 2.11 Corticospinal tract (Used with permissions from Jacobson and Marcus [4])

The *corticospinal tract* (Fig. 2.11) is a descending motor tract. It is responsible for voluntary movement of the contralateral side of the body. The cell bodies of first-order neurons are located in the primary motor cortex. Their axons traverse the corona radiata and course through the posterior limb of the internal capsule, through the cerebral peduncles of the midbrain, the ventral pons, and then the medullary pyramids where they decussate and enter the lateral white matter of the spinal cord. They then synapse with the second-order neurons in the anterior horn of the spinal cord. The second-order neurons exit the

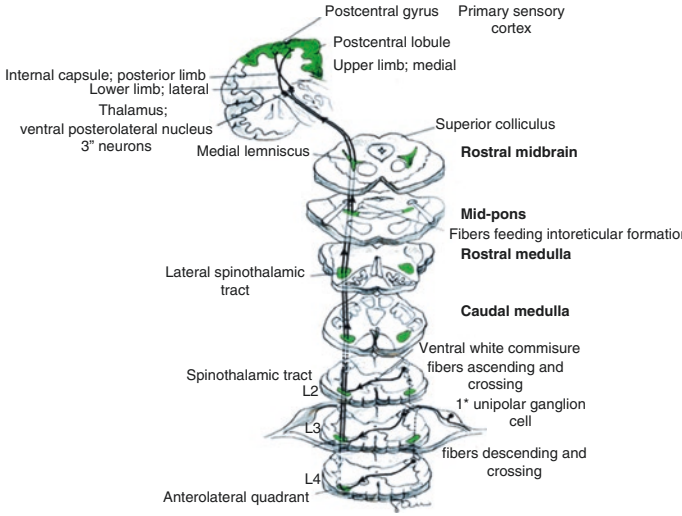

Fig. 2.12 Spinothalamic tract (Used with permissions from Jacobson and Marcus [4])

anterior horn, form the ventral spinal root, join the spinal nerve, and then relay information to muscles throughout the body [3].

The *spinothalamic tract* (Fig. 2.12) is the ascending sensory tract that relays pain and temperature sensation. First-order neurons enter the spinal cord through the spinal nerve and dorsal spinal root before immediately synapsing in the dorsal horn. Second-order neurons decussate over one to two levels and continue caudally in the contralateral anterolateral white matter of the spinal cord. They continue through the brainstem and then synapse in the thalamus. Third-order neurons project to the primary somatosensory cortex of the parietal lobe [3, 9].

The *posterior column tract* (Fig. 2.13) is an ascending tract that conveys the sensations of fine touch, vibration, and proprioception. The first-order neurons enter the spinal cord via the dorsal root and ascend through the ipsilateral dorsal column to the lower medulla, where they synapse. Second-order neurons

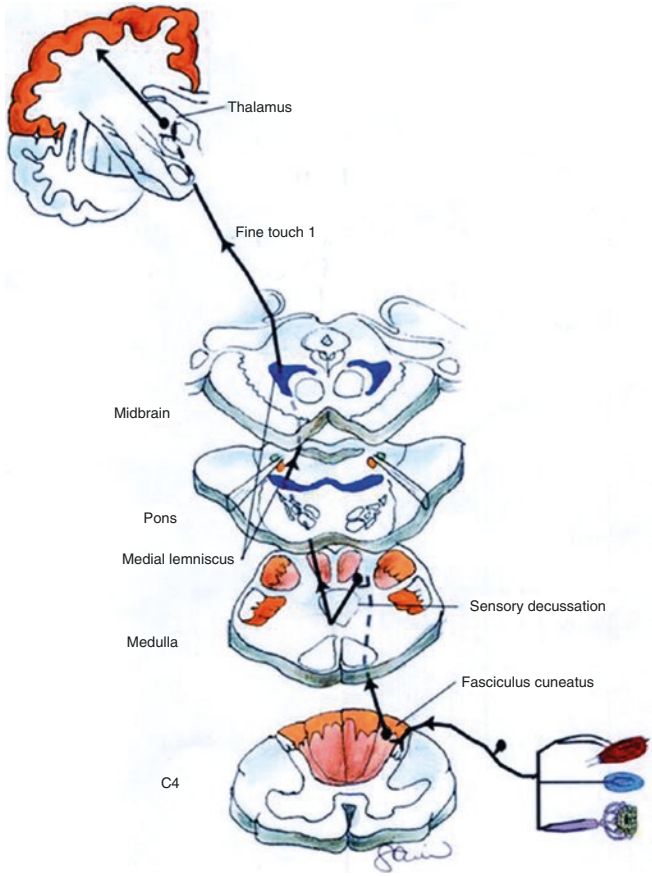

Fig. 2.13 Posterior column tract (Used with permissions from Jacobson and Marcus [4])

decussate immediately and ascend through the brainstem as the *medial lemniscus*. These neurons travel to the thalamus, where they synapse with third-order neurons which course through the posterior limb of the internal capsule and finally to the primary somatosensory cortex [1, 10].

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Chapter 3
Neuroradiology

Susan Yeager, Mohit Datta, and Ajay Malhotra

3.1 Introduction

A variety of imaging modalities are currently utilized to evaluate the brain. However, prior to the 1970s neurologic imaging primarily involved radiographs and invasive procedures for spinal and vessel imaging. In 1895, Roentgen discovered x-ray imaging, but it was years before neurologic application was realized. This was due to the fact that at that time, the brain was considered inaccessible to imaging and referred to as "the dark continent." In 1918 ventriculography was discovered with encephalography soon to follow. In 1925 the injection of contrast agent injections (Lipiodol) was introduced. In 1931, after years of experimentation, Moniz described contrast enhanced arteriography as a means to accurately describe vessel images

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and – indirectly – obtain information about non-vascular structures. In the 1960s, commercial manufacturers began work to improve scanning devices. Since that time, exciting advances in neuroradiology have moved the brain from being a "dark continent" to evaluation techniques that accurately describe the brain contents and pathology. The purpose of this chapter is to provide an overview for Advanced Practice Clinicians (APCs) on the anatomy, diagnostic principles, and clinical applications of brain imaging beyond plain radiographs.

3.2 Definitions

After becoming familiarized with neurologic anatomy (see Chap. 2), the next step in neuroradiologic learning is to become familiar with definitions of commonly used terms during radiographic interpretation.

Both computed tomography (CT) and magnetic resonance imaging (MRI) involve gray scale imaging. Structures are displayed through a variety of shades of white, black, and gray (Table 3.1). In general, the variation of shade is reflective of the density of the object. If the object is denser, fewer x-ray beams pass through it. For example, air is not dense, therefore enabling a large amount of radiographic beams to pass through and appearing black on an image. Alternately, bone is dense and presents as a white structure when using the same imaging

Table 3.1 MRI/CT greyscale summary

Normal tissue	T1	T2	CT
Dense bone	Dark	Dark	Bright
Air	Dark	Dark	Dark
Fat	Bright	Less bright	Dark
Water	Dark	Bright	Dark
Brain	Anatomic	Intermediate	Intermediate

methods. Figure 3.1 demonstrates a spectrum of gray scale structures seen on CT scan.

- *Hypo/hyperdensity*-This term is used in CT imaging to describe structures that are low on the grayscale (hypodense/dark) or high on the grayscale (hyperdense/white) (Fig. 3.2)

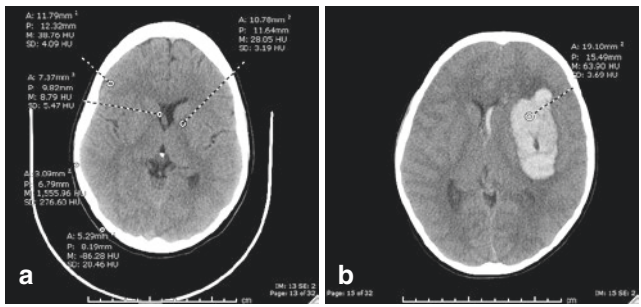

Fig. 3.1 (**a**) Axial noncontrast CT showing densities of different structures. Note: *Gray* matter is hyperdense (brighter) relative to white matter. (**b**) Noncontrast Head CT with hyperdense hematoma in the left putamen with mean density of 64 HU

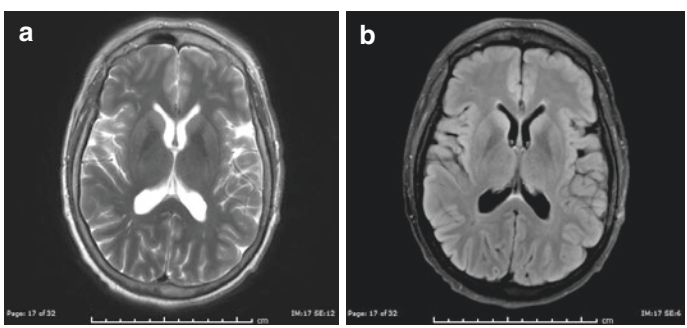

Fig. 3.2 MRI Axial T2 (**a**) and FLAIR (**b**) images- *Gray* matter is hyperintense (*bright*) relative to *white* matter. CSF is hyperintesne (*bright*) on T2 and hypointense (*dark*) on FLAIR

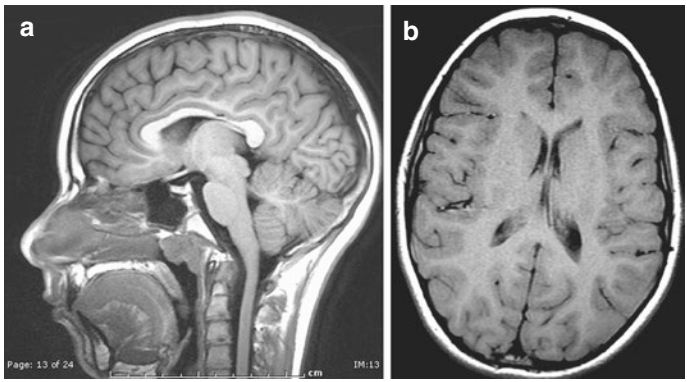

Fig. 3.3 Sagittal (**a**) and axial (**b**) T1 WI- *gray* matter is hypointense (*dark*) relative to *white* matter, CSF is *dark*, and *fat* is very hyperintense (*bright*)

- *Hypo/hyperintensity*-This term is used in MRI imaging to describe the proton density of tissues. Structures that are low on the grayscale (hypointense/dark) have low proton density (lungs, for example) whereas high/bright areas on the grayscale (hyperintense/white) have high proton density (Fig. 3.3).

The axis in which the image is captured is also important when interpreting images. The common planes of image acquisition are:

- *Axial*: transverse imaging plane that is perpendicular to the long axis of the body
- *Sagittal*: longitudinal plane that divides the body into right and left sections.
- *Coronal*: An imaging plane obtained through subsequent sections made from front to back.

In addition to understanding the plane of the image, a basic knowledge of imaging terminology is necessary to understand and be able to articulate what is being viewed.

- *Non-contrasted images* – These are images obtained without the administration of extrinsic contrast medium.

- *Contrasted images* – These are images obtained with the use of intravenous contrast medium. Contrast is used to facilitate visualization of adjacent body tissue as well as to highlight pathology which may have increased density/intensity due to increased vascularity or the breakdown of blood brain barrier. In CT scan imaging, the contrast material contains iodine and is denser (brighter) than the brain [1]. MRI contrast media are Gadolinium-based.
- *Gray matter* – Anatomic areas of the nervous system where the nerve fibers are unmyelinated. Contains the cell body and dendrites and nuclei of the nerve cells. i.e. cerebral cortex and deep gray structures (basal ganglia, thalami)
- *White matter* – Anatomic areas of the nervous system where the myelinated axons and white matter tracts occur, e.g.- corpus callosum. On CT, gray matter is hyperdense relative to white matter.

3.3 Basic Brain Imaging

3.3.1 Computerized Tomography (CT) Scan

Sir Godfrey Hounsfield, working at EMI Laboratories, first conceived of the idea of CT scan imaging in 1967. The first prototype was finished in 1971 and was only designed to scan the head. The prototype took several hours to get the data required to scan a single "slice" and required several days to compile the information into a single image. The images produced were very crude by today's standards, but allowed physicians to see soft tissue structures by imaging for the first time. This technology has evolved to the point of including vascular and perfusion CT scan technology.

Tomography stems from the Greek tomos, meaning "section". Like conventional x-rays, CT scans measure the density of studied tissues. The difference from conventional x-ray is that

rather than taking one view, the x-ray beam is rotated around the patient to take many different views of a single slice of anatomical structures. As the beam passes through the patient, the x-rays are partially absorbed by the tissues encountered. The amount of energy absorbed is determined by the density of the tissue traversed. Once obtained, the images are reconstructed by the computer to reflect detailed images of all the structures including air, bone, liquid, and soft tissue. With the addition of advanced computational resources, multiple slices can now be acquired simultaneously. Spiral (helical) CT can acquire data continuously without stops. This technology reduces radiation exposure and increases the resolution and speed [1].

Images obtained are displayed with different densities. Dense structures, like bone or calcifications, appear white on images. Less dense material, such as air, appears black. CT density is often expressed in Hounsfield units (HU) (Table 3.2).

CT is the preferred initial screening technique acute and hyperacute pathologies, including brain trauma, stroke, and altered mental status. It is also the preferred first line study for the identification of space occupying lesions. The speed, accessibility, relative safety, and high sensitivity to cortical bone and acute blood make CT imaging ideally suited for trauma evaluation. CT is not very sensitive for the detection of hyperacute strokes (less that 3 h from symptom onset); however, loss of gray/white differentiation may be seen very early in some cases. Beyond anatomic information of

Table 3.2 Common CT attenuation values

Structure	Attenuation value in HU
Air	From −500 to −1,000 HU
Fat	From −10 to −150 HU
Water	From 0 to 20 HU
Gray matter	From 32 to 45 HU
White matter	From 25 to 32 HU
Recent hemorrhage	From 60 to 90 HU
Calcifications	More than 100 HU
Bone	From 200 HU and above

parenchymal structures, useful indirect information about the status of the brain vessels can sometimes be obtained from a plain head CT. One example is the "hyperdense vessel sign," that reflects occlusion or extremely slow flow of a large vessel, usually the middle cerebral artery. CT is also helpful in assessing for space occupying lesions and evaluation of ventricle size and herniation.

A CT angiogram (see below) expands the role of the plain head CT in the acute setting by offering accurate details of the major brain vessels after a bolus of intravenous contrast. This technology serves to quickly detect proximal large vessel occlusions or injury in stroke and trauma patients [2]. It can also be used to identify underlying vessel abnormalities (i.e. arteriovenous malformations or aneurysms), vascular collateral vessels, vasospasm, or tumor vascularization patterns.

Typical indications for CT scan:

- Hyperacute and acute stroke (both ischemic and hemorrhagic)
- Head trauma (Fig. 3.4)
- Suspected subarachnoid hemorrhage (Fig. 3.5)

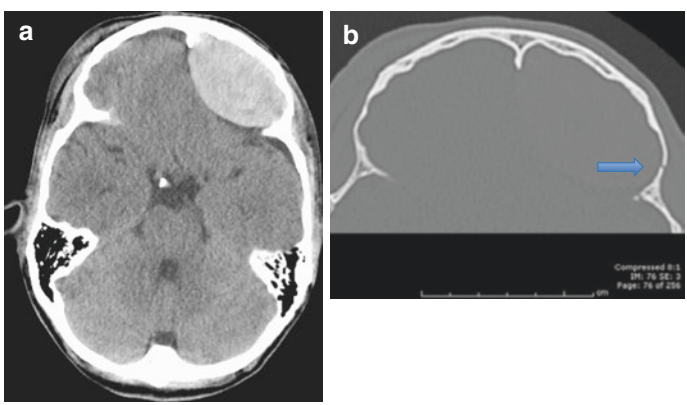

Fig. 3.4 Axial CT showing large left convexity biconvex epidural hematoma (**a**) confined by sutures and non-displaced fracture seen on bone windows (**b**)

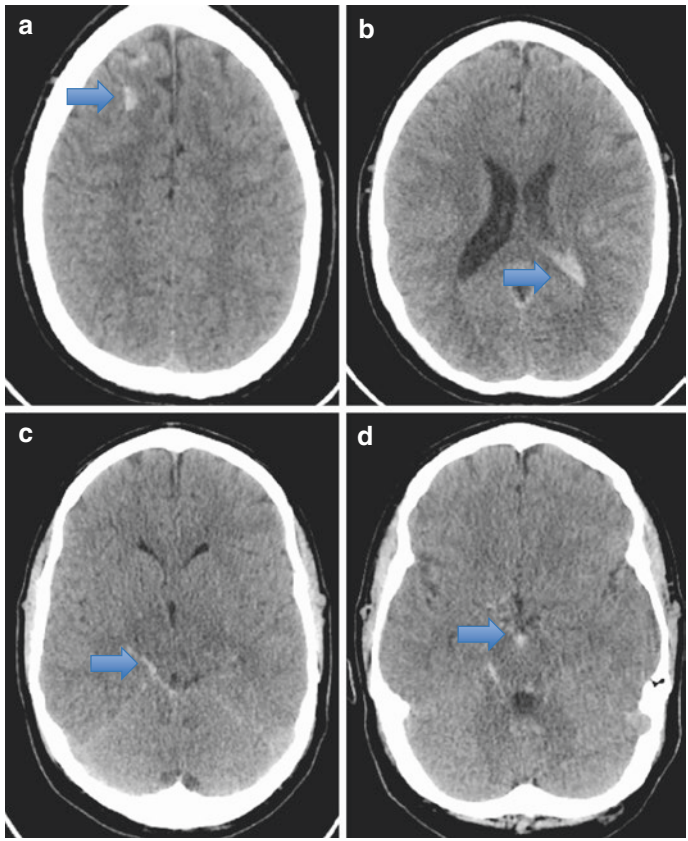

Fig. 3.5 Axial CT with blood in different locations. (**a**) At the *gray-white* matter- characteristic of shearing (traumatic axonal) injury. (**b**). Intraventricular layering in the occipital horn in dependent portion. (**c**) Subarachnoid blood in quadrigeminal cistern. (**d**) Subarachnoid blood in prepontine cistern

- Aneurysm evaluation
- Vascular occlusive disease or vasculitis (including use of CT angiography and/or venography)
- Detection or evaluation of a calcification

- Immediate postoperative evaluation following surgical treatment of tumor, intracranial hemorrhage, or hemorrhagic lesions
- Treated or untreated vascular lesions
- Suspected shunt malfunctions, or shunt revisions
- Mental status change
- Hydrocephalus and other causes of increased intracranial pressure
- Headache
- Suspected intracranial infection, especially to rule space occupying lesions before a lumbar tap in suspected meningitis
- Congenital lesions (such as, but not limited to, craniosynostosis, macrocephaly, and microcephaly)
- Evaluation of psychiatric disorders
- Brain herniation
- Suspected mass or tumor
- When magnetic resonance imaging (MRI) is unavailable or contraindicated

The potential advantages and disadvantages of CT imaging are summarized below:

Advantages

- Widespread availability, relatively low cost, and rapid acquisition time.
- Evaluation in patients with contraindications to MR scanning or when screening for MRI cannot be obtained.
- Speed and open set up of equipment creates ease of patient placement while alleviating the potential of claustrophobia
- Good for cortical bone pathology- best modality to assess for fractures
- High sensitivity to detect acute hemorrhage makes it the corner stone of imaging in stroke treatment and trauma. Blood remains hyperdense on CT (HU 60–100) for 7–10 days.

Disadvantages

- Uses ionizing radiation and hence risk of radiation exposure. Special considerations for pediatrics and pregnant women.

For the latter, the maximum risk occurs during the first 8–11 weeks of pregnancy.
- Radiation dose is additive so the more images obtained, the higher the dose of radiation to which the patient is exposed
- Posterior fossa structures of the brain are not as well visualized due to beam hardening from the dense petrous bones [3]
- Relatively poor soft tissue visualization due to inferior contrast resolution compared to MRI
- Iodinated IV contrast is required for CT with contrast, CTA, CTP and CTV imaging, which can be nephrotoxic and cause contrast-induced nephropathy
- Contrast allergies may exist to iodine-based contrast media

3.3.2 Magnetic Resonance Imaging (MRI)

MRI is an imaging modality that uses non-ionizing radiation to create diagnostic images. The concept of MRI was first described by Felix Bloch and Edward Purcell in 1946 and was initially called Nuclear Magnetic Resonance Imaging after its early use for chemical analysis. It was not until 1971 when the potential medical uses of this technology were realized.

A MRI scanner consists of a large and powerful magnet. A radio wave antenna is used to send signals to the body and returning signals are converted into images by a computer.

MRI images are created based on the absorption and emission of radiofrequency energy, without using ionizing radiation. MRI scanning involves the use of primary and secondary magnetic fields. The use of 1.5 or 3 Tesla (T) terminology refers to the strength of the magnetic field. The current FDA approval in terms of upper limit of field strength for adults is 8T and 4T for adults and children, respectively [4]. Most scanners in current clinical use are “electromagnets” or super conducting magnets, which implies that the static magnetic field is always turned “on” even when a patient is not being scanned.

Safety precautions are to be strictly followed at all times. "Quenching," the process of turning the scanner off, is rarely performed. "Open" MRI are useful in claustrophobic patients, although the upper field strength is usually limited to 1T.

For all practical purposes, if a patient develops a medical emergency while being scanned, it is best to get the patient out of the scanner before starting resuscitation. All equipment inside the scanner room must be MR compatible (non- ferromagnetic).

In addition to the main magnetic field, secondary fields are created using radio frequency pulses (RFP) and gradient pulses emitted from the scanner to spatially encode the signal in the x-, y- and z-axis. These secondary gradients cause the loud metallic banging noise inside the scanner. Image density depends on several contrast parameters intrinsic to the tissue being scanned (T1 recovery time, T2 decay time, Proton density, Flow and Apparent diffusion coefficient), as well as extrinsic parameters that are varied by the radiologist to change image quality (TR, TE, Flip angle, TI or inversion time, Turbo factor/Echo train length).

MRI Definitions:

- *Radiofrequency* (*RF*) *pulse* – MRI technique where short electromagnetic signals oscillate to change the direction of the magnetic field. They are cycled at a rate of pulses per second.
- *Relaxation time* – The time it takes for protons to regain their equilibrium state during MRI imaging. T1 and T2 are two types of relaxation phases.
- *T1*- T1 is considered the "*anatomic image*". Clues to recognizing T1: CSF is black, subcutaneous fat is white and gray matter (cortex) is hypointense relative to white matter (Fig. 3.2). The time it takes for 63% of longitudinal (parallel to the magnetic field) relaxation of protons to occur. Not all tissues get back to equilibrium at the same rate, and a tissue's T1 reflects the amount of time its protons' spins realign with the main magnetic field. Fat quickly realigns its longitudinal

magnetization, and therefore appears bright on a T1 weighted image. Conversely, water has much slower longitudinal magnetization realignment after a RF pulse. Thus, water has low signal and appears dark on T1 weighted imaging.

- *T2* – T2 is considered the "*pathologic image*". Most pathologies increase the fluid content of tissues and show up as high signal (bright) including surrounding edema. This is the time it takes for 63% of transverse (perpendicular) relaxation of protons during MRI image acquisition. T2 is a "fluid –sensitive" sequence and free fluid appears hyperintense/white on T2 imaging.
- *T2- FLAIR* (fluid attenuated inversion recovery) – This sequence is basically a *T2 image without the CSF brightness*. The CSF signal is nulled out (appears gray/black). This technique attempts to minimize distraction of the CSF brightness while highlighting underlying pathology (Fig. 3.3). This is especially important for detecting small lesions in periventricular and subcortical white matter, and FLAIR is the sequence of choice for evaluation of patients with Multiple Sclerosis. CSF should always be dark/low signal on FLAIR-presence of increased signal indicated presence of subarachnoid hemorrhage (SAH) or increased protein in cases of meningitis. FLAIR is at least as sensitive as CT for detection of acute SAH.
- *Diffusion Weighted Imaging (DWI)* – Follows the changes in the movement of water through tissues and uses these changes as a contrast medium. Free diffusion of protons occurs only when cell membrane integrity is lost. DWI sequence is sensitive to abnormal water motion and diffusion through the tissues. DWI is a manipulated T2 image and therefore high signal areas can be caused by true restricted diffusion or be T2 shine through. DWI is used in acute stroke identification as well as to differentiate abscess versus necrosis versus cystic brain lesions [5, 6]. DWI is considered the gold standard for infarct core estimation and is very sensitive early in the evolution of ischemia (Fig. 3.6).

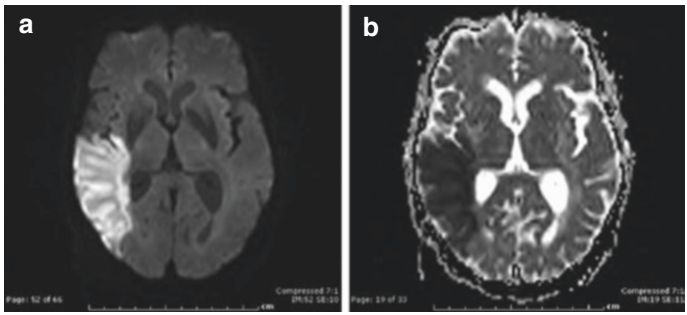

Fig. 3.6 Axial DWI (**a**) and ADC (**b**) maps demonstrating right MCA acute infarct. Involvement of the cortex helps distinguish cytotoxic from vasogenic edema, which is typically confined to white matter

- *Apparent Diffusion Coefficient* (*ADC*) – A measure of the magnitude of diffusion (of water molecules) within tissue, and is commonly clinically calculated using MRI with diffusion weighted imaging (DWI). ADC values are calculated automatically by the software and then displayed as a parametric map that reflects the degree of diffusion of water molecules through different tissues. The impedance of water molecule diffusion can be quantitatively assessed using the apparent diffusion coefficient (ADC) value. ADC maps are devoid of T2 effects that may mimic or obscure lesions on DWI [7].
- *Susceptibility Weighted Imaging* (*SWI*)- An echo MRI sequence which is particularly sensitive to compounds which distort the local magnetic field and as such make it useful in detecting blood products, calcium etc. Blood is dark in this sequence and shows the "blooming artifact" where it is much darker than any other sequence (Fig. 3.7).

MRI is rarely the initial imaging study in acute clinical scenarios. It follows, most often, an initial CT screening. In contrast, MRI is the preferred method of evaluation for many

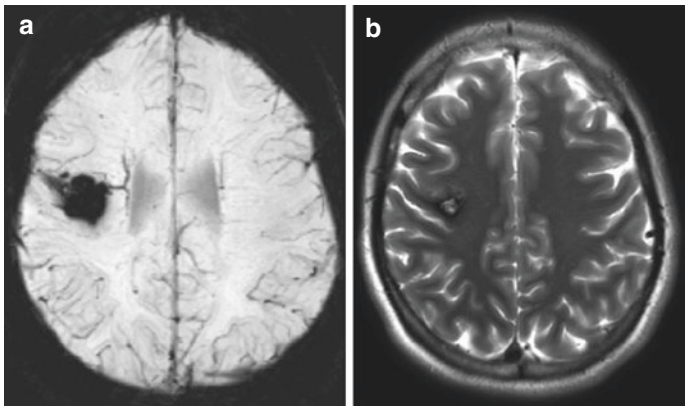

Fig. 3.7 Parenchymal bleed due to Cavernoma. GRE/SWI (**a**) is very sensitive to parenchymal blood and shows "blooming" or marked low signal relative to T2 WI (**b**)

non-acute pathologies. MRI is also more sensitive for visualization of posterior brain structures, regardless of the timing of presentation.

Typical indications for MRI:

- Acute stroke, following head CT (Fig. 3.7)
- Mass lesion characterization (Fig. 3.8)
- Posterior fossa evaluation
- Traumatic diffuse axonal injury
- Demyelinating disease
- Diplopia
- Cranial nerve dysfunction
- Seizures
- Ataxia
- Suspicion of neurodegenerative disease
- Developmental delay
- Neuroendocrine dysfunction
- Encephalitis (after a head CT)

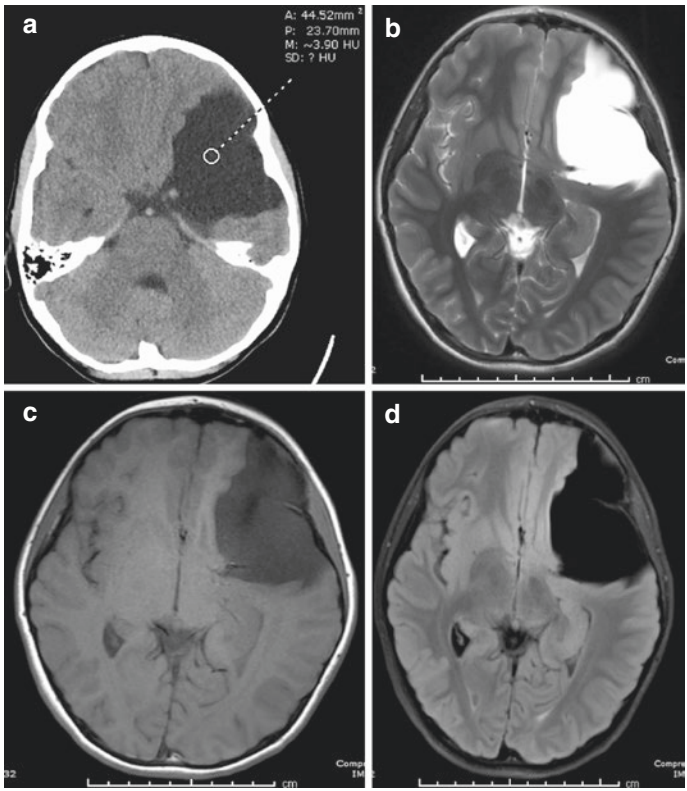

Fig. 3.8 Axial CT (**a**) density showing fluid density (0–20 HU) in the left frontotemporal region. Axial T2 (**b**), Axial T1 (**c**), and FLAIR (**d**) images confirm fluid nature, consistent with an arachnoid cyst

- Drug toxicity
- Cortical dysplasia, and migration anomalies or other morphologic brain abnormalities

The potential advantages and disadvantages of MRI imaging are summarized below:

Advantages

- The ability to image without the use of ionizing radiation (unlike x-ray and CT scanning)
- Superior soft tissue contrast over CT scans and plain films, making it the ideal examination of the brain, spine, joints and other soft tissue body parts
- The ability to visualize posterior structures of the brain better than CT imaging
- Angiographic images can be obtained without the use of contrast material, unlike CT or conventional angiography
- Advanced techniques, such as diffusion and perfusion, allow for specific tissue characterization rather than merely 'macroscopic' imaging
- Functional MRI allows the visualization of active parts of the brain during certain activities.

Disadvantages

- More expensive and less accessible than CT
- Longer scan times (patient dyscomfort is sometimes an issue).
- Length of the exam and decreased visualization of the patient throughout the exam can put certain patients at risk for clinical decompensation.
- Claustrophobia and patient size may preclude the ability to obtain images.
- Ability to lay still may be challenging for some neurological patients; intubation and/or conscious sedation is possible, but risks and benefits should be weighed carefully.
- MRI scanning is contraindicated for patients with some metal implants, cochlear implants, spine stimulators, cardiac pacemakers (relative contraindication) and metallic foreign bodies close to neurovascular structures. Careful attention to safety measures is necessary to avoid serious injury to patients and staff. This requires special MRI compatible

equipment and stringent adherence to safety protocols. A comprehensive list of MR safe equipment is available at- www.mrisafety.com
- Consideration needs to be given for how continuous infusions and ventilator support will be managed as not all equipment is MRI compatible.

3.4 Vascular Imaging

3.4.1 CT Angiography (CTA)

CTA is a method of rapid injection of iodine rich intravenous contrast. This contrast is used in combination with helical CT scan techniques to rapidly obtain images of the cerebral and neck vessels. This imaging approach allows the evaluation of the vessels' anatomy, as well as the presence of stenosis, vasculitis, occlusion, vasospasm, dissection and other vascular anomalies. The CTA of the neck begins at the aortic arch and extends to the skull base or 1 cm above the dorsum sella, if intracranial information is desired. CTA of the brain begins at C2 and extends to the vertex. Using conventional angiography as the gold standard, the specificity and sensitivity of CTA exceeds 90% for vascular stenosis and occlusion [2, 8].

3.4.2 MR Angiography (MRA)

MR angiography (MRA) can be used to evaluate cerebral and cervical vessels, with or without contrast (Time-of-flight technique). A routine MRA brain does not require contrast, but MRA Neck and MR Venography is usually performed before and after injection of Gadolinium contrast. Non contrast time of

flight (TOF) images of the neck tend to over-estimate the degree of stenosis. Because TOF MRA is flow dependent, absence of signal does not necessarily mean absence of blood flow and can be seen with extremely sluggish blood flow. Phase contrast MRA images are helpful in evaluating the blood flow velocity as well as direction.

3.4.3 CT/MRI Venogram Brain/Neck

CT venogram (CTV) and MR venogram (MRV) imaging modality assists with the identification of cerebral venous occlusion and other venous pathology such as arteriovenous malformations (AVMs) and dural venous anomalies (DVAs) [9]. These technologies utilize computer assisted generation of images which result from the difference in signal between flowing blood next to stationary tissue. 4D imaging or "time resolved imaging" displays temporal resolution and the passage of contrast through arteries, capillaries and veins can be assessed.

On an unenhanced CT, indirect signs of cerebral venous thrombosis include deep intraparenchymal hemorrhage, bilateral location and/or parenchymal edema which is atypical (non-arterial) in location. A direct sign is called the "empty delta sign" when there is hypodensity or filling defect in the sagittal sinus on a contrast CT image [10]. Because these findings are subtle, CTV or MRV imaging or conventional angiograms are indicated. MRV imaging with contrast MRI is both sensitive and specific enough to provide the best noninvasive method of diagnosis for cerebral venous thrombosis though it is prone to artifact caused by slow flow or met-hemoglobin and congenital anatomic variations and hypoplastic sinuses or arachnoid granulations.

3.4.4 Angiography

This is an invasive procedure done in the operating room under sterile conditions. A catheter is inserted in the femoral artery and navigated through the aortic arch into the carotid or vertebral arteries, and then to the intracranial cerebral vessels. Intermittently throughout the procedure, a contrast agent is injected into the vessels to enhance visualization of vessel anatomy. Real time fluoroscopy radiographs are taken in a series first as the contrast spreads from the arterial system and another as the contrast reaches the venous system. While CTA and MRA technology has rapidly improved and is increasingly being used as the first-line modality, angiography remains the gold standard for visualization of cerebral vessels.

Advantages

- High quality images – highest spatial resolution
- Selective vessel injection allows better delineation of anatomy
- Contrast injection can be repeated if required
- Ability to treat a pathology at the time of identification using endovascular devices

Disadvantages

- Expensive set-up and not readily available in all facilities
- Requires the presence of specialty trained interventional radiologists/neurosurgeons to perform
- Requires a contrast load which may cause renal insult or allergic reactions
- Radiation exposure during image acquisition
- Invasive procedure- risk of vessel/aneurysm rupture/perforation and plaque rupture and distal emboli resulting in periprocedural strokes.

- Difficult vascular access in patients with vascular disease and proximal occlusions/tight stenosis or abdominal/thoracic aortic dissections.
- Higher risk in patients with coagulopathy and bleeding tendencies due to risk of hematoma at vascular access site (generally groin) and risk of intracranial bleed in event of vessel rupture.

Angiography is the preferred study for confirmation of aneurysm, arteriovenous malformations, vascular malformations, venous thrombosis, vasculitis, and vasospasm.

3.5 Perfusion Imaging

Perfusion is defined as a steady-state delivery of blood to an element of tissue [9]. Perfusion weighted images help characterize tissue-level blood flow while providing insight into blood delivery to the brain parenchyma. Neurologic dysfunction is noted to occur if cerebral blood flow falls below 18–20 mL/100 g of tissue per minute with infarction occurring after only a few minutes of flow less than 10 mL/100 g. However, levels of 10–20 ml/100 g may take minutes to hours before cell death occurs [7]. Restoration of blood flow to arteries serving infarcted or ischemic arteries has the potential to produce reperfusion injury with resultant mass effect that could translate to herniation and possibly death. Thus, risk-benefit evaluation of increased perfusion techniques including artery recanalization remains under study.

Perfusion Imaging Definitions:

- *Perfusion weighted imaging* – radio-isotopic or contrast imaging that uses the difference in blood flow through organs as a means of diagnosing diseases such as stroke or malignancies. Perfusion imaging can be performed with CT, MRI or PET scanning.

- *Diffusion-perfusion mismatch* – Indicates a deficit on perfusion weighted images which exceed the zone of diffusion restriction on diffusion weighted images. The diffusion-perfusion mismatch reflects the ischemic penumbra/salvageable brain tissue that is at risk for infarction [1, 11].
- *Cerebral Blood Flow* (*CBF*) – The volume of blood moving through a given volume of brain per unit time. CBF helps detect hypoperfused tissue and is usually prolonged in acute ischemia (Fig. 3.9) [3, 12].

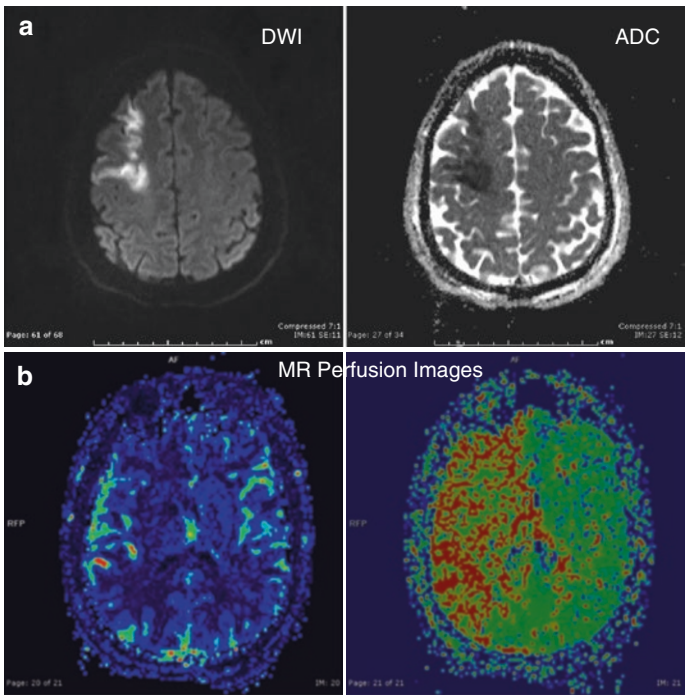

Fig. 3.9 Patient with significant diffusion-perfusion mismatch. Right anterior MCA territory infarct demonstrated on MRI (**a**) with a much larger area "at risk" on the MTT (**b**)

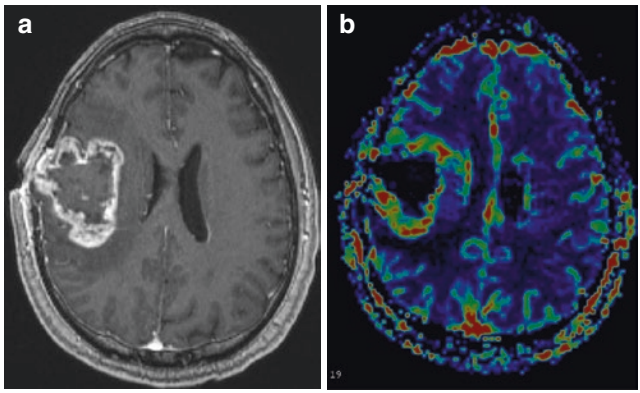

Fig. 3.10 Postoperative scans on a patient with Glioblastoma multiforme. (**a**) MRI with contrast showing avid enhancement along the margins of the tumor resection cavity. (**b**) Increased perfusion seen on CBV maps, consistent with recurrent tumor

- *Cerebral Blood Volume* (*CBV*) – It is the *total volume of contrast in* a given unit volume of the *brain*. This includes contrast in the tissues, as well as blood in the large capacitance vessels such as arteries, arterioles, capillaries, venules, and veins (Fig. 3.10). CBV is highly specific for critical hypoperfusion; less sensitive for mild/moderate hypoperfusion [11].
- *Mean Transit Time* (*MTT*) – This is defined as the average transit time of blood traversing through a given brain region. MTT is prolonged in cases of acute large vessel occlusion as blood takes longer time to reach area of interest through collateral flow. Mathematically MTT=CBV/CBF [1, 12].
- *Time To Peak* (*TTP*) – This is defined as the time it takes for contrast to flow into a specific area of the brain. Similar to MTT, this is a sensitive tool for determining decreased contrast flow as blood going through collateral or narrowed vessels increases the TTP in stroke patients [3, 12].

Table 3.3 Cerebral perfusion changes in infarct and penumbra

Tissue impact	CBV[a]	CBF	MTT[b]
Ischemic penumbra	Normal or increased	Decreased	Increased
Infarct	Decreased	Decreased	Increased

[a]CBV – parameter that most accurately describes infarct core
[b]MTT – parameter that most accurate to describe penumbral tissue within first few hours after onset of ischemic event

In both CT perfusion and MR perfusion, pre and post contrast images are evaluated for the presence of a mismatch to determine potentially salvageable tissue. In the event of ischemia, decreased perfusion pressure occurs, which prolongs the mean transit time (MTT) in both the ischemic core and the penumbra [13]. As integrity of cells is impacted by the ischemia, autoregulation induces vasodilatation of capillaries in an attempt to maintain cerebral blood flow. See Table 3.3 for summary of perfusion imaging changes in infarct versus penumbra tissue.

3.5.1 CT Perfusion

CT perfusion imaging relies on the speed of multi-detector row scanners to follow the entry and exit of radiographic dye through a section of tissue. Perfusion studies are obtained 70–90 s after injection. Current scanning technology permits whole brain imaging, but some older scanners might limit z-axis coverage to 8 or 12 cm [13]. As the contrast passes through the tissue, signal intensities are noted and translate to several perfusion parameters: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP) Mismatched images of CBF and CBV, and MTT and TTP indicate a perfusion mismatch with tissue noted to be at risk.

3.5.2 MR Perfusion

Several techniques for MR perfusion exist. Bolus-contrast tracking is the most common and quantifies the amount of contrast that reaches the brain tissue after a fast intravenous bolus injection. Signal intensity (concentration) versus a time curve that tracks the time of bolus transit is used to calculate the previously mentioned physiological parameters (CBF, CBV, MTT, TTP) [13].

While perfusion imaging is not required to determine IV tPA or endovascular treatment selection, valid clinical indications do include the following:

- Excluding stroke mimics (hypoglycemia, seizure, complex migraine headaches, conversion disorders, dementia, or brain tumor)
- Identifying early risk for stroke following a transient ischemic attack (TIA)
- Clarifying/confirming the presence or site of vessel occlusion
- Assessment of cerebral vasospasm
- Determining the need for blood pressure management or augmentation in eloquent brain regions
- Guiding disposition decisions such as ICU placement or frequency of neurologic checks
- Guiding prognosis discussions by more objectively defining the risk/benefit of treating certain pathology

3.6 Contrast Considerations

Iodine- based dyes are used as contrast for CT studies. Contrast imaging is suggested if the initial study suggests a tumor or potential infectious/inflammatory cause. Contrast is also needed for CTA, CTV and CT perfusion studies. The usual dose of contrast is 60–100 cc. Some patients can be allergic to iodine-based

dyes and if there is such a history, patients should be premedicated with anti-histamines and steroids.

CT contrast media also can potentially cause nephropathy and transient deterioration of renal function. Hydration with IV fluids (unless contraindicated) is helpful and recommended to minimize kidney damage.

Factors that increase risk of contrast induced nephropathy:

- Dehydration
- Baseline chronic renal insufficiency
- Diabetes
- Metformin use-risk of lactic acidosis
- Paraproteinemias

MR contrast media are Gadolinium (Gd) based. Free Gd can be toxic and is bound to a ligand when used as contrast. Macrocyclic, ionic agents have the highest stability and are considered the safest [14]. Presence of renal dysfunction can potentially cause a systemic lethal fibrosing condition called Nephrogenic Systemic Fibrosis (NSF). Gd can be safely used if the Glomerular Filtration rate (GFR) is above 60. For a GFR of 30–60, Gd should be used only if absolutely needed. When the GFR falls below 30, a nephrology consultation is usually recommended to weigh the risks and benefits. Of note, recent studies have shown that Gd accumulates in the brain, even in patients with normal renal function, after multiple injections of contrast over time (usually 4 or greater). However, the clinical significance of this finding is still unknown [15, 16].

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Chapter 4
Aneurysmal Subarachnoid Hemorrhage

Jessica L. White and Charles Matouk

4.1 Introduction

Subarachnoid hemorrhage (SAH) accounts for approximately 10% of all strokes, the majority of which are caused by ruptured aneurysms. Other etiologies of SAH include trauma, ruptured vascular malformations, head trauma, use of blood thinners, and primary central nervous system vasculitis/reversible cerebral vasoconstriction syndrome spectrum disorders. Aneurysmal SAH is a devastating disease with 12–15% mortality before hospital admission and overall mortality approaching 50%. Many of those surviving aneurysmal rupture remain functionally dependent and suffer long-term cognitive impairment [1]. The subarachnoid space exists between the arachnoid and pia mater adherent to the surface of the brain and contains cerebrospinal fluid. When this space is filled with blood, the brain can suffer from significant dysfunction secondary to inflammatory cascades, cerebral edema, and hydrocephalus.

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Aneurysms are common, with prevalence in the adult population of 1–5% [2]. Historically, the most common presentation of aneurysms has been SAH. However, aneurysms are increasingly discovered incidentally during workup of other conditions, such as headache or head trauma. Risk factors for aneurysm development include hypertension, smoking, sympathomimetic substance abuse, female sex, family history of cerebral aneurysms, and certain genetic disorders, including polycystic kidney disease, Marfan syndrome, and Ehlers-Danlos syndrome (type IV) [1]. Risk factors for aneurysm rupture include aneurysm-specific factors (size, location, morphology) and patient-specific factors (age, female sex, smoking, hypertension, prior SAH) [2]. Aneurysm formation typically occurs at vessel branch points, most commonly the anterior communicating artery (30%), posterior communicating artery (25%), middle cerebral artery bifurcation (20%), and, less commonly, the internal carotid terminus and basilar tip [2].

4.2 Case Example

A 61-year-old woman with past medical history of hypertension presents to the hospital complaining of severe, sudden-onset headache, nausea and vomiting, and photophobia. On examination she is somnolent and complains of an excruciating headache. She reports that this is the "worst headache of her life." While in the emergency department she becomes increasingly lethargic and then frankly unresponsive. CT head demonstrates starburst pattern subarachnoid hemorrhage and mild hydrocephalus (see Fig. 4.1, image a). She is intubated for airway protection, sedated, and her blood pressure controlled with IV nicardipine. CT angiogram demonstrates a small anterior communicating artery aneurysm (image b). A ventriculostomy is placed for treatment of hydrocephalus and intracranial pressure monitoring. Her aneurysm is successfully treated by endovascular coiling (images c and d). The following day she is alert, able to follow simple commands, and is successfully extubated. On post-SAH day 4

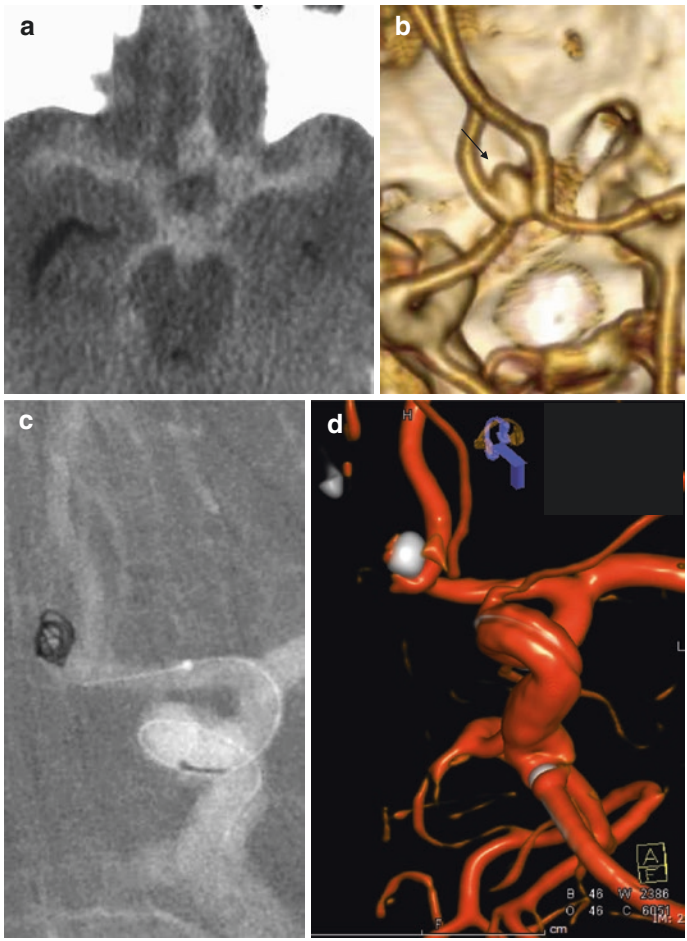

Fig. 4.1 This 61-year-old woman presented with a sudden-onset, severe headache. (**a**) A CT head (axial) demonstrates a starburst pattern of subarachnoid hemorrhage. (**b**) A 3D reconstruction of a CTA demonstrates a small anterior communicating artery (AComA) aneurysm (*arrow*). (**c**) A road map of a diagnostic cerebral angiogram (left internal carotid artery (ICA) injection, oblique view) during endovascular coiling of the ruptured AComA aneurysm. (**d**) A 3D (dual volume) reconstruction of a spin angiogram (left ICA injection, oblique view) demonstrates complete exclusion of the ruptured AComA aneurysm

she becomes confused with new lower extremity weakness. A repeat CT head confirms no interval rebleeding or worsening hydrocephalus. Transcranial Dopplers show elevated velocities in the anterior cerebral arteries, bilaterally. She is treated initially with blood pressure augmentation but fails to improve clinically. She is taken to conventional catheter angiography for intra-arterial administration of verapamil to the affected vascular territories. Induced hypertension is continued post-procedurally with an improvement in her clinical examination.

4.3 Initial Evaluation

4.3.1 Presentation

The most common presentation of aneurysmal SAH is sudden "thunderclap headache" or "worst headache of life." A smaller proportion, 10–15%, present in a comatose state. Additional exam findings may include nuchal rigidity, isolated cranial nerve palsy, and focal neurologic deficit [3]. Patients often report an antecedent, less severe headache syndrome referred to as a sentinel (or warning) headache. Several scales grade the severity of SAH. The Hunt and Hess scale (Table 4.1) is a clini-

Table 4.1 Hunt and Hess Scale

Grade	Neurologic symptoms
1	Asymptomatic, mild headache
2	Moderate-to-severe headache, no neurologic deficit other than cranial nerve palsy
3	Drowsy, confused, mild focal neurologic deficit
4	Stupor, moderate-to-severe hemiparesis
5	Coma, decerebrate posturing

Data from: Hunt [4]

Table 4.2 The World Federation of Neurological Surgeons Subarachnoid Grade

Grade	GCS	Motor deficit
1	15	Absent
2	13–14	Absent
3	13–14	Present
4	7–12	Present or absent
5	3–6	Present or absent

Data from: (1988). "Report of World Federation of Neurological Surgeons Committee on a Universal Subarachnoid Hemorrhage Grading Scale." *Journal of neurosurgery 68*(6): 985–986

cal scale and one of the most widely used. It assigns a grade based on severity of clinical symptoms. The World Federation of Neurological Surgeons Subarachnoid Grade (Table 4.2) is based on the Glasgow Coma Scale with special emphasis on the presence of a motor deficit. While these scales are helpful for quantifying the severity of SAH and facilitating communication, their utility in predicting patient outcome is debated.

4.3.2 Diagnostics

Non-contrast CT head is the recommended initial study for evaluation of suspected SAH with a sensitivity of 98% within 24 h of symptom onset. Classically, SAH appears as a starburst pattern of hemorrhage filling the basal cisterns [1, 2]. Intraventricular hemorrhage and parenchymal hematomas can be present as well, depending on the location and severity of aneurysm that has ruptured. Several grading scales based on CT hemorrhage pattern have been validated to predict the occurrence of symptomatic cerebral vasospasm, most notably the Fisher Scale (Table 4.3) and modified Fisher Scale (Table 4.4) [5, 6].

In cases where CT is negative for hemorrhage, but clinical suspicion for aneurysmal rupture remains high, a lumbar

Table 4.3 Fisher Scale

Grade	Blood on CT scan	% with vasospasm
1	No SAH identified	21
2	Diffuse or focal thin (<1 mm) SAH	25
3	Localized or thick (>1 mm) SAH, ± ICH or IVH	37
4	No SAH, + ICH or IVH	31

Data from: Fisher [5]

Table 4.4 Modified Fisher Scale

Grade	Blood on CT scan	% with vasospasm
1	Thin (<1 mm) SAH, − IVH	24
2	Thin (<1 mm) SAH, + IVH	33
3	Thick (>1 mm) SAH, − IVH	33
4	Thick (>1 mm) SAH, + IVH	40

Data from: Frontera [6]

puncture should be performed to evaluate the cerebrospinal fluid for presence of xanthochromia. Xanthochromia is the yellowish appearance of CSF due to the presence of bilirubin, produced by the metabolism of the heme groups released by red blood cells circulating in the CSF after an aneurysmal rupture. The presence of xanthochromia is over 99% sensitive for SAH and persists for several weeks after initial aneurysm rupture [3].

Once the diagnosis of SAH is established, the cerebral vasculature must be evaluated for a causative lesion. Digital subtraction angiography (DSA), or conventional catheter angiography, is the gold standard of vascular evaluation, although most institutions now utilize noninvasive imaging as a first-line diagnostic strategy. CT angiography is the modality of choice, with excellent sensitivity and specificity for aneurysms >3 mm in size [7, 8]. MR angiography is a reasonable alternative for patients with contraindications to iodinated contrast, e.g., renal impairment [1].

4.4 Interventions and Management

4.4.1 Prevention of Rebleeding

The focus of early management in SAH is to prevent aneurysm rerupture, a clinical scenario that portends a poorer prognosis. Patients are at highest risk for rebleeding within the first hours after aneurysm rupture, so rapid stabilization and treatment are paramount [9]. While aneurysm repair should be performed as soon as possible, several medical strategies can minimize the risk of rebleeding prior to repair.

Blood pressure should be closely monitored from the time of diagnosis. A treatment parameter of systolic blood pressure <160 mmHg is generally accepted as a target for management [1, 10]. Hypotension should be avoided as this can cause a precipitous drop in cerebral perfusion resulting in secondary neurological injury. While pulsed IV medications are helpful for acute stabilization, titratable infusions offer more rapid and sustained effect. Nicardipine (typical infusion rate 5–15 mg/h), a calcium channel blocker, has shown to be superior in achieving systolic blood pressure control than labetalol [11].

Antifibrinolytic medications (tranexamic acid and aminocaproic acid) are sometimes administered in the setting of delayed aneurysm repair to help stabilize fibrin formation in the ruptured aneurysm. Caution must be employed when considering these medications as they can precipitate clot formation and are contraindicated for patients with known coronary artery disease, peripheral vascular disease, and hypercoagulable states. Prolonged administration (>72 h) has the added concern of contributing to delayed cerebral ischemia [12]. When used in appropriate patients for a short duration, antifibrinolytic medications are recommended to reduce the risk of aneurysm rebleeding when aneurysm repair is going to be delayed [1, 10, 12].

Seizures, both convulsive and nonconvulsive, commonly occur after SAH. While most seizures occur at the onset of

hemorrhage, seizures are also associated with rebleeding, and patients remain at risk for seizure development throughout the disease course [13]. Patients with a seizure at presentation are placed on anticonvulsant therapy and should be monitored for further seizures. Prophylactic anticonvulsant medications are usually utilized in all patients until the culprit aneurysm is secured. This intervention is driven by the concern that uncontrolled seizure activity may precipitate rebleeding [10].

4.4.2 Aneurysm Treatment

Repair of ruptured aneurysms can be accomplished by surgical clipping or endovascular techniques, typically coiling, although other strategies are now emerging. The decision to clip or coil an aneurysm is highly individualized and is based on multiple factors including available expertise, aneurysm characteristics, and patient characteristics.

Surgical clipping via craniotomy is the tried-and-true approach to securing an aneurysm and results in its complete exclusion from the circulation. It is a durable strategy with a very low aneurysm recurrence rate on long-term follow-up. A major drawback, however, is its invasiveness.

Alternatively, coiling is a minimally invasive, endovascular approach that refers to the packing of an aneurysm with high-tech metallic thread deployed under fluoroscopic guidance. At Yale University/Yale-New Haven Hospital, a coil-first approach is recommended for most ruptured aneurysms. This is supported by the results of two randomized controlled trials, International Subarachnoid Hemorrhage Trial (ISAT) and Barrow Ruptured Aneurysm Trial (BRAT). Both studies showed improved clinical outcomes after endovascular coiling [14, 15].

More recently, a new endovascular device called flow-diverting stent became available for aneurysm repair. Currently, the only flow-diverting stents available for use in the United States are the Pipeline (and Pipeline Flex) Embolization Devices (Medtronic Neurovascular). These low-porosity stents are deployed in the par-

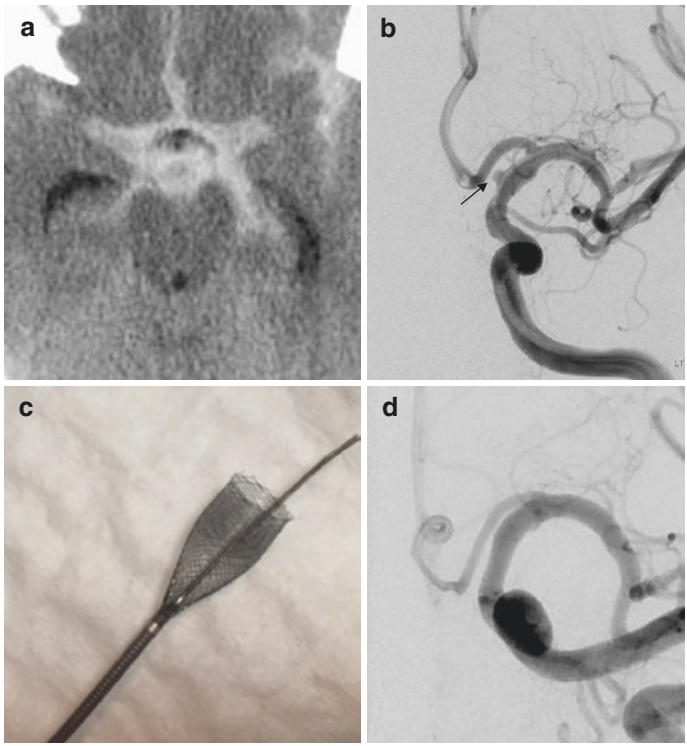

Fig. 4.2 This 51-year-old man presented with a sudden-onset, severe headache. (**a**) A CT head (axial) demonstrates a starburst pattern of subarachnoid hemorrhage. (**b**) A diagnostic cerebral angiogram (DCA, left internal carotid artery (ICA) injection, AP view) demonstrates a blister-like aneurysm of the supraclinoid ICA (*arrow*). (**c**) Photograph of a partially deployed (ex vivo) Pipeline Embolization Device (PED). A similar PED was deployed in the L ICA covering the neck of the small, ruptured aneurysm. Prior to this planned intervention, he was loaded with aspirin and clopidogrel. (**d**) A 6-month follow-up DCA (left ICA, AP view) confirms complete exclusion of the aneurysm

ent vessel and cover the neck of the aneurysm. In doing so, they promote aneurysm thrombosis and endothelialization across the neck of the aneurysm resulting in parent vessel reconstruction and exclusion of the aneurysm from the circulation (see Fig. 4.2 for

case example of Pipeline Embolization Device). A major disadvantage of these flow-diverting stents is their inherent thrombogenicity that mandate the use of dual antiplatelet therapy after deployment, even in the setting of aneurysmal SAH. Notwithstanding, limited off-label experience with these devices for difficult-to-treat, ruptured aneurysms like blister aneurysms, is overall positive [16].

Regardless of the chosen method, aneurysm treatment should be pursued as early as possible to prevent rebleeding.

4.4.3 Hydrocephalus

Hydrocephalus is a common complication of subarachnoid hemorrhage, resulting from impaired CSF reabsorption in the subarachnoid space and from obstructed cerebrospinal flow through the ventricles when intraventricular hemorrhage is present. Acute hydrocephalus can result in increased intracranial pressure and secondary neurological injury. Particularly in the setting of intraventricular hemorrhage, ventriculostomy is beneficial to both monitor intracranial pressure and to allow for CSF diversion. Some concern exists that significant CSF diversion in the setting of an unsecured ruptured aneurysm can precipitate rebleeding by altering the transmural pressure on the aneurysm wall. However, ventriculostomy placement and conservative CSF drainage have been proven beneficial, even in the setting of untreated ruptured aneurysms [17]. A significant number of patients will require long-term CSF diversion with ventriculoperitoneal shunt placement. This is often the case in the setting of extensive intraventricular hemorrhage and high Fisher Grade [18].

4.4.4 Cerebral Vasospasm and Delayed Cerebral Ischemia

Delayed cerebral ischemia (DCI) secondary to cerebral vasospasm occurs in 20–40% of patients following subarachnoid hemorrhage

and is a significant cause of morbidity and mortality [6, 19]. Though the mechanism is not completely understood, cerebral vasospasm is thought to be the result of inflammatory mediators produced during the degradation of blood products in the subarachnoid space. This inflammation causes spasm of cerebral vessels resulting in decreased cerebral blood flow, impaired regional perfusion, and ischemia [20]. Large vessel vasospasm is seen radiographically as focal or diffuse narrowing of arterial vasculature on CT angiogram or conventional angiogram. A greater degree of arterial vasospasm is more commonly seen in close proximity to the ruptured aneurysm. Though radiographic vasospasm and DCI symptoms often occur concomitantly, their relationship is not linear. Approximately 50% of patients who develop large vessel radiographic vasospasm will not have neurological symptoms of ischemia. Conversely, there are patients who develop symptomatic DCI without corresponding radiographic findings. Multiple factors are thought to influence this relationship, including collateral perfusion anatomy and variations in cellular ischemic tolerance [1].

Classically, vasospasm occurs 3–4 days after initial hemorrhage, peaks in occurrence at 7–10 days, and spontaneously resolves by 21 days [1]. Risk of vasospasm development is higher when patterns of thick subarachnoid hemorrhage and intraventricular hemorrhage are present (Tables 4.3 and 4.4) [21]. DCI occurs when vasospasm leads to decreased cerebral blood flow, decreased perfusion, and ischemia. Symptoms of DCI can include general decline in mental status or focal neurologic deficits corresponding to the affected vascular territory.

Rapid detection of cerebral vasospasm and DCI requires a combination of vigilant attention to fluctuations in neurological exam as well as the use of several monitoring modalities. Transcranial Doppler ultrasound (TCD) is used to trend the velocities of intracranial blood flow to observe for the development of vasospasm. As vessel diameter decreases due to spasm, blood travels through the vessel with increased force, resulting in increased blood velocity. Mean velocity in the MCA of <120 cm/s can be reliably used for ruling out vasospasm, while

Table 4.5 Lindegaard ratio

Lindegaard ratio (MCA/ICA velocity)	
<3	Normal
3–4.5	Mild vasospasm
4.5–6	Moderate vasospasm
>6	Severe vasospasm

Data from: Lindegaard [23]

a velocity ≥200 cm/s is indicative of severe vasospasm [22]. The Lindegaard ratio, defined as the mean velocity in the MCA divided by the mean velocity in the extracranial ICA, is helpful to confirm that these increased MCA velocities are due to vasospasm and not simply hyperemia (Table 4.5). TCD has the benefit of being a bedside, noninvasive modality and having a sensitivity of 0.73 and a specificity of 0.80 for detection of vasospasm in the anterior circulation [20, 22]. Trends in TCD velocities often precede symptomatic vasospasm.

In patients with poor clinical exams, the use of other multimodality monitoring including EEG, near-infrared spectroscopy, cerebral microdialysis, and brain parenchymal oxygen tension monitoring may be helpful in correlating cerebral ischemia with radiographic findings, although definitive supporting evidence to support the routine use of these techniques is still lacking. Please see Chap. 20 for further information on these technologies.

The mainstay of therapy for minimizing the detrimental effects of DCI is maintaining euvolemia and homeostasis. Close attention must be given to volume status, as a hypovolemic state equates to decreased intravascular volume and will result in decreased cerebral perfusion with the development of vasospasm.

Among the many medical therapies that have been evaluated in preventing or minimizing the effects of DCI, nimodipine, an oral calcium channel blocker, is the only medication shown to improve outcome related to subarachnoid hemorrhage. While

rates of radiographic vasospasm are not decreased, patients are shown to have lower rates of symptomatic vasospasm, infarction on imaging, and decreased rates of disability [24]. The standard dosing for nimodipine is 60 mg every 4 h, although this dosing can be adjusted (30 mg every 4 h, 30 mg every 2 h) if needed to avoid hypotension. Treatment is recommended for 21 days following SAH or until the patient is discharged from hospital.

In the setting of neurologic decline and concern for DCI, imaging is typically obtained to correlate exam findings with vasospasm and to rule out other diagnostic possibilities (rebleeding, hydrocephalus). CT angiography is the initial study of choice at most institutions and can be utilized to assess for large vessel vasospasm, although small-vessel spasm is difficult to diagnose. CT perfusion and MR perfusion may be helpful to identify areas of decreased cerebral blood flow in the setting of small-vessel vasospasm. These modalities can be particularly useful to evaluate vasospasm in patients with poor clinical exam [10]. Cerebral angiography is the gold standard for detecting vasospasm and provides the opportunity to treat the patient if the need arises.

Treatment of symptomatic vasospasm involves a combination of blood pressure augmentation and endovascular treatment (Table 4.6). Blood pressure is elevated in a stepwise fashion using a vasopressor (usually phenylephrine or norepinephrine) while the patient is evaluated for improvement in neurologic symptoms [10]. Subsequent increases of 20–30% of baseline

Table 4.6 Treatment approach in symptomatic vasospasm

Ensure homeostasis, euvolemia
Blood pressure augmentation (incremental increases of 20–30% above baseline MAP) using phenylephrine or norepinephrine
Increase CSF diversion by lowering ventriculostomy
Endovascular treatment with intra-arterial vasodilators or cerebral angioplasty

MAP are a generally acceptable paradigm. As mean arterial pressure increases, cerebral blood flow also increases and promotes cerebral perfusion. Boluses of isotonic IV fluid can be given to help augment blood pressure at the time of pressor initiation, but continued high-volume fluid infusion is not recommended for treatment. Caution should be utilized for patients with underlying cardiac disease, and patients should be monitored closely for signs of end-organ damage during blood pressure augmentation therapy. Increasing CSF diversion via ventriculostomy can also help to increase cerebral blood flow in vasospasm by decreasing the volume of CSF and allowing room for blood vessel expansion.

Endovascular treatment for symptomatic vasospasm is pursued when symptoms are not improving with blood pressure augmentation or when circumstances – such as cardiac disease or an unsecured aneurysm – preclude the implementation of this therapeutic approach. The severity and location of vasospasm are best characterized by catheter angiography, so treatment can be targeted to causative vessels. Intra-arterial injections of vasodilators, e.g., verapamil, and balloon angioplasty are examples of endovascular interventions for SAH-associated vasospasm. (see Fig. 4.3 for clinical example of balloon angioplasty treatment for vasospasm). Patients with significant symptomatic vasospasm often require serial endovascular treatments during their course.

Continued therapy is required to maintain cerebral perfusion following endovascular treatment for symptomatic vasospasm. Blood pressure augmentation is typically continued for a few hours and then weaned down in a stepwise fashion, observing for recurrence of neurologic symptoms. Imaging modalities, including TCD and CT angiogram, can be helpful in determining the timing of weaning therapies as improvement in radiographic vasospasm typically corresponds with lower risk of DCI recurrence. Similarly, weaning of CSF via ventriculostomy is completed in a stepwise fashion and is delayed until the risk of DCI is decreased.

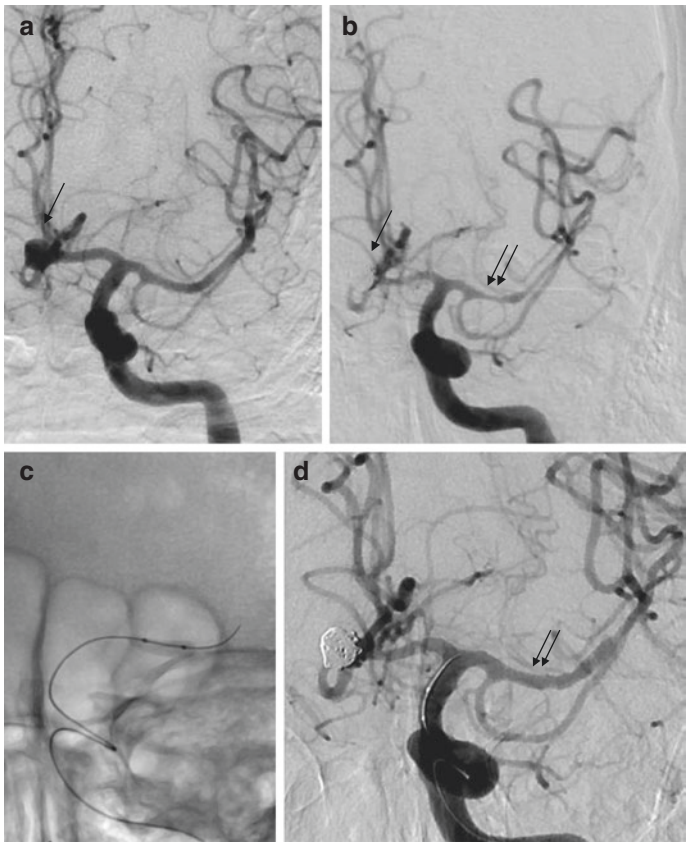

Fig. 4.3 This 53-year-old man presented with a sudden-onset, severe headache. A CT head demonstrated a starburst pattern of subarachnoid hemorrhage. (**a**) A diagnostic cerebral angiogram (DCA, left internal carotid artery (ICA) injection, AP view) demonstrates an AComA aneurysm (*arrow*). He underwent endovascular coiling of the ruptured aneurysm the next day. (**b**) On post-SAH day #5, he developed new-onset R-sided weakness and word-finding difficulty. These did not improve with a trial of induced hypertension. A DCA demonstrates the coiled AComA aneurysm (*arrow*) and interval development of moderate-to-severe vasospasm of the L MCA (*double arrow*). (**c**) Balloon angioplasty of the L MCA is demonstrated with an excellent angiographic result (*double arrow*) (**d**). His R-sided weakness and aphasia resolved in short course

4.4.5 Cerebral Salt Wasting

Cerebral salt wasting (CSW) is a condition frequently seen in aneurysmal subarachnoid hemorrhage and commonly occurs with the onset of cerebral vasospasm. CSW is characterized by a markedly elevated urine output (often >200 cc/h) accompanied by rapidly evolving hyponatremia. Laboratory studies reveal serum sodium <135 mmol/L, low plasma osmolality, and inappropriately elevated urine sodium and osmolality. It is necessary to distinguish CSW from SIADH as aggressive volume repletion is essential in CSW and may worsen symptoms in SIADH. Fludrocortisone and aggressive repletion of volume are utilized to correct hyponatremia and retain stable sodium levels (see Chap. 23 for further information on diagnosis and management of hyponatremia). If untreated, cerebral salt wasting can result in rapid depletion of the intravascular volume and subsequent development or worsening of cerebral vasospasm. Close monitoring of urine output and overall volume status is recommended through the time frame of cerebral vasospasm.

4.4.6 Cardiopulmonary Complications

Patients with SAH commonly develop cardiopulmonary complications, including neurogenic stunned myocardium (also referred to as stress cardiomyopathy or takotsubo cardiomyopathy) and neurogenic pulmonary edema. The primary mechanism contributing to the development of these conditions is thought to be the catecholamine surge that occurs at the time of aneurysm rupture and raised intracranial pressure.

Neurogenic stunned myocardium can be present at patient presentation but can also develop through the critical time frame of peak vasospasm occurrence. This disease process is a distinct entity from other cardiomyopathies in that incidence is not

associated with prior cardiac history or coronary artery disease. Identified risk factors include higher Hunt and Hess grade, history of smoking, lack of history of hypertension, and older age [25]. Initial presenting features include acute hypotension and hemodynamic instability, EKG changes (diffuse ST elevation or T-wave inversions), and troponin elevation. Echocardiogram will commonly demonstrate findings including reduced ejection fraction, global hypokinesis, dyskinesis of the apical or mid-ventricular segments, and diastolic dysfunction [26]. Management of neurogenic stunned myocardium is primarily supportive, utilizing vasopressors and balloon pumps in severe cases to maintain hemodynamic stability and cerebral perfusion. Spontaneous recovery of cardiac function is usually observed in days to weeks following onset [26].

Neurogenic pulmonary edema is similarly seen at presentation and can develop along the same time line as stunned myocardium. Pulmonary edema rapidly develops as a result of capillary dilation leading to interstitial and alveolar edema during initial catecholamine surge [27]. Treatment involves supportive management and maintenance of strict euvolemia (avoiding hypervolemia). The use of aggressive diuresis for management of pulmonary edema should be avoided during the peak time frame of cerebral vasospasm to avoid depleting intravascular volume and contributing to delayed cerebral ischemia.

4.5 Perimesencephalic Subarachnoid Hemorrhage

A subpopulation of patients presenting with subarachnoid hemorrhage have characteristic radiographic findings of aneurysmal SAH, but have no causative lesion identified, and have a benign clinical course. These patients typically present with symptoms of headache, meningismus, and nausea. The onset more commonly

occurs during physical exertion [28]. The hemorrhage pattern is focused centrally around the brainstem in the perimesencephalic cisterns without distal extension into the Sylvian and interhemispheric fissures. Vascular imaging (CT angiography or MR angiography) is recommended to exclude an underlying vascular lesion, but diagnostic catheter angiography can by deferred if clinical suspicion for aneurysmal rupture is low. Although perimesencephalic hemorrhage patients can develop hyponatremia and other systemic complications associated with SAH, their course is generally benign. Rebleeding and development of cerebral vasospasm are rare [29]. The etiology of perimesencephalic hemorrhage is debated but is likely to be venous in origin.

Summary Points

- Aneurysmal subarachnoid hemorrhage is a complex disease with significant associated morbidity and mortality.
- Early identification and treatment of ruptured vascular lesion are essential to prevent rebleeding and optimize neurologic outcome.
- Cerebral vasospasm is a major complication following aneurysmal subarachnoid hemorrhage and requires rapid diagnosis and treatment to prevent delayed cerebral ischemia.
- Aneurysmal subarachnoid hemorrhage is associated with multiple systemic complications.

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Chapter 5
Intracerebral Hemorrhage

Devra Stevenson and Kevin N. Sheth

5.1 Introduction

Intracerebral hemorrhage (ICH) occurs when intracranial vessels rupture and cause bleeding into the brain parenchyma. The present chapter discusses nontraumatic (or spontaneous) hemorrhages. ICH represents 10–15% of all strokes, second only to ischemic strokes, and is classified as primary and secondary [1]. Primary ICH is often the final manifestation of chronic small-vessel diseases of the brain, notably lipohyalinosis (also known as hypertensive vasculopathy because chronic hypertension is its main risk factor) and cerebral amyloid angiopathy (CAA). Etiologies of secondary ICH can be divided into several major categories including vascular malformations, coagulopathy, and underlying intracranial neoplasms. Within the category of vascular malformations, ICH can be further classified as caused by ruptured aneurysms, arteriovenous

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malformations (AVMs), or cavernous malformations. Coagulopathies include not only congenital coagulopathies such as hemophilia but also acquired causes of coagulopathy, including medication-induced (such as oral anticoagulation), or secondary to renal disease or liver disease. Intracranial neoplasms can also be further delineated into primary brain tumors versus metastatic disease. In clinical practice, the etiology of the hemorrhage is often inferred from the location of the hemorrhage identified on neuroimaging. The diagnosis is further supported by the history, clinical exam, and laboratory findings.

5.2 Case Presentation

A 70 year-old woman on acetylsalicylic acid + dipyridamole due to a prior stroke presented with acute-onset severe dizziness and vomiting followed by confusion. On arrival to the ED, her blood pressure was 248/72. On initial exam, she was lethargic, opened her eyes to noxious stimuli with no verbal output, localizing to painful stimuli with her right side and withdrawing on the left. Her neurologic status continued to decline and she was intubated in the ED for airway protection. The initial head CT revealed an acute right cerebellar ICH with intraventricular hemorrhage (IVH) extending to the lateral ventricles, third ventricle, and near-complete effacement of the fourth ventricle (Figs. 5.1 and 5.2). Her home acetylsalicylic acid + dipyridamole was held. Nicardipine was utilized to achieve SBP <180. A more detailed history revealed that the patient had long-standing history of uncontrolled hypertension.

Her ICH score was 3 (GCS 8, infratentorial, intraventricular hemorrhage).

She had a six-hour stability CT head with CTA which revealed noncommunicating hydrocephalus due to compression

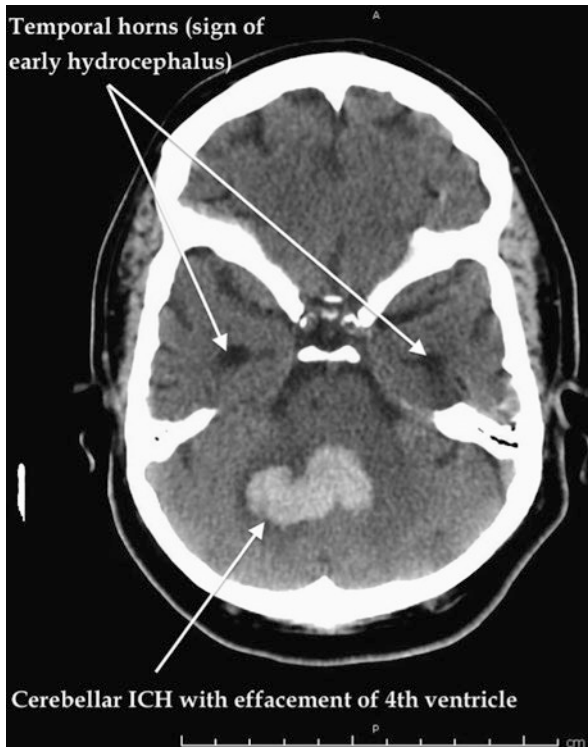

Fig. 5.1 Example of cerebellar ICH with early hydrocephalus

of the fourth ventricle and no evidence of underlying vascular lesion. Due to her lethargy, the location of the hemorrhage, and evidence of worsening hydrocephalus, an EVD was placed. After confirming the appropriate position on head CT, the EVD was opened to drain the CSF. Her exam rapidly improved with CSF drainage. Over the next several days she was weaned off the ventilator and extubated.

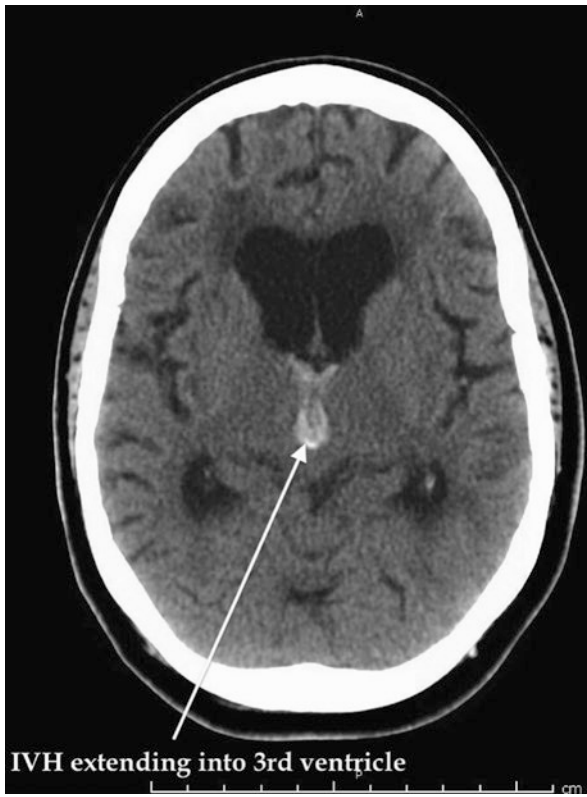

Fig. 5.2 Example of IVH

5.3 Initial Evaluation

5.3.1 Neuroimaging

One important component of the initial evaluation is to determine the underlying etiology of the ICH based on imaging, history, exam, labs, and other diagnostic tools. The primary

neuroimaging modalities used in ICH include CT, CTA, MRI, and cerebral angiography.

A head CT without contrast is the preferred imaging modality for the initial diagnosis of ICH. It is readily available, quick, and provides information about the size of the hemorrhage, location, edema, mass effect, midline shift, and any extension into the ventricles, also known as IVH [2]. Acute blood appears hyperdense on CT. A noncontrast head CT can also be used to calculate the hematoma volume. A common formula used for this calculation is *ABC/2,* where *A* is the greatest diameter of the hemorrhage on the CT slice with the largest area of hemorrhage, *B* is the largest diameter 90° to *A* on the same slice, and *C* is the approximate number of slices with hemorrhage multiplied by the thickness of the slice in centimeters [3]. *A* multiplied by *B* multiplied by *C*, divided by 2 gives the approximate volume of the hemorrhage in cubic centimeters. Referring to Fig. 5.3, *A* is measured at approximately 3.6 cm, *B* is approximately 2.0 cm, and *C* is determined to

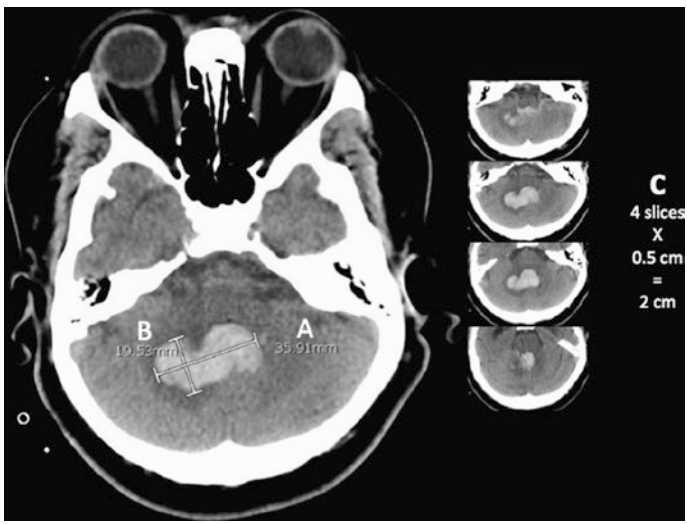

Fig. 5.3 Example of ABC/2 calculation

be 4 slices, which is then multiplied by the thickness of the slice (at our institution, 0.5 cm). Using the *ABC/2* formula these values are multiplied and then divided by 2, which estimates an ICH volume of approximately 7 cc.

A CT angiography of the head and neck with IV contrast is commonly used to assess for underlying vascular lesions. It is important to remember, however, that sometimes, underlying lesions can be obscured by the hemorrhage; therefore, this is often repeated in a delayed fashion. One useful finding for predicting hematoma expansion with CTA is the spot sign. This finding is defined as a focus of contrast enhancement within the hemorrhage on a postcontrast image and represents an area of active contrast extravasation [4, 5].

MRI with and without contrast is another commonly used imaging modality in ICH. Susceptibility-weighted imaging (SWI) and Gradient-recalled echo (GRE) are two sequences that can be helpful in identifying small areas of hemorrhage (microbleeds) that are not detected on CT and are useful in diagnosing CAA. Additionally, contrast studies can be helpful to identify underlying neoplastic lesions, as these lesions enhance with gadolinium.

Cerebral angiography, or digital subtraction angiography (DSA), is yet another tool available to identify the underlying cause of an ICH. This is more invasive than previously discussed modalities, but may be considered in specific patients where CTA or MRA are inconclusive and a vascular abnormality is high on the differential.

5.3.2 Diagnosis

Hypertension is the most common cause of ICH. Chronically elevated blood pressure is the main contributor to lipohyalinosis, a disease that affects the small deep-brain vessels, making them prone to rupture. Sudden fluctuations in blood pressure in

otherwise healthy individuals can also, in rare instances, cause ICH. Hypertensive hemorrhages are located in deep-brain structures: basal ganglia, thalamus, cerebellum, and midbrain. Obtaining a thorough history can be helpful, with attention to any history of hypertension, events leading to symptom onset (such as a strenuous physical activity or emotional event), or drug use. In patients with unknown past medical history, it may be helpful to look for evidence of left ventricular hypertrophy on EKG or echo. A toxicology screen on all ICH patients to rule out illicit drug use is also useful.

Cerebral amyloid angiopathy (CAA) is another common cause of ICH. CAA is characterized by the accumulation of amyloid deposits in the walls of small and medium-size brain vessels, also making them prone to rupture [6]. The incidence of CAA is strongly age dependent and is most often seen in patients greater than age 60. Some helpful findings on imaging to distinguish CAA from other causes of ICH include lobar (cortical) location and multiple hemorrhagic lesions including small hemorrhages (microbleeds). Despite these helpful clues, definitive diagnosis can only be made by pathology.

Coagulopathy is an important cause of secondary ICH. Coagulopathy can be divided into acquired and congenital. Acquired coagulopathies include those related to medications (warfarin) and those secondary to renal or liver disease. With anticoagulation-induced ICH, it is extremely important to determine the date and time the medication was last taken and obtain a full coagulation panel, as the highest risk of hemorrhage expansion is within the first six hours of hemorrhage. The reversal strategy should be tailored to the type of anticoagulation used. Renal disease causes increased risk of ICH through uremia-related platelet dysfunction, while liver disease increases the risk of ICH due to impaired synthesis of clotting factors. Congenital forms of coagulopathy include hemophilia A and B as well as other rare conditions.

Intracranial tumors are a less common cause of ICH, with rates ranging anywhere from 1 to 10% of all ICH cases [7].

Neoplastic lesions can be classified into two major groups: primary brain tumors and metastatic disease. Of the primary brain tumors, malignant gliomas, such as glioblastoma multiforme and oligodendroglioma, are particularly predisposed to hemorrhage. Among metastatic disease, breast and lung cancer are commonly associated with ICH due to their high prevalence in the general population, while melanoma, renal cell, thyroid cancer, and choriocarcinoma are also associated with ICH due to their proclivity to bleed.

Vascular lesions are yet another cause of ICH. Vascular lesions include aneurysms, cavernous malformations, and arteriovenous malformations. Rupture of these lesions can lead to multicompartmental hemorrhage including not only subarachnoid hemorrhage but also ICH. Subarachnoid hemorrhage is discussed further in detail in Chap. 4.

5.3.3 Prognosis

Prognostication in patients with ICH remains difficult. The ICH score is a clinical grading scale designed to capture baseline disease severity and approximate a prognosis. The ICH score is determined based on five features: Glasgow Coma Scale, IVH volume, presence of IVH, infratentorial origin, and patient's age [8]. Higher scores are associated with more severe baseline disease. Refer to Table 5.1 for scoring calculation.

The presence of IVH is another important factor not only in prognostication but also in guiding management. IVH occurs in approximately 45% of all patients with ICH [9, 10]. It is typically associated with worse outcomes, as patients are at increased risk of developing noncommunicating (obstructive) hydrocephalus.

Scoring systems, like the ICH score, should be used carefully to avoid self-fulfilling prophecies (patients labeled as having poor prognosis are more likely to have their care withdrawn, which in turn guarantees a poor prognosis). In other words, this scale constitutes one of the numerous factors to be considered

Table 5.1 ICH score

Scoring features	Values	Points
GCS		
	3–4	2
	5–12	1
	13–15	0
ICH volume (cm^3)		
	≥30	1
	<30	0
IVH presence		
	Yes	1
	No	0
Infratentorial origin of hemorrhage		
	Yes	1
	No	0
Age (years)		
	≥80	1
	<80	0

Total score 0–6

when prognosticating and making code-status decisions. Studies have shown that early do-not-resuscitate (DNR) orders (within the first 24 h of hemorrhage) are associated with an increased risk of in-hospital mortality after acute ICH, even after adjusting for patient and hospital characteristics, suggesting that DNR use may be a proxy for overall aggressiveness of care [11, 12].

5.4 Management and Interventions

5.4.1 Airway

Early assessment of the patient's respiratory status is essential. Patients may require urgent or emergent intubation for airway protection. Obtain an ABG, paying particular attention to CO_2. In the ICU setting, consider capnography and correlate this with the ABG.

5.4.2 Blood Pressure Management

Current studies do not support aggressive reduction of systolic blood pressure to <140 mm/Hg. On the contrary, ICH patients randomized to this aggressive blood pressure goal had a statistically significant increase in risk of acute kidney injury. In light of this evidence, it is reasonable to aim for a strict systolic blood pressure goal of <180 mm/Hg. Some experts would argue that few exceptions to this rule are patients who are deteriorating clinically and those who have concerning findings in the head CT, including enlarging hematoma and spot-sign presence [10, 13, 14].

5.4.3 Correct Underlying Coagulopathies

Ask about oral anticoagulant or antiplatelet use, obtain coagulation studies and a platelet count, and discontinue all anticoagulant and antiplatelet medications. Warfarin is the most commonly used oral anticoagulant [15]. To reverse warfarin, emergently give IV vitamin K and either four-factor PCC (prothrombin complex concentrates) *or* FFP (fresh frozen plasma) [16, 17]. PCC has faster time to INR correction, less volume administered during infusion, and does not require blood type matching, but purports an increased risk of thrombotic events. FFP is widely available and contains all coagulation factors, but takes longer to order, match, and prepare, provides large fluid volumes, carries a risk of allergic reaction and infections, and has the potential to cause transfusion-related acute lung injury (TRALI). Following reversal, it is paramount to repeat coagulation studies every 6 h, as patients may have rebound elevations in INR.

Heparin is another commonly used anticoagulant. Protamine sulfate is the reversal agent of choice for heparin.

In recent years, several newer oral anticoagulants, or NOACs, have become available and are increasingly being used as alternatives to warfarin. Some of the more commonly used agents include dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis). Currently, the only agent that has been approved by the FDA for the reversal of these NOACs is idarucizumab (Praxbind), which is specific for the reversal of dabigatran (Pradaxa). Another agent, Andexanet alfa, which has the potential to reverse rivaroxaban, apixaban, edoxaban, and low-molecular-weight heparin, has been submitted for breakthrough design therapy as well as orphan drug therapy to the FDA, but is not currently approved for human use [18, 19]. Reversal options for the other agents remain limited at this time, but may include activated charcoal for apixaban and rivaroxaban as well as dialysis in dabigatran-related bleeding [19]. The use of PCC, activated PCC (aPCC), or recombinant factor VIIa (rFVIIa) may be considered but has not been well studied. Several ongoing studies are investigating the safety and efficacy of other reversal agents. In any case, an emergent consult with hematology may provide valuable input to guide the reversal therapy in this setting.

Antiplatelet agents such as aspirin and clopidogrel (Plavix) have also been shown to be a risk factor for ICH. Platelet transfusion in patients with ICH is controversial. Current data indicate that platelet transfusions do not improve outcome and may actually worsen it. However, hospital policies vary greatly and some hospitals recommend platelet transfusion in patients planning to undergo a major procedure such as EVD placement or surgery. In terms of dosage, a transfusion of 10–12.5 units of platelets has been found to restore normal platelet function in patients on clopidogrel and aspirin [20].

In patients with coagulation factor deficiencies, administer the appropriate factor replacement.

5.4.4 Monitor for Hydrocephalus

Hydrocephalus can be monitored both clinically and radiographically. Clinical signs of hydrocephalus include gradual decline in level of consciousness as patients become progressively sleepier. Other helpful exam findings include impaired upward gaze and lateral rectus palsy.

Neuroimaging is another useful modality to monitor hydrocephalus. Maintain a low suspicion for repeating a noncontrast head CT to assess for increased size of ventricles, increased edema particularly near the third and fourth ventricle, or the presence of IVH that fills the ventricle (also known as "casting" of the ventricles), which can result in reduced CSF drainage. Also notable, the presence of temporal horns on CT can be a sign of early hydrocephalus. Patients with evidence of hydrocephalus and poor exam may require CSF diversion such as with an EVD. Some patients go on to require permanent CSF diversion with a ventriculoperitoneal (VP) shunt.

5.4.5 Glucose Management

Hyperglycemia in patients with ICH is associated with worse outcomes. In the first few days of admission, tight glucose control should be achieved, avoiding hyper- and hypoglycemia. One commonly accepted regimen is to start a patient on an insulin sliding scale and transition to an insulin drip for two readings of glucose >180.

5.4.6 Temperature Modulation

Fevers are associated with worse outcomes in patients with ICH. Consequently, it is important to both identify the source and treat fever early and aggressively. Central, or neurogenic fevers,

is a diagnosis of exclusion when no other clear source can be found. The risk of central fevers is higher in patients with IVH and those with larger hemorrhages. Options for fever control may include acetaminophen, ice packs, application of a cooling blanket, and if still refractory, to consider advanced cooling modalities (in intubated patients) to maintain normothermia. It is important to monitor for and avoid shivering in patients being cooled as this may increase metabolic demand. There are several techniques available to treat and prevent shivering including surface counter warming, magnesium repletion to a goal of greater than three, and medications such as buspirone (Buspar), meperidine (Demerol), diazepam (Valium), and dexmedetomidine (Precedex), among others.

5.4.7 Seizure Monitoring

Patients with ICH are at risk of developing seizures including nonconvulsive events. Seizures are more common in lobar hemorrhages compared to deep hemorrhages but can happen in both. EEG monitoring can be considered in patients with a fluctuating exam. Antiepileptic drugs (AEDs) are only recommended in patients with electrographic or clinical seizure; they are not recommended for seizure prophylaxis in this patient population [21, 22].

5.4.8 Surgical Interventions

There are currently several surgical interventions available for patients with ICH including intracranial pressure (ICP) monitoring, intraventricular thrombolysis, and surgical decompression and hematoma evacuation. Typical indications for ICP monitoring include patients with Glasgow Coma Score (GCS) less than or equal to eight, those with significant IVH, significant

hydrocephalus, or evidence of transtentorial herniation [10]. There are two main types of ICP monitors used in current practice. Diagnostic ICP monitors such as bolts are placed into the brain parenchyma and allow for ICP monitoring but no drainage of CSF. This is in contrast to therapeutic ICP monitors such as external ventricular drains (EVDs), which are placed within the ventricles and allow for both ICP monitoring as well as drainage of CSF. An ICP target goal is typically less than 25 sustained, with a typical cerebral perfusion pressure goal of 50–70 [10].

Another potential surgical option in ICH is intraventricular thrombolysis, during which a thrombolytic agent (tissue plasminogen activator, or tPA) is injected through an EVD into the ventricular system. The rationale is that tPA may help promote clot breakdown and clearance of blood [10]. However, this method is still undergoing investigation and is not routinely recommended at this time [23, 24].

Another available option is surgical decompression and hematoma evacuation. Surgery is only considered in patients with neurological decline, and the surgical approach is typically driven by the location of the hemorrhage—supratentorial versus cerebellar. In patients with supratentorial ICH, surgery is controversial and reserved for patients with life-threatening mass effect refractory to maximal medical therapy. Studies have shown similar rates of unfavorable outcomes between patients taken early for surgery versus those treated conservatively, although a survival benefit may exist in specific subgroups of patients, including those with poorer prognosis on presentation, those who deteriorated after presentation, and those with superficial ICH and no IVH [10, 25]. Patients with lobar clots >30 mL and within 1 cm of the surface may be considered for standard craniotomy for evacuation of the clot [10]. Surgery in patients with supratentorial ICH should only be considered as a life-saving procedure, and decisions should be made on a case-by-case basis.

Patients with cerebellar hemorrhage are at risk of brainstem compression and death. Common indications for suboccipital craniectomy include ICH >3 cm in diameter who are deteriorating clinically and evidence of brainstem compression and/or hydrocephalus due to obstruction of ventricles.

Summary Points

- Determine the underlying etiology. The location of the hemorrhage on imaging can be helpful in making this diagnosis.
- Hypertension and CAA are common causes.
- It is important to rule out a vascular abnormality early.
- Monitor for and treat hydrocephalus, paying close attention to level of arousal.
- Recognize and treat early any coagulopathy.
- ICH volume can be estimated using the formula ABC/2.
- Surgical intervention is made on a case-by-case basis, with low threshold for decompression in cerebellar IVH.
- Communication regarding prognosis in ICH should often include a range of possible outcomes.

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Chapter 6
Acute Ischemic Stroke

Karin Nyström and Joseph Schindler

6.1 Introduction

Stroke presentations are varied and complex. They are dependent upon the function of brain tissue that is affected or at risk. At the stroke onset, symptoms are typically at maximum severity. This may reflect a stroke that is caused by an embolus that abruptly occludes a cerebral arterial branch. Presentations that fluctuate or slowly progress may be dependent on perfusion, possibly from reduced blood flow in a preexisting or new fixed vessel stenosis.

It is beyond the scope of this chapter to detail the pathophysiology of all stroke types as this chapter is focused on the diagnosis and treatment of acute ischemic stroke. However, it is important to appreciate that for patients who experience an acute ischemic stroke, disruption of cerebral blood flow due to an obstruction of a blood vessel initiates a complex series of circulatory and metabolic events referred to as the ischemic cascade.

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The ischemic cascade occurs when blood flow in the brain measures less than 25 ml/min/100g. At this point, neurons are no longer able to maintain aerobic respiration; this switch to anaerobic metabolism generates large amounts of lactic acid and glutamate, changing the tissue pH and rendering cells incapable of producing sufficient quantities of adenosine triphosphate (ATP) to fuel cell depolarization processes [1]. Electrolyte balances begin to fail and the cells cease to function. Cell death at the site of vessel occlusion is referred to as the (*core infarct*). The surrounding area of affected brain tissue in which blood flow has been reduced is referred to as the *ischemic penumbra*. In selected patients, it is this stunned brain tissue that is deemed salvageable with early intervention, such as with thrombolysis (administration of intravenous tissue plasminogen activator or IV alteplase) [2] and/or with mechanical thrombolysis (clot retrieval with a specialized percutaneous catheter; see Chap. 7 [3].

The primary focus for the initial treatment of acute ischemic stroke is determining whether a patient who presents with acute neurological deficits is a candidate for intravenous thrombolytic therapy. Within the last two decades, the use of IV alteplase (commonly referred to as IV tPA) for acute ischemic stroke, together with the establishment of stroke systems of care, has changed the treatment "landscape" for both acute and recovery stroke care. Certified stroke centers are organizations recognized for the implementation of protocols that address the triaging and assessment of potential stroke patients quickly and that deliver selected treatments in a timely manner. At the forefront is the acute stroke team. Neurologists and non-neurologists including emergency department physicians, internists, and advanced practice clinicians comprise the modern-day providers (or LIPs – licensed independent practitioners) on the stroke team. All members of the team must understand the variable spectrum of acute stroke presentations, the critical elements of the neurological examination, the basis for imaging, the indications for treatment, and the need for specific order sets that outline subsequent inpatient care including post-lytic assessments.

6.2 Case Presentations

6.2.1 Case 1

Patient is a 48-year-old right-handed woman with a mechanical heart valve (taking warfarin) that presents with the acute onset of speech slurring, left-sided weakness, visual loss, and neglect. She arrives to the hospital within 1 h from the time of symptom onset. Her National Institute of Health Stroke Scale Score (NIHSS) is 15. Her INR is 1.1. She is taken for a STAT CT head (Fig. 6.1), which demonstrates no acute intracranial hemorrhage,

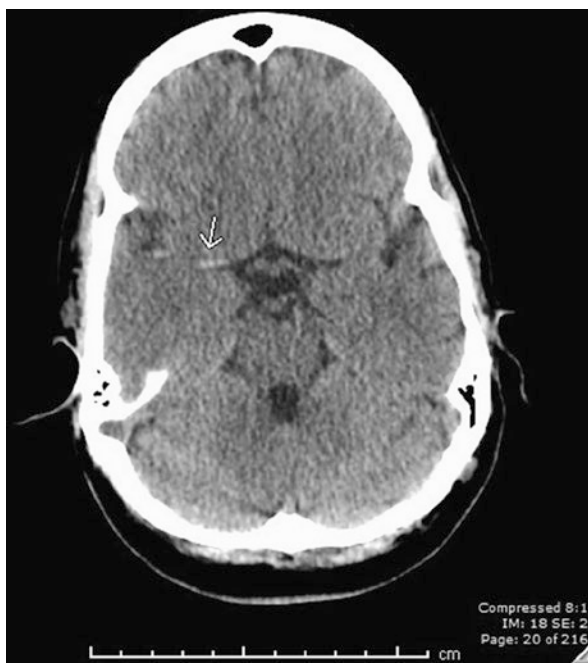

Fig. 6.1 Non-contrast head CT demonstrating a hyperdense right middle cerebral artery

but does show a hyperdense right middle cerebral artery suggestive of acute thrombus. She meets the inclusion criteria for intravenous thrombolytic therapy. IV alteplase is administered 1 h and 20 min after symptom onset. Over the next 24 h, the patient's symptoms improve with her NIHSS decreasing to 8. She is evaluated for and is accepted for acute rehabilitation. She undergoes a repeat CT scan to rule out any hemorrhage and is restarted on anticoagulation at 2 weeks after her stroke.

6.2.2 Case 2

Patient is an 87-year-old right-handed man with a history of hypertension, diabetes, and ischemic stroke (5 years ago) that presents with the onset of unsteady gait. He arrives to the hospital 4 h after the onset of his symptoms. On examination, the patient has rotary nystagmus at primary gaze, dysarthria, and right-sided dysmetria. His NIHSS is 2. The STAT head CT scan shows an area of early ischemic changes in the right cerebellum (Fig. 6.2). Despite a low NIHSS, the patient has disabling symptoms; however, his age (87 years) and comorbidities (history of diabetes and stroke) render him *not* a candidate for alteplase outside the 3 h time window. This patient is admitted to the stroke service for further diagnostic tests to understand the stroke etiology and to initiate secondary stroke prevention therapies. He is started on aspirin 81 mg daily, atorvastatin 80 mg daily and is deemed a candidate for physical and vestibular rehabilitation.

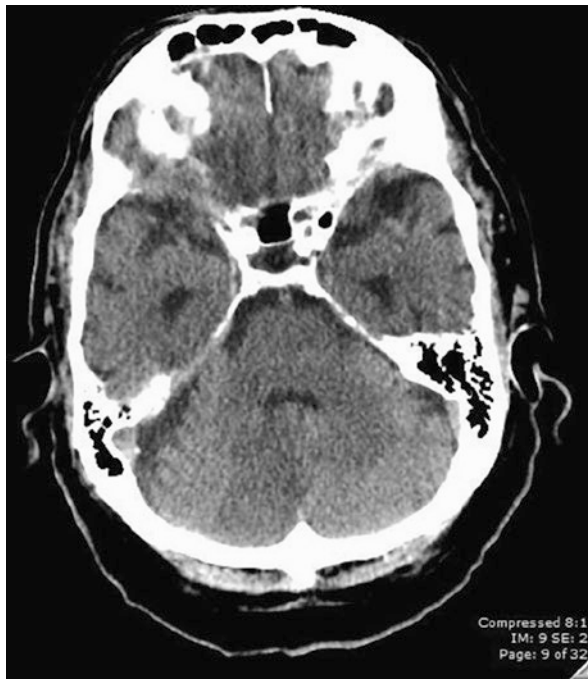

Fig. 6.2 Non-contrast head CT demonstrating a right cerebellar hypodensity

6.3 Initial Evaluation

The primary focus for the initial treatment of acute ischemic stroke is determining whether a patient who presents with acute neurological deficits is a candidate for intravenous thrombolytic therapy. This chapter focuses on a review of the pathophysiology of acute ischemic stroke, the critical thinking algorithms

that direct acute stroke care during the "golden hour" after presentation, and the role of the advanced practice clinician during the hyperacute, acute, and posttreatment recovery care process.

The two cases illustrate the diversity of acute stroke syndromes and their associated presentations, the importance of understanding neurovascular anatomy, the limitations of the currently recommended neurologic assessment (the National Institutes of Health Stroke Scale or NIHSS) in assessing posterior circulation strokes, the utility of imaging, and the criteria for IV alteplase treatment. Of the two stroke syndromes presented, the first patient has an anterior stroke syndrome and the second patient a posterior circulation syndrome. The significant contrast in the NIHSS assessments reflects the inadequacy of the NIHSS in appreciating disability caused by posterior circulation strokes.

A broad exposure to neuroanatomy and clinical correlation is important for prompt recognition of suspected acute stroke syndromes. Fortunately, many syndromes can be learned through pattern recognition (identifying specific symptoms that the patient presents with that can be correlated to and associated with loss of function in specific regions of the brain). For instance, strokes in the left hemisphere may be associated with aphasia and right-sided weakness. The patient from Case 1 had symptoms suggestive of right hemispheric dysfunction given that she had left-sided visual loss, left-sided weakness, and neglect. As shown in Case 2, posterior circulation strokes may be difficult to appreciate when depending on an NIHSS to make a diagnosis. A posterior circulation infarct must be considered if symptoms such as dysarthria, double vision, hemianopsia, and incoordination occur. Practitioners must also recognize a set of stroke syndromes that do not involve cortical signs on the examination. These strokes, called lacunar infarcts, occur in deeper brain perforating arteries commonly affecting the internal capsule,

thalamus, and pons. The associated syndromes include focal motor weakness, focal sensory disturbances clumsy-hand dysarthria, and ataxic hemiparesis.

A stroke classification scheme worth reviewing and that requires a rudimentary knowledge of neurovascular anatomy includes Bamford's Stroke Classification or the Oxfordshire Community Stroke Project [4]. Depending on the presence of cortical dysfunction and the extent of deficit, anterior strokes can be classified into a total anterior stroke or partial anterior stroke. If the patient has a cranial nerve palsy, bilateral motor deficits, conjugate eye movement problems, cerebellar dysfunction, or an isolated hemianopsia, patients can be classified as having a posterior circulation stroke. Pure sensory or motor deficits along with other small vessel syndromes described above can be categorized as a lacunar stroke.

Classification systems and scales are not a replacement for the neurological examination, which will refine localization and help the practitioner differentiate neurovascular from non-neurovascular presentations. The neurological examination will allow the stroke team to differentiate impairments stemming from the peripheral nervous system, such as hand weakness from a small cortical stroke as opposed to an ulnar neuropathy. It will also allow the advanced practice clinician to appreciate ocular findings, incoordination, and gait instability which are undervalued or not tested in the NIHSS.

Posterior circulation strokes are missed more frequently than anterior circulation strokes [5]. Vertigo evaluations can be challenging, especially when the patient has overwhelming nausea and head-motion intolerance. Additionally, focal signs on the exam may be absent in cerebellar strokes. For these cases, the neurologist and non-neurologist should be proficient in bedside testing that evaluates the vestibular-ocular reflex for

Table 6.1 Common stroke mimics

Acute vestibular neuritis
Cervical radiculopathy
Migraine
Seizure
Demyelinating disease
Hypoglycemia
Conversion disorder
Metabolic or toxic encephalopathy

corrective saccades, direction-changing nystagmus on eccentric gaze, and skew deviation. The acronym for the examination is called HINTS, which stands for head impulse testing, nystagmus, and test of skew deviation. A negative HINTS examination (which includes an abnormal head impulse finding, absence of nystagmus, and absence of a skew deviation) was found to be more sensitive than an early MRI of the brain for excluding stroke [6, 7].

It is estimated that up to 50% of acute presentations felt to be stroke are stroke mimics (Table 6.1) [8]. Most acute stroke responders will not have access to performing a brain MRI to confirm stroke, but will have to rely upon history, the neurological examination, and a head CT to determine whether to give IV alteplase [9]. Nevertheless, current practice supports have supported rapid treatment at the expense of a confirmatory diagnosis, citing that the risk of a complication from thrombolytics is very low.

6.4 Management and Interventions

For the purposes of understanding the time-sensitive nature of stroke, the assessment, stabilization, diagnosis, and management in the first few hours after symptom onset is referred to as the *hyperacute* phase of stroke care. This time window is more broadly defined as the first 24 h after contact with the healthcare

system and includes interaction with the pre-hospital personnel (EMS) and with the emergency department staff and acute stroke team (which may also include neurosurgeons, neurointerventionalists, and the critical care unit staff). The primary goal of care during this time frame is the rapid and efficient evaluation of patients presenting with neurological deficits that would benefit from early treatment therapies (to preserve the penumbra). Reference to the *acute* phase of stroke care includes the management of stroke patients during the early recovery stage and includes the time while hospitalized (several days) or the first 30 days after the index stroke, depending on the specific organization's scope of practice [10]. During the acute phase of care, diagnostic tests to understand the possible stroke etiology are ordered; secondary stroke prevention strategies are implemented; and promotion of early recovery and prevention of complications are outlined. For the individualized care plan, a patient- and family-centered education module for post discharge recovery is initiated.

In addition to the above operational phases of care, a key time frame within the stroke care trajectory is the time window from when the patient's symptoms begin (or when the patient was last known to be at his/her baseline) to the time when treatment is started. Depending on the available therapy options, patient-related variables, and clinical trial enrollment criteria, the treatment time window can vary from 3.0 h up to 12–24 h. The 3.0 h time window reflects the results of the 1995 NINDS trial which showed a significant outcome benefit for patients treated with intravenous alteplase [11]. The 4.5 h time window reflects the results of the 2008 ECASS III trial in which selected patients had a significantly improved outcome when treated with intravenous alteplase up to 4.5 h after symptom onset [12]. The stroke treatment time window that is extended out to 12–24 h reflects the additional treatment options such as mechanical thrombolysis and enrollment in acute stroke clinical trials for which specific pharmacologic or other experimental therapies might be offered.

So for the clinicians involved in the acute stroke code process, this time window defines "acute," it sets parameters for when the stroke code is activated, and it directs both the pre-hospital and stroke team efforts for early, efficient, and rapid evaluation.

6.4.1 Stroke Systems of Care

As mentioned earlier, there has been a revolutionary change in the organized capabilities of medical facilities to respond to the acute care needs of stroke patients. Over the last 15 years, hospitals have embraced the concept of disease-specific care certification for stroke as evidenced by the work of national certification entities such as The Joint Commission (TJC), Det Norske Veritas (DNV), and Healthcare Facilities Accreditation Program (HFAP). The impetus for the establishment of certified stroke centers was the 2000 publication of the consensus statement by Alberts et al. in the Journal of the American Medical Association, suggesting that elements of a stroke center would standardize and improve overall stroke care [13]. In collaboration with the American Heart Association (AHA)/American Stroke Association (ASA), The Joint Commission offers three levels of advanced stroke certification with specific requirements for meeting standards set forth by national clinical practice guidelines for stroke care. The goal is to afford every facility with the required resources to have the capability of caring for acute stroke patients across the continuum [14].

6.4.2 Acute Stroke Code

With the growing interest in organizing systems of care for stroke patients and with a shortage of vascular neurologists across the USA, opportunities for advanced practice clinicians to play a critical role in the evaluation and management of acute stroke patients have expanded across urban, suburban, and rural

acute care settings [15]. More healthcare organizations are taking an interest in achieving stroke center certification and are integrating APCs in the hyperacute phase of stroke care to meet the standards set forth by the certifying organizations to meet time targets and care metrics. In fact, for institutions seeking comprehensive stroke center certification, one or more APCs are required to take an active role in the delivery of stroke expertise in the clinical, education, and research domains [16, 17].

There are several acute stroke care delivery models that utilize stroke-trained APCs to link the pre-hospital, emergency department, diagnostic imaging, pharmacy, and other ancillary staff under the defined acute stroke code protocol. In some organizations, the APC is the designated first responder and is responsible for the initial neurological exam, gathering history, ordering imaging, and consulting with the on-call neurologist to review the case and determine treatment options. At larger facilities, the APC may be one member of a team of clinicians including neurology fellows, residents, or members of the ED staff. The evaluation and treatment decisions are a shared responsibility among the providers. With the expanded use of telestroke services, the APC at the remote site may be the key participant in the video-conferencing consult with the on-call telestroke vascular neurologist.

Many times EMS has provided notification of an acute stroke case before arriving at the hospital. Triage is performed in the field using one of several validated pre-hospital stroke assessment tools (Table 6.2). Based on prenotification, the acute stroke team will have been activated to provide a rapid and efficient evaluation of the patient's history (including time "last known well" or at baseline) and presenting neurological deficits (with an NIHSS assessment). A STAT non-contrast CT scan of the brain is the initial neuroimaging study ordered and performed to exclude cerebral hemorrhage as a cause for the patient's presenting symptoms. Based on a review of specific laboratory results and criteria for the administration of IV alteplase, in addition to making a clinical diagnosis of acute ischemic stroke, the stroke team will present the options for thrombolytic treatment with a

Table 6.2 Examples of pre-hospital neurologic screening assessments: the Cincinnati pre-hospital stroke screen and the Los Angeles pre-hospital stroke screen

Cincinnati pre-hospital stroke scale
Facial droop
Normal: both sides of face move equally
Abnormal: one side of face does not move as well as the other
Arm drift
Normal: both arms move the same or both arms do not move at all
Abnormal: one arm either does not move or drift down compared to the other
Speech
Normal: says correct words without slurring
Abnormal: says the wrong words, slurs words, or is unable to speak
Los Angeles pre-hospital stroke screen (LAPSS)
Last time patient known to be symptom free
Screening Criteria
Age > 45 y
No history of seizures or epilepsy
Symptom duration <4.5 hours
Not previously bedridden or wheelchair bound
Blood glucose 60–400 mg/dl
Exam
Facial smile/grimace: normal, droop
Grip: normal, weak grip, no grip
Arm: normal, drifts down, falls rapidly

full discussion of the risks and benefits associated with this treatment. The current time target from arrival in the emergency department to thrombolytic treatment is ≤60 min. Time elements of this process have been further divided with the following recommended time goals, as outlined in Table 6.3.

The acute stroke code actions described above represent the first tier of acute stroke care. A more detailed outline of additional imaging studies, relevant laboratory studies, and hemodynamic monitoring parameters is described in the 2013 AHA/ASA guidelines for the early management of patient with

Table 6.3 Recommendations for benchmark times during the stroke code

Emergency department team actions	Time
Arrival to provider evaluation	<10 min
Arrival to acute stroke team evaluation	<15 min
Arrival to CT scan "start"	<25 min
Arrival to CT scan interpretation	<45 min
Arrival to IV thrombolysis	<60 min
Arrival to disposition to the stroke unit	<3 h

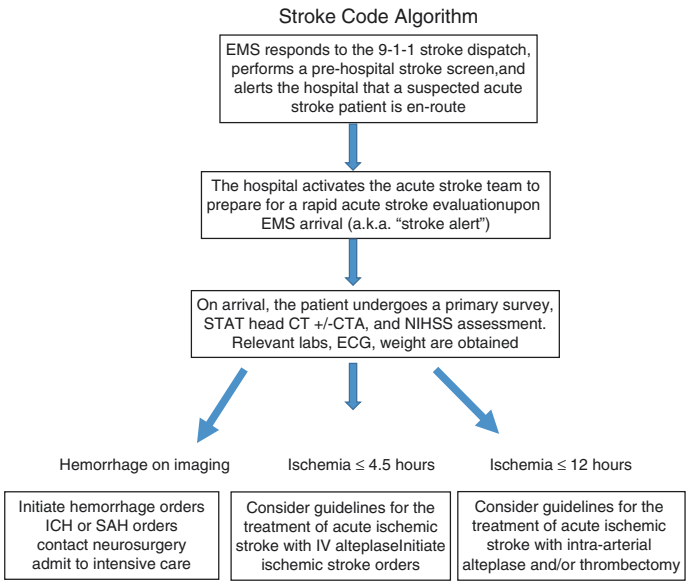

Fig. 6.3 Acute Stroke Algorithm

acute ischemic stroke. It is within the scope of practice of the APC to act as the stroke team's first responder or as a member of a larger stroke code team that may include neurology residents, emergency department staff, and/or a telestroke consultant service. Figure 6.3 outlines a typical stroke code algorithm that depicts the initial diagnostic evaluation.

6.4.3 National Institutes of Health Stroke Scale Score (NIHSS)

The NIHSS has become the standard neurologic assessment tool during the acute stroke evaluation. It is a 15-item impairment scale that evaluates the deficits from a impairment of a cerebral infarction on level of consciousness, dysarthria, language, neglect, visual loss, eye movement, sensory loss, motor strength, and coordination. This scale measures level of severity and has been shown to have concordance with infarct volume. This tool is also one of the standard assessments used in clinical trials evaluating efficacy in acute stroke therapeutics. With excellent inter-rater reliability, a major strength of the scale is that it can be learned by any member of the stroke team and it can be performed quickly. The certification is available online through the American Heart Association and the National Stroke Association and is typically mandatory for all stroke team members (Table 6.4).

The maximum recordable NIHSS score is 42 but given the laterality in most ischemic strokes, very severe strokes are scored between 25 and 31. Stroke severity has been characterized as 1–5 for mild strokes, 5–14 for moderate severity, and 15–24 for severe strokes. Outcomes and disposition are associated with NIHSS on admission. Patients with a score of 5 or less are likely to be discharged home, while patients with a scale greater than 14 more frequently require long-term skilled nursing care.

Since the NIHSS has replaced the neurological examination for many first responders to acute stroke, one must understand its weaknesses before basing treatment decisions on an isolated score. The NIHSS does not measure disability. Isolated symptoms of aphasia or a hemianopsia can yield low NIHSS that place the patient in a mild severity category but can be permanently disabling [18]. Furthermore, many institutions are using modified forms of the NIHSS which omit ataxia and dysarthria. Likewise, diplopia, dysphagia, gait instability, and nystagmus are not scored.

Table 6.4 National Institute of Health Stroke Scale (NIHSS)

1a. Level of consciousness 0 alert 1 drowsy 2 stuporous 3 coma	5a–b. Motor Arm (L/R) 6a–b. Motor Leg (L/R 0 no drift 1 drift 2 can't resist gravity 3 no effort against gravity 4 no movement
1b. LOC questions (month, age) 0 both correct 1 one correct 2 incorrect	7. Limb ataxia (finger-nose, heel-shin) 0 absent 1 present in 1 limb 2 present in 2 limbs
1c. LOC commands (close eyes, make fist) 0 both correct 1 one correct 2 incorrect	8. Sensation (pinprick) 0 normal 1 partial loss 2 severe loss
2. Best gaze 0 normal 1 partial gaze palsy 2 forced deviation	9. Best language 0 no aphasia 1 mild-mod aphasia 2 severe aphasia 3 mute
3. Visual fields 0 no visual loss 1 partial hemianopsia 2 complete hemianopsia 3 bilateral hemianopsia	10. Dysarthria 0 none 1 mild-mod 2 unintelligible
4. Facial palsy 0 normal 1 minor 2 partial 3 complete	11. Extinction and inattention 0 no neglect 1 partial neglect 2 complete neglect

A major weakness is that it undervalues posterior circulation symptoms, so acute stroke providers must maintain a high level of suspicion for stroke when these symptoms are present.

Another weakness is that the exam is highly dependent upon language. If two patients were to have identical NIHSS scores but were to have infarcts in opposite hemispheres, the patient with the right hemisphere infarct would have a larger median infarct volume [19].

Despite its weaknesses, the NIHSS stands as a common assessment tool that can be used to determine stroke severity, disposition, and outcome. The NIHSS also serves as a universal communication tool after the initial stroke assessment to detect worsening after IV tPA administration. Additionally, given the recent data supporting the use of mechanical thrombectomy in selected acute stroke patients, a new focus of stroke care has emphasized detection of large vessel occlusions. Within the first 3 h, the best cutoff NIHSS score with positive predictive value to show a large vessel occlusion is 9 or greater.

6.4.4 Neuroimaging

The gold standard imaging study for assessment of the acute ischemic stroke patient is the non-contrast head computed tomography (CT). Despite the advances made in neuroimaging, this study remains the primary modality given its accessibility and rapid interpretation. The initial objective of the study is to exclude cerebral hemorrhage which is an absolute contraindication for thrombolysis. Once hemorrhage is excluded, the next goal includes excluding a stroke mimic such as a mass lesion. Finally, it may be used to identify early ischemic changes guiding whether patients may benefit from thrombolysis and/or further catheter-based interventions.

Significant ischemic changes involving greater than one third MCA territory have generally been used as an exclusion criterion for IV thrombolysis because of its association with an

increased risk of hemorrhage after lytic therapy. The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point topographic CT scan evaluating affected brain tissue within standardized regions of the MCA territory (see link in *Helpful Links and Resources* for more information). A normal CT ASPECTS is 10, and a score of less than 7 is felt to approximate that greater than one third of the MCA is affected [20].

Many centers have access to multimodal CT and MRI; however, these studies should not delay the decision and administration of IV tPA if indicated. The American Heart Association guidelines for acute ischemic stroke recommend noninvasive intracranial vascular studies when endovascular studies are considered. Regardless, institutions vary on the patient population receiving selected imaging studies and are dependent on neuroimaging resources, radiological staff to interpret the studies, and treatment options at the local hospital.

Although not studied to affect outcomes, one can make the case that it is important to know the status of the extracranial and intracranial circulation on any acute stroke patient. This data may help provide mechanism such as diagnosing a vertebral artery dissection or carotid stenosis. In turn, the practitioner can facilitate prompt treatment paradigms to reduce the risk of recurrent stroke or worsening.

6.4.5 IV tPA

Intravenous alteplase (tPA) remains the only FDA-approved drug for the treatment of acute ischemic stroke, and its time dependence is the basis for creating a well-organized approach to diagnose stroke swiftly. During a stroke event, it is estimated that 2 million neurons die for each minute that the brain is not perfused [21]. The goal in thrombolytic therapy is to revascularize brain tissue, and IV tPA is the only FDA-approved drug for stroke that has shown to benefit acute stroke patient when administered up to 4.5 h after the onset of symptoms.

The NINDS tPA Stroke Trial part 2 evaluated the administration of IV tPA in acute ischemic stroke within 3 h. In 1995, the trial published that acute ischemic stroke patients who received IV tPA had 30% relative risk reduction (absolute risk reduction 11–15%) compared to placebo-treated patients in having minimal or no disability at 90 days. The primary outcome measures included the NIHSS, the modified Rankin Scale (mRS), the Barthel Index (BI), and the Glasgow Outcome Scale (GOS). To put this into perspective, the number of patients needed to receive treatment (NNT) to show a benefit of demonstrating minimal or no disability is 8.

Time to treatment has been demonstrated as being a critical variable that determines the benefit of thrombolysis. The most significant benefit is derived in the stroke population that is treated within 90 min. The NNT for any benefit in this population is 1.5. In 2008, the time window for demonstrated benefit from IV tPA was extended to 4.5 h in the European Cooperative Acute Stroke Study (ECASS) III. The study evaluated the efficacy of IV tPA between the 3 and 4.5 window in a restricted population. This population excluded patients over 80 years old, patients with a NIHSS >25, patients taking anticoagulation irrespective of the coagulation level, and patient with a previous history of diabetes and stroke. Results from this study revealed that the number of patients needed to treat with IV tPA within the 3–4.5 h window to demonstrate minimal or no disability is 15. Despite this data, the FDA has not extended the labeling to incorporate this change. However, the use of IV tPA within this window is endorsed by the AHA in the selected patient population.

The risk of intracerebral hemorrhage (ICH) after the administration of IV tPA provides the most angst for practitioners in the assessment of the acute ischemic stroke patient. There has been variance in the rate of symptomatic ICH (sICH) among trials, largely from varying radiographic and clinical definitions. The NINDS trial showed a sICH rate of 6.4%, and the ECASS

III trial demonstrated a rate of 2.4%. Predictors of intracerebral hemorrhage from the NINDS tPA study include patients with severe strokes and significant edema or mass effect on the baseline head CT. Thus many patients who do have symptomatic hemorrhages did not have their clinical course altered given the severity of the initial ischemic stroke. Nevertheless, overall benefit for the administration of IV tPA has still been shown in this population.

Other less common side effects of IV tPA include orolingual angioedema, systemic hemorrhage, and reportedly myocardial rupture. Orolingual angioedema reaction is typically mild, may be transient and often contralateral to the hemisphere affected by the stroke. Systemic hemorrhage can occur anywhere in the brain and occurred in 1.6% of IV tPA-treated patients in the NINDS trial. However, patients at elevated risk were excluded from the trial and included patients with evidence of active bleeding, patients with a gastric or urinary tract hemorrhage within 21 days, major surgery within 14 days, and an arterial puncture at a noncompressible site in 7 days.

Given the risk for bleeding and other potential complications, the current (2013) AHA guidelines for alteplase administration for acute ischemic stroke include inclusion/exclusion statements that assist clinicians with the decision-making process for treatment during the stroke code event (Table 6.5). The 1995 NINDS trial methods appropriately outlined conservative IV alteplase eligibility criteria, but since then, there have been several studies demonstrating broader considerations for thrombolysis and there have been revisions to the pharmaceutical company drug insert and a subsequent scientific statement proposing expanding eligibility criteria to afford more patients both treatment and potentially better outcomes. Demarschalk and his colleagues compared the current 2013 AHA guidelines with alteplase prescribing information and acknowledge that clinician experience and patient-specific factors together with the guidelines currently direct treatment recommendations. However, advanced

Table 6.5 Criteria for tPA administration

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 hours before treatment begins
Age > 18 years
Exclusion criteria
Significant head trauma or stroke in the previous 3 months
Symptoms suggestive of SAH
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, AVM, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (SBP >185 or DBP >110
Active internal bleeding
Acute bleeding diathesis, including but not limited to Plt count <100,000/mm^3, heparin received within 48 hours, or aPTT above normal, use of anticoagulant with INR >1.7 or PT >15 s, and use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated laboratory tests
Blood glucose <50 mg/dL
CT demonstrates multilobar infarction
Relative exclusion criteria
Minor rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within 14 days
Recent GI or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

practice clinicians should be familiar with their respective institution's protocols for thrombolytic therapies and the currently published guidelines.

Dosing of IV alteplase is weight-based and is prepared based on a 0.9 mg/kg (up to a maximum of 90 mg) formulation. It is administered in divided doses with 10% of the calculated

dose administered as a bolus over 1 min, and the remainder (90%) administered over the subsequent 1 h. Additional fluids are infused through the tubing to deliver the remaining drug. It is a focus of bedside nursing care to monitor for potential complications following alteplase administration. The stroke team directs the frequency of vital signs and neurologic assessments during the first 24 h after thrombolytic administration.

6.4.6 Post Thrombolytic Care

Most protocols direct patients to an intensive care unit for frequent neurologic and cardiovascular monitoring after IV alteplase treatment. Specific parameters are recommended for monitoring blood pressure, heart rate, oxygenation, and the neurological exam. Nurses specializing in acute stroke care follow post thrombolytic surveillance assessments to monitor for potential complications and neurologic deterioration for the first 24 h after treatment. Complications post stroke and post thrombolytics include bleeding, cerebral edema, aspiration, hypertension, cardiac arrhythmias, seizures, and subsequent neurologic deterioration. For a detailed understanding of the post thrombolytic intensive medical and nursing care, the AHA/ASA clinical practice guideline is a useful reference to guide clinical care during the first 24–48 h after admission. Stroke centers support evidence-based, multidisciplinary order sets or clinical pathways (specific to the care of an acute ischemic stroke patient) that outline the management during the acute phase of recovery care. The advanced practice clinician is ideally suited to direct the medical care based on a thorough understanding of the patient's stroke syndrome presentation, the affected cerebrovascular territory, possible stroke etiology, and recommended secondary prevention options.

Summary Points

- Organizations committed to the care of patients presenting with acute stroke syndromes support evidence-based protocols and necessary resources to deliver efficient and time-sensitive thrombolytic therapy.
- Stroke syndromes are variable; patients may present with a constellation of symptoms that require a knowledge of neurovascular anatomy and potential stroke mimics.
- Rapid interpretation of the non-contrast CT of the brain excludes hemorrhage; the diagnosis of acute ischemic stroke is clinical diagnosis that determines treatment eligibility.
- The NIHSS is the "gold standard" initial stroke assessment for quantifying neurological deficit(s) and is used to track the efficacy of thrombolytic treatment.
- Intravenous alteplase remains the only drug approved for the treatment of acute ischemic stroke.

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Chapter 7
Mechanical Thrombectomy for Acute Ischemic Stroke

Ketan R. Bulsara, Jennifer L. Dearborn, and Jessica L. White

7.1 Introduction

Mechanical thrombectomy is a tool to open the major arteries in the brain which are blocked after an ischemic stroke. One of the greatest advances in the care of stroke patients has been the definitive evidence that mechanical thrombectomy reduces the burden of disability that patients face after stroke. Patients who receive mechanical thrombectomy within 6 h of stroke syndrome onset are two times more likely to be independent 90 days after the stroke as compared to similar patients who do not receive the therapy. Despite the demonstrated clinical benefit, the selection of appropriate patients and timely administration of the therapy requires streamlined systems of care and triage of patients to comprehensive stroke centers.

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7.1.1 IV Thrombolysis and the Need for Better Treatments

Thrombolytic agents function by dissolving preexisting blood clots. The major thrombolytic agent is intravenous recombinant tissue plasminogen activator (IV-tPA). Overall, major therapeutic advancements such as IV thrombolysis have contributed to a decrease in the number of deaths from stroke by 23% between 1999 and 2009 [1]. However, the majority of patients do not qualify for IV thrombolysis, and many who survive still live with severe disabilities [2]. Fewer than 10% of patients meet the eligibility criteria for IV-PA because the standard treatment window is 4.5 h due to increased risk of intracranial hemorrhage with late administration of thrombolytic agents [3, 4]. Furthermore, as many as 20% patients who improve initially with intravenous thrombolysis experience clinical deterioration, possibly due to vessel reocclusion [5].

7.1.2 Mechanical Thrombectomy

An alternative strategy to thrombolytic agents is endovascular mechanical thrombectomy. Multiple studies have found that intravenous thrombolytic agents only yield 10–30% recanalization of large-vessel occlusions [6]. This is in contrast to mechanical recanalization with success rate of 83.6% [7].

Five recent multicenter randomized controlled trials using the mechanical thrombectomy technology known as stent retrievers have provided the necessary evidence to make this strategy the standard of care for large-vessel occlusions [8–12].

The Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) gave the first glimpse and is the largest of the four trials with 500 patients [13]. This trial compared endovascular

therapy plus usual care and usual care alone in participants with radiographically confirmed proximal arterial occlusion within 6 h of stroke onset. Of all the participants, 89% were treated with IV alteplase before randomization. Second-generation mechanical thrombectomy devices were used in 82% of the endovascular therapy group. Patients with endovascular therapy achieved lower mRS scores at 90 days (odds ratio of 1.67). Also, the rates of symptomatic intracerebral hemorrhage (SICH) (7.7% vs. 6.4%) and mortality at 30 days (18.9% vs. 18.4%) were statistically similar between the two groups.

The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial was the next major trial to show a benefit to endovascular therapy with standard care compared to standard care alone in ischemic stroke caused by proximal artery occlusion in the anterior circulation within 12 h of stroke onset in 316 participants [14]. A total of 75% of the patients received IV alteplase in the two groups. With multiphase CT angiography utilized to reduce patient motion artifact and for the rapid determination of collateral status, the study excluded patients with large infarct cores and poor collateral circulation. After an interim analysis performed by the Data and Safety Monitoring Board (DSMB), the study was terminated early due to the significantly better performance in the group receiving endovascular therapy. Participants with endovascular therapy had improved functional status at 90 days (modified Rankin score (mRS) 0–2; 53.0% vs. 29.3%) and lower 90-day mortality (10.4% vs. 19.0%).

The Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-IA) compared mechanical thrombectomy with the Solitaire FR device vs. IV alteplase in 70 patients [15]. After patients with core infarction volumes greater than 70 mL were excluded using CT perfusion imaging, the thrombectomy group reported higher rates of functional independence (mRS 0–2; 71% vs. 40%) without a difference in SICH rate (0% vs. 6%). The

DSMB also terminated the next study, the Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial [16]. This trial enrolled 196 patients, only used the Solitaire FR retrievers in the endovascular intervention group, and selected for patients with confirmed occlusion of a large artery in the anterior circulation within 6 h of symptom onset. Similar to the previous trials, significantly improved rates of functional status (mRS: 0–2; 60% vs. 37%) without statistically different rates of SICH (1% vs. 4%) or 90-day mortality (9% vs. 12%) were achieved in the mechanical thrombectomy group compared to IV tPA within 4.5 h of stroke onset.

Similar findings were replicated in Swift Prime and REVASCAT [16, 17].

7.2 Case Example

An 81-year-old man has a history of atrial fibrillation for which he takes apixaban. His apixaban was recently held for a dental procedure and restarted yesterday. He was last seen normal by his wife at 9:00 AM, and was found at 9:30 AM by his wife slumped in his chair. She noticed a right facial droop, right-sided weakness, and difficulty with speech. 911 was called and he arrived in the emergency department at 10:00 AM.

His initial evaluation revealed a blood pressure of 165/80, a pulse of 75 and a respiratory rate of 16, with oxygen saturation of 96%. On a brief neurological examination, he was

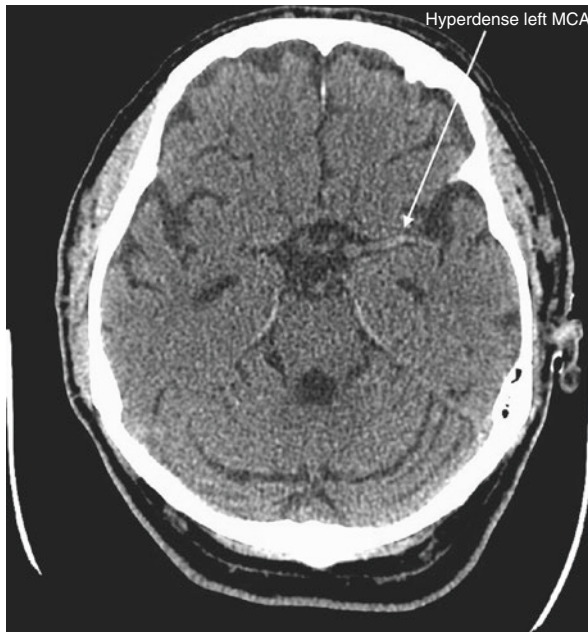

Fig. 7.1 Head CT with hyperdense left MCA sign

found to have global aphasia, left-gaze deviation, right facial droop, right arm plegia and right leg weakness. This tallied to an NIHSS of 19. Head CT demonstrated no early signs of ischemia and revealed a hyperdensity near the branch off the left middle cerebral artery (MCA) (see Fig. 7.1).

He was not a candidate for IV tPA due to his recent use of the blood thinner apixaban. After determining that he would be a good candidate for mechanical thrombectomy, the risks

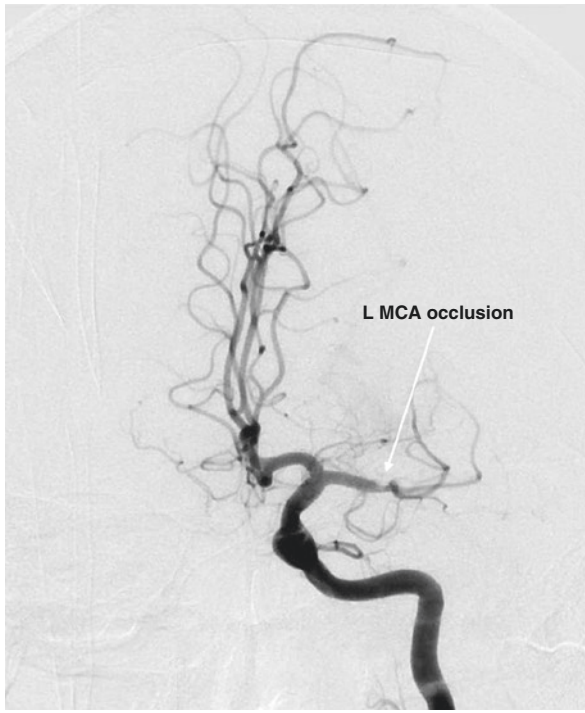

Fig. 7.2 Angiogram demonstrating left MCA thrombus

and benefits of the procedure were explained to his wife, who agreed to proceed. He was taken urgently to the interventional radiology suite. The cerebral angiogram confirmed a proximal occlusion of the left MCA (Fig. 7.2). A stent retriever was deployed and the clot was retrieved. A repeat angiogram showed near complete revascularization of the

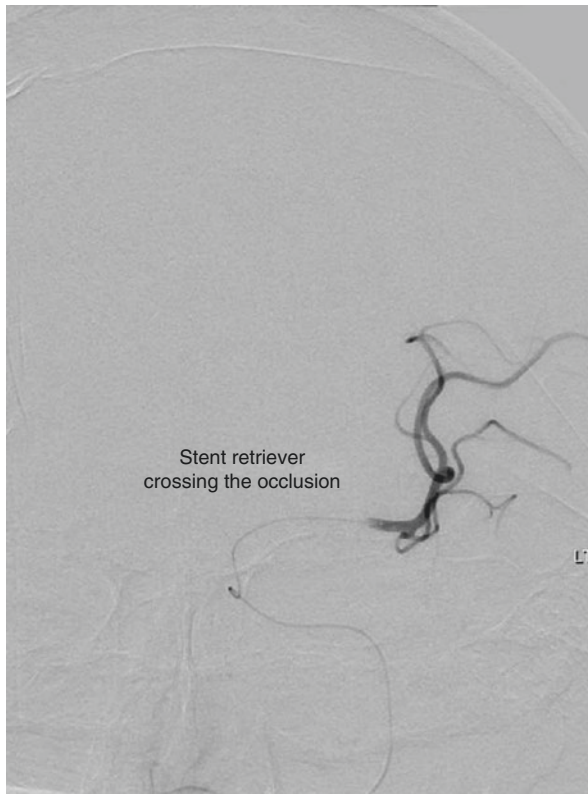

Fig. 7.3 Angiogram with stent retriever crossing thrombus

left MCA (Figs. 7.3 and 7.4). This was graded as TICI 3 revascularization. Postprocedure, the patient's neurological exam drastically improved, with resolution of his aphasia and near-complete resolution in his right arm's weakness

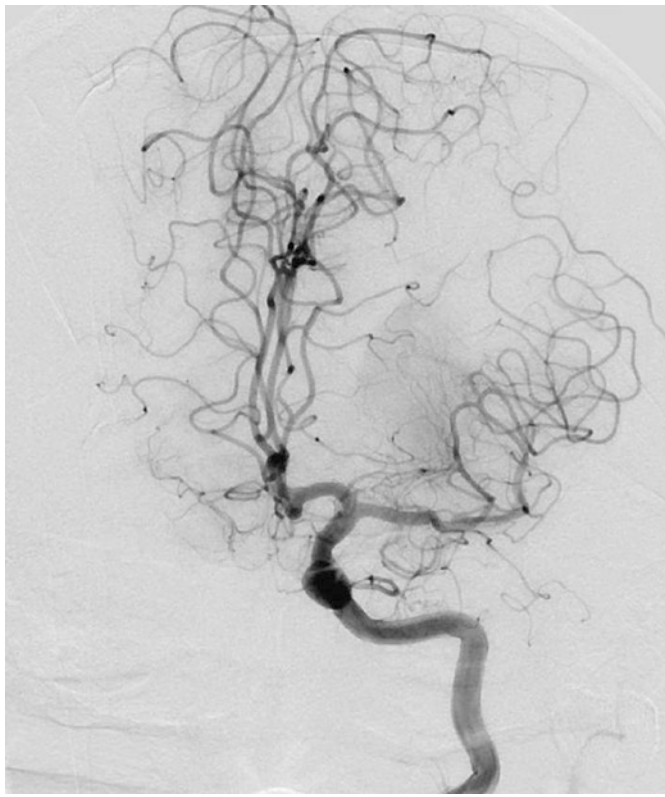

Fig. 7.4 Angiogram demonstrating restoration of flow in the left MCA

(NIHSS 4). He was admitted to the neurology service for further surveillance. MRI the following day demonstrated an ischemic stroke in the left basal ganglia, which was much smaller than the territory originally at risk at the time of presentation (Fig. 7.5).

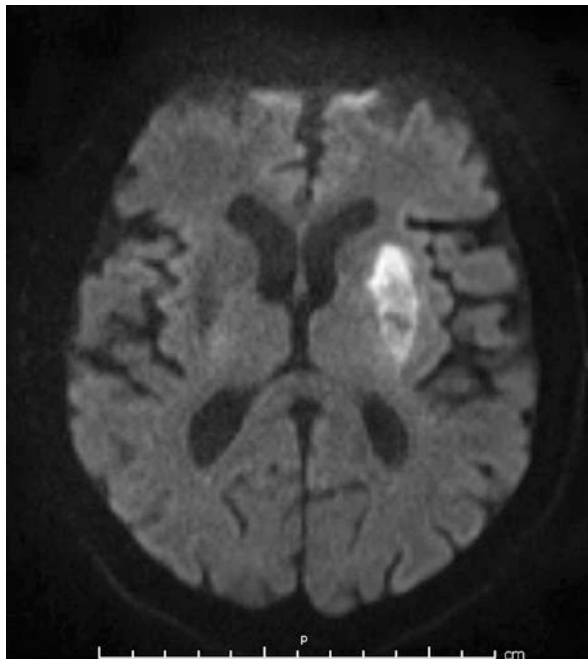

Fig. 7.5 MRI with resultant ischemic stroke

7.2.1 Stroke Systems of Care

Mechanical thrombectomy has demonstrated benefits in carefully selected patients; however most patients with acute ischemic stroke do not receive this therapy. The primary reason for this is delayed arrival to the hospital. As with IV-tPA, mechanical thrombectomy is a time-sensitive procedure with the greatest benefit if pursued early. Therefore, patient recognition of the

signs and symptoms of a stroke and calling 911 is the first step to ensure acute stroke care is delivered. The second challenge is the prompt triage of patients with acute ischemic stroke to a center that can offer mechanical thrombectomy [18]. In the US, certain hospitals are designated as Primary Stroke Centers, or Comprehensive Stroke Centers (CSC) by the Joint Commission. Primary stroke centers should have the capability to diagnose and treat stroke patients, including thrombolytics, but they may not have an ability to perform mechanical thrombectomy. Therefore, it is essential that prompt recognition of large-vessel occlusion occurs in hospitals that do not have the capability to administer such therapy, so that urgent transfer can occur to a CSC. At present, because of geographic distances and the difficulty of identifying a large-vessel occlusion in the field, patients with acute stroke may not be preferentially transferred to a CSC by emergency medical services. Patients may instead be brought to the closest hospital which is often a primary stroke center. Often times, the delay in transport to a CSC can cause the patient to be ineligible for thrombectomy, either because they arrive >6 h after symptoms onset, or sufficient time has passed to allow the infarct to fully develop. Future efforts in improving stroke systems of care need also focus on protocols for urgent transfer of patients to appropriate stroke centers where they can receive the full spectrum of care.

7.3 Initial Evaluation

The initial evaluation of a patient with acute ischemic stroke is summarized elsewhere (see Chap. 6 on Acute Ischemic Stroke). Here, we emphasize the aspects of clinical management specifically related to mechanical thrombectomy. During the teams' initial evaluation, a judgment is made as to whether the patient is likely to have a large-vessel occlusion. A large-vessel

occlusion is defined as acute thrombosis in the proximal segment of the anterior, middle, or posterior cerebral artery, the basilar artery, or the internal carotid artery. The presence of a large-vessel occlusion will determine if the patient can proceed to mechanical thrombectomy.

The determination of a large vessel occlusion can be made in several ways. In some centers, a neurologic examination suspicious for a "large-territory" infarction that would include a proximal vascular territory is enough evidence to warrant consideration for mechanical thrombectomy. A conventional cerebral angiogram to confirm a large-vessel occlusion is the first step in mechanical thrombectomy. Because of this, some centers have adopted a protocol to rely on the neurologic examination prior to transfer of the patient to the angiogram suite. However, all of the large-scale clinical trials that demonstrated a benefit of mechanical thrombectomy on functional outcome included at minimum a head CT and vascular imaging.

Other centers have created protocols which incorporate vessel imaging, or other advanced imaging techniques to examine the ischemic penumbra to confirm a large-vessel occlusion prior to recommending mechanical thrombectomy. These protocols are often the result of an ability to quickly obtain advanced imaging, and reflect the selection used in the published trials that confirmed the benefit of mechanical thrombectomy [13, 14, 16]. Options for advanced imaging include a CT or MR angiogram, a CT or MR perfusion study.

7.3.1 Patient Selection for Mechanical Thrombectomy Using Imaging

There are several methods supported by the literature to select patients that may benefit from mechanical thrombectomy. The most commonly used methods include the CT-based scoring

system of the ASPECTs score and CT and MR perfusion. The purpose of patient selection is to offer mechanical thrombectomy to patients that are most likely to benefit from revascularization. Examples of patients that are unlikely to benefit include those with a minimal ischemic penumbra, suggesting that there is no "tissue to save" or patients with a large stroke who are more likely to experience hemorrhagic transformation of the stroke if revascularization is achieved. The key principles, no matter what advanced imaging technique is used, is to select patients with a small ischemic core infarct, and large ischemic penumbra. The ratio of the penumbra to core would be large in patients who are most likely to benefit from reperfusion.

One method of image selection incorporates the CT-based ASPECTs score. The ASPECTS score was developed in 2000 as an attempt to quantify the size of the ischemic infarct on a CT scan in order to predict outcome after mechanical thrombectomy [19]. The benefit of this scoring system is that all centers that administer tPA have the ability to quickly obtain a CT scan. The ASPECTS scoring system is qualitative and ranges from 0 to 10, with higher numbers indicating less ischemia. In this scoring system, a point is subtracted for each of ten territories where there is evidence of ischemia. For information and training on this scoring system, see http://www.aspectsinstroke.com. Two large randomized controlled trials demonstrated benefit to mechanical thrombectomy in patients with an ASPECTS score > 6 or >7 [14, 17]. These trials help establish a cutoff from which treatment may be beneficial to select patients for mechanical thrombectomy.

The benefit of CT perfusion as compared with an ASPECTS-based scoring system is that the ischemic penumbra can be visualized along and the core infarct area can be estimated. Three of the recently completed trials that demonstrated a benefit for mechanical thrombectomy utilized CT perfusion for

some of the participants [14–16]. CT perfusion displays the physiologic function of the brain in the form of perfusion maps. A perfusion map is a view of the brain where each pixel measures blood flow to that area, with different colors assigned to represent a measurement over time. For example, one type of perfusion map is called the mean transit time (MTT). This map measures the mean amount of time it takes for the contrast to get to each pixel and can provide an estimate of the size of the ischemic penumbra. Other types of perfusion maps include the cerebral blood flow (CBF) and cerebral blood volume (CBV) maps [20]. Regions of the brain with reduced CBV and CBF can represent the area of core ischemic damage. There are several vendor software packages and institutional methods that are used to determine thresholds, or cutoffs to distinguish the ischemic core from the penumbra. These thresholds are based on a relatively few number of studies, and each institution that interprets CT perfusion should establish its own standards for decision-making.

In institutions where MRI scanning is readily and quickly available, MR perfusion techniques are often used to select patients for mechanical thrombectomy. The benefit of MRI over CT is that a more accurate determination can be made of the ischemic core. This is because of the higher sensitivity and specificity of MRI in detecting hyperacute ischemia [21]. Ischemic core can be accurately estimated using the diffusion-weighted imaging (DWI) sequence in the MRI protocol. MR perfusion begins with administration of gadolinium which allows for the generation of maps similar to those created during CT perfusion. The ischemic penumbra can be defined by MTT or time-to-maximum (T_{max}) maps which highlight areas of hemodynamic compromise. The ratio of the ischemic penumbra to the core infarction measured on DWI can be used to augment decision-making. As with CT perfusion, several different thresholds exist to measure the ischemic penumbra and

several vendor software packages are available to assist in the measurement of the volumes. In MRI, the amount of poorly perfused tissue that is still at risk of infarction is often called the diffusion–perfusion mismatch. It is this number which can accurately predict whether there is a substantial amount of "brain to save" through revascularization.

In summary, selecting patients for mechanical thrombectomy requires advanced decision-making, knowledge of advanced imaging, and the experience of multiple practitioners, including stroke neurologists, interventionalists, and radiologists. The decision on what imaging modality to use will depend on resource availability at each hospital.

7.4 Interventions and Management

7.4.1 Current Guidelines

The established benefit of mechanical thrombectomy in acute ischemic stroke has led to the revision of established guidelines in recent years [22]. The American Heart Association advises that patients presenting with acute ischemic stroke should continue to receive intravenous tPA if eligible and that intra-arterial treatment should be considered for all patients meeting the following parameters:

- Prestroke modified Rankin score of 0–1
- The causative occlusion is in the internal carotid artery or proximal middle cerebral artery
- Age ≥18 years
- NIHSS ≥6
- ASPECTS score of ≥6

Beyond these parameters, thrombectomy can be considered for patients presenting with other large-vessel occlusions,

Table 7.1 Thrombolysis in Cerebral Infarction (TICI) categories

Grade	Appearance on final angiographic image
0	No perfusion
1	Penetration with minimal perfusion
2	Partial perfusion
2a	Only partial filling (<2/3) of the entire vascular territory is visualized
2b	Complete filling of the vascular territory, but filling is slower than normal
3	Complete perfusion

Adapted from Higashida [26]

including basilar artery, vertebral artery, and M2 branches of the middle cerebral artery. In all cases, the goal of thrombectomy is to restore flow through the occluded vessel. The extent of revascularization is categorized using the Thrombolysis in Cerebral Infarction (TICI) Perfusion Categories (Table 7.1).

Clinical benefit is more clearly established for treatment within 6 h of symptom onset; however, continued advances are being made toward understanding the relationship between ischemic changes on neuroimaging (including MRI, CT, CT perfusion) and the potential benefits of delayed revascularization for salvaging the penumbra. The decision to pursue mechanical thrombectomy beyond 6 h of symptom onset requires a multidisciplinary approach best achieved at experienced stroke centers.

7.4.2 Postprocedure Care of Patients

The ICU care of patients receiving mechanical thrombectomy often mirrors that of patients after they receive tPA, and in fact many of these patients will have also received tPA. The primary reason for ICU triage is for neurologic monitoring for any deterioration. Patients are at high risk of reperfusion hemorrhage or

complications of the procedure, such as arterial dissection and progressive ischemia. Additionally, patients need to be monitored for the potential complications of a large ischemic stroke, like malignant cerebral edema. In most ICUs, nursing protocols include neurological exams and NIHSS scoring every hour for the first 24 h after tPA administration. Changes in neurologic examination often prompt notification of the advanced practitioner or physician, who must make a decision as to the cause of the neurologic decline.

Careful monitoring of blood pressure is essential after mechanical thrombectomy, especially if reperfusion has been obtained. There is no prospective randomized data which supports a recommended goal blood pressure after mechanical thrombectomy [23]. Therefore, the blood pressure goals must be decided on a per-patient basis or as per institutional policy. Patients who received tPA should have a goal blood pressure of at least <180 systolic and <105 diastolic. Many institutions recommend implementing a blood pressure goal of <140 systolic and <100 diastolic if revascularization was obtained, or allowing permissive hypertension if the large-vessel occlusion remains [24].

Reperfusion injury and hemorrhagic transformation is the feared complication of mechanical thrombectomy. Predictors of reperfusion hemorrhage include a large ischemic core infarct or delayed reperfusion. The key to treatment of reperfusion hemorrhage is early identification and prevention of hematoma expansion. If tPA has been given, its reversal is essential. Strict blood pressure control is a key component of prevention of hemorrhage expansion. Decompressive hemicraniectomy after reperfusion hemorrhage has not been studied specifically after mechanical thrombectomy and may represent a life-saving option for some patients [23].

Management of cerebral edema with hypertonic therapy or surgical decompression is reviewed in Chap 8. on Malignant Ischemic Stroke. The groin access site must also be monitored postprocedure for evidence of hematoma formation.

Summary Points

- Mechanical thrombectomy for large-vessel occlusion is now part of standard care [25].
- Currently the accepted time frame is last seen normal within 6 h from presentation.
- Patient selection for mechanical thrombectomy is a complex process utilizing clinician judgment and advanced imaging techniques.
- Postprocedure care revolves around close neurologic monitoring and early detection of neurologic decline.

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Chapter 8
Malignant Ischemic Stroke and Hemicraniectomy

Julian Bösel

8.1 Introduction

If the main stem of a brain-supplying vessel such as the distal internal carotid artery (ICA) or the proximal middle cerebral artery (MCA) is occluded, both the resulting infarct and associated clinical deficit will be substantial. Quite often, this type of stroke will not only lead to severe neurologic deficits but also result in impairment of vital functions such as circulation, breathing, or airway protection. This form of ischemic stroke will often have cerebral or systemic consequences requiring critical care interventions. "Severe" stroke may be defined by the following features: NIHSS >15, modified Rankin scale 4–5 (near-completed or complete dependency), deterioration of vital functions, association with extra-cerebral complications, and

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features of mass effect, raised intracranial pressure (ICP), or brain stem affection on imaging. Large ischemic stroke complicated by significant brain tissue swelling is referred to as "malignant" MCA infarction (MMI) due to its unfavorable and often fatal course [1–4].

8.2 Case Presentation

A 55-year-old male with history of atrial fibrillation presents to the hospital with dysarthria, left hemiplegia and sensory loss, and left hemibody neglect consistent with a large right middle cerebral artery territory infarct. NIHSS is 19. He is given IV tPA 2 h after symptom onset and admitted to the NICU for close neurological monitoring. CT scan 24 h after presentation shows a large right MCA distribution infarct with development of mild cerebral edema. Forty-eight hours after symptom onset, the patient becomes increasingly lethargic, requiring intubation for airway protection. Repeat CT scan shows increased edema associated with the infarct and increased midline shift (Fig. 8.1). Osmotherapy is administered with temporary improvement in neurological status; however, the patient continues to decline. He is taken to the operating room for right decompressive craniectomy (Fig. 8.2). Post-procedure he is more alert and able to follow simple commands.

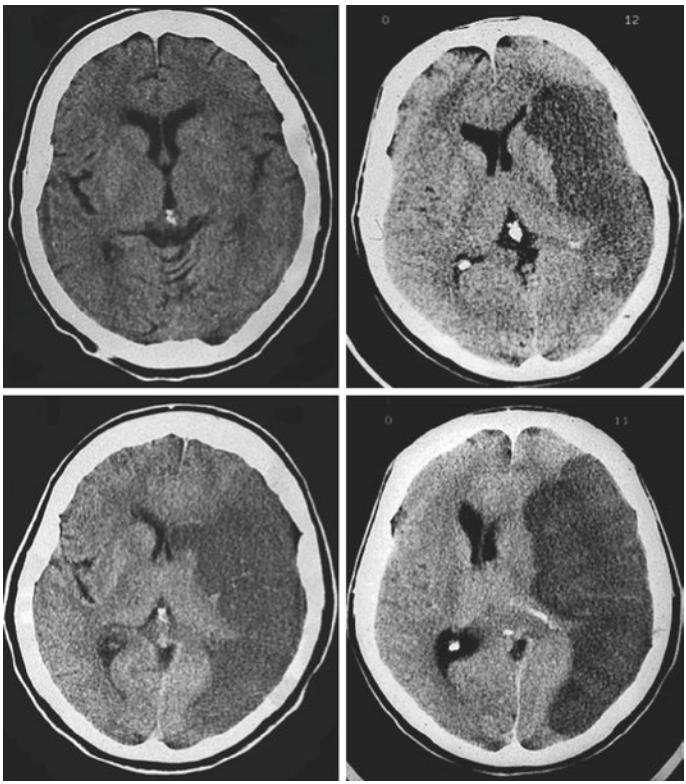

Fig. 8.1 Left-sided malignant middle cerebral artery infarction evolving over 4 days (Images courtesy of Eric Jüttler)

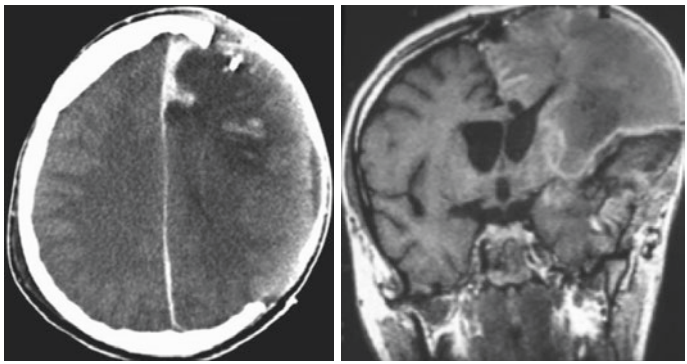

Fig. 8.2 Computed tomography (*left*, transversal) and magnetic resonance imaging (*right*, coronar) after decompressive hemicraniectomy for malignant middle cerebral artery infarction (Images courtesy of Eric Jüttler)

Table 8.1 Indications for transfer of acute ischemic stroke patients to the NICU

Instability during thrombolysis or thrombolysis-related intracerebral hemorrhage
Post-endovascular treatment if this involved intubation and general anesthesia
Progressive decline in level of consciousness
Compromise in airway protective reflexes with risk of aspiration
Respiratory failure and need of invasive ventilation
Substantial hemodynamic instability
Signs of swelling and/or mass effect on cerebral imaging
Need of neurosurgery (e.g., decompression) or invasive interventions

8.3 Initial Evaluation

Patients with severe ischemic stroke may well be managed in the stroke unit at first. The key point is that they must never be without monitoring in the acute phase. If they develop certain features of deterioration, they should be transferred immediately to the NICU (Table 8.1).

8.3.1 Diagnostic Imaging

Initial imaging should not only help to make the diagnosis of acute ischemic stroke (AIS) but also indicate the potential of an ischemic stroke to grow and swell. Magnetic resonance imaging (MRI) has been proposed for prognostication of severe stroke, including malignant hemispheric stroke. Studies yielded robust results on the predictive potential of certain sizes of the diffusion-weighted (DWI, >145 cm^3) and the apparent diffusion coefficient (ADC, <80%, >82 cm^3) lesions [5]. However, MRI is not part of the initial stroke work-up at several institutions and has not yet gained widespread acceptance for assessment and prognostication in these patients. This is due to wide availability of computed tomography (CT). Hence, CT is still the most popular imaging modality to judge the course of severe AIS. Horizontal displacement of the pineal gland of >4 mm within 48 h [6], loss of gray and white matter differentiation within the first hours [7], and hypoattenuation in more than 50% of the territory of the middle cerebral artery (MCA) [8] have all been found predictive of an unfavorable clinical course. However, patients show marked interindividual differences in their edema dynamics. Hence, quite often serial CT imaging during the first days post stroke is necessary to assess and anticipate the course of the patients. In large MCA infarction, total or subtotal hypoattenuation of the MCA territory, hypoattenuation in adjacent vessel territories, (partial) involvement of the basal ganglia, and space-occupying effect (e.g. compressed lateral ventricle or midline shift) are radiological criteria to seriously consider decompressive surgery at our institution.

8.4 Management and Interventions

Only a few high-quality studies on general critical care specific for ischemic stroke have been performed. Valuable information is available in guidelines [9] summarized in Table 8.2.

Table 8.2 Medical management of severe ischemic stroke

Airway and ventilation	Intubation indicated for threatening respiratory failure, decreased level of consciousness with loss of protective reflexes, impaired secretions management with risk of aspiration
	Target pCO_2 35–45, target pO_2 > 60, target SpO_2 95–98%
Hemodynamics	Continuous monitoring of EKG and BP
	Monitor and treat cardiac arrhythmias
	Avoid hypotension, tolerate initial transient hypertension
	Bring SBP to <180 mmHg in patients receiving IVT
	Utilize isotonic fluid to maintain euvolemia
Glucose	Target glucose 140–180 mg/dL
	Avoid hypoglycemia at all times
Temperature	Maintain normothermia
Miscellaneous	Administer subcutaneous low-molecular-weight heparin for DVT prophylaxis or intermittent pneumatic compression
	No indication for seizure prophylaxis

8.4.1 Brain Edema and Raised Intracranial Pressure

Extensive AIS leads to the generation of at first cytotoxic and later vasogenic edema, with considerable differences in extent and dynamics between individual patients [10]. On average, clinically relevant edema develops at day 2 or 3 from stroke onset. Basic measures to prevent brain edema comprise restriction of free water, avoidance of hypo-osmolar fluids, avoidance of excess glucose administration, avoidance of hypertension after reperfusion therapies, minimization of hypoxemia and hypercarbia, caution in application of drugs

causing cerebral vasodilation, and aggressive treatment of hyperthermia. If clinically relevant edema occurs and is detected by clinical signs (decline in level of consciousness, worsening of neurological deficit, nausea and vomiting, anisocoria), ICP monitoring and cerebral imaging, as well as pharmacological treatment, should be applied. Additionally, patients with severe stroke whose exams are difficult to assess due to sedation should have their ICP measured by parenchymal probe or external ventricular drain (if hydrocephalus is feared or present). The most common potential cause of neurologic worsening in large AIS is edema with mass effect and midline shift. Secondary hemorrhage, seizures, and reduced venous return are additional potential causes. There do not exist specific data on optimal ICP-lowering therapy in severe stroke, so it is recommended to follow a stepwise approach common in other brain injuries (Table 8.3).

The order of steps may vary individually. Hyperventilation and barbiturate administration can be deleterious and should be only considered cautiously.

Table 8.3 Stepwise approach to lowering ICP in MMI

Elevate head of bed to about 20°, keep neck straight to support venous return
Start or increase analgesia and sedation
Start mechanical ventilation
Apply hyperventilation, but only short term (!)
Treat seizures, fever, hyperglycemia, respiratory distress, etc. if present
Start osmotherapy
Consider barbiturates
Consider muscle relaxation
Consider surgery
Decompressive hemicraniectomy for large hemispheric stroke
External ventricular drain for hydrocephalus
Consider mild to moderate hypothermia

8.4.2 Malignant MCA Stroke and Decompressive Craniectomy

Occlusion of the distal ICA or proximal MCA leads to infarction of the total or subtotal MCA territory, possibly combined with infarction of the adjacent anterior cerebral artery (ACA) and/or posterior cerebral artery (PCA) territory. This type of brain infarct is called large hemispheric stroke. As mentioned above, MMI refers to a large hemispheric stroke complicated by significant brain tissue swelling, severe enough to compress critical neural structures.

Patients initially present with a severe hemisyndrome, combined with aphasia or neglect depending on the affected hemisphere, and display quite stereotypical deterioration over the first few days, such as decline in level of consciousness and anisocoria, reflecting swelling of the affected hemisphere. Despite maximal conservative critical care efforts, the mortality of MMI is between 70% and 80% due to massive swelling of the infarcted area leading to horizontal displacement of the brain stem, and intracranial pressure increases within the rigid skull (Fig. 8.1). Medical options to prevent or reduce brain edema have been disappointing so far. Classical osmotherapy is not sufficient to improve clinical outcome in MMI [1, 2, 13–17].

The previously bleak perspective of these patients has changed over the last 15 years, since recent evidence has been obtained on the benefits of decompressive craniectomy (DC). This surgical measure, by which a large (>12 cm diameter) bone flap is removed over the affected hemisphere combined with duraplasty, allows for outside swelling of the affected tissue leaving the contralateral unaffected parts of the brain uncompromised (Fig. 8.2). The bone flap is stored frozen or subcutaneously and reinserted after rehabilitation and shrinking of the affected hemisphere, usually between 3 weeks and 3 months from the insult.

After first encouraging results from observational studies [16], the pooled data on 93 patients from 3 European randomized trials

showed that DC within 48 h from onset for patients <60 years suffering from MMI reduces mortality by 50%, (number needed to treat (NNT) 2) and severe disability by 40% (NNT 2); on the downside, the number of those surviving with moderate to severe disability increases by 30% [17]. This evidence of survival and outcome benefits from the procedure led to international recognition of DC and to implementation into guidelines for MMI patients under 60 years of age. Recently, the DESTINYII trial on DC for MMI in 112 patients >60 years confirmed the highly significant survival benefit (33% vs. 70%, NNT 4) that was mainly responsible for an "outcome benefit" (mRS 0–4 38% vs. 18%), but showed survival after 6 months with moderate to severe disability (mRS 4) in 32% and with severe disability (mRS 5) in 28% of the surgical patients [18]. These and more randomized trials on DC for MMI have been nicely reviewed by Zha and colleagues [19]. These data provide fairly solid grounds for patient and family counseling on the option of DC, which is a very important element of care in this type of stroke (see below). Surgical treatment of MMI involves optimal and maximal neurocritical care before and after the operation.

Another option to reduce or prevent swelling might be therapeutic hypothermia. Small studies suggested that cooling the MMI patient is safe and feasible, reduces ICP, and may reduce mortality to 38–50%, i.e., not as effectively as DC [20–23]. Whether the addition of hypothermia to DC may further improve outcome [24] is currently investigated in the DEPTH-SOS trial [25] that just finished recruitment. The rewarming phase can be critical in MMI and lead to rebound edema, increased ICP, and herniation [26].

8.4.3 Ethics

The decision for DC on behalf of a patient not able to communicate may be very challenging, even though the alternative of treating

MMI by conservative intensive care measures is death in 70–80% of cases. The decision should involve the clinical and radiological situation, the current evidence, the premorbid state and age of the patient, and – of particular importance – the patient's putative will. It will be easier to pursue DC in a 50-year-old patient with no major comorbidities with a good rehabilitation potential. But it will be much more difficult in an older and sicker patient with a family who is uncertain whether he would rather live with considerable disability than die. According to a few randomized trials on DC for MMI, about 70–80% of survivors retrospectively consent to the DC decision, including some substantially disabled and dependent [18, 27]. Some observational studies have yielded inconsistent data on quality of life of MMI survivors, but largely echoed these patients' retrospective consent to measures allowing them to survive despite disability [28–33]. Not few of these survivors have a quality of life comparable to patients with common diseases of the respective age. Attitudes of health-care professionals as to what is "a life worth living," however, differ considerably and tend to be more pessimistic than that of family or patients in this setting [34].

Summary Points

- Severe ischemic stroke results from the occlusion of a major vessel of the cerebral vasculature, such as the internal carotid artery or proximal middle cerebral artery.
- Neurological decline and hemodynamic instability are associated with severe ischemic stroke, requiring intensive care monitoring and aggressive medical management.
- Imaging must be utilized to predict which patients are at risk for a malignant course.
- Malignant cerebral edema results from severe stroke and often requires medical management for increased intracranial pressure. Patients may early require decompressive craniectomy, which has been shown to improve mortality and morbidity.

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Chapter 9
Cerebral Venous Thrombosis

Gretchen Crabtree and Chad Miller

9.1 Introduction

Cerebral venous thrombosis (CVT), is a rare cause of stroke primarily affecting young adults and children. CVT may include narrowing or occlusion of the major dural sinuses or the more superficial cerebral veins. The incidence is approximately three to seven cases per million, is three times more prevalent in women than men, and constitutes less than 1% of all strokes [1]. Various medical conditions are known to predispose to CVT formation. A person with an inciting injury has at least one underlying risk factor (Table 9.1). It is important to recognize the multiple manifestations of CVT. Venous occlusion may result in elevated venous pressure which ultimately can reduce local cerebral perfusion and subsequent venous infarction. The infarct is often associated with

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Table 9.1 Risks for cerebral venous thrombosis

Category	Causes
Hypercoagulable state	Protein C, S, or antithrombin III deficiency; factor V Leiden mutation; prothrombin gene mutation; antiphospholipid syndrome (lupus anticoagulant/anticardiolipin antibody); nephrotic syndrome; hyperhomocysteinemia
Infectious	Encephalitis; cerebritis; meningitis; mastoiditis; otitis; sinusitis; mouth, face, and neck infections
Obstetric	Pregnancy and puerperium (about 12 cases per 100,000 deliveries)
Malignancy	Central nervous system tumors with invasion of the venous sinus, hematologic cancers, hypercoagulable state due to malignancy
Inflammatory diseases	Vasculitis, lupus, Wegener's granulomatosis, inflammatory bowel disease (Crohn's and ulcerative colitis), Behcet's disease, thromboangiitis obliterans, sarcoidosis
Hematologic diseases	Polycythemia, thrombocythemia, paroxysmal nocturnal hemoglobinuria
Drugs	Oral contraceptives (especially third generation contraceptives), hormone replacement therapy, asparaginase, tamoxifen, steroids, androgens
Trauma	Head injury, lumbar puncture, neurosurgical procedures, jugular catheter occlusion
Other	Dehydration, congenital heart disease, thyroid disease

significant vasogenic edema caused by breakdown of blood brain barrier with blood plasma leaking into the interstitial space and/or cytotoxic edema caused by ischemia around the area of injury. Petechial hemorrhages can form and have

the potential to merge causing large hematomas. Occasionally, these processes lead to development of intracranial hypertension. This obstruction causes increased venous pressure and inability to absorb cerebral spinal fluid at the end of its transport pathway, thus a pressure gradient does not develop between the ventricles and subarachnoid spaces on the brain's surface. This is important to note because it typically does not cause hydrocephalus since the ventricles do not dilate [2]. Focal edema, hemorrhage, and venous congestion may also serve as an ictal focus. A seizure can be the presenting symptom of CVT.

9.2 Case Presentation

A 36 year old female with no significant past medical history was brought to the emergency department after suffering a seizure in a movie theater. She had complained of onset of a diffuse and slowly worsening headache earlier in the day. She has no prior history of seizures and is a regular one pack per day cigarette smoker. She takes no over the counter medications and is on oral contraceptive therapy for prevention of pregnancy. She denies prior history of thrombotic events and denies a family history of clotting disorders. Upon initial assessment, she was post-ictal, with improving alertness. She exhibited some difficulty with language expression, but did not demonstrate any focal motor or sensory abnormalities. A non-contrast head CT (Fig. 9.1) showed a small amount of subarachnoid blood in the left parieto-occipital cortex. Further vascular imaging revealed thrombosis of her left transverse venous sinus and associated distal jugular vein

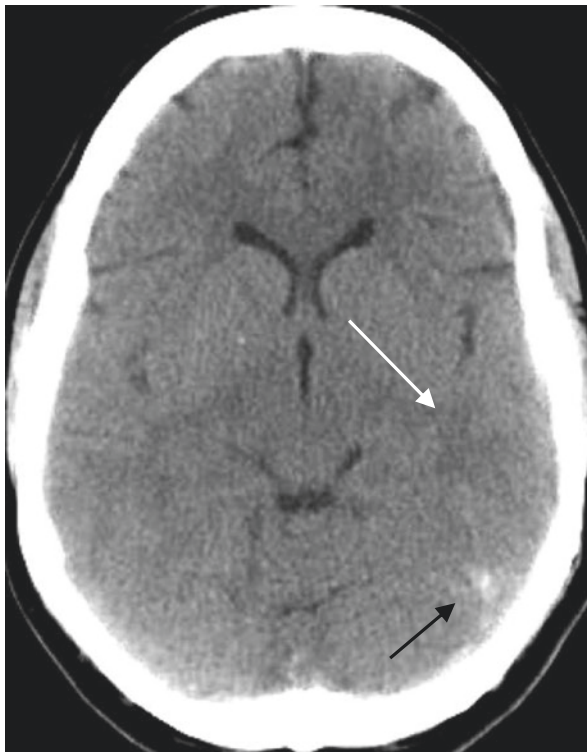

Fig. 9.1 Non-contrast head CT of a 36 year old female presenting with headache, seizure, and language difficulty. Subarachnoid hemorrhage is present within the left parieto-occipital lobe (*black arrow*) and small amounts of edema are present in a non-arterial distribution in the temporo-partietal lobe (*white arrow*)

(Fig. 9.2). She was diagnosed with a cerebral venous thrombosis and placed on intravenous unfractionated heparin. Her anticoagulation was transitioned to oral warfarin and she was eventually discharged on an anti-seizure medication. At

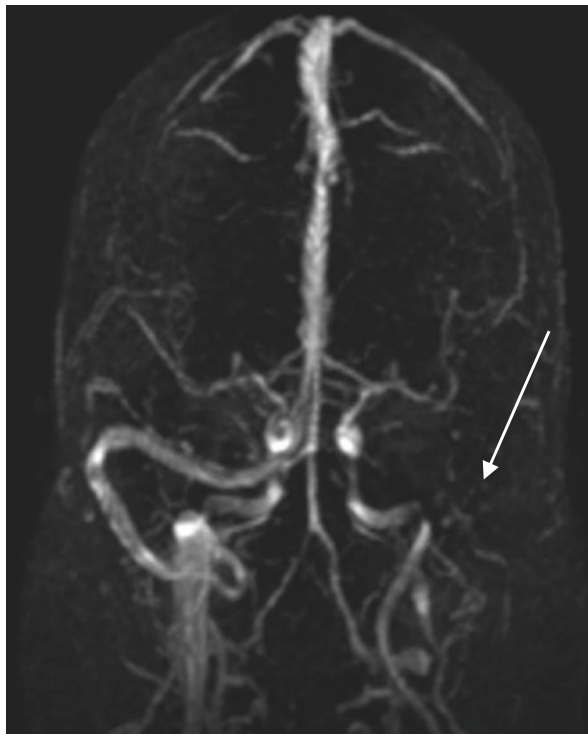

Fig. 9.2 Magnetic resonance venogram (MRV) of 36 year old female presenting with headache, seizure, and language impairment. The MRV shows absence of the L transverse sinus consistant with occlusion (*white arrow*)

3 month follow up, the patient reported no further clinical events and repeat vascular imaging showed recanalization of her thrombosed transverse sinus. The patient was successful in smoking regimen cessation and was placed on an alternative contraception. Her anticoagulation and seizure prophylaxis were discontinued.

9.3 Initial Evaluation

9.3.1 History

When taking a history on patients with CVT, it is important to assess for hypercoagulability, pregnancy, recent infection, dehydration, drug use (especially oral contraceptives or hormone replacement therapy with a smoking history), malignancy, or an inflammatory disease. Patients can present acutely with an onset of less than 48 h (28%), subacutely (42%), or chronically at greater than 30 days (30%) with symptoms [5]. An acute onset is often associated with pregnancy or infectious etiology. Although a patient may present with a variety of symptoms, 90% of the time they will have a chief complaint of a headache [1]. A headache is the only complaint for patients 14% of the time [3]. Other symptoms include vision loss, seizures (often associated with Todd's paralysis), motor and/or sensory deficits, and encephalopathy. Some patient may experience fluctuating symptoms secondary to incomplete or ongoing thrombus.

9.3.2 Neurological Examination

A patient's initial presentation can vary from decreased level of alertness to coma. Symptoms vary depending on the location of injury as well. A superior sagittal sinus thrombus occurs approximately 62% of the time can elicit motor symptoms primarily in the lower extremities and can be bilateral or alternating (Fig. 9.3). Patients can also experience seizures or psychiatric symptoms. Thromboses in the transverse sinus occurs most frequently (86%) and can be complicated with symptoms of intracranial hypertension. If the left transverse sinus is occluded, aphasia can be present as well. Motor and/or sensory deficits

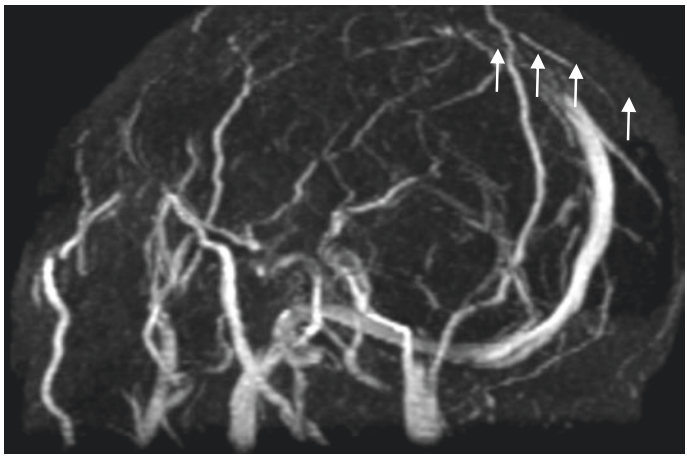

Fig. 9.3 Magnetic resonance venogram of a patient presenting with progressive paraparesis. The *white arrows* demonstrate thrombus in the superior saggital sinus

and focal seizures occur with cerebral cortical vein thromboses in 17% of patients. A thrombus of the deep venous system occurs approximately 11% of the time and can lead to coma and changes in mental status as well as bilateral motor deficits. Cavernous sinus thromboses are rare but cause cranial nerve III, IV, V1, V2, or VI palsies, orbital pain, chemosis, or proptosis [4]. The cavernous sinus is the only anatomic location where a single lesion can produce all of these neuropathies. Therefore, this unique clinical presentation should strongly raise suspicious of a vascular or mass lesion in the cavernous sinus.

When performing a fundoscopic exam, papilledema may be present. The patient will experience an enlarging blind spot with ensuing color desaturation. A late sign includes vision loss. Other vision changes can include hemianopsia as seen with a thrombosis of the vein of Labbé.

9.3.3 Differential Diagnosis

It is important to perform a thorough history and physical exam to establish differential diagnoses upon patient presentation. Some of which are listed below:

- Cerebral sinus thrombosis. Common etiologies include pregnancy and puerperium, local infections, oral contraceptives, and hypercoagulable states. Forty-four percent of patients present with more than one cause, however reversely 15% have no inciting factors [4].
- Stroke. A stroke can present with the same symptoms including seizure and acute deficits. Hemorrhagic strokes often will present with headache and mental status changes. Of note, a sinus thrombosis can cause intracerebral hemorrhage (ICH) as well as venous infarction.
- Brain tumor. Patient presentation can include sudden onset of symptoms/deficits or seizures, headache, elevation of intracranial pressure secondary to malignant edema, and/or intracranial hemorrhage.
- Dural arteriovenous fistula (DAVF). An abnormal direct connection between arteries and veins or venous sinuses on the surface of the brain including dura mater or arachnoid. There are three different types depending on where the drainage occurs. Patient may present with hemorrhagic strokes, intracranial hypertension, seizure, or progressive neurological deficits.
- Abscess/encephalitis/cerebritis. Assess for signs/symptoms of infection such as fever, chills, elevated white blood cell count, or a lumbar puncture suggestive of infection with pleocytosis, elevated protein, and low glucose levels. An infection could lead to a CVT and a thrombosis may be present as well.

These life threatening conditions can have a favorable prognosis if treated early. Elevations in intracranial pressure should be treated urgently and the underlying cause should be determined in order to preserve brain tissue and function. Infections

within the central nervous system need empiric antibiotic coverage until further testing is completed and antibiotics can be adjusted to specificity and sensitivity. If infections are left untreated further brain damage and sepsis leading to other organ failure can ensue. Lastly, if brain tumors, CVT, and DAVF are discovered and treated early further complications can be prevented such as intracranial hemorrhage and edema related deterioration.

9.3.4 Imaging

A computed topography (CT) of the head is the first step in diagnostic evaluation of neurological patients. Although CT is normal 30% of the time, one-third of patients will show a direct sign of CVT, the most frequent being the cord sign. This demonstrates a spontaneously hyperdense thrombosed cortical vein in 25% of patients. The dense triangle sign, is a hyperdensity in the torcular and/or posterior superior sagittal sinus. If a contrast CT of head has been performed, subsequent scans will reveal an empty delta sign in approximately 16–46% of patients. There will be a lack of filling of the posterior superior sagittal sinus and/or torcular. Other signs of CVT revealed on a CT are brain edema (20–50%), gyral enhancement, powerful contrast enhancement of tentorium and falx, and an infectious process within the ears, sinuses, and mastoids which could lead to CVT and hemorrhagic lesions [5].

A more reliable diagnostic option, which is being increasingly used, is the CT venography (CTV). It can be used for patients who have pacemakers or other conditions that preclude magnetic resonance imaging (MRI). A direct filling void will be seen if a CVT is present, especially in the major dural sinuses. Limitations of CTV include risk of reaction to the contrast, difficulty imaging the deep venous system and cortical veins, and exposure to radiation. Occasionally, it is challenging to

differentiate congenital atresia of venous sinus from presence of acute thrombus. Comparison with prior imaging and assessment of cranial foraminal openings can be helpful in distinguishing these differences.

An MR venography (MRV) is a diagnostic tool with extreme sensitivity and used for follow up as well. A thrombus less than 5 days old will appear isointense on T1 weighted images and hypointense on T2 weighted images. If the thrombus is greater than 5 days old, it will appear hyperintense in both T1 and T2 weighted images. When interpreting an MRI, it is important to ensure that slow flow or a nondominant transverse is not being misdiagnosed as thrombosed. The latest guidelines published by the American Stroke Association in 2011 state MRV and CTV are of equal efficacy for diagnostic testing.

The last imaging modality that can be used in CVT is a digital subtraction angiography (DSA). This is used when other diagnostic imaging has been inconclusive or a therapeutic intervention is necessary. A DSA is ideal for assessment of DAVF and cortical vein thrombosis. Abnormal findings include absent filling of venous sinuses or deep veins, sudden cessation of cortical vein, collateral drainage of veins around venous thrombosis. Similar to MRI, it is important to caution diagnosing hypoplasia or a non-dominant transverse sinus as an abnormality.

9.3.5 Other Diagnostic Testing

Neuroimaging is the only confirmatory testing for a patient suspected to have CVT, however there are other diagnostic tests which can help establish a competing etiology. Patients who present with a high suspicion for an infectious etiology for CVT may require a lumbar puncture (LP). An abnormal LP

will demonstrate pleocytosis, elevated protein, low glucose, and elevated pressure. Of note, patients with elevated intracranial pressure secondary to CVT may have an improvement in headache or vision changes secondary to draining of CSF. Caution must be taken to avoid lumbar puncture in individuals with focal mass lesions or edema under pressure, as cerebral spinal fluid aspiration from the lumbar region may exacerbate pressure gradients and precipitate brain herniation in this scenario. Other important laboratory studies include complete blood count, chemistry panel, coagulation studies (PT/INR, aPTT), liver function tests, coagulation panel (antinuclear antibody, homocysteine, prothrombin gene mutation, factor V Leiden mutation, lupus anticoagulant, antiphospholipid/anticardiolipin antibodies, antithrombin III, and protein C/S activity and level. A D-dimer can also be sent. It can be used as a screening tool for patients who present with CVT, however a normal level does not exclude the diagnosis.

9.4 Management and Interventions

The treatment of cerebral venous thrombosis can be divided into three steps. The first step is to control acute complications, such as seizures, and elevated ICP. As with all neurologic emergencies, maintenance of adequate airway, breathing, and circulation are vital. Studies have shown it is not necessary to use prophylactic anti-epileptic drugs (AEDs), nor do patients need to be on lifelong AEDs once the acute phase is complete. However, it is important to control seizures if they occur in order to limit further complications such as progression of brain edema. It is unclear how long AEDs should be continued when implemented for symptomatic seizures at presentation.

Management of elevated ICP is important as well. Ensuring the head of bed is elevated to at least 30° is a basic early intervention. Prolonged rotation of the head away from the midline position may lead to compression of the jugular veins, which may further preclude venous drainage. Treatment of aggravating factors including fever, hyponatremia, or elevated CO2 is required. If the elevated ICP persists, hyperosmolar therapy should be initiated using hypertonic saline or Mannitol. Since dehydration is a precipitating factor for CVT formation and propagation, mannitol and other diuretics should be used with caution to avoid intravascular volume depletion. In severe refractory cases, a patient may need to be placed in a barbiturate coma. Another option includes neurosurgical intervention with evacuation of a hematoma, external ventricular drain, or decompressive craniectomy.

The use of anticoagulation is recommended by experts and intravenous heparin is often first initiated. A reasonable goal PTT is 80–100 s. Anticoagulation inhibits the progression of the thrombus. Even if a hemorrhage is present, the benefit of heparin with reduction in mortality, morbidity, and disability outweighs the risk of worsening hemorrhage. If heparinization fails, another alternative is endovascular, catheter guided, localized thrombolysis [8, 9]. A thrombectomy with clot retrieval or aspiration can be performed as well. This can be considered for patients who have a rapid decline in mental status and function. These treatments are often implemented after failure of systemic anticoagulation or when the patient is experiencing complications related to a substantial venous clot burden. As a result, data supporting the use of thrombectomy and intra-sinus thrombolysis are predominantly anecdotal. Once the patient has stabilized, the heparin drip can be used as a bridge to oral anticoagulation with warfarin. Oral medications should be continued for 3–6 months and lifelong if a prothromobotic condition is present [6].

9.4.1 Prognosis

Cerebral venous thrombosis is a treatable condition with approximately 57–86% of patients experiencing a full functional recovery with treatment [7]. The mortality rate is approximately 5–18%. Poor outcomes are typically found in infants or elderly patients, sudden onset of severe neurological deficits including coma, and massive deep venous system thrombus. The recurrence rate is 12–14%.

Summary Points

- Cerebral venous thrombosis is a disease which is difficult to diagnosis based on clinical presentation and lab values alone.
- Imaging is imperative to diagnosis and should be completed quickly in order to ensure a rapid diagnosis and treatment.
- Early treatment is essential to give the patient the best chance at a functional recovery and limit morality and disability.

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Chapter 10
Traumatic Brain Injury

Megan T. Moyer and Monisha A. Kumar

10.1 Introduction

Traumatic brain injury (TBI) is a leading cause of morbidity and mortality worldwide. It remains the leading cause of death and disability among young people in developed countries. In the United States alone, 2.5 million emergency department visits and hospitalizations are attributed to TBI annually and more than 50,000 individuals die each year from TBI [1]. Thirty-percent of all trauma-related deaths in the United States are related to TBI [1]. Nearly five million Americans live with TBI-related disability [1]. The financial toll of TBI on the United States economy is over $76 billion annually in medical care, disability, and lost productivity [1].

Traumatic brain injury (TBI) is caused when a blow, blast or object penetrates the skull and damages brain tissue, disturbing

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normal brain function. The severity of TBI ranges from mild to severe. It is important to note that TBI is comprised of diverse pathological disorders that have a distinct clinical presentation, pathophysiology, natural history, treatment, and prognosis.

Primary cerebral injury from TBI may be classified as blunt, penetrating, or blast type. Blunt injuries are caused by direct impact and/or rapid acceleration/deceleration. Blunt trauma causes a cascade of events leading to tissue distortion, compression, shearing, and swelling causing contusions, extra-axial hematomas (epidural, subdural, and subarachnoid hemorrhages), and diffuse axonal injuries. Acceleration/deceleration injuries generally cause contusions, which are areas of hemorrhagic necrosis that can be seen in the orbitofrontal and anterior temporal regions. Contusions that occur ipsilateral to the site of impact are termed 'coup' lesions; those contralateral to the site of impact are called 'contrecoup'. Initial neuro imaging may demonstrate multifocal areas of patchy hemorrhage. Over time, these hemorrhages may coalesce into a larger parenchymal hematoma, with radiographic evidence of hematoma expansion or "blossoming".

Blunt injuries may manifest as focal hemorrhagic lesions. Epidural hematomas (EDH) are typically associated with skull fractures involving the middle meningeal artery (MMA) and occur in about 5% of TBI. Although MMA lacerations are the most common cause of EDH, epidural bleeding may also be caused by injury to the diploic veins or the venous sinuses. EDH are bound by (i.e. do not cross) skull suture lines, and can be described as lenticular or convex in shape. When the bridging veins rupture, a subdural hematoma (SDH) develops, generally over the cerebral convexities or less frequently, along the tentorium or the falx. SDH can be described as crescent-shaped or concave, and may cross skull suture lines. SDH are often associated with severe underlying brain injury and high mortality. When small pial vessels tear, subarachnoid hemorrhage (SAH) ensues; subarachnoid blood may enter the basal cisterns or the ventricles [2].

Rapid acceleration and deceleration injuries of the head result in diffuse axonal injury (DAI). The rapid acceleration and deceleration typically occurs in the lateral plane and can be a form of primary and a form of secondary cerebral injury. Primary injury may affect the structural integrity of axons as a result of immediate mechanical damage. Secondary axonal injury leads to axotomy, or progressive axonal swelling and bursting, and is the consequence of cellular cascades initiated by the trauma. DAI occurs in severe, moderate, and even mild TBI (concussion). DAI often affects the gray matter – white matter junction, white matter structures including the corpus callosum, the brainstem and the cerebellum [2, 3].

Penetrating TBI is caused by projectiles that tear the brain parenchyma. The hallmark of penetrating injury is parenchymal and vascular laceration. Complex pressure waves that are generated by explosions and transferred directly to the brain through the cranium represent blast injuries [3]. Blast pressure waves may be propagated through fluid-filled structures and therefore manifest with significant ocular and vestibular symptoms. Blast injury is also associated with arterial vasospasm without SAH (Fig. 10.1) [4].

TBI may be categorized by features other than mechanism of injury, such as clinical severity, radiographic appearance, neuropathology, or injury distribution [1]. Severe TBI is defined as a Glasgow Coma Scale Score (GCS) of 3 to 8 and includes both closed head injuries and penetrating injuries [1]. Investigators of the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) developed prognostic models to better characterize 6-month outcomes in large cohorts of adult patients with moderate – severe TBI [5].

The leading cause of TBI in the U.S. is falls (40.5%), disproportionately affecting both the youngest and oldest populations (<15 years and >64 years) [1]. Unintentional blunt trauma (15.5%) follows in second place and motor vehicle crashes

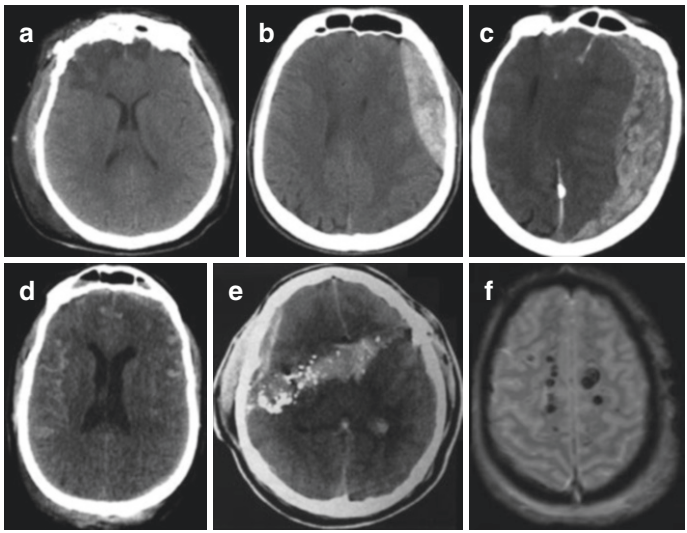

Fig. 10.1 Typical radiological appearance of the various primary injuries in TBI. (**a**) Non-contrast axial CT demonstrating *right* > *left* frontal lobe contusions with hemorrhage; (**b**) non-contrast axial CT demonstrating *left* convexity epidural hematoma; (**c**) non-contrast axial CT demonstrating *left* convexity subdural hematoma with mass-effect, effacement of the *left* lateral ventricle, and *left* to *right* midline shift; (**d**) non-contrast axial CT demonstrating traumatic subarachnoid hemorrhage; (**e**) non-contrast axial CT demonstrating trans-hemispheric laceration from bullet with hemorrhage, bullet fragments, and bone fragments in the tract; (**f**) axial gradient echo MRI sequence demonstrating punctate foci of hemorrhage (*black spots*) consistent with diffuse axonal injury

(14.3%) are now third, likely due to the standard use of airbags. Assaults (10.7%) rank fourth. Men are three times more likely to die from TBI and have higher rates of hospitalizations and Emergency Department (ED) visits than women. Children ages 0–4 have the highest rates of ED visits.

10.2 Case Presentation

A 26 year-old female college graduate student with no significant past medical history was struck by a motor vehicle while running and allegedly "flung 40 feet." Primary trauma survey demonstrated a comminuted fracture of the left scapula and a non-comminuted fracture of the right inferior pubic rami as well as a left fronto-temporal intra-parenchymal hemorrhage (IPH), SAH, and a left cerebral convexity SDH (Fig. 10.2). A brain tissue oxygen monitor was placed after getting a single dose of mannitol for elevated intracranial pressure (ICP). Off sedation, the patient's ICP increased to the 40 mmHg, and hypertonic saline was administered. ICP decreased to 20–25 mmHg with preservation of cerebral perfusion pressure (CPP). Intracranial pressure remained elevated despite maximal medical therapy and brain tissue oxygen ($PbtO_2$) values were below target. The patient was taken to the operating room (OR) emergently for a

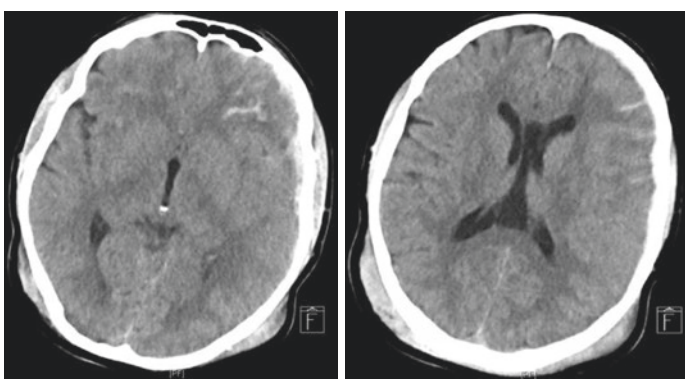

Fig. 10.2 Case study head CT: *left* frontotemporal IPH, SAH, and a left cerebral convexity SDH

decompressive hemicraniectomy; $PbtO_2$ values improved after surgery. On post-injury day #2, the $PbtO_2$ fell to 10 mmHg; cerebral perfusion was augmented with induced hypertension and intravenous fluids. By post-injury day# 6 she was following commands and the brain tissue oxygen monitor was removed. She was extubated successfully the following day. On post-injury day #13 she was discharged to an acute brain injury rehab. She presented for an autologous cranioplasty 11 weeks post-injury and was noted to be weight bearing in therapy. Six-months post-injury she completed a 5 K race, returned to school and resumed working part-time. One year after her injury she ran a half-marathon.

10.3 Initial Evaluation

Published guidelines and best practice statements have attempted to standardize the treatment and management of TBI [2, 3, 6]. The Brain Trauma Foundation (BTF) has developed evidence-based guidelines for both pre-hospital and in-hospital management of patients suffering from TBI. The BTF also created guidelines for special populations including children, soldiers and for those with concussion. The American College of Surgeons also recently published a Best Practice Statement for the management of TBI [3].

The initial evaluation of the TBI patient is guided by the BTF and focuses on basic life support, cervical stabilization and appropriate triage. Triage is based on the Glasgow Coma Scale (GCS) (Table 10.1). The GCS provides a standardized classification to the neurological assessment. The GCS encompasses a score of three assessed components (eye, verbal, and motor) for each individual patient. The three individual component scores, as well as the sum total, should be tallied and reported for use. If a sub-component cannot be tested due to intubation, sedation, or other factor, the reason should be noted.

Table 10.1 Glasgow Coma scale

Category	Response	Score
Eye opening	Spontaneous	4
	To voice	3
	To pain	2
	None	1
Verbal response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	None	1
Motor response	Obeys commands	6
	Localizes to pain	5
	Withdraws from pain	4
	Flexion posturing to pain	3
	Extensor posturing to pain	2
	None	1

Table 10.2 Abbreviated injury score

AIS score	Injury
1	Minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Non-survivable

Severe TBI is defined as a GCS of 3–8, moderate TBI as a GCS of 9–12, and mild TBI by a GCS of 13–15 [1]. Although the GCS was established to triage patients in the trauma bay, serial assessments of the GCS may be useful to trend changes in exam and document response to interventions.

Patients with a GCS of ≤13 should be transported to the highest level trauma centre in the region for assessment and possible intervention by a neurosurgeon. Patients with a GCS of ≤15 and moderate severe extra-cranial injuries and Abbreviated Injury Score (AIS) (Table 10.2) of ≥3 should also be transferred

to the highest level trauma centre in that region for assessment and possible intervention by a neurosurgeon and a multidisciplinary team [3].

The patient, bystanders, and/or emergency medical personnel typically provide the history leading to the diagnosis of TBI. Initial assessment should include documentation of abrasions, lacerations, soft tissue swelling of the head, presence of entrance and exit wounds, retro-auricular ecchymosis (Battle's sign), periorbital ecchymosis (racoon's eyes), hemotympanum, and CSF otorrhea or rhinorrhoea [2]. If no history is available, providers typically use clinical assessment and radiographic findings to determine the TBI diagnosis.

10.4 Interventions and Management

Initial treatment in the emergency department is guided by Advanced Trauma Life Support (ATLS) recommendations. Treatment includes monitoring of systemic oxygenation and blood pressure and targeting therapeutic thresholds (Table 10.3) [3]. Neurological assessment should be performed serially and neuroimaging should be obtained to guide operative intervention. Clinical signs of intracranial hypertension (e.g. Cushing response or pupillary dilation) should prompt empiric treatment and consideration of an ICP monitor. Laboratory assessments including blood alcohol level and urine toxicology screen should be performed and any coagulation derangement should be rapidly corrected, when appropriate.

Table 10.3 Goals of treatment

Pulse oximetry ≥95%	ICP 20–25 mmHg	Serum sodium 135–145
PaO_2 ≥100 mmHg	$PbtO_2$ ≥15 mmHg	INR ≤1.4
$PaCO_2$ 35–45 mmHg	CPP ≥60 mmHg	Platelets $\geq 75 \times 10^3/mm^3$
SBP ≥100 mmHg	Temperature 36.0–38 °C	Hemoglobin ≥7 g/dl
PH 7.35–7.45	Glucose 80–180 mg/dL	

10.4.1 ICP Monitoring and Surgical Indications

Intracranial pressure (ICP) monitoring should be initiated in patients with a GCS of ≤8 and evidence of structural brain damage. For patients with a GCS >8 with structural brain damage and at high risk for progression, ICP monitoring should also be considered. Similarly, it may be reasonable to consider ICP monitoring for patients with a GCS of <8 without a mass lesion if there is a clinical suspicion for DAI. If urgent surgery is considered for extra-cranial injuries within the first 72 h of trauma, placement of an ICP monitor should be considered to guide intraoperative anesthesia management [3]. Additionally, ICP monitoring should be considered if neuroimaging demonstrates progression of pathology, or the patient is clinically deteriorating. A tiered approach to ICP management adapted from the ACS TQIP TBI Management Best Practice Statement is detailed in Table 10.4.

Historically, the method of ICP monitoring was not strictly prescribed. Parenchymal monitors were favoured as cerebral

Table 10.4 Tiered approach to the management of intracranial pressure

Tier	Management
Tier 1	Head of bed elevated at 30°
	Short-acting sedation and analgesia
	Intermittent ventricular drainage
	Repeat CT imaging and neurological examination to rule out the development of a surgical mass lesion and guide treatment
	If ICP remains ≥20–25 mmHg proceed to Tier 2
Tier 2	If parenchymal monitor is indicated, EVD should be considered
	Intermittent (not routine) hyperosmolar therapy as needed for ICP elevation
	In the absence of cerebral autoregulation, CPP goal should be lowered
	$PaCO_2$ goal 30–35 mmHg, as long as brain hypoxia is not encountered
	Additional neuromonitoring may help determine optimal PaCO2 and CPP
	Repeat CT imaging and neurological examination
	Neuromuscular paralysis should be considered if test dose lowers ICP
	If ICP remains ≥20–25 mmHg proceed to Tier 3
Tier 3 (includes potential salvage therapies)	Decompressive hemi-craniectomy or bilateral craniectomy
	Neuromuscular paralysis via continuous infusion titrated to train of four
	Barbituate or propofol (anesthesia dosage) coma may be induced
	Hypothermia (<36 °C) is not currently recommended as an initial TBI treatment

edema often complicated placement of external ventricular devices (EVDs). These devices are catheters attached to an external drain-gauge transducers and are the gold standard for ICP monitoring as they can serve as a diagnostic tool to measure ICP as well as therapeutic modality to treat elevated ICP via cerebral spinal fluid (CSF) drainage. In the current iteration of the TQIP Guidelines, EVD placement is recommended in lieu of parenchymal monitors for these reasons.

While invasive monitoring of ICP is considered the standard of care [2, 3, 7], it has not been shown to improve outcome. The Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST TRIP trial) multicentre randomized controlled trial failed to demonstrate a difference in outcome between treatments guided by clinical examination and use of an ICP monitor. These study findings may not be generalizable to developed countries where use of invasive monitors is the current practice standard; future trials conducted in developed countries will provide direction of best practice [8].

Cerebral perfusion pressure (CPP) is the driving pressure for cerebral blood delivery. Given its relationship to mean arterial pressure (MAP) and ICP (CPP = MAP – ICP), CPP is easily calculated in patients with an ICP monitor. The CPP provides a surrogate estimate of cerebral blood flow (CBF), or the delivery of blood flow to a certain volume of brain tissue. Targeting CBF may allow determination of judicious blood pressure goals and may minimize ischemia (compromised blood flow) and hyperemia (excessive blood flow).

Maintaining adequate brain tissue oxygenation is pivotal in the care of TBI patients. Preventing secondary cerebral injury, which evolves over hours to days following the initial insult, begins with the initial pre-hospital assessment and remains the focus of care throughout the hospital stay. Secondary injury involves cellular and molecular cascades that promote cell death; secondary injury is clinical manifest by cerebral edema,

ischemia, hemorrhage and seizure. Injured cells are more vulnerable to further physiologic insult. ICP monitoring remains the gold standard of neuro monitoring however it is not sensitive in detecting regional and focal cerebral ischemia. Other forms of advanced neuro-monitoring include, but are not limited to, continuous electroencephalography, transcranial Doppler ultrasound, jugular bulb oxygen saturation (SjvO2), CBF monitoring, near-infrared spectroscopy, and cerebral microdialysis [7–12].

Recommendations for surgical management of mass lesions are detailed in Table 10.5 [2, 13–17]. Hyper-metabolic and catabolic states exist with TBI, thus increasing systemic and cerebral energy requirements. Early nutrition, as defined by starting within 24–48 h of injury and achieving full nutritional supplementation within 7 days of injury, should be the goal and is associated with fewer infections and lower mortality rates. Enteral nutrition is preferred over the use of parenteral nutrition [18].

Although there have been a few trials of neuroprotective agents for patients with TBI, none have been proved effective. In the National Acute Brain Injury Study: Hypothermia II (NABISH II) multi-center randomized controlled trial, therapeutic hypothermia was not associated with improved outcome, although it may have been associated with reduced ICP in the treatment arm [19]. The Progesterone for Traumatic Brain Injury, Experimental Clinical Treatment (PROTECT III) was a randomized, multicentre trial that did not demonstrate utility of progesterone in improving the outcome of patients with acute TBI over the placebo [20].

Table 10.5 Recommendations for surgical management of TBI

Lesion	Treatment recommendations
Subdural hematoma [13] (SDH)	Acute lesion >10 mm or >5 mm MLS should be evacuated
	Comatose patients with SDH <10 mm or MLS <5 mm should undergo evacuation if GCS decreases by ≥2 (if indicated, should be performed via craniotomy)
	All patients with GCS <9 should have ICP monitoring
Epidural hematoma [14] (EDH)	EDH ≥30 cm^3 should be evacuated regardless of GCS
	EDH <30 cm^3, <15 mm or <5 mm MLS may be managed non-operatively with close serial neurosurgical evaluation
	EDH in coma with anisocoria should undergo evacuation
Parenchymal hematoma [15]	Mass lesions with related neurological deterioration, refractory intracranial hypertension, or radiographic signs of mass effect should be treated operatively
	GCS 6–8, frontotemporal contusions >20 cm^3 and MLS ≥5 mm and/or cisternal compression should be treated operatively
	Any lesion >50 cm^3 should be treated operatively
	Parenchymal lesions without neurological compromise, with controlled ICP, and no mass effect may be monitored
	Bifrontal decompressive craniectomy within 48 h of injury is an option for patients with diffuse, refractory posttraumatic cerebral edema and resultant intracranial hypertension [15]

(continued)

Table 10.5 (continued)

Lesion	Treatment recommendations
Posterior fossa hematoma	Patients with radiographic mass effect or with neurological dysfunction referable to the lesion should undergo intervention
	Mass effect on the fourth ventricle; compression of the basal cisterns, or the presence of obstructive hydrocephalus
	Patients with lesions but no significant mass effect on CT scan and without signs of dysfunction may be managed expectantly
	In patients with indications for surgical intervention, evacuation should be performed as soon as possible
Depressed skull fractures	Compound cranial fractures depressed > the thickness of the cranium should undergo operative intervention
	Compound depressed fractures may be treated non-operatively in the absence of dural penetration, ICH, depression <1 cm, frontal sinus involvement, gross cosmetic deformity, wound infection, pneumocephalus, or gross wound contamination
	Simple depressed fractures may be expectantly managed
	Early operation is recommended to reduce infection
	Primary bone fragment replacement is a surgical option in the absence of wound infection at the time of surgery
	All management strategies for open (compound) depressed fractures should include antibiotics [7]

10.4.2 Other Systems and Considerations

For patients unable to liberate from ventilator support, or deemed not likely to improve rapidly, a tracheostomy tube should be considered, ideally within 8 day of initial injury. It is recommended the tracheostomy be held off until persistently elevated ICPs, hemodynamic instability, and severe respiratory failure have resolved [3]. Similarly, non-intracranial procedures should be delayed until neurological status is stable. Orthopaedic surgeries should be delayed 24–48 h after ICP stabilization. Intravenous anaesthesia is preferred over regional techniques in the setting of intracranial hypertension. Anaesthesia should be monitored closely to prevent intracranial hypertension, hypotension, hypoxia, and hypo or hypercarbia [3].

VTE is common in the TBI population. Nearly 20–30% of TBI patients develop venous thromboembolism (VTE); therefore, VTE prophylaxis should be initiated once intracranial bleeding has stopped. Inferior vena cava filters may be considered in patients that cannot receive pharmacologic prophylaxis [3].

Paroxysmal sympathetic hyperactivity (PSH) is thought to occur in 15–33% of comatose patients with severe brain injury. PSH is a diagnosis of exclusion characterized by the rapid onset and paroxysmal cycling of agitation and dystonia associated with autonomic symptoms including: tachycardia, hypertension, tachypnea, fever, pupil dilation, decreased level of consciousness, diaphoresis, and ventilator dyssynchrony. The pathophysiology of PSH continues to be poorly understood. When the parasympathetic feedback mechanism fails, sympathetic outflow is uninhibited; leading to hyperactivity and ultimately PSH. Pharmacologic therapy aims to inhibit afferent sensory processing to limit the development of allodynia, inhibit central sympathetic outflow, and block end organ responses of the sympathetic nervous system. Medications are used to target specific cell surface proteins, including voltage gated calcium channels, GABA A and GABA B receptors, alpha and beta-adrenergic receptors, dopamine receptors, and opiate receptors [21].

Summary Points

- ICU care of the TBI patient revolves around monitoring and supportive care, with the goal of pre-empting or preventing secondary cerebral injury.
- There is no effective drug treatment for TBI; however, improvements in pre-hospital care, advanced imaging techniques and adherence to guidelines have been associated with improved outcomes.

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Chapter 11
Intracranial Pressure Management

Danielle Bajus and Lori Shutter

11.1 Introduction

Because the skull is a closed, non-compressible vault, constant equilibrium must be maintained between the skull contents, including brain tissue, cerebrospinal fluid (CSF) and blood. The Monro-Kellie hypothesis states that an increase in one of these components must be accompanied by a relative volume adjustment. The brain has a dynamic capacity for self-protection and compensation in the early stages of an injury including autoregulation, restriction of blood flow, decreased production and shunting of CSF. However, when a critical volume change has occurred, compensation is lost and an elevated intracranial pressure (ICP) is the result. Sustained intracranial hypertension is defined as ICP >20 mmHg for >5 min [1–3]. Cerebral

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perfusion pressure (CPP) is an estimate of the cerebral blood flow and is calculated by subtracting ICP from the mean arterial pressure (MAP) or CPP=MAP − ICP. The normal adult value is a range of 70–100 mm Hg. Data from several studies support a CPP goal of >50–60 mm Hg to prevent cerebral ischemia in traumatic brain injury patients [4]. Interventions to modulate blood pressure may be used to increase or decrease CPP as necessary.

Compliance is a measure of the adaptive capacity of the brain to maintain intracranial equilibrium in response to physiological and external challenges to the system. Compliance represents the ratio of change in volume to change in pressure ($C = \Delta V/\Delta P$) [5]. When compensatory mechanisms are intact, there is adequate volume shift intracranially leading to normal ICP measurements or adequate compliance. When compensatory mechanisms are overwhelmed, ICP may rise quickly because of poor compliance. Compliance can be lost with even the smallest volume shifts depending on the patient's underlying pathology (See Fig. 11.1).

Cerebral edema is a common cause of elevated ICP and is classified in two categories: vasogenic and cytotoxic. Vasogenic cerebral edema is characterized by an increase of fluid in the extracellular space and occurs when there is a breakdown in the blood brain barrier. Trauma, brain tumors, infection, hemorrhage and surgical procedures are common causes. Cytotoxic cerebral edema is characterized by an excess of fluid within the intracellular space. Sodium and water shift into the cell, causing swelling and, eventually, cell death [1, 2, 5]. This type of cerebral edema is typically seen in acute hypoxic injury, cerebral ischemia, and hypo-osmolality, but can also occur in trauma, inflammation, and hemorrhage. Both types of cerebral edema, if not managed effectively, can lead to herniation syndromes (see Table 11.1).

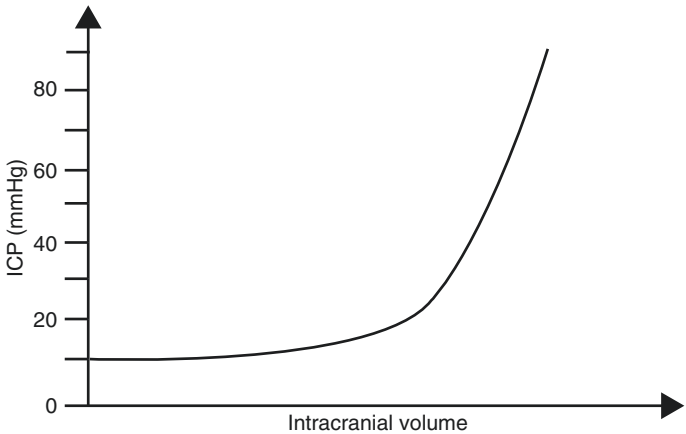

Fig. 11.1 Intracranial compliance curve. Initial increases in intracranial volume are well tolerated. Continued increase in intracranial volume results in loss of compliance and rapid elevations in ICP. Sustained increases can lead to secondary brain injury and herniation syndromes (No re-print premission needed)

Table 11.1 Signs of increased ICP

Changes in level of consciousness:
Confusion
Lethargy
Agitation
Changes in vital signs:
Hypertension
Bradycardia
Widening pulse pressure
Irregular respiratory pattern
Headache
Visual disturbances
Nausea and vomiting
Pupillary changes
Hemiplegia/hemiparesis

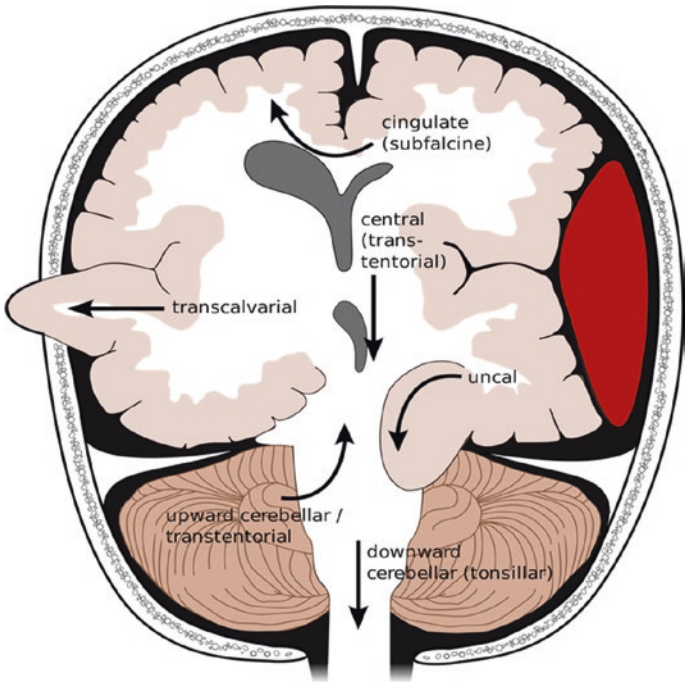

Fig. 11.2 Herniation Syndromes. The brain tissue herniates from an area of increased pressure to an area of lesser pressure causing clinical exam changes leading to poor outcomes if not treated immediately. The different types of herniation syndromes are illustrated below (Retrieved from Wikimedia Commons, a free medical repository. No re-print permission needed)

Herniation syndromes include uncal, transtentorial, subfalcine, and cerebellar [5] (See Fig. 11.2). Each is related to mass effect and compartmental pressure changes because of the rigid intracranial boundaries. The brain tissue herniates from an area of increased pressure to an area of lesser pressure causing

clinical exam changes leading to poor outcomes if not treated immediately. Patients with herniation syndrome will present with progressive somnolence, decreased respirations and Cushing's Triad of symptoms: sudden hypertension, bradycardia, and respiratory irregularities.

11.2 Case Presentation

A 23-year-old male with no past medical history was brought to the emergency department following a motor vehicle collision (MVC). He was an unrestrained driver T-boned by another vehicle at approximately 50 mph. Extrication from the vehicle was required. He was unresponsive in the field and immediately intubated upon arrival of EMS in the field for airway protection. Trauma scans revealed a right tentorial subdural hematoma with mild mass effect, a right pontine/midbrain intraparenchymal hemorrhage, fracture of the right occipital condyle, and fracture of the eighth tooth. No other injuries were identified. An external ventricular drain (EVD) and intraparenchymal ICP monitor, temperature, and brain tissue oxygen probes via a triple lumen intracranial bolt were placed. He was admitted to the Neuro ICU in hemodynamically stable condition. Proper positioning, sedation, analgesia, and seizure prophylaxis were immediately implemented. Because of ICP elevations to 55 mmHg sedation was increased; a paralytic administered, and 3% hypertonic saline was started. The patient subsequently had a temperature spike and surface cooling with a goal of normothermia was initiated. Acetaminophen was given and empiric antibiotics began to prevent further fever. The paralytic was gradually weaned off. Over the course of a week, his ICP was maintained <20 mmHg and the intracranial bolt was removed. EVD was removed on hospital day 13.

11.3 Initial Evaluation

It is the role of the neurocritical care clinician to recognize physiologic signs of elevated ICP and take any necessary steps to prevent secondary brain injury and herniation. Initial evaluation should include baseline vital signs and a complete neurologic exam. Symptoms to be evaluated include changes in vital signs, mental status, and pupil size; in addition to headache, visual disturbances, vomiting and motor function abnormalities (see Table 11.2). If there is sudden or unexplained ICP elevation, the patient must be examined immediately. Interventions to lower the ICP must be initiated urgently prior to any diagnostic studies. Head CT should be repeated to rule out new mass lesion that may require surgical evaluation such as new subdural hematoma, epidural hematoma, or hemorrhagic transformation of stroke.

Most ICP lowering therapies are effective for variable amounts of time and early management goals should include placement of an ICP monitoring device. The purpose of ICP monitoring is to improve the clinician's ability to maintain

Table 11.2 Common causes of increased ICP

Primary causes
Edema
Trauma
Brain tumors
Infection/inflammation
Hemorrhage
Ischemic injury/infarction
Hypoxic injury
Hydrocephalus
Secondary causes
Agitation
Hypertension
Seizures
Fever

adequate cerebral perfusion pressure and oxygenation to the brain. The diagnosis of elevated ICP is made from clinical findings based on the patient's exam, imaging, and past medical history.

Any patient that is suspected to be at risk for elevated ICP should be considered for placement of an ICP monitoring device. There are four common sites used for ICP measurements; intraventricular, intraparenchymal, subarachnoid, and epidural. Intraventricular monitors are the gold standard of ICP monitoring catheters. They are placed through the skull into the ventricular system and attached to a pressure transducer with collection bag (See Fig. 11.3 for example). The major advantage of an intraventricular system is that CSF can be drained. Disadvantages are infection and potential hemorrhage during placement. Intraparenchymal devices are built around a thin cable with a fiber optic transducer at the tip. These devices are inserted through the skull directly into the brain parenchyma. Their main disadvantage is the lack of ability to drain CSF; advantages include ease of placement and lower risk of infection. Subarachnoid bolts are fluid filled systems within a hollow screw that are placed through the skull adjacent to the dura. The dura is punctured and the CSF communicates with the fluid column and the transducer. Advantages of subarachnoid monitors are low rates of infection and hemorrhage. The major disadvantage is frequent clogging of the system, which renders the measurements unreliable. Epidural ICP monitors contain and optical transducer that rests against the dura once passed through the skull. They are often inaccurate and have limited use clinically.

Once ICP monitors are in place, the waveforms can be easily accessed to help the clinician evaluate intracranial compliance. There are three peaks to the waves that are referenced for clinical significance. P1 is the percussion wave, which reflects arterial pulsation. P2 (tidal wave) represents intracranial compliance and P3 is the dicrotic wave signaling closure of the aortic valve

Fig. 11.3 Extraventricular drain (EVD). This is a temporary method to reduce ICP that can be regulated manually. The drain is attached to a bag that is transduced to atmospheric pressure and leveled to the midbrain. The drain can then be raised or lowered to different anatomical reference points to facilitate drainage (Photo courtesy of University of Pittsburgh Medical Center)

[1, 2]. Normal intracranial compliance is depicted by a sharp, high P1, followed by a P2 that is lower than P1, followed by an even lower P3 wave. Poor intracranial compliance is seen as a P2 wave that is equal to or higher than that of P1 (See Fig. 11.4).

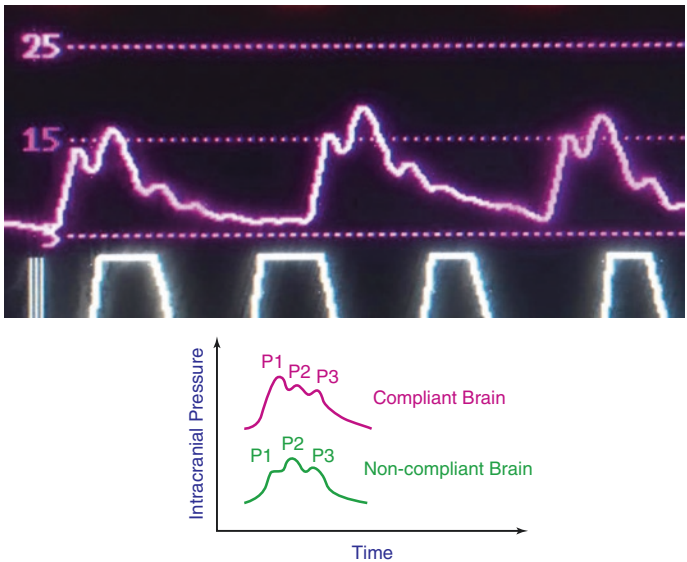

Fig. 11.4 ICP Waveforms. Normal intracranial waveforms depicted by a high P1, followed by a P2 that is lower than P1 followed by an even lower P3 wave. Poor intracranial compliance is seen as a P2 wave that is equal to or higher than that of P1 (Photo courtesy of University of Pittsburgh Medical Center)

11.4 Management and Interventions

There are several ICP management options used in neurocritical care. A step-wise approach to treatment is suggested and consists of some simple techniques such as positioning maneuvers to more complicated treatments for refractory patients (see Table 11.3). Many of the treatments currently in use are outlined in the following pages.

Table 11.3 Stepwise treatment of increased ICP

Positioning
Sedation/analgesia
Normothermia
CSF diversion
Hyperventilation
Osmotherapy (may repeat treatments)
Hypothermia
Pentobarbital Induced coma
Decompressive hemicraniectomy

11.4.1 Head Elevation

One of the easiest interventions to help manage ICP is proper positioning of the patient. The head should be positioned forward and straight without the neck being flexed backwards or forwards. This promotes adequate perfusion and drainage of the cerebral vessels. Head of bed at a maximum of 30° is acceptable to maintain adequate CPP. Special care should also be taken if a cervical collar is in place. The collar should be properly positioned and should not be so tight as to restrict venous outflow.

Flat positioning is acceptable for patients who do not have a large abdominal girth, but because of the risk of aspiration or gastric reflux, reverse Trendelenburg could be considered. For those with a large abdomen, head of bed should be raised slightly to decrease intra-abdominal pressure. Trendelenburg is always contraindicated because of obstruction of venous return, which increases cerebral blood volume and in turn increases ICP. In general, proning and extreme hip flexion are also discouraged, as they will also increase abdominal pressure and raise ICP. However, in a patient with ARDS where proning may be a life saving measure, it can be done if necessary. There should be close teamwork and communication with neurosurgical colleagues in this situation.

11.4.2 Sedation and Analgesia

Adequate sedation and pain control are important early interventions for ICP management. Sedation can decrease cerebral oxygen demand in addition to controlling a multitude of other factors that elevate ICP. Restlessness, agitation, coughing, and ventilator asynchrony can all be prevented or minimized with adequate pharmacological support. This is best achieved with short acting narcotics for analgesia and propofol or similar short acting agents for sedation [6]. These drugs are ideal for interruption for neurologic exams because of their short half-lives (See Chap. 22 for information on commonly used sedation and analgesia agents).

11.4.3 Temperature Control

Fever increases cerebral oxygen demand and may contribute to cerebral ischemia and elevated ICP. Cerebral blood flow and cerebral metabolic rate increase about 5% for every 1 °C temperature increase [5]. Cooling blankets and acetaminophen can be instituted quickly and easily. The goal is for normothermia (37.0 °C) to be maintained throughout the patient's course.

Hypothermia is reserved for refractory cases of elevated ICP. If core temperature remains uncontrolled, surface cooling and cooling catheters may be necessary. Hypothermia lowers ICP but there is no evidence that it improves outcomes. Moderate hypothermia with a target core temperature of 32–34 °C is associated with a predictable reduction in ICP [4].

11.4.4 Cerebrospinal Fluid Diversion

Insertion of extra ventricular drains (EVD) allows CSF to be displaced and can facilitate treatment of elevated ICP related to

hydrocephalus. The EVD catheter itself gives the clinician direct ICP measurements. As the fluid is removed, ICP decreases and creates more room inside the cranial vault. This is a temporary method to reduce ICP that can be regulated manually. The drain is attached to a bag that is transduced to atmospheric pressure and leveled to the midbrain. The drain can then be raised or lowered to different anatomical reference points to facilitate drainage (see Fig. 11.3).

11.4.5 Osmotherapy

Osmotherapy decreases the amount of cerebral edema by creating an osmotic gradient across the blood-brain barrier and facilitating the movement of free water out of the cerebral tissue. There are a few different osmotherapy options available. Mannitol is an osmotic diuretic that pulls free water from the brain, decreasing brain volume and lowering ICP. Mannitol works quickly and lowers ICP within minutes. It should be given as a single bolus dose of mannitol 20% 1 gm/kg rapid IV infusion. There is large volume diuresis seen with mannitol administration; consequently, accurate documentation of intake and output is essential. Measures should be taken to avoid systemic hypovolemia when this agent is used. Additionally, impaired renal function reduces the utility of this medication and patient can develop acute kidney injury with prolonged use.

Hypertonic saline (HTS) is also a well-recognized form of osmotherapy to help control ICP. HTS has minimal side effects and has been shown to produce a significant reduction in ICP when compared to mannitol [7]. However, there is a lack of consensus over optimal concentration and length of use. Current available concentrations are 1.5%, and 3%, given as a bolus dose followed by continuous infusion, or 7.5% and 23.4% given as bolus doses up to every 6 h. Serum sodium, electrolytes and osmolality should be checked routinely while the patient is

receiving osmotherapy [8–12]. See Chap. 22 for osmotherapy administration and monitoring information.

11.4.6 Hyperventilation

Carbon dioxide is a known cerebral vasodilator. Lowering CO_2 can cause a rapid vasoconstriction of cerebral blood vessels causing a decreased cerebral blood flow and leading to a decrease in ICP. The goal is a $PaCO_2$ of 32–36 mm Hg and can be achieved by increasing the ventilator rate for an intubated patient. An ambu bag can be used to hyperventilate the non-intubated patient. While this works in acute episodes of intracranial hypertension, the effectiveness is transient in nature. Prolonged hypocarbia may reduce cerebral blood flow to the point of ischemia so careful monitoring with frequent blood gas sampling or end tidal CO_2 detector is necessary and hyperventilation should only be used as a bridging measure toward alternative therapies.

11.4.7 Pentobarbital

Continuous pentobarbital infusion should be considered in patients with ICP elevations refractory to treatment with osmotherapy, hyperventilation and sedation. The mechanism of action of pentobarbital is a profound reduction of cerebral metabolic rate. Pentobarbital should be given as a bolus dose of 10 mg/kg. If this initial dose results in an ICP reduction, then a continuous infusion can be started. The initial rate is usually at 1 mg/kg per hour, but can be titrated upward as needed [13]. Continuous EEG should be applied to these patients to monitor brain activity and watch for burst suppression. The goal of pentobarbital infusions is a burst-suppression pattern on EEG consisting of a 1–2 s burst of activity followed by 8–10 s of suppression. Titration of pentobarbital above the level to produce this pattern should be undertaken with

extreme caution, and only if a decrease in the ICP occurs in response to upward titrations. Hemodynamic support may also be required as the most common side effect is hypotension.

11.4.8 Decompressive Hemicraniectomy (DHC)

DHC can be performed when other methods of ICP reduction fail, or the area of injury is expected to swell and herniation syndromes are anticipated. Part of the skull is removed, the dura is opened, and the skin is closed to allow the brain additional room outside of the cranial vault. Cranial skull flaps are typically replaced weeks to months later. Management after DHC consists of aggressive medical care to optimize patient outcomes and avoid complications such as respiratory failure leading to tracheostomy and DVT. Some institutions have incorporated DHC into ICP treatment algorithms as an early intervention although there is no strong evidence supporting this practice [14].

11.4.9 Additional Therapies

11.4.9.1 Paralysis

Paralytics, or neuromuscular blockade, can be used in addition to sedation to help control elevated ICP. Vecuronium and cisatracurium are common agents. All patients with neuromuscular blockade on board should have adequate sedation and must be monitored for appropriate level of blockade to be achieved. Side effects can be minimized by carefully monitoring the dosage and degree of blockade attained with a train-of-four peripheral nerve stimulator applied to the ulnar or facial nerve. Because of the neuromuscular blockade, seizure activity would be undetectable; therefore, it is helpful to have continuous EEG monitoring in place during paralysis.

11.4.9.2 Steroids

Patients with vasogenic edema in the non-traumatic population are often started on high dose corticosteroid therapy, such as dexamethasone, to help decrease intracranial pressure. Steroids have *not* been shown to be effective for cytotoxic cerebral edema, and are contraindicated in traumatic brain injury [15]. Consideration must be made for blood glucose levels and subsequent initiation of insulin therapy to maintain normoglycemia.

11.4.9.3 Seizure Control

Seizures cause elevated ICP by increasing the cerebral metabolic rate and oxygen consumption. Patients with elevated ICP from brain injury are prone to seizures, which may further elevate ICP. There should be a low threshold for either routine or continuous EEG monitoring. Any seizure activity should be treated aggressively with antiseizure medications [16].

Summary Points

- The skull is a closed, non-compressible vault. The Monroe-Kelli Hypothesis states that an increase in one of the three internal components of the skull (brain, blood or CSF) should be followed by a relative decrease in one of the other components. Compliance is the adaptability of the brain. When compliance is lost an increase in ICP may result.
- Frequent neurological and vital sign assessments can help clinicians detect early changes in ICP and lead to earlier treatment.
- Treatments of ICP can consist of simple techniques such as positioning maneuvers to more complicated treatments like pentobarbital for refractory patients. Management should be done in an organized step-wise approach.

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Chapter 12
Seizures and Status Epilepticus

Catherine Harris and Emily Gilmore

12.1 Introduction

Seizures are a common phenomenon in intensive care units (ICU). The prevalence of seizures in the ICU, including patients with brain injury, varies widely in studies from 7% to 68% [1–4]. In patients without a primary neurological disorder, the prevalence is much less at 8–11% [1–4]. Seizures in critically ill patients can be provoked or unprovoked, focal or generalized, and with (convulsive or myoclonic) or without (nonconvulsive) prominent motor features. The majority of ICU seizures are classified as nonconvulsive and may be

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secondary to focal injury, as seen in ischemic and hemorrhagic stroke, encephalitis, or diffuse injury (as seen in traumatic brain injury, aneurysmal subarachnoid hemorrhage, and hypoxic-ischemic encephalopathy). Seizures occur when there is excessive neuronal excitability. The focus of electrical activity comes from the neurons of the cortex and possibly the brain stem, although brain stem origin has not been well established. Most excessive electrical activity causing a seizure will stop on its own in a couple of minutes. Seizures lasting more than 5 min are less likely to stop spontaneously and require urgent treatment.

A thorough description and classification of seizures can help clinicians determine etiology and guide treatment:

- *Provoked* vs. *unprovoked*. Provoked seizures can be the result of primary neurological disorders, systemic disorders, or drugs that lower the seizure threshold, outlined in Table 12.1. Unprovoked seizures occur without a clear precipitating event.
- *Focal* vs. *generalized.* Generalized seizures include tonic-clonic, absence, myoclonic, clonic, tonic, or atonic. Focal seizures can occur with or without impairment in consciousness. Semiology of focal and generalized seizures are outlined in Table 12.1.
- *Discrete* vs. *continuous.* Seizures should be described in reference to the time course of seizure activity. Descriptions of seizures should include onset, duration and frequency, or if the seizures are continuous or intermittent.

Seizures present with a spectrum of clinical manifestation and severity. The following terms are used frequently to define the spectrum of seizure activity [5, 7, 8]:

Table 12.1 Seizure semiology [5, 6]

Semiology for focal-onset seizures	
Frontal lobe	Disinhibited behaviors
	Confusion
	Automatisms
Temporal lobe	Confusion
	Auditory hallucinations
	Chewing, lip smacking
Parietal lobe	Paresthesias (warmth, cold, tingling, numbness)
	Loss of awareness
	Confusion
Occipital lobe	Scotomas
	Visual hallucinations
	Confusion
Semiology for generalized seizures	
Tonic	Increased muscle tone
Clonic	Rhythmic jerking
Tonic clonic	Increased muscle tone with rhythmic jerking
Atonic	Loss of muscle tone
Myoclonic	Muscle contractions

- Seizure – uncontrolled electrical impulses in the brain that manifest as focal or generalized rhythmic activity lasting 10 s to 5 min.
- Status epilepticus (SE) – a single seizure lasting more than 5 min or recurrent seizures without return to neurologic baseline in the intervening period(s).
- Generalized convulsive status epilepticus (GCSE) – status epilepticus that is clinically evident, e.g., tonic-clonic, clonic, or myoclonic movements.

- Nonconvulsive status epilepticus (NCSE) – status epilepticus without tonic-clonic, clonic, or myoclonic movements, but often with impairment in mental status with or without subtle signs (e.g., eye, facial, or finger movements) and associated with electrographic evidence of seizure activity. Similar to convulsive status epilepticus, more than 5 min or >30 min of total ictal activity in any hour of recording is consistent with NCSE. Can be focal or generalized. NCSE is common among critically ill comatose patients and accounts for 20% of all SE [9].
- Refractory status epilepticus (RSE) – can initially be GCSE or NCSE; it is defined by failure to respond to first- or second-line antiepileptic therapy. RSE occurs in a significant number of patients who present with GCSE.
- Super refractory status epilepticus (SRSE) – status epilepticus that persists or recurs more than 24 h after appropriate anesthetic therapy
- New-onset refractory status epilepticus (NORSE) – refractory status epilepticus without an obvious etiology after an initial workup.

The most common cause of SE is a prior history of epilepsy. For these patients, a number of circumstances can lower seizure threshold including recent alterations in antiepileptic medication dosing, systemic infection, or new drug exposure. Patients in the Neuro ICU can develop SE as a result of old or new cerebral insult including stroke, tumor, subdural hemorrhage, hypoxic-ischemic injury, metabolic disarray, and ethyl alcohol withdrawal (Table 12.2). The increased utilization of continuous EEG monitoring in the ICU setting has proved very useful in the evaluation of patients with fluctuating neurologic symptoms and unexplained coma. Timely identification of NCSE can focus treatment and improve outcome in neurologically ill patients.

Table 12.2 Provoked seizure etiologies

Primary neurologic disorders	Systemic disorders	Drugs that lower seizure threshold
Head trauma	Hypo/hyperglycemia	Antibiotics
CNS infections	Hyponatremia	Antidepressants
Stroke	Hypomagnesemia	Antipsychotics
Cerebrovascular diseases	Hyperthyroidism	Stimulants
Encephalopathy	Sleep deprivation	Chemotherapy drugs
Anoxic brain injury	Hyperthermia	Beta-blockers
Intracranial hemorrhage	Uremia	Narcotics
CNS structural abnormalities	Withdrawal ETOH	Antihistamines
Neurodegenerative disease	Withdrawal sedatives	Analgesics

12.2 Case Study

A 78-year-old man is transferred from another hospital to the Neuro ICU. The wife initially states that he was in his usual state of health watching TV when his eyes rolled back and he began to shake all over. Paramedics arrived at the scene, where the patient had stertorous breathing and depressed level of consciousness. He was intubated in the field and taken to the local hospital. While in the CT scan, he had a "GTC" seizure. He was treated with a benzodiazepine IV push and the seizure terminated. CT scan revealed an 8 mm acute on chronic left subdural hemorrhage with 4 mm of midline shift. He was loaded with fosphenytoin and admitted to the ICU for further management. On the way to the ICU, he begins "jerking" on the right side and the nurse administers more Ativan. On arrival to the ICU, a continuous infusion of midazolam and continuous EEG monitoring are ordered STAT.

Upon further questioning, the wife states that her husband was tripped by the dog about 2 months ago and has become increasingly unsteady but attributed it to an old knee injury. The patient's cEEG showed lateralized periodic discharges over the right temporal parietal region that evolved into frank electrographic seizures despite antiseizure therapy. He was started on a propofol infusion titrated to seizure suppression and remained seizure-free for 30 h. The infusion was slowly tapered over several hours at which point the nonconvulsive seizures recurred. He was bolused with IV midazolam and started on an infusion. Given his refractory seizures, the decision was made to go to the OR for SDH evacuation.

12.3 Initial Evaluation

12.3.1 Airway

The inability to maintain the airway is the most immediate risk to a patient with CSE. Factors that affect adequate oxygenation and ventilation include a clenched jaw, paradoxical or poorly coordinated respirations, secretions, and vomitus. Implementing precautions, including placing the patient on their side and supplying 100% oxygen via a face mask while performing continuous cardiopulmonary monitoring, are essential to minimizing the need for intubation secondary to hypoxic respiratory failure. However, despite these efforts intubation may be necessary and should be determined on a case-by-case basis. Short-acting paralytics should be used so as not to mask clinical seizure activity for a prolonged period of time.

12.3.2 Abortive Therapy

Benzodiazepines are first-line agents to control seizures [10–12]:

- Lorazepam 4 mg IV push over 2 min, if still seizing after 5 min, repeat ×1 to a max of 0.1 mg/kg IV.
- See Fig. 12.1 for status epilepticus management algorithm.

If no IV access is available, other options include:

- Rectal diazepam gel (10–20 mg, 0.2 mg/kg)
- Intranasal/buccal/IM midazolam 10 mg IV solution

12.3.3 History

Since etiology of seizures and SE varies significantly, a thorough evaluation of seizure characteristics and patient history is essential in guiding patient management:

- Seizure characteristics – Describe the seizure including onset, semiology (gaze deviation, face or extremity jerking, automatisms, altered mental status), evolution (progressing generalization), how did it cease (e.g., on its own or with medication).
- Seizure duration – Determine when the patient last seen normal or at baseline.
- History of present illness – Obtain a thorough understanding of the events leading up to the seizure including preceding illness, cognitive or behavioral changes, trauma, recent changes in medications, lifestyle, use of illicit substances or alcohol, etc.

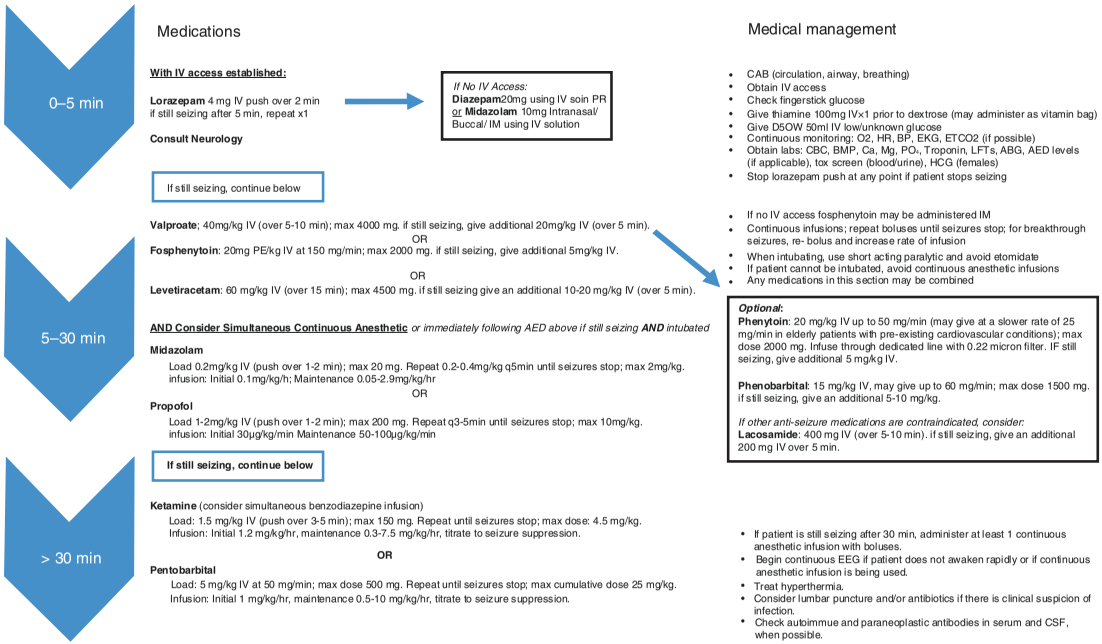

Fig. 12.1 Status epilepticus treatment algorithm

- Past medical history – This should include questions about prior seizures, history of epilepsy, and epilepsy risk factors (e.g., prior trauma, stroke, CNS infection, febrile seizures) as well as psychogenic non-epileptic seizures.
- Medication history – Special attention should be made to medications that lower seizure threshold. If the patient has a history of epilepsy, obtain information about antiseizure medication regimen recent dosing adjustments or a history of medications noncompliance.

12.3.4 Neurological Evaluation

A neurological assessment is imperative in the initial evaluation and will be fundamental in narrowing the list of differential diagnoses. A full assessment should include mental status, cranial nerves including fundoscopy, motor and sensory functioning, reflexes, and cerebellar exam.

Patients in NCSE can have pupillary abnormalities, including asymmetry and hippus. However, if the pupils are dilated, pinpoint, or unreactive, other life-threatening neurologic emergencies should be entertained, prompting an emergent neurology or neurosurgical consultation. Additionally, in NCSE the eyes may be open, but the patient is mute (eye open mutism), the eyes may be deviated with or without head version. Not all eye deviation is secondary to seizure and can be seen in cortical, thalamic, and brain stem lesions. In general, with ongoing seizures the eyes will deviate away from the brain lesion (especially if frontal), but with stroke or other lesions, they will deviate toward the side of the lesion. The exception to this rule involves lesions to the paramedian pontine reticular formation, in which lesions in the pons may cause contralateral eye deviation. Facial, eye, or limb twitches may be observed and may be induced with stimulation. Tone may be symmetrically or asymmetrically increased with hyperreflexia and clonus. “Awake” patients are more likely to exhibit automa-

tisms (e.g., picking, lip smacking) and behavioral changes (perseveration, agitation, emotional lability, aggressiveness).

After a self-limiting convulsive seizure, a patient's exam should return to their baseline functioning over a short period of time. Patients who do not return to their baseline level of consciousness within 30–60 min should be evaluated for nonconvulsive seizures and status epilepticus and undergo monitoring with cEEG as soon as possible. Immediately in the post-ictal phase, the patient may have a focal motor deficit (Todd's paralysis) that resolves over minutes to days.

Sometimes seizures are clear-cut and obvious in a clinical setting where the provider knows the patient and the history of the patient. However, many patients present without a diagnosis or history of seizures. The differential diagnoses for seizures can be extensive, so it is important to consider life-threatening diagnoses. There are several conditions that should be ruled out immediately or considered during the workup for a patient with seizures:

- Basilar artery thrombosis – patients may present in coma or have multiple cranial neuropathies (papillary abnormalities, diplopia, dysphagia), cerebellar signs (ataxia, nystagmus, nausea/vomiting), weakness (hemiparesis, quadriparesis), paroxysmal spasms or posturing (decerebrate). Patients with concerns for basilar thrombosis require emergent recognition of signs/symptoms and neuroimaging for possible thrombolysis.
- Ischemic stroke – patients can present with a wide range of symptoms depending on the location of the stroke and can easily mimic seizure activity or rarely be associated with ictal activity. Management of stroke requires early detection and treatment. Patients with focal deficits should be evaluated for possible TIA/stroke in case emergent treatment is warranted.
- Meningitis/encephalitis – patient may complain of headaches, but typically have flu-like symptoms; patients may

also present in a comatose state. Patients with fever and altered mental status need a lumbar puncture and antibiotics imminently; neuroinfections can cause seizures that should be treated concurrently. Lumbar puncture and antibiotics should not be delayed for other diagnostic testing if there is a strong concern for meningitis.

- Sepsis – patient may present with encephalopathy, which is often an early sign in sepsis. Again treatment of sepsis with antibiotics should be prioritized. These patients are also at increased risk for seizures, especially nonconvulsive, that would otherwise be missed without the use of cEEG.
- Hypoglycemia – patients with hypoglycemia may present in a coma, focal neurologic deficits, or seizure activity that is best treated with glucose administration. All patients with altered mental status should have a finger-stick glucose done to evaluate for the hypoglycemia as a potential etiology of their neurologic deterioration.
- Nonconvulsive status epilepticus – GCSE is generally apparent and easy to identify, but NCSE may be more insidious. Patients may be in a coma for various reasons, which can all be complicated by NCSE, especially if it is not considered or recognized as delays in diagnoses are associated with worse outcomes. If identified, NCSE should be treated aggressively.
- Venous sinus thrombosis – patients with venous sinus thrombosis may have some convulsive movements from either the thrombosis or associated hemorrhage from the venous sinus thrombosis. Treatment is typically anticoagulation as the seizures are provoked; however antiseizure medication may be appropriate if seizures persist or recur acutely.
- Other diagnoses to consider include cardiac conditions (syncope, cardiac arrhythmias), psychiatric disorders (panic attacks, conversion, malingering), and other neurological disorders (movement disorders, migraines, narcolepsy, transient global amnesia, delirium).

12.3.5 Diagnostics

Laboratory evaluation of patients presenting with seizures and SE should include metabolic studies to evaluate for hypo/hypernatremia, hypo/hyperglycemia, electrolyte disturbances, hyperammonemia, and thyroid dysfunction. Urine toxicology should be sent for cocaine and methamphetamines and ethyl alcohol, which lower seizure threshold. Drug levels of known AEDs, benzodiazepines, antidepressants, and antipsychotics can be helpful in determining seizure etiology. Complete blood count may show signs of systemic infection; however seizures can precipitate a leukocytosis, so other signs of infection should be taken into consideration. Seizures can also cause elevated lactate and CK levels due to rigorous muscle activity. Prolactin, if drawn within 30 min of seizure activity, may be helpful in distinguishing epileptic from psychogenic non-epileptic seizures, but not from syncope.

Lumbar puncture should be performed and tailored to the clinical scenario. Typically, a basic CSF panel will include gram stain and culture, cell count, protein, and glucose. See chapter *Neurological Infections* for further outline of diagnostic workup and treatment for infectious encephalitis and meningitis. Occasionally, seizures can be attributed to a paraneoplastic, autoimmune, or parainfectious encephalitides. A detailed history will help guide what can be a very extensive investigation.

Non-contrast head CT should be performed for any patient with new-onset seizures to evaluate for a neurological insult including occult trauma, hemorrhage, or tumor. CT angiography can be performed if acute ischemic stroke is considered as an alternative diagnosis. Similarly, CT venography can be considered to evaluate for cerebral venous thrombosis as potential seizure etiology. MRI can be considered once patient is clinically stabilized to evaluate for a number of conditions related to

seizures including but not limited to infection (including abscess), malignancy, hypoxic-ischemic injury, posterior reversible encephalopathy syndrome (PRES), and limbic encephalitis. MRI may demonstrate diffusion and FLAIR abnormalities due to seizure activity. These changes can be seen in the cortex as well as the deep gray nuclei (pulvinar of the thalamus) and the corpus callosum [13].

12.4 Interventions and Management

12.4.1 Continuous EEG Monitoring and Interpretation

Continuous EEG (cEEG) monitoring (>24 h duration) must be contextualized to the clinical scenario. Not all epileptiform activity is consistent with the presence of seizures, and conversely the absence of epileptiform activity does not always negate the presence of focal seizures. CEEG patterns can be caused by a wide variety of neurologic conditions, and not all cases of neurologic injury are associated with EEG abnormalities. It is critical to understand the descriptive terminology of EEG waveforms and to assess for patterns over time.

An electrographic seizure can be defined by [5, 8, 13]:

- Paroxysmal pattern that evolves in morphology, frequency, and/or spatial distribution OR
- Generalized spike-wave discharges ≥3 per second
- Clearly evolving discharges of any type that reach a frequency of >4 per second (focal or generalized)
- Paroxysmal electrographic pattern that is different from the background EEG pattern and associated with a clinical correlate

Activity observed on cEEG can be defined as epileptiform, strongly associated with seizures, or as nonepileptiform, or as features commonly seen in critically ill patients, but not associated with seizures:

- Epileptiform activity [14–19]
  - Interictal epileptiform discharges (IED) – Highly suggestive of seizure activity. IED can also be seen from withdrawal from short-acting barbiturates and benzodiazepines, metabolic derangements, and some medications.
  - Periodic discharges (PDs) – Can be lateralized (LPDs), generalized (GPDs), or bilaterally independent (BIPDs). PDs are commonly seen in brain lesions such as stroke, intracerebral hemorrhage, encephalitis, and hypoxic-ischemic encephalopathy. They are also common in patients with symptomatic seizures and are all strongly associated with seizures.
  - Rhythmic delta activity (RDA) – Can be lateralized (LRDA) or generalized (GRDA) as well as bilaterally independent (BI). Similar to PDs, RDA can be seen across the spectrum of brain injury and when lateralized is strongly association with seizures.
- Nonepileptiform activity – Can be relatively common in critically ill patient population resulting from a multitude of causes, not associated specifically with seizures, but frequently occurring after seizures.
  - Slowing – diffuse, regional, or localized. Commonly seen in post-ictal states and with focal structural lesions.
  - Frontal intermittent rhythmic delta activity (FIRDA) - Bilateral slow activity, nonspecific finding associated with encephalopathy of all causes. Can be seen in normal individuals as well. Defined by changes in amplitude or asymmetry and deviations from normal patterns.

12.4.2 *Seizure Management [11, 20–22]*

GCSE is a neurologic emergency warranting rapid triage and treatment. Most patients will respond to first-line medications if begun within 30 min of seizures onset, however <40% respond after 2 h of ongoing seizures [23]. Additionally, withholding antiepileptic medication because of fear of respiratory compromise has been shown to increase the risk of acute respiratory failure [10]. Figure 12.1 provides an algorithm for treatment of SE.

Benzodiazepines are the first line for treatment in initial management of seizures (see Sect. 12.3.2, above). The second-line treatment for seizures is IV AED administration. There are many options for choosing antiepileptic drugs for patients with seizures; however, not all are appropriate for use in the ICU. There are several commonly used AEDs in the ICU that are available in IV form for rapid titration and emergent administration. Please refer to section on antiepileptic drugs used in status epilepticus found in Chap. 22 *Pharmacology in the Neuro ICU* for further drug administration, level monitoring, and drug interaction information. Commonly utilized medications include valproate sodium, fosphenytoin/phenytoin, levetiracetam, phenobarbital, and lacosamide. For patients with new-onset seizures, levetiracetam is frequently used because of its relatively low-side-effect profile, limited drug interactions, and rare need for drug level monitoring when starting therapy.

Continuous infusion of AEDs is recommended to suppress seizures not controlled by first- and second-line therapies. None of the following therapies have been shown to be superior and often the choice is dictated by the patient's clinical status (e.g., arrhythmia, hypotension, fulminant liver failure, etc.). Several infusions can be utilized at this point in treatment: midazolam, propofol, ketamine, or pentobarbital. Once

seizure suppression is achieved for 24 h, it is reasonable to begin tapering continuous infusions while on cEEG to monitor for recurrent and rebound seizures, the latter of which are more common with rapid weaning. Recurrent seizures should trigger rebolusing with the infusion and/or switching to another infusion. Antiseizure medications, typically IV formulations due to potential absorption-related issues from ileus or gastroparesis in the setting of anesthetics, can facilitate weaning.

There are several additional options for the treatment of refractory SE that may be utilized if initial therapies are ineffective. Immunomodulatory treatments including high-dose corticosteroids, intravenous immunoglobulin, and plasmapheresis can be considered. These treatments may be useful in NORSE where the cause of seizures is unknown. Therapeutic hypothermia may have anticonvulsant properties; however, only low-grade evidence is available at this time. Ketogenic diet, by means of achieving the state of ketosis, may provide some benefit in seizure termination; however, while studies are promising, they are ongoing. In cases where an irritable foci can be identified, a lesionectomy can be considered. Finally, electroconvulsive therapy remains exploratory and limited to case reports.

Treatment options will vary and may become complex based on patient condition and response (or nonresponse) to therapies. However, there are five general principles to guide the management of SE:

- General supportive care – maintain airway and hemodynamic support
- Achieve cessation of seizure activity
- Prevent seizure recurrence
- Identify and correct the underlying cause, when feasible
- Management of complications resulting from seizures as well as adverse effects from AED therapy

12.4.3 Systemic Complications of Status Epilepticus

Patients suffering from seizures and status epilepticus are at risk for developing a number of systemic complications during the course of their illness. From a respiratory standpoint, hypoxemia can occur from airway obstruction, acute onset neurogenic pulmonary edema, aspiration pneumonia/pneumonitis, and respiratory failure from depressed mental status and failure to protect their airway. In the setting of prolonged ICU stays, patients are also at risk for recurrent mucous plugging, atelectasis, pleural effusions, ventilator-associated pneumonia, pulmonary emboli, and the need for tracheostomy. Cardiac injury may also occur, often manifesting as stunned myocardium (Takotsubo's cardiomyopathy), demand ischemia (Type II MI), or arrhythmias. Medications used to treat status epilepticus can cause hypotension and result in the need for hemodynamic support with pressors when volume resuscitation isn't adequate.

Excessive muscle contraction can lead to the production of lactic acidosis, and if severe, rhabdomyolysis and renal failure hyperglycemia can result from a metabolic stress response or infection in the setting of critical illness and should be appropriately treated with insulin therapies. Hyperpyrexia is also seen secondary to excess metabolic activity from seizures, and patients should be aggressively treated to achieve normothermia, especially in the early phases of acute brain injury.

12.4.4 Prognosis [24–29]

Prognosis will vary with age and etiology of the seizures. Table 12.3 shows a mortality prediction score for SE. Mortality is highly associated with anoxic brain injury, whereas sei-

Table 12.3 Mortality prediction score for status epilepticus [29]

	Features	Score
Level of consciousness	Alert, somnolent, confused	0
	Stuporous or comatose	1
Seizure type	Simple or complex partial	0
	Generalized	1
	NCSE + Coma	2
Age	<65	0
	>65	2
Previous seizures	Yes	0
	No	1
Total		0–6

Using cutoff ≥3 predicts mortality within the following statistical parameters: sensitivity 81%, specificity 65%, PPV 25%, NPV 96%, accuracy 73%

zures from benzodiazepine or alcohol withdrawal has a much lower rate of mortality. Another risk factor for increased mortality risk is no obvious cause and persistent duration of seizures; however outcomes may be marred by the nihilistic fate of the self-fulfilling prophecy when withdrawal of life-sustaining therapy is initiated too early. When compared to convulsive status epilepticus, NCSE is associated with worse outcome. Outcome in RSE, which is often nonconvulsive, is associated with significant mortality (nearly 50%) and morbidity with only a minority of patients returning to previous functional baseline. However, young patients without overt evidence of catastrophic brain injury should be treated aggressively.

Seizures can be traumatizing for anyone to witness. Families may be in a state of shock on initial encounter and may have difficulty comprehending the situation or what is being communicated to them by the healthcare team. Remember to involve the family in discussions in management and goals of care, when appropriate, on a regular basis.

Summary Points

- Seizures are considered a neurologic emergency – always manage airway and hemodynamics first; many seizures can be self-limiting and resolve spontaneously
- NCSE and CSE are common in the ICU and may only be diagnosed with EEG monitoring
- Treatment regimens can be complex and vary from patient to patient; however the general principles of management are the same.
- Prognosis varies widely based on etiology, duration of seizures, and patient's age.
- Families will require significant amounts of resources and support in order to make informed decisions related to the management of the patient.

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Chapter 13
Neurological Infections

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13.1 Introduction

Meningitis and encephalitis are life-threatening central nervous system (CNS) infections or inflammatory states that most advanced practice clinicians (APC) will encounter at some point in their careers, much more so if they practice in the neurocritical care realm. These conditions differ from other infectious processes, such as pneumonia or urinary tract infections, because of the high morbidity and mortality associated not only with the conditions themselves, but also with a delay in the initiation of appropriate empiric therapy. In this chapter we will discuss the diagnosis and management of this constellation of diseases from initial presentation to initial management goals and ongoing tailoring of therapies as more data becomes available. We will also

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dive deeper into the epidemiology of the most common etiologies with specific considerations if a specific pathogen or etiology is suspected.

Meningitis is defined as the inflammation of one, two, or all three meningeal layers: the dura, arachnoid, and pial membranes. Encephalitis is an inflammation of the brain parenchyma. An inflammation that includes both the brain and the spinal cord is called encephalomyelitis. The etiologies of these CNS inflammatory states can be divided into infectious and noninfectious. Infectious etiologies underlying CNS inflammation include bacterial, viral, and, more rarely, fungal and parasitic. Presentations vary widely and depend on the etiology and progression of the disease. A timely assessment for the possibility of CNS infection is of the utmost importance, as initiation of treatment is emergent, and a delay can significantly affect morbidity and mortality.

13.2 Case Presentation

A 28-year-old woman is brought to your emergency department by her roommate because of fever, severe headache, and stiff neck. On initial exam, she is sleepy but arousable and generally ill appearing. Her vital signs are temperature, 38.7 °C; heart rate, 122; blood pressure, 116/60; and respiratory rate, 12. Her neck and back are very stiff and rigid, particularly to flexion and extension. Inspection of her eyes and retina with the ophthalmoscope demonstrates optic nerve head swelling (papilledema). She has no other pertinent findings. Given the high clinical suspicion, emergent empiric antibiotic therapy with vancomycin, ceftriaxone, and dexamethasone is started immediately after the clinical exam and before any other diagnostic method is pursued. A head CT is performed and is read by both you and the radiologist as normal. Her pertinent laboratory values

include a blood white blood cell count of 18,000 with 89% neutrophils. Her serum glucose is 110 mg/dl. A lumbar puncture (LP) is performed, demonstrating a glucose of 33 mg/dl [normal value: 50–100], protein of 123 mg/dl [50–90], a CSF white blood count of 8,000 (90% neutrophils) [0–5], and 6 RBC [0–5]. On gram stain, there are gram (+) diplococci seen. You admit her to the general medicine floor with neurology consult. Her LP culture eventually grows out *S. pneumoniae.* You discontinue the dexamethasone on hospital day 5, and once you get back the sensitivity profile from the LP culture, you narrow to just ceftriaxone. The patient is discharged on hospital day 9 with neurology and primary care provider (PCP) follow-up. Her deficits at the time of discharge were persistent headache and transient short-term memory deficits.

13.3 Initial Evaluation

13.3.1 Presentation

Meningitis presents with fever, severe headache, nausea, vomiting, photophobia, meningeal signs, and, in some cases, decreased level of arousal and papilledema. Encephalitis presents with meningitic signs and symptoms plus focal signs. Myelitis presents with meningitic symptoms plus complete or incomplete cord syndromes. The key difference between patients with a CNS infection and those patients with stroke-like symptoms alone, and from whom you cannot get the stiff neck or headache story from, will often be the patient's temperature. In a recent study of 696 patients with community-acquired bacterial meningitis, the mean initial temperature was 38.8 °C, and fully 77% were febrile at initial presentation. In a large pooled study of patients with meningitis, 95% had two of the three symptoms of the classic triad of symptoms of

meningitis: fever, stiff neck, and change in mental status [27]. Bacterial meningitis will have a rapid and severe progression, usually a matter of hours. Manifestations of viral meningitis or encephalitis are more subtle, with possibly days of worsening symptoms before presentation to the emergency department.

13.3.2 Stabilization

The initial management of a patient admitted to the emergency room with suspected CNS infection begins the same as with any other infectious patient. ABCs should be assessed and measures taken to support airway, breathing, and circulation. Vital signs should be measured in triage including core temperature whenever possible. Assessment of neurological status should also be obtained immediately, paying particular attention to the presence of focal neurologic deficits. Two large bore IVs should be placed and an initial liter bolus of normal saline started. Many patients with bacterial meningitis will present with sepsis and septic shock. Therefore, the initial resuscitation of these patients will proceed as any other patient in septic shock. This chapter won't dive into the debate of sepsis care, but fluid resuscitation and if necessary vasopressor initiation (norepinephrine) should be started without delay. In most cases of CNS infection, but particularly in bacterial meningitis, the patient's intracranial pressure (ICP) is usually elevated. Therefore, ensuring an appropriate mean arterial pressure and cerebral perfusion pressure is paramount. Initial laboratory studies of peripheral blood should include cultures, CBC with differential, chemistries, serum lactate, and coagulation studies. If the patient is capable of giving a history, particular care should be taken to elicit the timing of the illness. Refer to Fig. 13.1 for suggested diagnostic and therapeutic approach for suspected CNS infection.

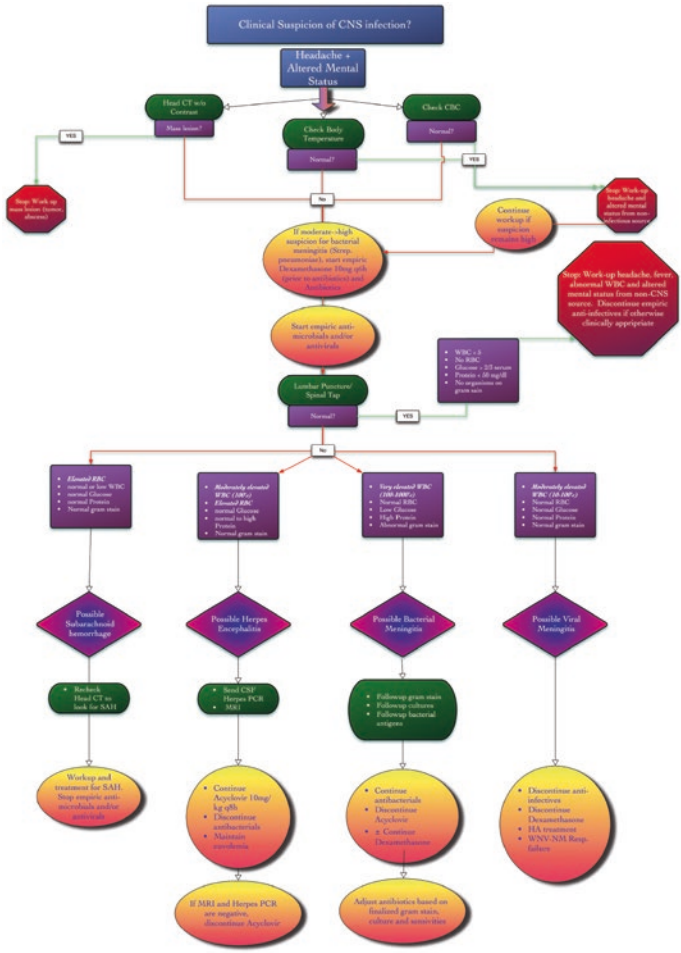

Fig. 13.1 Neurological infection workup and management algorithm

13.3.3 Empirical Antimicrobial Therapy

The next step in the management of CNS infections is to start antibiotic treatment. Antibiotics should be started immediately after completing the physical exam, even before obtaining a CT scan and performing an LP. Importantly, timely administration of appropriate antimicrobial therapy improves both morbidity and mortality. A retrospective case record study of 119 patients diagnosed with adult acute bacterial meningitis aged greater than or equal to 16 years assessed the association between meningitis mortality and door-to-antibiotic time. If appropriate antibiotic therapy was delayed 6–8 h mortality rose to 45% and if delayed to the 8–10 h range the mortality increased to 75% [20]. In ICU patients with community acquired pneumococcal meningitis, in-hospital antibiotic delay exceeding 3 h was the strongest indicator of mortality, with a 14-fold increase in the mortality risk over the group receiving antibiotics in less than 3 h of admission [3]. Another study found that in the first 12 h from admission, the odds for an unfavorable outcome increased 30% with every hour that antibiotics were delayed [17].

The significant predictors for delay in initiation of antibiotics were found to be no antibiotic prior to transfer from another hospital; the diagnostic–treatment sequence of CT of the head followed by lumbar puncture followed by antibiotics; partial meningitis treatment; and absence of the meningitis triad at presentation/atypical presentation, lack of fever, and patients with concomitant pneumonia [3, 20].

Choice of initial antimicrobial therapy will differ between institutions based on formulary availability; generally speaking, for adult patients with normal renal function, the empiric regimen of choice includes:

- Vancomycin 15–20 mg/kg IV every 12 h
- Ceftriaxone 2 G IV every 12 h (or alternative third-generation cephalosporin at CNS dosing)

- +/− Acyclovir 10–15 mg/kg IV every 8 h for suspected (when encephalitic signs are present). In patients with a prior history of severe penicillin allergy, vancomycin and trimethoprim–sulfamethoxazole is a reasonable first-line regimen, with acyclovir for those with suspected viral encephalitis. Many institutions have fairly rapid polymerase chain reaction (PCR) testing for the most common viral causes of meningitis, so you should feel comfortable starting acyclovir empirically, knowing that you will likely have a confirmatory or rule out result soon. Older and immunocompromised adults are at higher risk of *Listeria monocytogenes* and should be prescribed ampicillin in addition to the agents listed above.

13.3.4 Dexamethasone

There is evidence for the use of dexamethasone in bacterial meningitis, particularly in CNS infections caused by *Streptococcus pneumoniae*. One trial enrolled 301 patients with the treatment group receiving 10 mg of dexamethasone every 6 h for 4 days [8]. Note that the first dose was given prior to, or at the time of, antibiotic administration. The trial demonstrated significant improvement in outcome in those patients receiving dexamethasone. This improvement in outcome and decrease in mortality was almost exclusively in the group of patients that were identified as having pneumococcus. Analysis for different bacteria causing meningitis showed that patients with meningitis due to *Streptococcus pneumoniae* (*S. pneumoniae*) treated with corticosteroids had a lower death rate (29.9% versus 36.0%), while no effect on mortality was seen in patients with *Haemophilus influenzae* (*H. influenzae*) and *Neisseria meningitidis* (*N. meningitidis*) meningitis. Dexamethasone increased the rate of recurrent fever, but was not associated with other adverse events [4].

In situations where it is clearly evident that the suspected organism is not *S. pneumoniae*, dexamethasone may be withheld.

Otherwise, empiric use of dexamethasone until cultures return is reasonable [11]. The Infectious Disease Society of America's practice guidelines state: "some authorities would initiate dexamethasone in all adults with suspected bacterial meningitis because the etiology of meningitis is not always ascertained at initial evaluation" [26]. Patients should be given 10 mg of IV dexamethasone immediately and every 6 h thereafter for a duration of 4 days [8]. Ideally, the steroid should be given prior to or at the start of antibiotic therapy [11, 26]. The rationale for dosing the dexamethasone prior to antibiotic administration is to diminish the inflammatory response triggered by endotoxins from bacterial lysis that occurs following antibiotic administration.

13.3.5 Imaging

Early on in the workup of this type of patient an emergent noncontrast head CT should be ordered. In the management of the patient with a suspected CNS infection, certain findings on head CT such as subarachnoid or intraparenchymal hemorrhage or mass lesion which adequately explain the patient's neurologic deficits will abort the workup for CNS infection and the provider should proceed with management of the alternate diagnosis found on the CT. The initial antimicrobial orders can then be canceled as they will not significantly affect the ongoing management of a bleed or lesion.

If the patient's head CT is grossly normal, the provider should proceed with lumbar puncture as soon as possible. Various studies have been done on CSF analysis after antibiotic administration and show that even the most antibiotic-sensitive pathogens will still be present and culturable in CSF for the first 4 h after antibiotic administration. Collection of CSF for culture and immunohistochemical testing for viral and other rarer pathogens will be the single greatest driver of antimicrobial therapy adjustment going forward, as it is always best to narrow your antimicrobial regimen as early as possible to avoid very real medication side effects.

13.3.6 Lumbar Puncture

Ideally a lumbar puncture (LP) would be performed prior to antibiotic administration. Administration of antibiotics prior to performing an LP raises the issue of the diagnostic value of the CSF examination. Gram stain has 92% sensitivity and greater than 99% specificity in diagnosing bacterial or fungal meningitis in those who have received no treatment [9]. Michael et al. show that CSF culture is still likely to be positive in adults with bacterial meningitis if the LP is performed within a few hours of starting the antibiotics. Beyond 4 h, the chance of positive cultures drops significantly, and beyond 8 h, no culture was positive [18]. Another study also found that beyond 4 h after antibiotic administration, chances of a positive CSF culture are low [14].

Performing a lumbar puncture before obtaining a head computed tomography (CT) is a source of controversy due to the risk of brain herniation which may occur in patients with elevated intracranial pressure and or mass-occupying lesions. A CT scan of the brain is typically not required or needed to diagnose bacterial meningitis, but it is useful in excluding other diagnoses. CT is also useful for excluding mass-occupying lesions that might complicate the lumbar puncture done for diagnosis. There is minimal evidence supporting the need for a CT scan of the brain prior to LP. Somewhere between 3% and 5% of patients with meningitis develop fatal herniation syndromes within the first 7 days of hospitalization, around 60% of those within the first hours post LP [10]. There are also studies demonstrating that normal CT scans do not eliminate the risk for herniation nor do abnormal CT scans predict herniation after LP [12].

Head CT should be expedited prior to lumbar puncture in patients with any of the following: altered mental status, focal neurologic deficits, papilledema or loss of venous pulsations on fundoscopic examination, new onset seizures or a history of CNS disease such as stroke or intracranial mass lesions, and known or

suspected immunosuppression [26]. Unfortunately, from a diagnostic standpoint, most patients who present with symptoms consistent with acute bacterial meningitis will likely meet criteria for a head CT prior to LP.

13.3.6.1 Opening Pressure

The opening pressure is usually elevated in cases of bacterial meningitis. Over 80% of patients have an opening pressure greater than 20 cm water, and 20–40% of patients have an opening pressure greater than 40 cm water [10, 27]. Some recommend that if the spinal fluid pressure is found to be greatly elevated (i.e., greater than 40 cm water), the needle stylet should be left in place and mannitol administered. The risk is that with such an elevated pressure, the CSF will continue to leak from the LP site and increase the risk of herniation. It may be prudent to recheck the pressure after a few minutes to determine that it has declined, before removing the needle [11].

13.3.6.2 CSF Analysis

A 12-year study of 100 patients aged 16 years or older found that the vast majority exhibited some degree of CSF leukocytosis; approximately 10% of quantified samples had CSF leucocyte counts of <100 white blood cells/millimeter^3 (WBC/mm^3), 90% had counts >100 WBC/mm^3, and 56% had greater than or equal to 1,000 WBC/mm^3, with about 14% of all samples exceeding 10,000 WBC/mm^3. Ninety percent of differentiated samples displayed neutrophil predominance. Seventy-eight percent of all CSF samples were cloudy [13].

Gram staining of CSF revealed no bacteria in 53% cases; of those, 47% subsequently became culture positive for a total of 64% culture-positive CSF. Around 78% of the patients were either CSF and/or blood culture positive [13]. Almost all patients will have CSF protein levels above 45 mg/dL, with 66%

above 200 mg/dL [10, 13]. Ten percent of positive cerebrospinal fluid smears were misinterpreted. The most frequent error (occurring in 7 of 17 cases) was misidentification of listeria as *Strep pneumoniae* [10].

One study found that half of all patients had hypoglycorrhachia (defined as CSF glucose <40 mg/dL). In another study 70% of patients had hypoglycorrhachia, defined as glucose less than or equal to 50 mg/dL; of the cases with CSF glucose >50 mg/dL, 55% had levels less than or equal to 50% of serum values at the time of collection [10, 13].

See Tables 13.1 and 13.2 for summary of initial CSF evaluation and results.

Table 13.1 Initial CSF studies

Tube 1	Cell count and differential
	Gram stain and cultures
Tube 2	Glucose
	Protein
	Lactate
Tube 3	HSV PCR
	VZV PCR
Tube 4	Cell count and differential

Table 13.2 CSF values for most common diagnoses

	Glucose	Protein	WBC's	Lymphocytes	Neutrophils	RBC's
Normal CSF	50	50	<5	<5	<5	0[a]
Bacterial meningitis	− −	+	(+ +) 1 k–10 k+	+	+++	0
Viral encephalitis (HSV, EVB, VZV, WNV, etc.	50 or (−)	+	(+) 100–1 k	+ +	+	0 or (+ in HSE)
Aseptic meningitis *aka* viral meningitis	50 or (−)	+	(+) 100–1 k	+ +	+	0
Subarachnoid hemorrhage	(−)	+	(+)	+	+	(+++) 1 k to >1 m

[a]In traumatic tap will be high in tube 1 and low to 0 in tube 4

13.3.7 Differential Diagnosis

There are many differential diagnoses for patients with suspected CNS infection (Table 13.3). Bacterial meningitis is at the top, followed by non-bacterial meningitis, usually referred to as aseptic meningitis (a vast majority of which are viral). Patients with aseptic meningitis have clinical and laboratory evidence for meningeal inflammation inconsistent with bacterial infection and bacterial cultures of CSF that are negative. Encephalitis and intracranial abscess or empyema can have similar presentations. Additional etiologies include other non-bacterial infections (mycobacteria, e.g., tuberculosis and other mycobacterium (very rare), fungi, protozoa, e.g., amoeba, trypanosomes, malaria, toxoplasma, and helminths (parasitic worms), e.g., trichinosis, cysticercosis), but these

Table 13.3 Differential diagnoses for CNS infection

Diagnosis	Clinical features
Bacterial meningitis	Toxic appearing, very low CSF glucose
Aseptic meningitis	Slower onset than bacterial, days not hours
Viral encephalitis	History of HSV, isolated mental status changes, seizures
Chemical meningitis	Difficult to diagnose, many times is misdiagnosed as psychosis and patients often get admitted to psychiatric units, can be due to NSAIDs, anti-tNFa drugs, seizure medications (lamotrigine or carbamazepine)
Brain abscess/ subdural empyema	Usually has history of distinct vector: neurosurgery, dental procedure, sinusitis, recurrent otitis media, and endocarditis but can also be hematogenous in the immunocompromised patient
Subarachnoid hemorrhage	Thunderclap headache, severe instantaneous decline in mental status, “worst headache of my life”
Migraine/atypical migraine	Usually unilateral with associated photophobia / phonophobia

are quite rare. There are also noninfectious causes of meningeal symptoms which include subarachnoid hemorrhage, postictal state, complex migraine headache, brain tumors, carcinomatosis, cysts, illicit drug, or alcohol intoxication. Although rare, there are also prescription drug-related cases of aseptic meningitis, also known as chemical meningitis, including from antibiotics, particularly trimethoprim-sulfamethoxazole, trimethoprim alone, and amoxicillin; NSAIDs, especially ibuprofen; immunosuppressive immunomodulatory drugs including monoclonal antibodies, (mainly tumor necrosis factor inhibitors) and intravenous immunoglobulins; and the antiepileptics lamotrigine and carbamazepine [19].

13.3.8 Disposition

Most of these patients will require ICU care and monitoring, even if mechanical ventilation or hemodynamic support with vasopressors is not needed.

13.4 Interventions and Management

13.4.1 Community-Acquired Bacterial Meningitis (CABM)

13.4.1.1 Epidemiology

In adults, the annual incidence of CABM in the United States is between two and six cases per 100,000 persons [24, 27]. Mortality from bacterial meningitis can be as high as 34% [28] and is highest with *Streptococcus pneumonia*e and *Listeria monocytogenes*.

Long-term neurologic deficits occur in about half of all patients [8, 22, 33]. Bacteria reach the subarachnoid space via the bloodstream and less often from a contiguous infection such as from the ears or sinuses. The predominant causative organisms are *Streptococcus pneumonia*e (pneumococcus) and *Neisseria meningitidis* (meningococcus), which are responsible for about 80% of all cases [1, 23, 28].

13.4.1.2 Presentation

Symptoms of acute CABM develop over several hours to 1–2 days with non-bacterial forms of meningitis *generally* being less acute. Because meningitis by definition affects the meninges, there is less likelihood of focal deficits compared to encephalitis or brain abscess. However, as the disease progresses, the brain parenchyma frequently becomes involved in the inflammatory response leading to *meningoencephalitis*. As a result, focal neurologic deficits are seen in about 20–33% of patients on presentation and many more during the course of their illness [3, 13, 27].

Obtain the patient's history, including identifying sources of possible exposure and previous and recent infections. Examine for general symptoms of infection (fever, chills, myalgias, fatigue) as well as for signs suggesting central nervous system infection (photophobia, headache, stiff neck, nausea, vomiting, focal neurologic symptoms, and changes in mental status).

Classic signs of meningeal irritation include nuchal rigidity and Kernig's and Brudzinski's signs. *Nuchal rigidity* is present when the neck resists passive flexion. *Kernig's sign* is elicited with the patient in the supine position. The thighs and knees are flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. *Brudzinski's sign* is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. The presence of Kernig's sign, Brudzinski's sign, or

nuchal rigidity has good positive, but no negative predictive value. One study of 297 patients found that Kernig's and Brudzinski's signs had poor sensitivity (5%) but high specificity (95%), while nuchal rigidity had a sensitivity and specificity of 30% and 68%, respectively [25].

The absence of all three signs of the classic triad of fever, neck stiffness (nuchal rigidity), and an altered mental status virtually eliminates a diagnosis of meningitis [2]. In a nationwide prospective study of 696 adults with CABM [27], the classic triad of fever, nuchal rigidity, and a change in mental status was present in only 44% of patients. However 95% of patients with CABM had at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status. There was headache in 87% of cases, nuchal rigidity in 83%, fever (>38 °C) in 77%, and impairment of consciousness (<14 on the Glasgow Coma Scale) in 69% of cases. Hypothermia can also be consistent with CNS infection.

13.4.1.3 Treatment Monitoring

If there is no clinical improvement after 48 h of antimicrobial therapy, repeat CSF analysis should be performed [26]. Resolution of hypoglycorrhachia and reduction of the cerebrospinal fluid lactate level are the earliest indicators of improvement [7]. Rule out persistence of source of primary infection, e.g., pneumonia, bacterial endocarditis, mastoiditis, or otitis, and consider secondary infection [6]. Another mainstay of therapy is narrowing of antimicrobial spectra based on PCR, culture, and repeat culture data. All antibiotics and antimicrobials have side effects, and the patient with suspected CNS infection will be getting big doses of multiple agents until further data can drive the narrowing of therapy. Whenever possible, narrow therapy. This will help prevent secondary infections, antibiotic resistance, and even antibiotic-induced delirium.

13.4.1.4 Seizures

Seizures occur in 15–23% of patients with bacterial meningitis [13, 27]. Electroencephalographic (EEG) monitoring, especially in patients with history of seizure or fluctuating mental status, should be considered [28]. Although the need for an anticonvulsant as seizure prophylaxis for all patients with bacterial meningitis is not clear, the use of anticonvulsants is warranted once clinical or electrographic evidence of seizure is noted.

13.4.1.5 Hydrocephalus

Acute hydrocephalus occurs in 3–8% of cases of bacterial meningitis [28]. Hydrocephalus can develop because the flow of cerebrospinal fluid may be blocked at the third or fourth ventricles due to tissue swelling from inflammation (obstructive hydrocephalus) and/or due to exudate from the infection interfering with CSF reabsorption at the arachnoid villi (communicating hydrocephalus). Elevated opening pressure may suggest the presence of hydrocephalus, and the diagnosis is confirmed by cranial imaging. A repeat lumbar puncture, ventriculostomy, or ventricular shunt placement should be considered to treat acute hydrocephalus or elevated intracranial pressure [21, 26, 28].

There have been no randomized clinical trials published in regard to treatment of increased intracranial pressure without hydrocephalus. Any literature available is inconclusive. It is unclear whether treating intracranial hypertension with hypertonic agents such as mannitol or hypertonic saline is useful, as the impaired blood–brain barrier associated with meningitis which may reduce their utility. Therapeutic hypothermia has been tested for ICP control. Although hypothermia does lower ICP, the outcomes generally were not better and possibly even worse. The methodology was also questionable. However, given what we know about fever and the increased metabolic demands

of the brain and the associated increased ICPs, maintaining euthermia may be a safe and helpful strategy.

13.4.1.6 Dysnatremia

Approximately 25–28% of patients with bacterial meningitis develop hyponatremia [28]. Etiologies of hyponatremia can be multifactorial, such as salt wasting, SIADH, or adrenal insufficiency. Transient diabetes insipidus has been known to occur with bacterial meningitis, but it is uncommon. Most causes of hypernatremia are related to fluid resuscitation, insensible losses, etc.

Frequent electrolyte monitoring and correction are recommended. See Chap. 23 *Common Complications in the Neuro ICU* for more information on evaluation and treatment of dysnatremias.

13.4.1.7 Others

Raised intracranial pressure from cerebral edema or obstructive hydrocephalus is a rare, but serious and life-threatening complication of meningitis. If one of these pathologies is suspected based on clinical exam (acute decline in mental status, papilledema on fundoscopic exam, or Cushing's response), expeditious neuroimaging should be obtained and measures taken to treat increased intracranial pressure. Please refer to the Chap. 11 for further details. Vascular complications (arteritis or venous sinus thrombosis) leading to cerebral ischemia again are rare but very serious complications. These are very difficult to diagnose clinically and require CT angiogram or venogram vs. digital subtraction angiography or MRI/MRA/MRV to diagnose. In such cases close consultation with vascular neurology or vascular neurosurgery will be crucial. Failure of appropriate response to appropriate antimicrobial therapy

should also raise your suspicion for epileptic seizures (specifically: non-convulsive status epilepticus (NCSE)) and would warrant routine or continuous electroencephalography (EEG.) In patients in closely monitored units who you are suspicious of NCSE, a trial dose of benzodiazepine would be reasonable (lorazepam or midazolam.) And finally, always consider persistence of source of primary infection (e.g., pneumonia, bacterial endocarditis, mastoiditis, or otitis) [6].

13.4.1.8 Prognosis

Indicators of poor outcome include the presence of symptoms for less than 24 h before admission, seizures, pneumonia, an immunocompromised state, a heart rate below 60 bpm or greater than 120 bpm, and hypotension (defined as a diastolic blood pressure of less than 60 mm Hg). The causative organism has been shown to have an independent effect on outcome with an unfavorable outcome being six times that among patients infected with *S. pneumoniae* compared with patients infected with *N. meningitidis*, even after adjustment for other clinical predictors [27]. The average mortality rate in this study was 21% and varied depending on the causative organism; it was 30% for pneumococcal meningitis, compared with 7% for meningococcal meningitis and 20% for meningitis due to other pathogens. The most common neurologic deficits identified were hearing loss and hemiparesis [27]. However cognitive dysfunction, behavioral changes, seizures, and motor impairment are additional common complications of meningitis.

13.4.1.9 Immunizations

There are at least 12 serogroups of *Neisseria meningitidis*. Serogroups A, B, C, W, and Y cause most meningococcal dis-

ease, and there are vaccines for all five. Recently approved by the FDA in Oct 2014 and Jan 2015 are two new *Neisseria meningitidis* serogroup B vaccines known as Meningococcal B or MenB. Previously established vaccines for causative agents include Meningococcal ACWY (MenACWY), Pneumococcal conjugate vaccine 13-valent (PCV13), Pneumococcal polysaccharide vaccine 23-valent (PPSV23), and *Haemophilus influenzae* type B vaccine (Hib). All of these vaccines are included in the CDC's Advisory Committee on Immunization Practices (ACIP), recommended immunization schedules. *Haemophilus influenzae* type B was historically most common cause of CABM, mostly affecting young children. However, since the introduction of the Hib vaccine in 1985, the number of cases of invasive Hib disease (not specifically meningitis) has decreased by more than 99% in children under the age 5 according to the CDC. Many more cases of community-acquired bacterial meningitis can be prevented with proper vaccination [5, 15].

13.4.2 Nosocomial Bacterial Meningitis

Nosocomial bacterial meningitis is usually the result of an invasive procedure, e.g., intracranial surgery, internal or external ventricular catheter placement, lumbar puncture, and intrathecal infusions – including spinal anesthesia, complicated head trauma (complicated requires intracranial neuroimaging abnormalities), or rarely as a complication of hospital-acquired bacteremia [4, 30].

There is a broad spectrum of causative organisms in the hospital setting. Meningitis from an invasive procedure is most often caused by one or more the following: *Pseudomonas aeruginosa, Staphylococcus aureus*, *Staphylococcus epidermidis*, *Propionibacterium acnes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *group A beta-hemolytic Streptococci*, *Enterococci spp.*, and *Acinetobacter spp.* [16, 29]. The key point being that broad-spectrum antibiotic coverage should be started urgently to include

coverage of gram-negative and atypical organisms in addition to typical organisms. If there is access to CSF via an existing invasive device, a sample should be collected prior to initiation of the antibiotics. Or alternatively, an LP can be safely performed without delay to aid in diagnosing the infectious species.

13.4.3 Acute Encephalitis

A variety of different organisms, such as herpes simplex virus, arbovirus, rabies, and listeria can cause encephalitis. The most common cause of sporadic fatal encephalitis in the United States is herpes virus (HSV). HSV encephalitis occurs in patients previously infected with either HSV 1 or 2 and is a reactivation of the dormant virus. Cases of HSV encephalitis tend to have higher incidence of seizure versus bacterial meningitis, and such a finding can be a helpful clue in differentiating the HSV encephalitis patient. HSV encephalitis also has characteristic MRI findings which will further confirm or heighten your suspicion for the disease. MRI findings in HSV encephalitis may include parenchymal T1 enhancement after gadolinium and/or T2 hyperintensity in limbic structures including the insula, temporal lobe, cingulate gyrus, and orbitofrontal regions including the gyrus rectus [32]. As encephalitis can present similarly to meningitis, the initial approach to diagnosis and empiric treatment should be initiated as discussed in above Sect. 13.3.

13.4.3.1 Neuroimaging

The CT scan of a patient with herpes simplex virus (HSV) may rarely show mass effect and low density in the temporal lobes. There may also be increased density consistent with a hemorrhagic lesion. The classic MRI abnormality in HSV-1 encephalitis is high signal on T2-weighted images of the medial and inferior

temporal lobe often extending into the insula. HSV also has a predilection for the inferior frontal lobes. Gadolinium enhancement around the periphery of the infection may also be seen.

13.4.3.2 CSF Examination

In the CSF of those patients with HSV encephalitis, the opening pressure may be elevated. The cell predominance is typically lymphocytes rather than the neutrophil predominance of bacterial meningitis. Note should be made, however, that early in the course of the infection, the cell counts can have as many as 40% neutrophils. Red blood cells and/or xanthochromia may be present. The protein content is typically elevated beyond 50 mg/dL but may be normal in up to 25% of patients. The culture and gram stains are negative. Herpes PCR has a sensitivity of 95% with a specificity approaching 100% [9]. One study of 43 patients with herpes encephalitis diagnosed by brain biopsy or necropsy showed positive PCRs for fully 5 days after initiation of acyclovir [9].

Treatment of HSV encephalitis includes acyclovir, standard dosing 15 mg/kg q8 hours. High-dose acyclovir has been known to cause acute renal dysfunction, so it is important to ensure adequate hydration and closely monitor renal function though the duration of prescribed therapy.

Other forms of viral encephalitis, such as those caused by the arboviruses, may also have a subacute presentation. There are no pharmacotherapeutic interventions for these encephalitides, but until exclusion of HSV can be verified, empiric acyclovir is reasonable. For suspected CNS infections that evolve over days in an immunosuppressed patient, fungal meningitis should be considered. Prior history of the CNS disease or systemic fungal infections and rapid disease progression should raise the index of suspicion for fungal meningitis. Empiric amphotericin B should be administered in these cases during diagnostic testing.

13.4.4 CNS Space-Occupying Infective Lesions

Examples of space-occupying lesions of the central nervous system include parenchyma abscesses, epidural abscesses, and empyemas. Because the treatment of subdural empyema is emergent neurosurgery, it is important for the clinician to recognize not only the classical triad (sinusitis, fever, and neurologic deficit) but the signs of cortical inflammation such as focal deficits (75%), seizures (50%), and raised intracranial pressures such as headache, vomiting, and papilledema (50%) [31].

13.4.4.1 Brain Abscess

Treatment of brain abscess is both surgical and medical. Abscesses greater than 2.5 cm in diameter or those associated with mass effect require CT-guided aspiration or excision. Brain imaging should be followed with repeat scans every 1–2 weeks. In patients not considered surgical candidates, such as those with associated ependymitis or meningitis, hydrocephalus requiring shunting, or those with inaccessible abscesses, medical treatment alone can be attempted. Broad-spectrum antibiotics are used with, initially, weekly brain imaging. This can be spaced out to every 2 weeks during the remainder of the 6–8 week antibiotic course, with follow-up scans every 2–4 months for the following year to assess for recurrences. Empiric drug regimens for immunocompetent patients should include vancomycin, metronidazole, and cefotaxime, typically for 6–8 weeks.

In immunosuppressed patients, treatment should be more individualized depending on relative suspicion for specific entities. In patients who have not been receiving prophylactic therapy who have positive toxoplasmosis serology, empiric treatment with pyrimethamine and sulfadiazine (or clindamycin in those

with sulfa allergies) is reasonable with repeat brain imaging to assess response.

Diagnostic testing may be helpful in differentiating infection from neoplasm. For instance, there will be increased uptake of thallium-201 on SPECT scan in lymphoma, but not in toxoplasmosis. Cerebrospinal fluid polymerase chain reaction (CSF PCR) for the John Cunningham virus (JC virus) formerly known as the *papovavirus* can be helpful in differentiating progressive multifocal leukoencephalopathy (PML) from other lesions in AIDS patients. As the presence of Epstein–Barr virus by PCR in CSF highly correlates to lymphoma, this may add diagnostic value to the evaluation of focal brain lesions in AIDS patients. In other immunosuppressed patients, such as those with neutropenia or those who are post-transplantation, amphotericin B should be empirically used given the high rates of fungal infections, specifically aspergillosis, in this population [8]. Lumbar puncture should not be performed in those with brain abscesses given the risk of herniation.

13.4.4.2 Subdural Empyema

The treatment of subdural empyema is neurosurgical. Treatment within 72 h of symptom onset resulted in less than 10% disability among patients, whereas 70% of patients died or were disabled if the treatment was prolonged beyond 72 h [23].

13.4.5 Postoperative Neurosurgical Infections

Among cases of meningitis that develop in patients after craniotomy, approximately one third occur in the first week after surgery, one third in the second week, and one third after the second week, with some cases occurring years after the initial surgery [16]. Treatment depends largely on source control and whether further

neurosurgical intervention is required. If surgery is not required, these infections are treated like any other meningitis.

13.4.6 Ventriculostomy Infections

Many conditions treated in the neurocritical care setting eventually require placement of an external ventricular drain (EVD) for measurement and control of ICP. Of note, 0–30% (with an average of about 12%) of these catheters result in ventriculitis. Several risk factors have been identified in the development of CNS infections after implantation of an EVD. Factors leading to an increased risk for infection include:

- Intraparenchymal hemorrhage, especially with intraventricular extension
- Repeated sampling or irrigation of the system
- The number of attempts needed to pass the catheter into the ventricular system
- Systemic infection

Although it is clear that the longer a catheter remains in place the higher chance there is of an infection, it is also evident that prophylactic changing of the catheter is of no benefit [31]. Care bundles have been shown to be effective in reducing EVD infection rates and include measures such as maintaining a closed drainage system whenever possible, use of antibiotic-coated catheters, and strict adherence to sterile technique during insertion regardless of setting. See Chap. 23, for example, of EVD care bundle.

Once EVD-associated meningitis/ventriculitis is confirmed, treatment of the infection is similar to that of standard meningitis with three main caveats. First, the offending EVD should be removed at the earliest possible instance. If the patient requires extraventricular drainage of CSF, a new catheter should be placed in another site if possible. Second, since this infection is nosoco-

mial, coverage for *Pseudomonas* should be considered with agents such as cefepime or meropenem. And third, given the higher bacterial burden in the CSF of EVD-associated infections, there may be a role for intrathecal antibiotics, usually vancomycin and or gentamicin depending on the offending organism. This extreme measure should be done in close consultation with the entire care team from pharmacy, to neurosurgery, and infectious diseases.

Summary Points

- CNS infections are life-threatening conditions that require prompt recognition and early treatment to minimize morbidity and mortality.
- Initiation of treatment should not be delayed for diagnostic evaluation and should include broad-spectrum antibiotics, and antivirals until the causative organism is identified with the addition of dexamethasone if infection with *S. pneumonia* is suspected.
- Lumbar puncture for CSF analysis is the most useful diagnostic tool in evaluating for CNS infection and guiding treatment from broad empiric therapy to targeted management. Studies should include differential cell count, culture, protein, and glucose evaluation as well as viral PCR studies for VZV and HSV.
- Space-occupying infectious CNS lesions require emergent neurosurgical intervention until proven otherwise as well as prolonged antibiotic therapy for curative treatment.
- CNS infections often cause serious and even life-threatening complications ranging from increased ICP to seizures. Close monitoring and early aggressive treatment for such complications is a mainstay of CNS infection management.

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Chapter 14
Brain Tumors

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14.1 Introduction

Brain tumors encompass a wide range of clinical entities, including primary and metastatic lesions and benign and malignant pathologies. Although they are not nearly as prevalent as other neoplasms, brain tumors often require complex, multidisciplinary care. Furthermore, patients with brain tumors frequently require intensive care unit (ICU) management, both at time of initial presentation and in the post-operative period. Primary brain tumors include lesions that originate in the central nervous system (CNS); in contrast, metastatic (or secondary) brain tumors originate outside of the CNS (Fig. 1).

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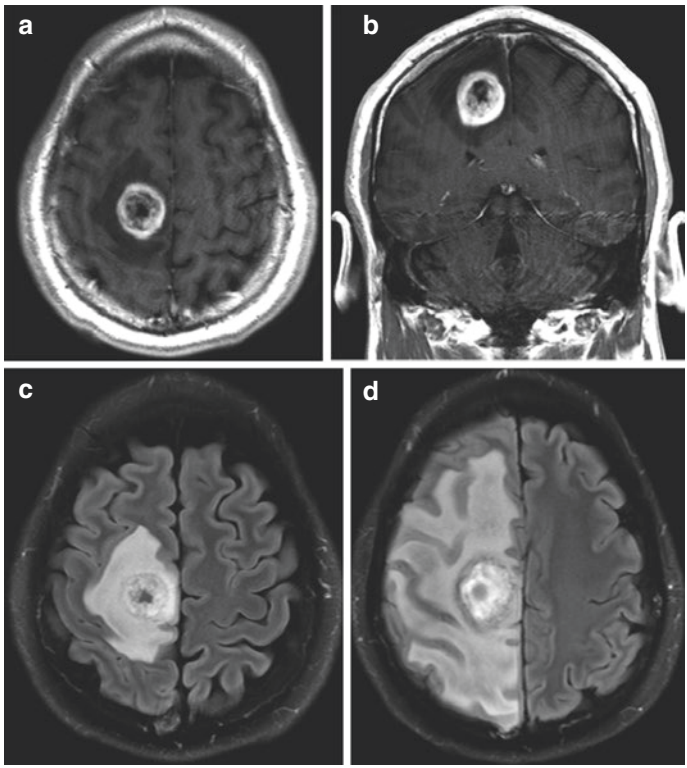

Fig. 14.1 Case 1 Imaging. (**a**, **b**) Pretreatment axial and coronal T1 post-contrast MRIs demonstrate a ring-enhancing intra-axial mass with central necrosis. (**c**) Pretreatment axial FLAIR MRI demonstrates surrounding vasogenic edema that was managed with corticosteroids. (**d**) Posttreatment axial FLAIR MRI demonstrates a significant increase in vasogenic edema, which is now diffuse and encompasses the majority of the right cerebral hemisphere

According to Central Brain Tumor Registry of the United States, the annual incidence of primary CNS tumors is 22.36 cases per 100,000 people. Thus, it is estimated that there will be ~79,270 new cases of primary CNS tumors diagnosed in the

United States (USA) in 2017. This includes both malignant (~26,070 new cases) and benign (~53,200 new cases) pathologies. The most common malignant primary CNS tumor is glioblastoma (GBM), a highly aggressive type of glioma that arises from glial cells. The most common benign primary CNS tumor is a meningioma, which arises from the arachnoid cap cells of the meninges. In the United States, ~17,000 deaths will be attributed to primary malignant CNS tumors in 2017 [1].

Metastatic CNS neoplasms are much more common than primary CNS neoplasms. It is estimated that 100,000 new cases of metastatic brain tumors are diagnosed in the United States each year. Furthermore, approximately 20–40% of cancer patients will develop brain metastases at some point in their disease course. The most common cancers to metastasize to the brain include lung, breast, and melanoma [2].

Patients with brain tumors present to medical attention with a wide variety of signs and symptoms, depending on the size and location of the tumor. Tumors in relatively ineloquent locations (i.e., right frontal pole) often grow to a large size and present with generalized signs of mass effect such as headache, nausea/vomiting, and fatigue. In contrast, tumors in highly eloquent locations (i.e., left frontal operculum) may present at a much smaller size by causing focal neurologic deficits. Brain tumor patients also commonly present with seizures, vision changes, cognitive decline, sensory or motor deficits, and ataxia.

In general, treatments for brain tumor patients are directed toward two synergistic goals: improvement of neurologic function and improvement of oncologic outcome. These treatments can include surgical resection, chemotherapy, radiation, and medical management. Benign tumors are most often treated with surgical resection alone, although radiation may be required for surgically inaccessible skull base tumors. Malignant tumors most often require a combination of surgical resection, chemotherapy, and radiation. In this chapter, we will focus our attention on reviewing the management of common critical care issues that occur in brain tumor patients.

14.2 Case Presentations

14.2.1 Case 1

Thirty-eight-year-old right-handed male presents to medical attention with a rapidly progressive left hemiparesis. Intracranial imaging revealed a right frontal, intra-axial, enhancing mass lesion within the subcortical motor pathway (Fig. 14.1a–c). The patient was started on high-dose dexamethasone (10 mg initial bolus, followed by 4 mg every 6 h) and noted to have improvements in his motor exam the next day. Due to the location of the lesion, a stereotactic biopsy was performed; pathology revealed a glioblastoma. The patient was subsequently treated with adjuvant chemotherapy (temozolomide) and radiation, and steroids were slowly tapered.

Approximately 3 weeks later, the patient presented to medical attention with headache, lethargy, nausea/vomiting, and increased left-sided weakness. Repeat intracranial imaging revealed a significant increase in peritumoral edema with new mass effect, midline shift, and early obstructive hydrocephalus (Fig. 14.1d). The patient was admitted to the ICU and started on high-dose IV dexamethasone as well as hyperosmolar therapy (3% saline and mannitol). Within 12 h, he reported improvements in his headaches and had objective improvements in his left-sided strength. He was then started on bevacizumab, with resolution of his headaches. He subsequently resumed his combined chemotherapy and radiation therapy 2 weeks after admission.

14.2.2 Case 2

Sixty-one-year-old right-handed female presents to medical attention after experiencing a generalized tonic-clonic seizure at work. Intracranial imaging revealed a large, en plaque right

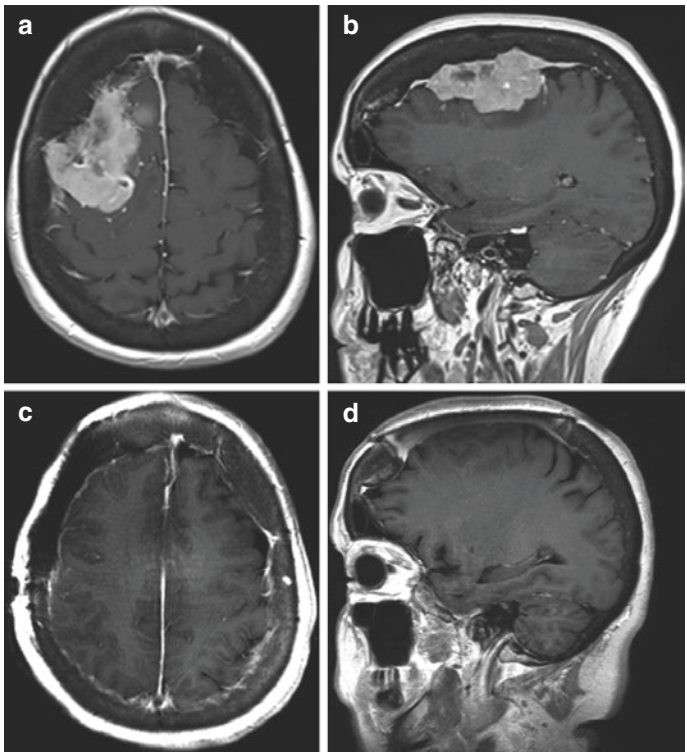

Fig. 14.2 Case 2 Imaging. (**a**, **b**) Preoperative axial and sagittal T1 post-contrast MRIs demonstrate an extra-axial enhancing right frontal mass with a "dural tail" and local mass effect, consistent with an en plaque meningioma. (**c**, **d**) Postoperative axial and sagittal T1 post-contrast MRIs demonstrate gross total resection with resolution of the mass effect

frontal meningioma with hyperostosis of the overlying calvarium (Fig. 14.2a, b). She was started on levetiracetam and taken to the operating room several weeks later for elective surgical resection (Fig. 14.2c, d).

Immediately postoperatively, she remained clinically stable and was neurologically intact. Subsequently, on the first night after surgery, the patient developed focal motor seizures of her left arm. Intracranial imaging was obtained and revealed expected changes, without evidence of hematoma or infarct. The seizures persisted despite several 2 mg boluses of lorazepam and increasing doses of levetiracetam. Over the next several hours, she developed focal status epilepticus and soon became lethargic. She was intubated, started on continuous video EEG, and ultimately required burst suppression with propofol and a fosphenytoin load to control seizures. Approximately 48 h later, the sedation was lifted and the patient was noted to slowly awaken. Over the next 24 h, she became fully alert and was noted to be neurologically intact. She was maintained on levetiracetam and phenytoin and has remained seizure-free.

14.2.3 Case 3

Thirty-two-year-old right-handed female presented to medical attention with a 1-week history of progressive headache, nausea/vomiting, and blurry vision. Intracranial imaging was obtained and revealed a colloid cyst with resultant obstructive hydrocephalus (Fig. 14.3a, b).

The patient was admitted to the ICU and noted to be awake and alert. Given her preserved mental status, an emergent external ventricular drain (EVD) was not required; however, an EVD kit was placed at bedside while operative preparations were made. The patient was started on high-dose IV dexamethasone and taken to the operating room the following morning for resection of the colloid cyst. Postoperatively, the patient had complete resolution of her symptoms; intracranial imaging revealed gross total resection of the lesion and resolution of the hydrocephalus (Fig. 14.3c, d).

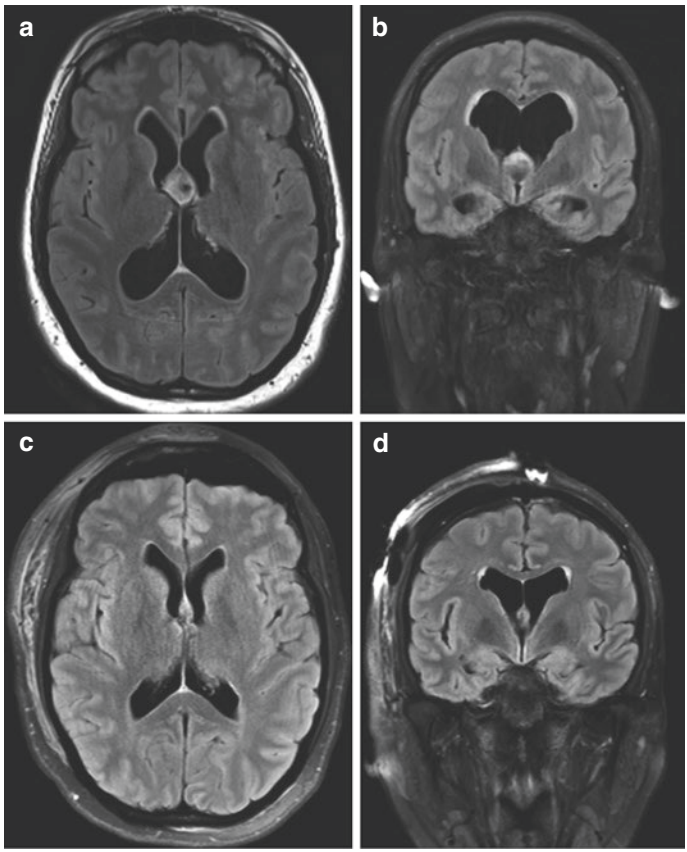

Fig. 14.3 Case 3 Imaging. (**a**, **b**) Preoperative axial and coronal FLAIR MRIs demonstrate an intraventricular mass centered at the foramina of Monro, consistent with a colloid cyst. Note the dilated ventricular system, a sign of obstructive hydrocephalus. (**c**, **d**) Postoperative axial and coronal FLAIR MRIs demonstrate gross total resection with resolution of the hydrocephalus

14.3 Initial Evaluation

As with all neurocritical care patients, the initial evaluation of a brain tumor patient should begin with a thorough neurological exam. In particular, providers should focus on the patient's mental status and assess for the presence or absence of focal neurologic deficits. The initial evaluation should also include a review of the available intracranial imaging, typically a CT and/or MRI. In general, if a brain tumor patient presents in an emergent fashion, a non-contrast CT of the head should be obtained to evaluate for an acute neurologic emergency (i.e., hemorrhage, infarct, herniation). However, in non-emergent cases, the preferred imaging modality is an MRI of the brain with and without contrast, which provides superior delineation of the tumor and brain parenchyma. Most brain tumors have unique imaging characteristics, which help to identify them from one another (Fig. 14.4). Following review of the exam and imaging findings, the patient should be quickly stabilized and treated in accordance with the interventions described below.

14.4 Interventions and Management

14.4.1 Routine Postoperative Management

The majority of brain tumor patients are admitted to the ICU for routine postoperative care. In most hospitals, patients undergoing a cranial tumor surgery will spend one night in the ICU immediately after surgery. This allows for close monitoring and rapid identification of changes in neurological exam. If a change in neurologic status is identified, brain imaging (typically, a non-contrast CT Head) must be obtained expeditiously to

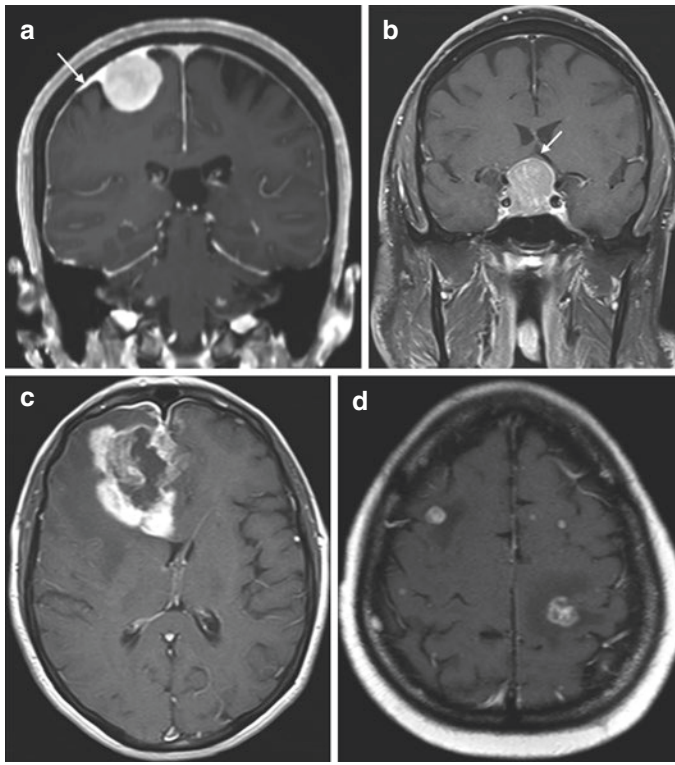

Fig. 14.4 MRI images depicting the most common primary and secondary CNS tumors. (**a**) Coronal T1 post-contrast MRI demonstrating a convexity meningioma. Note the extra-axial location, homogenous enhancement, and presence of a "dural tail" (*arrow*). (**b**) Coronal T1 post-contrast MRI demonstrating a pituitary macroadenoma with suprasellar extension and compression of the optic chiasm (*arrow*). (**c**) Axial T1 post-contrast MRI demonstrating a glioblastoma. Note the intra-axial location, thick peripheral enhancement, and central necrosis. (**d**) Axial T1 post-contrast MRI demonstrating multiple brain metastases. Note the numerous intra-axial enhancing lesions near the grey-white junction with associated vasogenic edema

evaluate for frequent postoperative complications, including hemorrhage, infarct, and pneumocephalus. Additionally, the ICU setting allows for prompt treatment of pain, nausea, and vomiting, symptoms which are common in the first 24 h following cranial surgery. The routine care of most postoperative brain tumor patients includes the administration of intravenous fluids, corticosteroids (most commonly, dexamethasone), narcotics, and antiemetics. Additionally, TED hoses and sequential compression devices are utilized to decrease the risk of deep venous thrombosis. Neurological exams are performed every hour. Systolic blood pressure is typically maintained <140 mmHg (using labetalol, hydralazine, and/or nicardipine). Foley catheters are utilized to record strict urine input and output. A non-contrasted CT of the head is typically obtained 24 h after the procedure to evaluate the surgical cavity. If the CT scan demonstrates expected findings and the neurological exam is stable, the patient can be transferred to the general floor.

14.4.2 Management of Cerebral Edema

Brain tumor patients often present with symptomatic peritumoral edema. Edema is defined as the abnormal accumulation of fluid within tissues. Cerebral edema can be subdivided into two main types: vasogenic and cytotoxic. Cytotoxic cerebral edema occurs when fluid accumulates within cells as a result of injury, most commonly, an ischemic event. Vasogenic edema occurs when a disruption in the blood-brain barrier (BBB) allows plasma proteins and fluid to shift into the brain parenchyma and is commonly associated with brain tumors (particularly high-grade gliomas and metastatic lesions) [3].

Vasogenic edema can be a major cause of morbidity and mortality in brain tumor patients. Significant vasogenic edema may result in elevations in intracranial pressure (ICP), mass effect on critical neurovascular structures, and herniation

syndromes [4]. The initial treatment for vasogenic edema is corticosteroids. Since the 1950s, dexamethasone has been the steroid of choice due to its longer half-life and low mineralocorticoid effects [5]. When starting dexamethasone, most patients are given an initial bolus of 10 mg intravenously, followed by a maintenance dose of 4 mg every 6 h. However, this dosing schedule may vary considerably depending on provider preference. Improvements in neurologic symptoms are typically seen within the first 24 h. Once maximum clinical benefit has been achieved, steroids should be slowly tapered to the lowest effective dose [6]. In addition to their use for symptomatic vasogenic edema, corticosteroids are also used in the immediate postoperative care of brain tumor patients. This practice has been demonstrated to decrease perioperative morbidity and mortality. Typically, patients are placed on a dose of 4–6 mg every 6 h following surgery, and this is tapered over the subsequent 1–2 weeks.

Although corticosteroids have improved clinical outcomes for brain tumor patients, these medications can have significant adverse effects that must be recognized, especially with prolonged use. Although relatively uncommon, these include gastrointestinal (GI) issues (bowel perforation, gastric ulcers), proximal myopathy, pneumocystis pneumonia, and osteoporosis. Other more common but less severe side effects include hyperglycemia, behavioral changes, weight gain, insomnia, and immunosuppression. Thus, for patients on corticosteroids, frequent blood glucose checks and either proton pump inhibitors or H2 blockers should be included in the treatment plan.

In addition to corticosteroids, other medications can be considered for the treatment of peritumoral cerebral edema. Hyperosmolar agents can reduce the amount of edema by increasing serum osmolality and drawing fluid out of the brain via an osmotic gradient. The most commonly used hyperosmolar agents are hypertonic saline and mannitol. When administering these medications, the patient's serum osmolality, osmolar

gap, and sodium should be carefully monitored; these measurements should not exceed 320 mOsm/kgH_20, 12, and 160 mEq, respectively. Additionally, because these medications are administered intravenously, they can only be utilized transiently in an emergent setting. See Chap. 11 for further information on use of osmotic agents for edema management. Another pharmacologic option for the treatment of refractory peritumoral edema is the VEGF-A inhibitor, bevacizumab. In randomized trials, this medication was found to have only modest oncologic benefit in malignant gliomas; however, it was found to have remarkable efficacy in the treatment of vasogenic edema [7]. Thus, for patients with severe edema that cannot be controlled by steroids alone, bevacizumab may be a valuable adjunctive option.

14.4.3 Management of Seizures

Many brain tumor patients frequently experience seizures; as a result, good seizure control is essential for patient management. Approximately 20–40% of brain tumor patients will present with seizures, while another 20–45% of patients will develop seizures at some point during their clinical course [8]. There are several factors that influence the likelihood of developing a seizure. In general, primary brain tumors tend to have a higher incidence of seizures as compared to metastatic lesion. Of the primary tumors, low-grade gliomas are more epileptogenic than high-grade gliomas. The location of tumors also correlates with risk of seizures; cortical and temporal lobe lesions have higher rates of seizures than infratentorial or deep, subcortical tumors [9].

If a brain tumor patient experiences a seizure, the risk of developing a subsequent seizure is high. Thus, it is important to start antiepileptic drugs (AEDs) immediately. Seizures themselves can lead to profound neurologic morbidity and significantly impact a patient's quality of life. Choosing an anticonvulsant regimen can

present a challenge; both its therapeutic efficacy and potential side effects must be considered [10]. The newer AEDs (including levetiracetam, lacosamide, lamotrigine, topiramate, zonisamide, gabapentin, pregabalin) are generally preferred over older medications (phenytoin, valproic acid, phenobarbital) because of their fewer side effects and drug-drug interactions [3, 10]. Most often, brain tumor patients experience localization-related epilepsy, due to the physical presence of the tumor. Thus, if the tumor can be surgically resected, this has the potential to cure the patient's seizure disorder.

The available data suggests that prophylactic AEDs are not effective in preventing first seizures, and given that many AEDs have significant side effects, prophylactic use is not supported [8]. Despite the lack of supporting data, many providers still prescribe prophylactic AEDs in the perioperative period, arguing that a seizure during this critical time could have significant clinical impact. If AEDs are given prophylactically in the perioperative period, it is generally accepted that they should be discontinued within 7 days following surgery [11].

14.4.4 Management of Hydrocephalus

Hydrocephalus is defined as the abnormal accumulation of cerebrospinal fluid (CSF) within the ventricular system of the brain. Broadly, hydrocephalus can be either obstructive (non-communicating) or communicating in nature. Obstructive hydrocephalus occurs when there is a blockage within the ventricular outflow system. Depending on the location of the obstruction, various parts of the ventricular system will be dilated, while other portions may be normal in caliber. Communicating hydrocephalus occurs when the entire ventricular system is dilated; there is no focal point of obstruction. Thus, the anatomic abnormality lies within the absorptive portion of the CSF pathway, at the level of the arachnoid granulations.

Overall, obstructive hydrocephalus is more common in brain tumor patients than communicating hydrocephalus, although both conditions may occur. Obstructive hydrocephalus is caused by physical compression of the ventricular outflow pathway by the tumor itself. Communicating hydrocephalus occurs when a tumor secretes abnormal proteinaceous material into the CSF, which impairs the ability of the arachnoid granulations to absorb the CSF.

Patients with hydrocephalus most often present with signs and symptoms of elevated ICP. This typically includes headaches, nausea/vomiting, vision changes, and lethargy. On physical exam, notable findings may include papilledema and altered mental status. The severity of symptoms is related to the degree of hydrocephalus and the rapidity of onset. Slowly evolving hydrocephalus allows the brain time to accommodate, while rapidly evolving hydrocephalus does not. Similarly, mild hydrocephalus can often be compensated for, while severe hydrocephalus is typically symptomatic.

While the definitive treatment of hydrocephalus is generally surgical in nature, several medical interventions are important during the initial stages of management. Patients with symptomatic hydrocephalus should be admitted to the ICU for close neurologic monitoring. Additionally, they should be placed on high-dose corticosteroids to reduce any peritumoral edema that may be contributing to an obstructive phenomenon. Finally, bedside placement of an external ventricular drain (EVD) may be required, to temporarily divert CSF from the ventricular system and control ICPs. After the patient has been stabilized, obstructive hydrocephalus is typically treated by resection of the tumor, while communicating hydrocephalus often requires placement of a ventriculoperitoneal shunt, even if the tumor has been removed.

14.4.5 Prevention of Venous Thromboembolism

Brain tumor patients are known to have an increased risk of postoperative deep venous thrombosis (DVT) and pulmonary embolism (PE), with a reported incidence of 3–8% in the immediate postoperative period [12, 13]. It is postulated that the increased rates of DVT and PE in brain tumor patients are due to the local synthesis of tissue factor and/or higher rates of immobility in this population. Despite this, there is no consensus recommendation regarding the use of mechanical and/or chemical prophylaxis for these patients [14].

Numerous retrospective reviews have demonstrated that a practice of combined mechanical and chemical prophylaxis in the immediate postoperative period can reduce the risk of DVT and PE by more than half [14]. While almost all surgeons initiate mechanical prophylaxis in the operating room via TED hoses and sequential compression devices, there is considerable variability in the administration of subcutaneous chemical prophylaxis (both heparin and low-molecular-weight heparin, LMWH) [13]. Some surgeons begin chemoprophylaxis in the operating room, others wait until postoperative day 1, and others do not ever utilize chemoprophylaxis. In general, the reluctance to start chemoprophylaxis is due to the perception that this class of medications increases the risk of surgical site hemorrhage. While some case series do report an increased risk of minor bleeding with chemical prophylaxis, there have been no consistent reports demonstrating an increased risk of clinically significant surgical site hemorrhages with chemoprophylaxis [14]. Thus, at most institutions, for brain tumor patients, the practice has evolved to begin mechanical prophylaxis in the operating room and chemical prophylaxis on the morning of postoperative day 1.

14.4.6 Hospice/Palliative Care

Most patients with malignant brain tumors will eventually succumb to their disease. This is particularly true for glioma patients. As their disease progresses, these patients may experience a myriad of neurologic symptoms, including seizures, focal weakness, lethargy, cognitive changes, and headache. These symptoms may, in turn, prompt ICU admission. Thus, it is critical for the ICU provider to understand the natural progression of malignant brain tumors and to be prepared to provide supportive care to these patients via corticosteroids and AEDs, as needed. In addition to medical management, the critical care provider should engage the patient's primary oncologist to assist with family discussions regarding goals of care, and, when appropriate, consult the hospice/palliative care team. Although these efforts are not livesaving, by design, attention to end-of-life care is critical to the overall management of brain tumor patients and may start in the ICU. Keen attention to maintaining the comfort of both the patient and their family cannot be overemphasized.

Summary Points

- Brain tumor patients represent a wide range of clinical pathologies and can present to medical attention with a variety of signs and symptoms.
- Many brain tumor patients will require ICU care for the initial management of cerebral edema, seizures, and/or hydrocephalus.
- Almost all brain tumor patients will require transient ICU care in the immediate postoperative period.
- Close neurologic monitoring is essential; most neurologic changes, when identified early, can be treated with good long-term outcomes.

- Critical care providers who are treating brain tumor patients should be comfortable with the use of dexamethasone, hyperosmolar agents, and anticonvulsant medications.
- The ability to read and interpret intracranial imaging is essential to the management of brain tumor patients.

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Chapter 15
Spinal Cord Injury

Jennifer Massetti and Deborah M. Stein

15.1 Introduction

Spinal cord injury (SCI) is one of the most devastating neurological injuries in both developed and developing nations. Worldwide, the incidence of SCI ranges from 3.6 to 195 per million [1]. In the United States, the incidence and prevalence of traumatic SCI are higher than in other developed countries [2]. The estimated annual incidence of SCI in the United States is 40 cases per million, totalling 12,000 new cases per year [3]. There are between 238,000 and 332,000 people with spinal cord injury currently living in the United States [1]. The incidence of SCI in men is four times higher than in women, and the average age of the SCI is increasing as the population continues to age [2]. Mean age of SCI occurrence has shifted from 29 in the 1970s to 40 in the 2010 [3]. While the occurrence of SCI is increasing, its severity is decreasing [2]. The most common syndromic presentations include incomplete tetraplegia

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(41%), incomplete paraplegia (19%), complete paraplegia (18%) and complete tetraplegia (12%).

15.1.1 Morbidity and Mortality

An estimated 4,800 victims of SCI die before ever reaching the hospital [4]. For those alive when reaching the hospital, the overall mortality is highest in the first year after the injury, as well as in patients with advanced age and severer clinical pictures. Long term causes of death include infections (septicemia from urinary tract infections, respiratory infections, and decubiti) and pulmonary thromboembolism secondary to deep vein thrombosis. There has been no change in the mortality rate for septicaemia in the past 40 years and only a slight decrease in mortality due to respiratory diseases [5]. SCI is an extremely costly disease. In 2014, the annual expenses during the first year ranged from $347,000 to $1 million, depending on the severity of injury [5]. Each subsequent year ranged from $42,000 to $184,000 [5].

15.1.2 Mechanism of Injury

Motor vehicle collisions remain the leading cause of traumatic SCI in the United States, accounting for 38% of new SCI [5]. Falls, at 30%, are the leading cause of SCI in the geriatric population. Violent injuries account for 14% and sports injuries account for 9%. These mechanisms of injury are more often seen in the younger population [2, 3, 5]. Causes of non-traumatic SCI include disc herniation, metastatic disease of the spine, and spinal stenosis [7].

The majority of traumatic SCI cases compromise the cervical spine, resulting in increased short- and long-term morbidity when compared to thoracic and lumbar injuries [6]. Predictors of mortality include age at injury, neurologic level and clinical presentation (incomplete vs. complete injury) [7].

Spinal cord injuries typically occur when a powerful impact is applied to the spine resulting in fractures, ligamentous disruptions, and cord damage. The classification of SCI is based on location (craniocervical, subaxial cervical or thoracolumbar) or mechanism (flexion, extension, or axial load). There are four mechanisms of primary injury to the spinal cord [8].

- Impact with persistent compression: Seen in burst fractures, whereby bone fragments or an acute disc disruption impinges the spinal cord.
- Impact with transient compression and rapid realignment of the vertebral bodies: Seen in extension injuries causing varying levels of damage to the spinal cord. Transient compression of the cord can be caused by a bulging disc or osteophyte and thickened ligamentum flavum.
- Spinal Cord Injury Without Radiographic Abnormality (SCIWORA): Seen in patients with cervical spondylosis. This is characterized by an absence of radiological evidence of trauma on routine imaging, but a spinal cord contusion and/or edema may be noted on MRI.
- Laceration of the spinal cord: Caused by penetrating trauma, stab or gunshot, or by a bony fragment dislocation.

In thoracolumbar injuries, the "three column" concept states that at least two of the three columns of the spine need to be disrupted for an injury to be unstable, posing risk of further injury to the spinal cord [9]. Medical conditions such as ankylosing spondylitis and spinal spondylosis are the exceptions to this theory, as the underlying abnormalities of the spinal column can result in significant injury to the spinal cord with minimal bony injury.

15.1.3 Primary and Secondary Injury

There are two distinct pathophysiological phases in SCI. The primary phase occurs at the time of the event and is the result of the mechanical insult; this stage constitutes the perfect target for

preventive strategies. The secondary phase occurs minutes to days after the injury and is the focus of currently used medical interventions. Mechanisms for secondary injury include inflammation and edema, as well as vascular, electrolyte and biochemical changes. The severity of the secondary insult is determined by severity of the primary insult and the development of other systemic factors, such as hypotension and hypoxia. The goal of management following SCI is to minimize secondary injury by maintaining hemodynamic stability and optimizing medical status.

15.2 Case Presentation

A 40-year-old man presented to a trauma center following a motor vehicle collision. Upon presentation, his primary survey was significant for a blood pressure of 80/44 mm Hg with a pulse rate of 49. He is breathing comfortably but complaining of shortness of breath. On the secondary survey, he is awake, alert and oriented with 5/5 muscle strength in his biceps bilaterally, 4/5 strength in his wrist extensors on the right, 4/5 strength in his wrist extensors on the left, and 3/5 triceps muscle strength bilaterally. His only sensation below the nipple line was rectal sensation (American Spinal Injury Association (ASIA) 24 B). He is fluid resuscitated until target blood pressure is achieved proceeding with imaging studies. CT scan showed bilateral interfacet dislocation at C6–C7 and anterolithesis of cervical spine 6 over 7, interspinous process widening, and severe canal narrowing. Before MRI he developed worsening respiratory function with the development of “quad breathing” and was intubated. A central line was placed and a norepinephrine infusion was started for a blood pressure of 95/44 mm Hg. The MRI showed injury at C6–C7 with cord signal abnormality extending

from the C5 through T1 levels and C6–C7 anterior and middle column diskoligamentous injuries with a partial tear of the ligamentum flavum. After the MRI, the patient was placed in cervical traction to reduce the fracture, but one facet of the bilateral dislocation could not be reduced under fluoroscopic guidance. He was taken to the operating room for open reduction and posterior spinal fusion. Postoperatively, an MRI showed an increase in the signal abnormality starting at C3 and expending to T2. The patient was transferred to the intensive care unit (ICU) and a mean arterial pressure greater than 85 mm Hg was achieved using norepinephrine. He underwent an anterior cervical diskectomy and fusion on his second day of hospitalization. Reevaluation by the physical therapy team revealed an ASIA of 18 B. Post operatively, his course was complicated by hypotension and bradycardia, treated with enteral albuterol and midodrine and infusions of vasoactive medications. Five days post injury he developed acute ventilatory failure. He underwent a tracheostomy on the seventh day of hospitalization. With aggressive secretion clearance, he was weaned to tracheostomy collar on the 18th day of hospitalization and transferred to an acute rehabilitation facility on the 22nd day of hospitalization.

15.3 Initial Evaluation

The goal of management in patients with SCI is prevention and minimization of secondary injuries. The initial management for a patient with a traumatic SCI is the same as for any patient who sustains a traumatic injury as suggested by the American College of Surgeons' Advanced Trauma Life Support (ATLS®) course [10].

The primary survey identifies life threatening injuries requiring emergent intervention and rapid and systemic evaluation

Table 15.1 Indications for intubation of the patient with traumatic cervical spinal cord injury

Absolute indications
Complete spinal cord injury above C5 level
Respiratory distress
Hypoxemia despite attempts at oxygenation
Severe respiratory acidosis
Relative indications
Complaint of shortness of breath
Development of quad breathing[a]
Vital capacity of <10 mL/kg or decreasing vital capacity
Consideration should be given
Need to travel remote from emergency department (e.g., MRI, transfer to another facility)

[a]Quad breathing refers to the stereotypical breathing pattern in patients with cervical and upper thoracic spinal cord injury in which the chest wall retracts and the abdominal wall protrudes with inspiration (Adapted from Stein et al. [11])

which should be completed in the first minutes of the patient's arrival. See Table 15.1. Following the "ABCDE" approach (airway, breathing, circulation, disability, and exposure), risk of airway loss, inadequate oxygenation and ventilation, and hypotension require immediate attention.

Patients with cervical and high thoracic injuries experiencing impending respiratory failure often describe heaviness in the chest or inability to catch their breath, or may appear breathless while speaking. Loss of chest wall and abdominal innervation produce a pattern where the chest goes in and the abdomen goes out with diaphragmatic contraction, so call "quad breathing". Treatment of respiratory insufficiency in a patient with SCI should include urgent endotracheal intubation [12, 13]. Caution should be employed during intubation as tetraplegic patients can develop bradycardia and hypotension due to autonomic instability.

Once hemodynamic stability it achieved, the secondary survey should begin with a detailed exam to quantify neurologic disability.

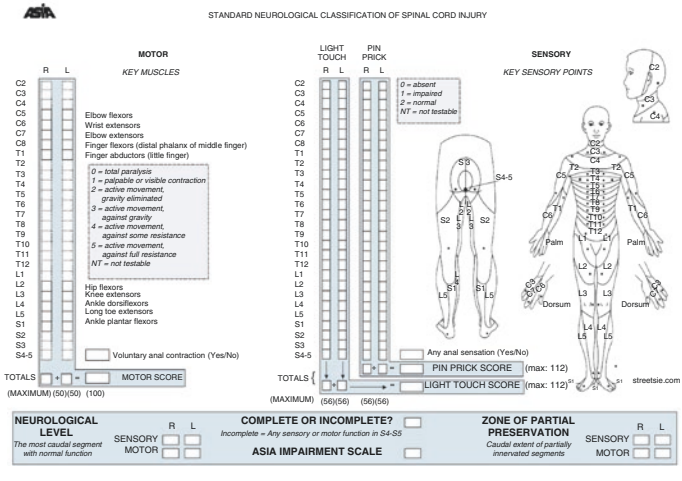
15.3.1 Imaging

CT scan is the modality of choice for initial evaluation. It detects bony injury and dislocation [14].

MRI is useful in detecting injury in the obtunded patient with a suspected SCI where physical exam is less reliable. Additionally, MRI is used for diagnosis, to plan operative interventions, and for prognostication, as it is the modality which determines the degree of edema and hemorrhage in the spinal cord [15].

15.3.2 Evaluation and Classification of SCI

The American Spinal Injury Association (ASIA) developed a standard classification of SCI which is widely used [16] (Fig. 15.1). The ASIA examination tests 2 components; sensory and motor. The sensory examination tests 28 dermatomes bilaterally for two aspects of sensation, light touch and pin prick. The motor examination tests ten paired myotomes bilaterally for strength. The American Spinal Injury Association has also described the ASIA Impairment scale which is the standard for determination of completeness of an SCI. Complete injuries are losses of all sensory and motor function below the level of injury ASIA A. Incomplete injuries retain some neurologic function below the level of injury ASIA B-D. ASIA should be assessed at least daily as a decreased score is usually a result of spinal cord edema ascension, new or worsening spinal cord hemorrhage, or ischemia.



MUSCLE GRADING

0 total paralysis

1 palpable or visible contraction

2 active movement, full range of motion, gravity eliminated

3 active movement, full range of motion, against gravity

4 active movement, full range of motion, against gravity and provides some resistance

5 active movement, full range of motion, against gravity and provides normal resistance

5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present

NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture.

ASIA IMPAIRMENT SCALE

☐ **A = Complete:** No motor or sensory function is preserved in the sacral segments S4-S5.

☐ **B = Incomplete:** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

☐ **C = Incomplete:** Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

☐ **D = Incomplete:** Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

☐ **E = Normal:** Motor and sensory function are normal.

CLINICAL SYNDROMES (OPTIONAL)

☐ Central cord
☐ Brown-Sequard
☐ Anterior cord
☐ Conus medullaris
☐ Cauda equina

STEPS IN CLASSIFICATION

The following order is recommended in determining the classification of individuals with SCI.

1 Determine sensory levels for right and left sides.

2 Determine motor levels for right and left sides.
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level.

3 Determine the single neurological level.
This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4 Determine whether the injury is Complete or Incomplete (sacral sparing).
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0** AND any anal sensation = **No**, then injury is COMPLETE*
Otherwise injury is incomplete.

5 Determine ASIA Impairment Scale (AIS) Grade:
Is injury Complete?
NO → **If YES,** AIS=A Record ZPP (For **ZPP** record lowest dermatome or myotome on each side with some (non-zero) preservation)
Is injury motor incomplete?
YES → **If NO,** AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side.)
Are at least half of the key muscles below the (single) neurological level graded 3 or better?
NO → AIS=C
YES → AIS=D

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

Fig. 15.1 ASIA Standard neurological classification of spinal cord injury (From International Standards for Neurological Classification of Spinal Cord Injury [16])

15.3.3 Specific Clinical Syndromes [11]

Central cord syndrome

- Most common, seen in older adults
- Extensive weakness noted in the upper extremities compared to the lower extremities
- Existing degenerative ligament and/or osteophytic changes to spine prior to hyperextension injury of the neck causing the spinal cord to be squeezed or pinched
- Usually not associated with a bony injury or evidence of spinal instability

Brown-Sequard syndrome

- Typically from penetrating spinal cord injury or a lateral mass fracture of the spine
- Hemiplegia with ipsilateral loss of light touch and proprioception with contralateral loss of pain and temperature sensation

Anterior cord syndrome

- Motor and sensory pathways in the anterior part of the spinal cord are injured
- Cause is not usually traumatic
- Ischemic insult from disruption of flow in the anterior spinal artery
- Poor prognosis for recovery

Posterior cord syndrome

- Result of vascular compromise to the spinal cord
- Rarely occurs from trauma
- Posterior aspect of spinal cord affected
- Loss of proprioception with preservation of motor function, pain and temperature sensation and light touch

Cauda equina syndrome

- Traumatic cause is typically retropulsion of a fracture fragment in the lumbosacral region resulting in lower spinal nerve root compression
- Non traumatic cause most commonly results from a massive herniated disc in the lumbar region
- Other non-traumatic causes are spinal lesions/tumors, lumbar stenosis, spinal hemorrhages, spinal arteriovenous malformations, birth abnormalities, spinal anesthesia
- May include one or more symptoms:
  - Severe low back pain
  - Motor weakness/sensory loss or pain in one or both legs
  - Saddle numbness
  - Recent onset of bladder dysfunction (incontinence or retention)
  - Recent onset bowel dysfunction
  - Abnormal sensation in the bladder or rectum
  - Recent onset of sexual dysfunction
  - Loss of reflexes in the lower extremities

15.3.4 Spinal Shock

Spinal shock was first described by Whytt in 1750 as the loss of sensation with motor paralysis with gradual recovery of reflexes [17]. Following spinal cord injury, the reflexes above the injury level remain intact while the reflexes below the injury level become depressed or absent. In SCI, the term ‘shock’ does not refer to the circulatory system, and should not be confused with neurogenic shock. Ditunno et al. [18] described spinal shock in a four phase model.

- Phase 1: areflexia or hyporeflxia, 0–24 h post injury.

- Phase 2: reflexes return, 1–3 days post injury.
- Phase 3: early hyper-reflexia, day 4 to 1 month post injury.
- Phase 4: spascity/hyper-reflexia, 1–12 months post injury.

15.4 Management and Interventions

The majority of treatment for patients with spinal cord injury is supportive, with focus on minimizing secondary injury, and preventing and treating complications as they occur. Patients with injury in the cervical or high thoracic spine are at high risk of organ failure and require high-level intensive care support [19]. It should be expected that over hours to days following injury the neurologic deficits will worsen, which in turn will trigger further cardiovascular and respiratory dysfunction.

15.4.1 Neurogenic Shock

Neurogenic shock can occur in patients with SCI on or above T6. It is caused by the loss of supraspinal control of the sympathetic nervous system [20, 21]. This causes hypotension and stimulation of the vagus nerve, with unopposed parasympathetic activity leading to bradycardia and the block of the atrioventricular node [21]. Neurogenic shock is a form of distributive shock with excessive vasodilatation and the characteristic finding of bradycardia. Patients are usually hypotensive with warm and dry skin. Neurogenic shock may not be present on admission but can develop over days to hours and last for 1–3 weeks. The first line therapy is fluid resuscitation to maintain euvolemia. Second line treatment is the use of pressors, inotropes or a combination of both (Table 15.2). Treating hypotension and hypoperfusion is

Table 15.2 Vasoactive agents used to treat neurogenic shock

Agent	α Activity	β Activity	Considerations
Norepinephrine	+++	++	Probably the preferred agent
Phenylephrine	++	None	May worsen bradycardia
Dopamine			
Low dose (3–10 mcg/kg/min)	+	++	May lead to inadvertent diuresis at low dose
High dose (10–20 mcg/kg/min)	++	+++	
Epinephrine	+++	++	Rarely needed
Dobutamine	None	+++	May cause hypotension if not euvolemic

Adapted from Stein et al. [11]
+ small effect, ++ moderate effect, +++ large effect

paramount, as these are known mediators of secondary injury. Severe hemodynamic abnormalities will ultimately resolve after the first 2–6 weeks post injury, however patients with SCI can have life-long alterations in cardiovascular function.

15.4.2 Cardiovascular Evaluation and Management

Aggressive management of hypotension is recommended and is associated with improvements in neurologic outcome [14, 22]. Treatment of hypotension and neurogenic shock following spinal cord injury initially involves volume resuscitation followed by pressor administration as outlined above. Current recommendations are to maintain mean arterial blood pressure between 85 and 90 mm Hg for the first 7 days following acute cervical spinal cord injury [22]. Oral α-receptor agonists, such as midodrine hydrochloride and pseudoephedrine, can be used

with IV vasoactive medications and may be helpful in the subacute stages following injury for management of persistent hypotension [23].

Treatment of bradycardia following spinal cord injury is typically reserved for symptomatic patients. For symptomatic cases, use of β-agonist therapy with enteral albuterol may be helpful, atropine can be used for episodic bradycardia, and pacemaker placement may be indicated if patients have persistent symptomatic bradycardia.

Some patients will have recurrent and sustained bradycardia that can progress to asystole if left untreated [20, 21].

15.4.3 Respiratory Evaluation and Management

Respiratory dysfunction occurs in over 65% of patients with cervical SCI. Of these, 40% meet criteria for respiratory failure by standardized organ dysfunction scales [19]. The primary cause of respiratory failure is intrinsic dysfunction from denervation of the muscles essential for adequate ventilation, resulting primarily in hypercarbia. Trauma patients may have concomitant injuries such as pulmonary contusions, hemothoraces and pneumothoraces also compromising respiratory function through hypoxemic failure. Patients with high cervical and thoracic injuries who do not require immediate intubation need close observation as the injury progression in the spinal cord from edema and ischemia may worsen respiratory function. Increased respiratory secretions, ineffective cough, and increased bronchial tone are additional contributory factors in respiratory dysfunction.

Tracheostomy placement is sometimes indicated for both prolonged ventilation and secretion management. In general, admission ASIA score of less than 10 will require tracheostomy [24].

If tracheostomy is indicated, early tracheostomy may reduce ICU length of stay and decreased time of mechanical ventilation.

15.4.4 Ventilator Management

Patients with spinal cord injury have a high incidence of pneumonia and benefit of a protocolized ventilator management [25]. Complete high cervical spine injury at the C1 to C3 with invariably need mechanical ventilation due to loss of diaphragm innervation (Table 15.3). Ventilator weaning can be challenging for many SCI patients and high and/or complete injuries may require long-term mechanical ventilation.

Initial ventilation of the tetraplegic patient should be aimed at a higher tidal volume; risk of barotrauma should be reduced if peak airway pressure is kept under 40 [22].

Table 15.3 The three major muscle groups of the respiratory system

Muscle group	Function	Innervation
Diaphragm	Major muscle of respiration	C3 to C5
	During inhalation, the diaphragm contracts and moves downward	
	During exhalation, the diaphragm relaxes, allowing for passive recoil	
Intercostal muscles	During inhalation, the external intercostal muscles contract and elevate the rib cage	T1 to T11
	During exhalation, the internal intercostal muscles contract and pull the ribs down	
Abdominal muscles	Essential for an effective cough	T6 to L1
	During exhalation, the abdominal muscles contract and compress the abdominal contents and push the diaphragm up	
Accessory muscles	Elevate the rib cage and assist in deep ventilation	C1 to C3
	Inadequate alone for effective ventilation	

Adapted from Stein and Sheth [26]

Early aggressive pulmonary therapy is associated with decreased time on the ventilator, fewer pulmonary complications and improved survival [27]. These include:

- Assisted coughing techniques including manual assistance and devices that assist by delivering a deep breath and during exhalation with a rapid reversal of flow which helps expectoration of secretions
- Chest physiotherapy and positioning
- Intrapulmonary percussive ventilation (IPV) which can be utilized for patients to mobilize mucous and improve delivery of nebulized medications

Abdominal binders are helpful during the acute phase as they keep the abdominal contents from protruding and have a traction effect on the diaphragm [27]. Or in prolonged cases, diaphragmatic pacer implantation for patients with high cervical SCI allows for the possibility for these patients to wean from full ventilator support [28].

15.4.5 Other Systems and Considerations

Complications are the leading cause of morbidity and mortality in SCI patients. The leading cause of death is infection. Screening and treatment of infection is extremely important. These patients are also susceptible to deep vein thrombosis (DVT), skin breakdown, gastrointestinal hemorrhage and pulmonary embolism.

15.4.6 Urinary Tract

Timely Foley catheter removal and urinary tract infection (UTI) prevention are of paramount importance. Consider removal of indwelling urinary catheter once the patient is hemodynamically stable.

Once Foley catheters are removed, patients often require intervention to ensure adequate bladder emptying. Intermittent catheterization of the bladder can be done every 4–6 h, with the goal of keeping bladder volume below 500 ml to prevent over-distention. Suprapubic catheters should be considered with urethral abnormalities, recurrent urethral obstructions, and difficulty with urethral catheter insertion. If patient is voiding without catheterization, scan bladder or catheterize at least once after voiding to ensure the bladder is emptying and there is not a high post-void residual.

15.4.7 Gastrointestinal Tract

Maintenance of adequate nutrition is extremely important and enteral nutrition should be started as soon as feasible. A formal swallow evaluation is recommended prior to oral food and liquids as dysphagia can be present in up 41% of patients with tetraplegia [14, 27]. Acute SCI patients are at high risk for gastrointestinal bleeding and should be prescribed stress ulcer prophylaxis.

Initiate a bowel training program early as patients with SCI can have decreased bowel motility. Bowel distention, ileus, and inadequate evacuation can occur and lead to nausea, vomiting, and high gastric residuals which could lead to aspiration and other complications. Aim for one bowel movement per day with the combined use of oral and rectal medications and digital stimulation as needed.

15.4.8 Venous Thromboembolism (VTE) Prevention

At a minimum, pneumatic compression stockings and mechanical compression should be used in all patients from the time of admission. Prevention of VTE with chemical prophylaxis such

as low molecular weight heparin is typically acceptable to start within 72 h of injury. Discuss timing with surgeon if the patient underwent operative fixation.

The placement of a prophylactic inferior vena cava filter (IVC) recommended only when use of chemical VTE prophylaxis is contraindicated. Recommended duration of treatment is 3 months.

15.4.9 Skin

Skin breakdown is one of the more common complications following SCI and prevention must start in the acute setting. Skin assessment and pressure reduction using specialty mattress and padding with frequent turning and repositioning is required. Temperature should be monitored and regulated. The disruption of the autonomic nervous system in patients with cervical and high thoracic SCI can result in poikilothermia where surrounding temperature will be assumed by the body [14].

15.4.10 Pain

Pain can be muscular or neuropathic or both. Consider the use of muscle relaxants to treat spasm as well medications to treat neuropathic pain in addition to opioids. Patients with an incomplete SCI may have allodynia – a hypersensivity to touch. In these patients attempt to minimize pain by decreasing contact with the area as much as possible.

15.4.11 Autonomic Dysreflexia [29]

Autonomic dysreflexia can occur following SCI and may affect patients in the acute or chronic phase. It is more typically seen in patients with high thoracic or cervical spinal cord injuries.

Any noxious stimulus (bladder distension or fecal impaction) which occurs below the level of injury can lead to a dangerous rise in systolic blood pressure due to hyperactive thoracic sympathetic reflex activity, a loss of supraspinal sympathetic control, and inadequate parasympathetic response. Autonomic dysreflexia is defined as a greater than 20% increase in systolic blood pressure with a change in heart rate and at least one sign (e.g., sweating, piloerection, facial flushing) or symptom (e.g., headache, blurred vision, stuffy nose).

Although prevention is ideal, once autonomic dysreflexia occurs, first-line therapy is to remove the stimuli. If hypertension persists, pharmacologic intervention should be instituted with calcium channel blockade or nitrates. If left untreated, malignant hypertension can result in intracranial hemorrhage, retinal detachment, seizures, coma, myocardial infarction, pulmonary edema, and death.

15.4.12 Prognosis

Patients and families will ask about potential for neurologic recovery. The ASIA impairment scale offers some information when discussing prognosis as complete injuries are less likely to recover neurologically than incomplete injuries. Overall life expectancy is shorter for patients with SCI as compared to the general population. Mortality rates are the highest in the first year following injury regardless of age or severity of injury.

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Chapter 16
Neuromuscular Disease

Peter Reuter and Alejandro Rabinstein

16.1 Introduction

The presence of neuromuscular disease is common in critical care, especially in the Neuroscience intensive care unit. Patients may present with acute, subacute, or chronic neuromuscular failure. Early identification, treatment, and management are the keys to preventing further complications. The field of neuromuscular disease encompasses a wide array of conditions that affect the upper and lower motor neurons. Etiologies include genetic, infectious, autoimmune and degenerative. The most severe cases may result in respiratory failure.

APCs play a crucial role in the management of patients with neuromuscular disease, from early diagnosis to recognition of decline and monitoring of treatment. This chapter begins with a discussion on the basics of neuromuscular respiratory failure

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and then details the most common neuromuscular diseases seen in the Neurocritical care unit.

16.2 Case Example

A 46-year-old female presents to the emergency department for evaluation of what she describes as “pins and needle” sensation starting in her toes and ascending to her mid-thigh. She states that the “pins and needles” sensation started 36 h ago. As the sensation progressed also noticed that she was tripping and having a hard time lifting her feet up. She explains that she feels like she is tripping over a rug when there is nothing beneath her. She is concerned that her symptoms are getting worse. Her past medical history if significant for hypothrydoism, for which she takes levothyroxine. She describes herself as “healthy.” The patient does describe recent cold/flu like symptoms she experienced 10 days ago. She states that her symptoms went away on their own with rest and fluids.

Over a 2-h course in the emergency department, the patient lost 75% of her lower extremity strength and experienced drooling, dysarthria and double vision. She was intubated for airway protection given concern about her ability to appropriately clear secretions. Intubation was successful but large variations in her blood pressure were observed. This was likely secondary to autonomic dysfunction.

After stabilization, an EMG showed slow conduction velocities in motor nerves, representing demyelination and supporting a diagnosis of Guillain-Barre syndrome. The patient was started on IVIG immunotherapy at 0.4 g/kg daily for 5 days. Over the course of her ICU stay she developed complete paralysis. She received a second course of IVIG and gabapentin for dysautonomia and neuropathic pain secondary to nerve demyelination. Tracheostomy and percutaneous gastric tube were placed on ICU day 14 for long term mechanical ventilation and nutrition. After hemodynamic and airway stability were achieved, the

patient was transferred to an acute rehab facility where she was eventually weaned off the ventilator. She recovered the ability to walk and swallow over her 6-month rehabilitation. The patient re-gained much of her functional status and was able to return home with the help of her husband.

16.3 Initial Evaluation

16.3.1 Neuromuscular Respiratory Failure

Neuromuscular respiratory failure is a type of ventilatory failure caused by weakness of the respiratory muscles, followed by ineffective ventilation and subsequent hypercapnia. While some patients may become hypoxemic, it is important to emphasize that this phenomenon appears late in the course of the clinical event. Oropharyngeal muscle weakness can also lead to airway obstruction with secretions, increasing the risk of aspiration and pneumonia [1]. Neuromuscular respiratory failure in the neurocritical care unit can be caused by primary neuromuscular diseases, like Myasthenia gravis, Guillain-Barre syndrome or amyotrophic lateral sclerosis; or can be the result of critical illness neuromyopathy and deconditioning [5].

Signs and symptoms of neuromuscular respiratory failure include shortness of breath, staccato speech, restlessness, tachycardia, tachypnea, diaphoresis, accessory muscle use and paradoxical breathing (inward rather than outward movement of the abdomen during inspiration) [2]. Decreased level of arousal due to hypercarbia can be seen in advanced stages.

When diagnosing neuromuscular respiratory failure, a complete history of present illness should be taken into account. Details regarding the events leading up to presentation may be helpful to diagnose the underlying disease process causing the respiratory failure. A complete physical examination should be

Table 16.1 Pulmonary function test critical values

Parameter	Normal value	Critical value
Forced vital capacity (FVC)	40–70 mL/kg	20 mL/kg
Maximal inspiratory pressure (MIP)	Men: >−100 cmH_2O Women: >−70 cmH_2O	−30 cmH_2O
Maximal expiratory pressure (MEP)	Men: >200 cmH_2O Women: >140 cmH_2O	40 cmH_2O

Table adapted from Wijdicks et al. [8]. By permission of Mayo Foundation for Medical Education and Research

performed. Chest x-ray, arterial blood gas (ABG) and pulmonary function tests (PFT) are all helpful in classifying the type of respiratory failure [2]. Table 16.1 outlines general parameters and values for patients exhibiting signs of neuromuscular respiratory failure. Critical values can be remembered in the "20-30-40" sequence. It is important for the APC to use the information in the table below in conjunction with the patient assessment and ABG.

It is important to identify if the patient requires ventilatory assistance, which can be provided in the form of non-invasive ventilation using the Bilevel Positive Airway Pressure (BiPAP), or via orotracheal intubation and conventional invasive mechanical ventilation. BiPAP may be particularly helpful in patients in myasthenic crisis and may prevent an intubation. Patients with Guillain-Barre syndrome experiencing respiratory distress secondary to neuromuscular failure should undergo prompt endotracheal intubation and mechanical ventilation as BiPAP is contraindicated. Patients may require long-term respiratory management and tracheostomy [6].

The role of the APC is essential for the prevention and timely recognition of secondary complications such as infection, gastric ulcer and deep vein thrombosis. Aggressive pulmonary toileting, early and frequent mobilization and volume management should also be priorities in the management of these patients.

16.4 Interventions and Management

16.4.1 Guillain-Barre Syndrome

Guillain-Barre Syndrome (GBS) is an autoimmune, inflammatory disease causing peripheral nerve damage to the myelin sheath portion of the nerve cell (Fig. 16.1). The inflammatory damage interferes with nerve conduction. GBS often presents after a bacterial or viral illness, thought to be the precipitating event for the development of auto-antibodies. The incidence is slightly higher in men than women, and increases with age. There are a few variants to this disease, although in this chapter we will discuss the most common, generalized and demyelinating form (acute inflammatory demyelinating polyradiculoneuropathy) [4].

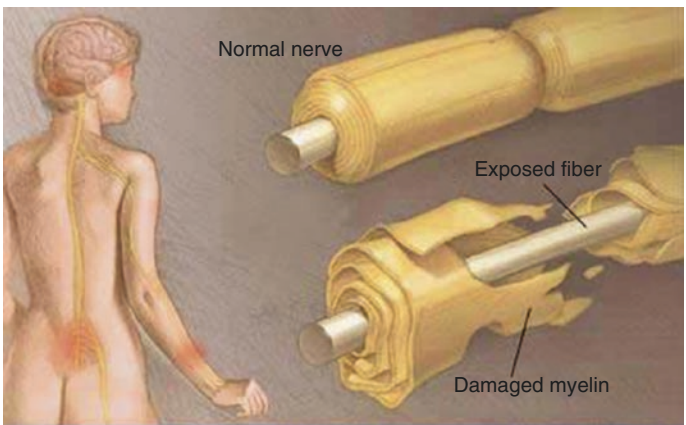

Fig. 16.1 Demyelination in nerve roots and peripheral nerves in Guillain-Barre Syndrome

16.4.1.1 Clinical Presentation

The most common clinical presentation consists of acute, symmetric, ascending weakness, sensory changes and decreased to complete absence of deep tendon reflexes. Initial symptoms often include paresthesias (or "pins and needles" sensation), especially in the feet and legs. Low back pain is also a frequent early complaint. Motor symptoms follow shortly after and subsequently predominate. As the disease progresses, the neuropathy can be mild, moderate, or severe.

Motor weakness is progressive, starting in the lower extremities and ascending to the hips and trunk followed by shoulders, arms and neck. Cranial nerves are frequently involved. Patients may develop ophthalmoparesis causing diplopia and bulbar muscle weakness (bilateral facial weakness, oropharyngeal muscle weakness) causing dysarthria and dysphagia. The degree of motor weakness may range from mild to complete (paralysis). The speed and severity of weakness are strong indicators of the risk of respiratory failure. Bulbar muscle weakness also predicts need for intubation and mechanical ventilation [4].

Respiratory failure requiring mechanical intubation occurs in one third of cases of GBS. Careful assessment and monitoring is needed to intervene when respiratory failure is imminent. Presence of paradoxical breathing pattern signifies diaphragmatic failure and should be considered a sign of impending neuromuscular respiratory failure. Bulbar muscle weakness may impair coughing and result in inability to manage secretions [7].

Autonomic dysfunction is another major manifestation of GBS. Patients may present with arrhythmias, dramatic swings in blood pressure (both hypotension and hypertension), ileus, bladder dysfunction and body temperature dysregulation.

16.4.1.2 Diagnosis

Initial evaluation consists of taking detailed history of present illness and conducting a thorough neurological examination. Patients may present anywhere on the symptom spectrum and may rapidly progress.

Nerve conduction studies (NCS) and electromyography (EMG) are helpful diagnostic tools that assess nerve conduction and degree of denervation. In the patient with the most typical form of GBS, acute inflammatory demyelinating polyradiculoneuropathy, NCS studies will show slowing of the motor nerve conduction velocity. The degree of slowing velocities in the motor nerves represents a good indicator of the severity of the demyelination. Some patients have more severe axonal form of GBS and those cases show decreased amplitude of the motor nerve action potentials. NCS/EMG is helpful in initial diagnosis and may be helpful to repeat later in the disease course to gauge the peak severity of the disease and monitor recovery [2].

Cerebrospinal fluid (CSF) should be obtained via lumbar puncture. Most often, CSF will have an elevated concentration of protein but normal cell count.

Baseline and serial pulmonary function tests (PFTs) should be obtained to monitor the degree of weakness of respiratory muscles. PFTs are a reliable measure of weakness progression in GBS, but only when patients are appropriately coached before the testing. APCs should become familiar with the technique of PFTs to assist respiratory therapists during their performance.

16.4.1.3 Treatment

Management of GBS includes supportive care and administration of immunomodulatory therapies. Prevention and early

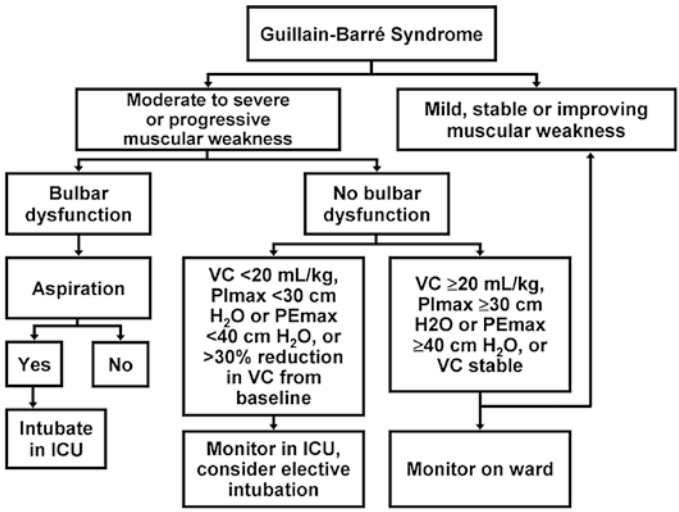

Fig. 16.2 Algorithm for respiratory management of Guillain-Barre Syndrome (Wiley-Blackwell, "The Practical Management of Guillain Barre Syndrome and myasthenic crisis" in *Emergency Management in Neurocritical Care.* Image used with permission from the Mayo Foundation for Medical Education and Research)

identification of secondary complications should always be a priority in the mind of the APC, in particular the recognition of early signs of respiratory failure. It is important for the APC to use critical thinking skills when monitoring for respiratory failure. Not all patients need mechanical ventilation. A general rule is that the GBS patient should be intubated if their forced vital capacity (FVC) falls below 15–20 ml/kg (Fig. 16.2). However, this rule does not apply to every patient and each case should be individually assessed considering all relevant factors (presence of bulbar weakness, dysautonomia, comorbid conditions, etc.) [4].

Patients should be closely monitored for breathing pattern and airway safety. It is worth emphasizing that pulse oximetry

may show acceptable saturation values even in the setting of severe muscle weakness, especially when the patient is receiving supplemental oxygen. Once the patient develops signs of respiratory failure or airway compromise, orotracheal intubation is indicated without delay. Non-invasive ventilation is not safe in patients with severe GBS. Tracheostomy may be necessary for long-term respiratory management.

Dysautonomia is common in GBS. Patients should be monitored on cardiac telemetry for bradycardia and tachyarrhythmias. Blood pressure variations may be sudden and profound. Hypertension should be treated cautiously. Short acting agents such as captopril and hydralazine should be first line medications. Beta-blockers are not preferred as they may cause prolonged hypotension and bradycardia with pauses. Hypotension should be managed conservatively with the use of positioning changes and volume expanders. These interventions are recommended to prevent large blood pressure variations. The APC must be cautions when performing nasotracheal and endotracheal suctioning, as it may induce a vagal response causing hypotension and bradycardia.

Patients with GBS often need enteral nutrition due to dysphagia. Placement of a nasogastric tube may be necessary to reduce the risk of aspiration and to meet caloric requirements. Gastroparesis and ileus are commonly caused by dysautonomia. Patients may require intermittent nasogastric suctioning if high gastric residuals are present or ileus develops. Stool softeners should be administered routinely as constipation is common with decreased gastrointestinal motility.

Neuropathic pain in GBS may be mild to severe, requiring opioid medications and frequent repositioning to keep the patient comfortable. However, it is necessary to keep in mind that opioids can worsen ileus and therefore must be used sparingly in patients with GBS. Gabapentin and other antineuropathic pain medications can be helpful to patients who are experiencing neuropathic pain.

GBS is an autoimmune, inflammatory disease and treatment with immunomodulatory therapies has been proven to be effective in accelerating the recovery from the disease. Available options are intravenous immunoglobulin (IVIG) and plasma exchange (PLEX). Both are equally effective in treating the disease.

IVIG is often the first line treatment because it does not require a central venous line and can be given peripherally. Proposed mechanisms of action include inhibition of activated complement and favorable modification of cytokine patterns. Treatment dose is 0.4 g/kg daily for 5 days initially, although repeated courses may be necessary. Side effects include headache (sometimes with meningeal signs), transfusion reactions, and increased risk of acute kidney injury and thrombotic events [4].

PLEX consists of removing large volumes of plasma from the circulation in exchange for replacement fluid with the objective of eliminating inflammatory mediators. PLEX requires a central venous line. The typical regimen is exchanging 1.5–2 plasma volumes per treatment session and to pursue five treatments alternating every other day. More treatments may be needed and efficacy is best if initiated early in the disease course and symptom onset. Complications from PLEX are mostly related to the placement of the central venous catheter. There is also the possibility of hypotension while pulling fluid from a patient who may have labile blood pressures. If the patient's blood pressure is unstable, PLEX needs to be initiated cautiously [4].

16.5 Myasthenia Gravis

Myasthenia Gravis (MG) is an autoimmune neuromuscular condition caused by autoantibodies that interfere with normal neuromuscular synaptic transmission. The antibody attaches to the

post-synaptic acetylcholine receptor, thus decreasing the amount of acetylcholine able to bind those receptors. This reduces the strength of muscle contraction and is responsible for the characteristic fatigability with repeated effort.

MG can remain restricted to the ocular muscles (Ocular Myasthenia), but most commonly affects all muscle groups (Generalized Myasthenia). Respiratory failure caused by MG is known as Myasthenic Crisis [4].

16.5.1 Clinical Presentation

The most defining symptom of MG is muscle fatigability, which is weakness that becomes progressively worse over periods of activity followed by recovery with rest. Signs and symptoms of MG, or an exacerbation of known MG, may occur after a recent illness or medication change. This fluctuating weakness often worsens in the afternoon and evening causing ptosis, diplopia and a nasal speaking voice.

Unlike GBS, patients with MG do not typically have any sensory symptoms as the disease affects the neuromuscular junction. Also in contrast with GBS, deep tendon reflexes are normal or only slightly decreased in MG [4].

16.5.2 Diagnosis

Presentation of MG can be distinct and specific, allowing for a purely clinical diagnosis. Response to medications that enhance acetylcholine transmission may confirm the diagnosis. Yet, the diagnosis is typically supported by serological and electrophysiological data.

NCS in patients with MG may display a decrease in the compound muscle action potential (CMAP) of at least 10% from the first to the fourth stimulus upon repetitive stimulation at a rate

of 2–5 Hz before and after isometric voluntary contraction. Findings on single-fiber EMG may show neuromuscular dysfunction in the form of jittering.

Acetylcholine receptor antibodies should be tested first because they are the most common (nearly 80% of patients with generalized MG have these antibodies). When acetylcholine receptor antibodies are not detected, it is advisable to check for antibodies against muscle-specific receptor tyrosine kinase (MuSk), which may produce MG with greater involvement of bulbar and respiratory muscles. Patients with a new diagnosis of MG should have a chest CT to evaluate the thymus for abnormalities (hyperplasia is common, but thymoma is also possible).

PFT should be used to assess for respiratory failure. PFT may not be as helpful in patients with MG experiencing bulbar weakness as they may not have the ability to create an appropriate seal on the mouth of the spirometer. Also, the fluctuating nature of the weakness may result in varying results with this testing [4].

16.5.3 Treatment

Treatment of MG in the ICU consists of providing respiratory support when necessary and administering immunomodulatory and anti-inflammatory therapies, immunosuppressant and cholinesterase inhibitors. A proposed algorithm is presented in Fig. 16.3.

Non-invasive ventilation may be invaluable in patients with severe myasthenic exacerbation and early myasthenic crisis. When initiated early – particularly before the development of hypercapnia – non-invasive ventilation with BiPAP may avert orotracheal intubation and substantially reduce the length of stay in the ICU. Most patients with MG tolerate BiPAP well, even if respiratory secretions are increased. In fact, the risk of

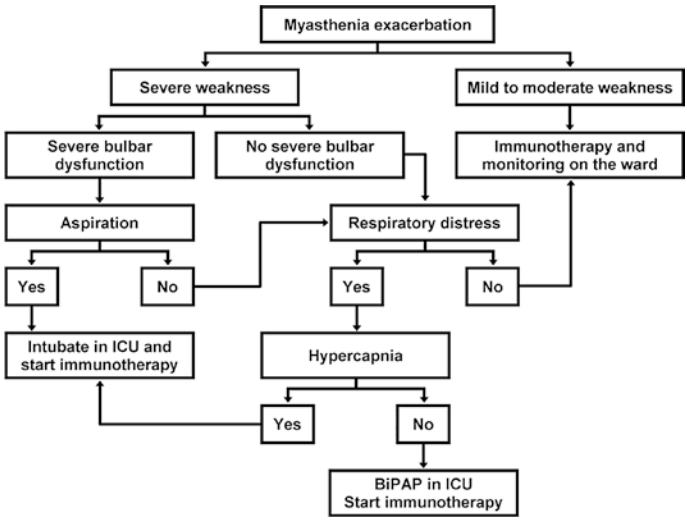

Fig. 16.3 Algorithm for the early management of myasthenia gravis exacerbation (Wiley-Blackwell, "The Practical Management of Guillain Barre Syndrome and myasthenic crisis" in *Emergency Management in Neurocritical Care*. Image used with permission from the Mayo Foundation for Medical Education and Research)

pneumonia is greater in patients treated directly with intubation and invasive mechanical ventilation compared with patients started on non-invasive ventilation [6].

IVIG or PLEX may be used to treat myasthenic exacerbations and myasthenic crisis. There is no evidence that one treatment is superior to the other. IVIG should be dosed 0.4 g/kg and administered for 5 days. The course may be lengthened if necessary. PLEX treatment should be administered every other day for five treatments.

Oral or IV steroids should be used in the patient with MG to reduce the inflammatory response. Steroids should be started with caution as they can produce weakness per se before

improving the myasthenia. Thus, the starting dose varies according to the patient's condition. When patients are already on steroids before hospitalization, the dose should not be reduced unless complications attributed to steroids are identified. For long-term maintenance, steroids may be partially or completely replaced by immunosuppressants (steroid-sparing agents) with better side-effect profile, such as azathioprine or mycophenolate mofetil.

An acetylcholinesterase inhibitor, typically pyridostigmine, should be part of the regimen for any symptomatic patient with MG. The purpose of this medication is to increase the amount of acetylcholine available at the level of the neuromuscular synaptic terminal by reducing its degradation. Thus, it represents a symptomatic treatment that complements the immune therapies aimed at correcting the underlying pathophysiology. Yet, it is crucial to use a sufficient dose of pyridostigmine when trying to avoid intubation in patients being treated with non-invasive ventilation and to liberate patients from invasive mechanical ventilation. Side effects include cramps, fasciculations, diarrhea, increase in respiratory secretions and bradycardia. Increased respiratory secretions be problematic in myasthenics with weak cough. The usual dose can range from 60 to 90 mg three to five times a day, but higher doses may be necessary in the most severe cases.

Thymectomy, surgical removal of the thymus, may be necessary in patients with thymoma or thymus hyperplasia. Thymectomy is indicated in the first year after symptoms and diagnosis [4].

16.6 Critical Illness Neuromyopathy

Critical Illness Neuromyopathy (CINM) is a term used to encompass polyneuropathy and myopathy acquired throughout

the course of a critical illness. It is also referred by the term ICU-acquired weakness. Patients with CINM may experience a wide variety of symptoms such as muscle weakness, atrophy and neuromuscular respiratory failure. The diagnosis of CINM is primarily clinical. Characteristically it is seen after septic shock complicated with multi-organ failure and resultant prolonged mechanical ventilation. However, it may occur after any critical illness and may develop within days of the ICU admission. It is most often recognized when patients are no longer receiving continuous sedation and cannot be weaned from mechanical ventilation. NCS and EMG may be helpful to confirm the diagnosis and exclude other causes of neuromuscular weakness. However, these electrophysiological studies may be confounded by peripheral edema, cold limbs, or inability of the patient to cooperate with the examination (e.g. when the patient is not awake enough to try to contract the muscles when instructed to do so during the needle examination). The term CINM has been favored to name this condition because there is often a coexistent involvement of peripheral nerves (critical illness polyneuropathy) and muscles (critical illness myopathy) in this disorder [3].

Critical Illness polyneuropathy affects the nerves and may cause axonal degeneration. Weakness is usually generalized affecting the body symmetrically. Respiratory muscle and core weakness are often affected which can lead to prolonged mechanical ventilation. NCS typically show reduced amplitude of motor/sensory nerve action potentials. EMG may show denervation.

Critical illness myopathy is characterized by myosin loss on biopsy specimens. Yet, muscle mass may decrease during critical illness due to inadequate nutrition and decreased mobility. On NCS nerve conduction velocity may be normal or minimally reduced, amplitude may be reduced and duration of compound muscle action potentials may be increased. Electromyography can confirm the diagnosis by showing spontaneous electrical

activity when the needle electrode penetrates the affected muscles.

16.6.1 Treatment/Prevention

There is no specific treatment for CINM. Thus, the best strategy is prevention. Early mobilization of patients in the ICU has been shown to reduce deconditioning and ICU-acquired weakness. Sedation holidays with spontaneous breathing trials have been shown to be helpful. Prolonged used of paralytic medications should be avoided when possible. Treating severe hyperglycemia may be helpful in avoiding nerve damage [3].

Summary Points

- Respiratory failure may be a result of primary neuromuscular diseases such as Myasthenia gravis, Guillain-Barre syndrome or amyotrophic lateral sclerosis; or it may occur after the development of weakness in the ICU (critical illness neuromyopathy and deconditioning).
- The APC should identify if the patient requires ventilatory assistance, which can be provided in the form of non-invasive ventilation using the BiPAP mask or via orotracheal intubation and conventional invasive mechanical ventilation.
- BiPAP is most beneficial in patients with myasthenic crisis and may prevent an intubation. Patients with Guillain-Barre syndrome should not be initiated on BiPAP and instead mechanically ventilated if respiratory failure is evident.

- Guillain-Barre Syndrome (GBS) is an autoimmune, inflammatory disease causing peripheral nerve damage to the myelin sheath portion of the nerve cell.
- Management of GBS includes supportive care, such as intubation and administration of immunomodulatory therapies.
- Myasthenia Gravis (MG) is an autoimmune neuromuscular condition caused by autoantibodies that interfere with the normal neuromuscular synaptic transmission.
- Treatment of MG in the ICU consists of providing respiratory support when necessary and administering immunomodulatory and anti-inflammatory therapies, immunosuppressant and cholinesterase inhibitors.

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Chapter 17
Hypoxic-Ischemic Injury After Cardiac Arrest

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17.1 Introduction

There are 350,000–450,000 out-of-hospital cardiac arrests each year in the United States [1]. Cardiopulmonary resuscitation (CPR) is attempted in 100,000 of these cases, and 40,000 are admitted to the hospital [2]. Cardiac arrest is often related to a primary cardiac arrhythmia but may also result from respiratory arrest or profound hypotension. Neurological injury, such as a devastating acute brain injury, traumatic brain injury, or aneurysmal subarachnoid hemorrhage, may also result in cardiac arrest.

Unfortunately, survival to discharge after cardiac arrest is less than 10%, and prognosis is unknown with patients remaining comatose for weeks [1]. Patients that survive cardiac arrest may have numerous consequences including brain injury, cardiac dysfunction, and systemic ischemia. The pathophysiology of brain injury caused by cardiac arrest is understood; however,

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less is known about the biological mechanisms and cellular pathways mediating recovery in this population. Once return of spontaneous circulation (ROSC) has occurred, the chances of survival may be determined by several clinical observations. Patients hospitalized following cardiac arrest will be admitted to an intensive care unit and will frequently be in refractory cardiogenic shock, requiring multiple vasopressors.

This chapter addresses the pathophysiology, clinical assessment, and identification of poor prognostic indicators in patients with anoxic-ischemic brain injury after cardiac arrest. Expert consultations for assessment of comatose patients after CPR are quite common. The assessment and management of patients with anoxic-ischemic injury after ROSC is a major clinical task for the interdisciplinary team caring for these patients in the intensive care unit.

17.1.1 Pathophysiology of Anoxic-Ischemic Injury: The Basic Principles

The brain is able to tolerate anoxia for approximately 2–4 min before irreversible neuronal damage occurs. In cardiac arrest, whether it is due to asystole or ventricular fibrillation, there is no measurable blood flow to the brain. With standard CPR techniques, only one third of the pre-arrest cerebral blood flow can be achieved. Cardiac arrest is the most profound injury to the brain, even worse than traumatic brain injury. Hypoxic injury alone may result in temporary synaptic dysfunction, but when asystole, hypotension, and minimal cerebral perfusion occur during chest compression, ischemic brain injury results. Ischemia leads to the dysfunction of cell membrane ion pumps and a rapid unraveling of the cellular machinery causing the opening of calcium channels and release of excitatory amino

acids, particularly glutamate and aspartate, which causes calcium overload and cellular death. Restoration of the systemic blood circulation does not automatically result in reperfusion of cerebral tissue. There are several areas in the brain that are not reperfused, which is related to endothelial edema caused by ischemia, blood sludging, early intravascular coagulation, and leukocyte adhesion [1–3].

Ischemia results in activation of the N-methyl-D-aspartate (NMDA) and *a*-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, causing the opening of calcium and sodium channels and an apoptosis pathway [4]. This biochemical pathway happens very quickly and is not preventable, thus allowing the neurons to be very susceptible to hypoxic-ischemic injury. Selected regions of the brain are specifically susceptible to global ischemia including the hippocampus, neocortex, cerebellum, corpus striatum, and thalamus [1, 2].

After reestablishment of circulation, reperfusion and reoxygenation can cause further neuronal damage over a period of hours to days, which is often referred as "reperfusion injury." Alterations in the inflammatory response can cause endothelium activation, leukocyte infiltration, and further tissue injury. Other contributing factors include hypotension, hypoxemia, impaired cerebrovascular autoregulation, and brain edema, which can further impede the delivery of oxygen to the brain [2].

Therapeutic hypothermia is initiated to limit neurologic injury by slowing down brain metabolism. This aids in decreasing the amount of oxygen and adenosine triphosphate (ATP) being consumed [2]. Apoptosis is prevented by means of calcium overload and glutamate release, as well as the initiation of antiapoptotic Bcl-2 and the destruction of the proapoptotic factor BAX [5]. Therapeutic hypothermia has also been shown to suppress inflammation that appears after global cerebral ischemia and to decrease hyperemia and delayed hypoperfusion [1].

17.2 Case Presentation

A 40-year-old female with past medical history of diabetes mellitus type II, hyperlipidemia, hypertension, smoker who was in her usual state of health during the day developed chest pain on and off over the late afternoon and early evening, presented to the local emergency department (ED). Soon after arrival in the ED, she went into ventricular fibrillation and required 45 min of CPR, with a total of 12 shocks delivered. Patient received a total of 450 mg of amiodarone, followed by initiation of an amiodarone drip. The patient was intubated, 12 lead ECG completed that revealed ST elevation. The patient received aspirin and clopidogrel. Patient was transferred to the CCU and underwent cardiac catheterization, resulting in stent placement of the LAD coronary artery. Upon neurological examination, the patient had pupils 4 mm and reactive to light bilaterally, cough, gag and corneal reflexes intact, no facial droop, and moved all four extremities to painful stimuli mostly flexion. Targeted temperature management to 36 °C was initiated. CT scan of the brain showed no evidence of brain edema. Neurological examination following the rewarming period demonstrated the patient did not open eyes to voice or tracking, roving eye movements, withdrawal in all four extremities or possibly decorticate posturing, intact brainstem reflexes, and triggering the ventilator. EEG shows diffuse suppression with questionable reactivity but no epileptiform activity. SSEP shows normal N20 responses. Serum neuron-specific enolase is normal. We are asked to assess the neurologic injury and prospects of improvement. Several days were allowed before prognostic neurological exam to allow sedative medications to metabolize. The patient did not improve neurologically and remained comatose. MRI was performed 4 days after CPR which showed diffuse cortical infarction. After failure to improve neurologically 14 days after CPR, family made the decision to withdraw support.

17.3 Management and Interventions

17.3.1 Targeted Temperature Management and Its Practice

Induced hypothermia, or targeted hypothermia, aims to reduce the body's core temperature. Recent randomized clinical trials enrolling out-of-hospital cardiac arrest patients demonstrated that aggressive hypothermia (33C) does not provide additional benefit over mild hypothermia (36C). Detailed hypothermia protocols are usually developed by each institution, and providers may see substantial variation from hospital to hospital.

Cooling requires reduction in core temperature with ice packs, rapid infusion of cold intravenous fluids, and the use of external cooling devices or endovascular cooling systems [6]. Therapeutic hypothermia should be initiated as soon as possible following cardiac arrest and continued for 24 h prior to the rewarming phase. Shivering is expected and should be treated with sedatives, opioids, or neuromuscular blockade (see section in Chap. 23 for shivering management recommendations). The absence of shivering during hypothermia treatment indicates severe brain injury in the hypothalamus and purports a poor prognosis [1, 7]. During therapeutic hypothermia treatment, hyperglycemia may occur and result in a decreased urine output. Other complications that may occur include pneumonia, cardiac arrhythmias, and pancreatitis. Vasopressors may be needed, but this is likely for treatment of cardiogenic shock from myocardial stunning [3]. Therapeutic hypothermia may also result in electrolyte imbalances such as hypokalemia, hypomagnesemia, hypophosphatemia, and hyperglycemia. Therefore, monitoring of serum electrolytes at regular intervals will be pertinent to guide the appropriate therapies [2]. Seizures may also occur during therapeutic hypothermia and the rewarming phase of the treatment. Typically, subclinical seizures are not identified, so it

would be recommended to monitor patients with continuous electroencephalographics (EEG) monitoring and treat the seizures if they transpire to improve patient outcomes.

Following the therapeutic hypothermia period, the patient will need to be rewarmed slowly to normal core body temperature. Clinical trials have demonstrated an improved patient outcome of 55% in the therapeutic hypothermia group, when compared to 39% in the control group [4]. It is important to know that patients may persist in a coma for a period of time following cardiac arrest and still have neurological recovery.

17.3.2 Neurologic Evaluation of the Comatose Patient After Cardiac Arrest

How do we interpret a comatose patient? How do we assess the clinical consequences of acute loss of multiple cortical layers, loss of watershed areas as a result of no flow, and loss of neurons in extremely susceptible areas such as the global pallidus?

First, no blood flow to the brain or a fraction of blood flow during resuscitation first damages the deep basal ganglia and thalami, followed by the cortical mantle, and finally the brainstem. Few patients become brain dead (which requires involvement of brainstem reflexes clinically) after CPR because the brainstem is resilient to major systemic injury. Pathology shows ischemic injury to the cortical laminae, globus pallidus, and cerebellum, and these changes can be found on MR imaging. Thus, most patients will have clinical signs of bi-hemispheric damage with no localizing signs. Common exam findings include increased tone, no motor response to pain or reflexive responses, gaze preference up or down (indicative of thalamic injury), and normal brainstem reflexes. If cortical areas (including most vertical cortical layers) are damaged, myoclonus status could appear. Myoclonus status epilepticus is an unusual presentation, often seen after prolonged cardiopulmonary

resuscitation or exsanguination and is vigorous, forceful with jerks involving all four limbs and with significant facial distortions, all in association with upward eye jerks. Shivering, rigor, or non-sustained clonus is often misinterpreted as myoclonus. Myoclonus status may be associated with continuous seizures on EEG, a burst suppression pattern, or marked decrease in amplitude. Myoclonus status epilepticus is also more frequently associated with CT scan abnormalities. Thus it is a telltale sign of a major severity of injury. Patients with different degrees of cortical injury are more difficult to prognosticate.

Second, patients with dilated pupils, loss of pupil reflexes, and corneal reflexes indicating pontomesencephalic involvement will do very poorly (unless these reflexes are muted by drugs used to manage shivering as a result of targeted temperature management protocol). Loss of brainstem reflexes may occur from prolonged anoxic injury allowing more injury or may occur as a result of brain edema also a result of more severe injury to the cortex. These core fundamentals of correlating pathophysiology in conjunction with clinical findings help in understanding the spectrum of anoxic-ischemic injury.

A complete neurologic evaluation should occur following the ROSC post-cardiac arrest. It will be vital to assure that no extenuating factors will confound the examination such as (obviously) paralytic or sedative medications and persistent hypotension (SBP less than 90 mmHg). Early awakening after cardiac arrest, ability to localize to painful stimulus, or the ability to follow simple commands are indicators of a positive outcome. However, a significant percentage of post-cardiac arrest patients will have a poor neurologic outcome, and it becomes important to sort out who might have a probable chance to survive cognitively intact. Devastating neurologic outcomes leave providers and families to be burdened with hard decisions related to goals of care, acceptable outcomes, and end-of-life decisions [1].

The most important concept is to understand that particular elements of the neurologic examination are vital when determining the severity of anoxic-ischemic injury. Clinical neurological examination should follow a standard procedure. The standard examination should include motor response to pain, with specific attention to myoclonus and spontaneous or elicited eye movement abnormalities and brainstem reflexes [6–8]. When performing brainstem reflex testing, it is important to include pupillary light reflex, corneal reflex, and cough and gag reflexes if the patient has spontaneous respirations. The brainstem is far more resilient to anoxic-ischemic injury than the cortex, so when evaluating the brainstem reflexes and the pupil response to light, it is frequently found to be within normal limits. If you find an absent pupil response, consider that it may be a result of high doses of atropine used during resuscitation. Fixed and dilated pupils examined several hours post-cardiac arrest is a clinical indicator of a poor outcome. Fixed and dilated pupils would rarely be an isolated examination finding but more commonly seen with brainstem involvement. Corneal reflexes may be absent initially but often return over time. Identifying eye movement abnormalities provides more clinical information; for example, having a persistent upward gaze indicates significant global bi-hemispheric injury that may also include involvement of the thalamus. Persistent upward gaze is often a clinical indicator of a poor functional outcome but in 10% of cases was found to be consistent with survival. When eliciting the vestibulo-ocular reflex or rapid head movement, the examiner may see a downward gaze. Other eye abnormalities may include the ping pong gaze, lateral gaze deviations, or continuous blinking which are not examined for prognostic value [6].

An essential clinical indicator is myoclonus status epilepticus or more clearly explained as continuous and forceful jerking movements involving facial muscles, limbs, and abdominal muscles [6]. These jerks can be provoked by touch or hand clapping and may include the diaphragm which affects ventilation of the patient [6]. Myoclonus status epilepticus signifies a poor prognosis [7].

17.3.3 Ancillary Diagnostics

Other diagnostic tests can be considered to assist in the neurologic examination including electroencephalogram (EEG), somatosensory evoked potentials (SSEPs) biochemical markers, computed tomography (CT), and magnetic resonance imaging (MRI). The most common EEG finding is episodic low-amplitude events (ELAE). ELAEs are often correlated with medication effect and therefore not suggestive of hypoxic-ischemic cerebral injury. When there is background EEG motion that reveals generalized slow wave motion, the patient has an increased chance of a better outcome. When a burst suppression pattern is identified on EEG that is often suggestive of a fatal outcome or vegetative state, EEG with the existence of faster frequency with spontaneous fluctuation and reactivity to stimuli provides the indication of a better neurologic recovery [4]. When EEG indicates seizures, the consideration of continuous EEG and treatment of the seizures will need to be considered.

SSEPs are another test used to assist with identifying neurological recovery. SSEPs are not confounded by medications, temperature, or metabolic abnormalities and therefore are a reliable tool for aiding neurologic prognostication [6]. SSEP involves the peripheral stimulation of the median nerve that results in a potential at the brachial plexus, cervical spinal cord, and bilateral cortex potentials (N20), evaluated with scalp electrodes. In order for the SSEP to be considered trustworthy, the cervical spine potential has to be acknowledged, as this could be a possible concern in patients with severe anoxic-ischemic injury involving the cervical spinal cord. The bilateral absence of cortical potentials (N20 component) is approximately 100% definite in calculating poor outcomes when completed between day one and day three post-cardiac arrest [6, 7]. Nevertheless, the existence of cortical N20 responses does not assure awakening from a coma will transpire. SSEP along with the clinical examination does offer adequate and reliable information for prognostication of neurologic recovery [8].

Biochemical markers that have been identified to detect cerebral damage post-cardiac arrest include serum neuron-specific enolase (NSE) and S100 [9]. NSE is a gamma isomer of enolase that is found in the neurons, and S100 is a calcium-binding astroglial protein [6]. Elevated levels of NSE and S100 are linked to hypoxic-ischemic brain injury and poor neurologic outcomes; however, we need to keep in mind that there is absence of standardization in how we measure these markers. Therapeutic hypothermia may also play a role in the effects of metabolism and clearance of these biomarkers, thus hindering the prognostic value [6].

17.3.4 Imaging

A majority of CT scans post-cardiac arrest will be normal; however, additional CT scans over the next couple of days may demonstrate changes. CT changes that may occur are related to widespread cerebral edema. Often these patients have several additional clinical indicators signifying a poor neurologic outcome. MRI imaging is more reliable in prognosticating for outcome and provides details such has diffuse cortical injury that involves bithalamic and putaminal injury [4]. A normal MRI does not necessarily indicate a better outcome because clinicians have seen numerous patients in a persistent vegetative state or minimally conscious states with normal MRI scans, with brain atrophy seen months following initial injury [4].

There are numerous diagnostic tests, including neuroimaging, electrophysiology, and laboratory testing, that may aid in evaluating neurologic recovery, but there is no one stand-alone test that is satisfactory in prognostication [7]. Some guidance is shown in Fig. 17.1. Timing of tests is not known, but we can expect MRI, EEG, and SSEP abnormalities within 24 h after the event.

MRI may become abnormal if repeated, but there are patients with repeatedly normal MRI who never awaken only to demonstrate generalized brain atrophy later.

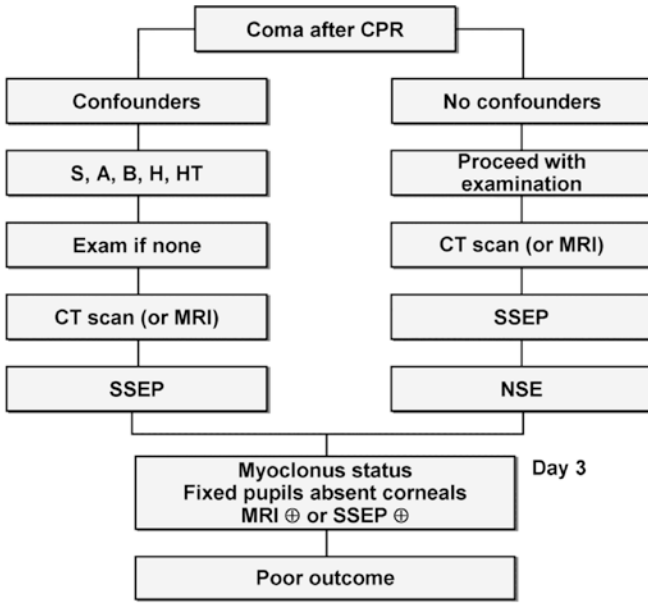

Fig. 17.1 Evaluation of hypoxic ischemic injury algorithm. *S* sedatives, *A* analgesics, *B* neuromuscular junction blockers, *H* hypothermia

17.3.5 Prognostication Summary

Anoxic-ischemic injury remains the primary cause of disability post-cardiac arrest [10]. Targeted hypothermia is standard of care in many hospitals with modern ICUs, but the practice varies. Uncertainties about the timing of initial therapy, duration of therapy, best means to cool, and target temperature during therapeutic hypothermia exist. Prognostication in these comatose patients remains unreliable if there is (1) no myoclonus status, (2) present brainstem reflexes, (3) no suppression of EEG background or burst suppression pattern, (4) normal or near normal MRI, and (5) normal SSEPs. This means that in the majority of patients, outcome cannot be clearly established in the first

weeks. Failure to improve motor response to localization implies longstanding cognitive deficits and even failure to awaken beyond a minimally conscious state. Neurologic assessment remains key and cannot be replaced by any ancillary test. Thus, neurologists and neurology specialty trained providers will continue to be consulted to perform thorough neurological examinations on patients post-cardiac arrest and provide their expertise in treating and prognostication to guide the primary care providers and families in determining goals of care.

Summary Points

- Targeted hypothermia is the primary treatment strategy following cardiac arrest to preserve neurological function.
- Shivering is expected with therapeutic hypothermia and should be treated with sedatives, opioids, or neuromuscular blockade agents.
- Repeat neurologic examination without confounders often predicts poor outcome.
- MRI and SSEP are helpful for determining degree of injury.
- The absence of brainstem reflexes indicates poor outcome.
- Uncertainty remains regarding the presence of seizures or seizure activity in comatose patients following cardiac arrest in identifying if it is a treatable complication or indicator of substantial brain injury.

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Chapter 18
Brain Death and Organ Donation

Dea Mahanes and David Greer

18.1 Introduction

In the United States and many other countries, death can be determined by either cardiorespiratory or neurological criteria. The scope of this chapter is limited to declaration of death by neurologic criteria ("brain death") in the United States. Standards may differ slightly in other countries. While death by cardiorespiratory criteria is marked by the cessation of heart function and breathing, death by neurological criteria (DNC) is marked by cessation of whole brain function, including the brain stem [1]. When performed according to the nationally accepted standards, brain death is irreversible; there are no substantiated cases of recovery when the appropriate procedures

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are followed [2]. The first steps in declaring a patient dead by brain criteria are to identify the cause of neurologic devastation, to establish its irreversibility, and to rule out confounders or alternative explanations for the patient's condition. The next step is a clinical examination, typically performed by an attending physician, to evaluate for any signs of brain function. A second clinical exam by a different physician may be required by state law or institutional policy. Finally, an apnea test is performed to assess the patient's respiratory drive in response to significant hypercarbia and acidosis. If prerequisites are met, the clinical examination reveals no brain function, and the patient does not attempt to breathe on the apnea test in the setting of adequate stimuli (hypercarbia and acidosis), then the patient is declared legally dead. If any part of the clinical examination is unreliable or cannot be performed, ancillary tests may be used to demonstrate loss of brain perfusion (conventional angiography, nuclear perfusion study, or transcranial Doppler) or electrical activity (electroencephalography). Some patients who are declared brain dead may become organ donors, based on their previously documented wishes or with family authorization. Advanced practice clinicians (APCs) play a key role in managing patients before, during, and after the process of declaring death by brain criteria.

18.2 Case Presentation

E.H., a 36-year-old male with a history of hypertension, was found unresponsive by his roommate about 7 h after last being seen normal. He was found lying on the couch, with a bottle of ibuprofen lying nearby. EMS was called, and E.H. was transported to the local emergency department (ED). His BP on arrival in the ED was 258/102 (MAP 154), and a brief neurological exam revealed extensor posturing of his extremities, pupils

6 mm and nonreactive bilaterally, no gag reflex, and a minimal cough reflex. E.H. was intubated, his BP controlled, mannitol administered, and a CT scan performed that revealed a large intracerebral hemorrhage with intraventricular extension. Following placement of an external ventricular drain and surgical clot evacuation, E.H. was transferred to the neuroscience ICU where his exam remained unchanged. E.H.'s sister and his mother, identified as his surrogate decision-maker by state law and institutional policy, arrived at the bedside and were updated. A post-op CT/CTA scan revealed diffuse cerebral edema and minimal cerebral blood flow, especially in the left hemisphere, and signs of herniation. E.H. was managed aggressively according to the hospital's devastating brain injury guidelines, but over the next 24 h his exam continued to decline with loss of all movement and brainstem reflexes. With family present at the bedside and supported by the social worker, brain death was declared approximately 48 h after admission. The local Organ Procurement Organization (OPO), initially contacted by the ED, was on-site and approached E.H.'s family regarding organ donation. E.H.'s mother authorized donation, stating that E.H. recently had a friend who received a kidney transplant and E.H. expressed his wishes to donate his organs if anything ever happened to him. Approximately 72 h after ICU admission, E.H. was taken to the OR where he donates his heart, lungs, liver, kidneys, and pancreas.

18.3 Principles of Brain Death

For APCs, comprehensive care of patients in the neuro ICU includes identifying and supporting patients who are likely to progress to brain death. Although there are some earlier references to brain death, criteria for brain death diagnosis were first outlined in a report by the Harvard Ad Hoc Committee in 1968

[3]. In 1981, a report from the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Biobehavioral Research formed the basis of the Uniform Determination of Death Act (UDDA) [1]. The UDDA states "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards" [1]. In the United States, laws consistent with the UDDA have been adopted in all states, although New Jersey, New York, Illinois, and California require certain accommodations for religious or moral beliefs [4]. Most state laws and organizational policies for determination of brain death closely follow practice parameters from the American Academy of Neurology [2, 5]. The American Academy of Neurology (AAN) practice parameters, initially published in 1995 and updated in 2010, provide the "accepted medical standards" referred to in the UDDA. Despite these established practice parameters, a recent review demonstrated marked variability in policies for determination of death by neurologic criteria across the United States [6]. Organizational policies (and in some cases state law) often require an attending physician to make the declaration of brain death [6], but the APC in the neuro ICU plays a key role in managing these patients. A comprehensive understanding of brain death will allow the APC to better manage patients and support families throughout the evaluation process.

Declaration of brain death requires a clinical examination that is consistent with loss of whole brain function, including the brain stem. The patient must be comatose due to a known cause, typically established by neuroimaging. Patients with alternative causes of unresponsiveness such as fulminant Guillain-Barré syndrome will not have imaging findings sufficient to explain their condition, or the clinical history will give insights to the underlying condition. In addition, other confounding factors that might impact the clinical exam must be excluded [2].

18.4 Brain Death Evaluation and Clinical Management

When patients present with devastating neurological injury, the care team's first priority is to provide interventions that promote physiological stability, target the underlying cause of the injury, and prevent secondary brain injury, unless such interventions are inconsistent with the patient's previously expressed wishes. "Devastating brain injury guidelines (DBIGs)," sometimes called "catastrophic brain injury guidelines (CBIGs)," are implemented when patient survival is uncertain or unlikely because of neurological insult. DBIGs focus on maintaining the patient's physiologic stability, with the goals of promoting recovery when possible, allowing time for family to arrive at the bedside, and maintaining the option of organ donation if curative interventions are not possible [7]. Table 18.1 provides one example of DBIGs.

In some cases, the injury to the brain is so severe that compression of the brain stem occurs, or loss of perfusion to the entire brain occurs due to highly elevated ICP, resulting in loss of function of the entire brain, including the brain stem. These patients can be declared dead by neurologic criteria (DNC). Clinical or imaging findings must reveal a reason for the patient to be unresponsive; examples include but are not limited to large SAH or ICH, traumatic injury, or diffuse cerebral edema. Potential confounders that must be excluded include the effects of CNS depressant drugs; neuromuscular blockade; and severe electrolyte, acid-base, or endocrine disturbance [2]. Body temperature must be normal, with a lower limit of 36 °C recommended by the AAN practice parameters. Blood pressure must also be adequate, defined by the AAN practice parameter as ≥100 mmHg, with or without vasopressor support. Once the cause of unresponsiveness has been identified and possible confounders have been eliminated, testing for DNC can proceed.

Table 18.1 Devastating brain injury guidelines

The purpose of implementing devastating brain injury guidelines is to promote physiologic stability in order to support potential for neurological improvement, allow time for family presence, and preserve the opportunity for organ donation

Target	*Interventions*
Oxygenation and ventilation: maintain PaO2 > 100 and pH 7.35–7.45	1. Adjust ventilator as appropriate 2. Maintain pulmonary hygiene interventions (turn q 2 h, suction)
Blood pressure: maintain MAP >60 mm Hg and SBP > 100 mm Hg	1. Administer IV fluids (NS or LR unless lab values indicate otherwise) to maintain euvolemia. Adequate intravascular volume is critical to hemodynamic stability 2. Vasopressor support: if patient remains hypotensive once euvolemic, start vasopressors and titrate to keep MAP >60 mm Hg and SBP > 100 mm Hg Note: tachycardia and hypertension may be seen immediately prior to brainstem herniation. If treatment is desired, use only short-acting medications
Temperature: maintain normothermia. (Note: for some populations, hypothermia may be used as a therapeutic measure)	1. Monitor temperature at least q 1 h 2. Maintain temperature 36 °C–37.5 °C using cooling devices as needed. In general, active rewarming of neurologic patients is not recommended, but may be necessary prior to assessment of death by neurologic criteria
Urine output: maintain urine output >0.5 ml/kg/h and <400 ml/h	1. If <0.5 ml/kg/h, reassess hydration and need for BP support 2. If >400 ml/h, consider diabetes insipidus and check serum sodium. Treat DI with desmopressin (DDAVP) 1–2 mcg IVP or an infusion of vasopressin 1–2.5 units/h, and replace urine output ml for ml with 0.45% saline
Labs: monitor labs and treat as appropriate	1. BMP, Mg, Phos, CBC, PT/PTT, blood bank sample for ABO typing initially and PRN 2. Maintain Hgb > 8 g/dL and HCT > 24%. 3. Replete electrolytes as needed 4. Maintain blood glucose between 80 and 180 mg/dL

Examination for DNC encompasses three cardinal features: coma, absence of brainstem reflexes, and apnea. One examination, performed according to the AAN guidelines, is clinically sufficient to declare DNC in adults [2], but a period of observation and a second exam is sometimes required by state law or organizational policy.

18.4.1 Coma

Assessing for response to noxious stimulus is the first part of the clinical exam for DNC. Patients who are DNC exhibit no eye opening or movement and no body movement in response to central and peripheral pain stimulus, except for reflexes mediated by the spinal cord. One of the most common reflexes mediated by the spinal cord is triple flexion, characterized by stereotypical flexion at the hip, knee, and ankle. Other movements that may be observed after DNC include toe movements, finger movements, and the Lazarus signs, characterized by a rising up motion with the torso and arms [2, 8]. Spinally mediated movements can occur in response to stimulation and are most common in the first 24 h after DNC [8]. Any movement, even spinal reflexes, can be very disconcerting to the patient's family and to the staff, and a clear explanation of the nature of the movement should be provided. If there is any question about whether or not a movement is initiated by the brain, ancillary testing is recommended (see below).

18.4.2 Brainstem Areflexia

The next step in the evaluation of DNC is assessment of brainstem reflexes and cranial nerve function, as outlined in the AAN guidelines (see Table 18.2) [2].

18.4.3 Apnea

The final step in the clinical exam is apnea testing, which assesses for spontaneous respirations in response to an elevated carbon dioxide level and acidosis. There are several acceptable methods for completing the apnea test [2, 9]. The most common and validated is apneic oxygenation, in which oxygen is provided through a cannula inserted to the level of the carina or via a T-piece, but the patient is not ventilated. The patient is observed for spontaneous respirations, and reconnected to the ventilator if any respirations are noted. The test is also aborted if the patient's oxygen saturation or blood pressure drops below established limits, defined in the AAN practice parameters as an oxygen saturation of less than 85% for more than 30 s or a systolic blood pressure less than 90 mmHg [2]. If no spontaneous respirations are observed with the patient disconnected from the ventilator, a blood gas is drawn, typically 8–10 min after the test is initiated. A $PaCO_2$ of >60 mmHg, or a rise in $PaCO_2$ of >20 mmHg in a patient with baseline elevations in $PaCO_2$ due to COPD or OSA, is consistent with DNC [2]. The patient is reconnected to the ventilator while results are reviewed and shared with the family. The patient's time of death is the time the blood gas result consistent with DNC is reported. Transcutaneous CO_2 monitoring may be a useful adjunct to guide the timing of blood gas measurements, but arterial blood gas measurements are still required [9].

The APC has a key role in preparing the patient for apnea testing and maintaining patient stability during the test. Hypovolemia is common in brain death due to the development of diabetes insipidus, and will increase the likelihood of hypotension during apnea testing. Careful attention to fluid balance is paramount. Many patients undergoing apnea testing will be on vasopressors, and upward titration may be

Table 18.2 Brainstem reflexes and cranial nerve function in DNC evaluation

Pupillary light reflex	Pupils are nonreactive to bright light. Size varies from mid-position to dilated. Smaller pupils should alert the clinician to the possibility of drug effect
Oculovestibular reflex	The head of bed is elevated to 30°, and the integrity of the tympanic membrane and auditory canal is confirmed. Ice water is instilled into the external auditory canal for 60 s continuously, one ear at a time, while observing for eye movement with the patients' eyelids held open. In patients with DNC, no movement is seen. An interval of 5 min should transpire before testing the contralateral ear
Oculocephalic reflex	Except in cases where cervical spine instability cannot be ruled out, the oculocephalic reflex is tested by rotating the patient's head rapidly side to side, while holding the eyelids open and observing for eye movement. Movement in response to rapid vertical head movement may also be tested. Any eye movement precludes the declaration of DNC
Corneal reflex	No eyelid movement is seen when the cornea is stimulated. For brain death determination, an adequate stimulus must be provided, such as pressing with a sterile cotton swab on the cornea adjacent to the iris. Care must be taken not to injure the cornea to maintain the option of subsequent donation
Facial movement to noxious stimulation	No grimacing or other facial movement is observed in response to deep pressure on the supraorbital ridge and temporomandibular joint.
Pharyngeal (gag) reflex	The posterior pharynx is stimulated, most often with a rigid suction catheter or tongue blade. There is no response in patients who are DNC.
Tracheal (cough) reflex	No cough reflex is noted in response to insertion of a suction catheter down the endotracheal tube to the level of the carina

required. If not already in use, vasopressors and/or intravenous fluids should be made available during apnea testing. Prior to starting apnea testing, the patient's systolic blood pressure should be >100 mmHg, and a buffer of at least 110–120 mmHg is recommended. Careful adjustment of ventilator settings in preparation for apnea testing is needed. Prior to starting the apnea test, the patient's CO_2 should be normal (35–45 mmHg) and preoxygenation is mandatory to a PaO_2 of >200 mmHg. At no point during the apnea test should the patient become hypoxic, and hypoxia is not the stimulus for respiration (hypercarbia, and more importantly, acidosis is what simulates the medullary respiratory centers). As outlined in the AAN practice parameters, body temperature should be ≥36 °C; CO_2 is produced more slowly at lower temperatures, which could potentially lengthen the amount of time required to complete apnea testing. Close collaboration with the patient's bedside nurse is essential to optimize the patient's physiologic stability prior to and during apnea testing. With adequate preparation (especially preoxygenation) and careful management, apnea testing can be safely completed in most patients [10].

Of note, it is common practice at some institutions to complete apnea testing with the patient attached to the ventilator but placed on CPAP with a pressure trigger of −2 cm H_2O. Use of this method is not recommended because the cardiac cycle may be enough to trigger a ventilator breath in some patients.

18.4.4 Ancillary Tests

Death by neurologic criteria is clinically determined. In cases where one or more elements of the clinical exam cannot be reliably assessed, ancillary tests are used to support the diagnosis, but are

not a substitute for the clinical exam. Ancillary tests may also be useful when complex motor movements are present and there is question as to whether they are spinally or cerebrally mediated. Four ancillary tests are recognized by the AAN guidelines as adequately tested and reliable to support the determinations of DNC: catheter angiography, cerebral radionuclide scintigraphy using single photon emission computed tomography, electroencephalography (EEG), and transcranial Doppler (TCD) ultrasound [2]. Each of these ancillary tests has limitations. EEG is easy to perform but subject to artifact from the electromagnetic interference in the ICU environment, and assessment of subcortical structures is poor. Both catheter angiography and radionuclide studies require patient transport, and false positives are possible if perfusion has been reestablished to devitalized brain tissue. TCDs do not require patient transport and are noninvasive, but can be technically challenging, with the absence of flow due to brain death potentially confused with absence of flow because of limited bone windows. Thus, reversal of flow or zero flow during diastole is required, signifying no effective forward cerebral flow. While CT angiography (CTA), MR angiography, and evoked potentials have been investigated as potential ancillary tests for DNC, these studies currently lack the evidence necessary to support their use [2] and CTA has been associated with false positive findings [11].

Please refer to Fig. 18.1 for a sample criteria checklist for determination of death in adults by neurologic criteria, provided by Yale New Haven Hospital.

18.5 Family Communication

DNC is a challenging concept for many family members to understand. The ventilator provides mechanical respiratory support, and cardiovascular function is often supported by flu-

UNIT NO.

NAME

BIRTH DATE:

VISIT NUMBER:

(If handwritten, record name, unit no., birth date, and visit no.)

Yale-New Haven Hospital

Worksheet for the Determination of Death in ADULTS by Neurological Criteria

If the clinical examination cannot be performed adequately and an ancillary test is necessary, two examinations are NOTrequired.

I. PREREQUISITES	I. FIRST EXAM	I. SECOND EXAM
A. Clinical or neuroimaging evidence of acute CNS catastrophe that is compatible with irreversible loss of brain function	A. Yes ☐ No ☐	A. Yes ☐ No ☐
B. Absence of complicating medical conditions		
1. absence of severe electrolyte, acid base or endocrine disturbance or severe hyperammonemia	1. Yes ☐ No ☐	1. Yes ☐ No ☐
2. absence of drug intoxication or poisoning	2. Yes ☐ No ☐	2. Yes ☐ No ☐
3. core temperature 96.8°F / 36°C or greater	3. Yes ☐ No ☐	3. Yes ☐ No ☐
II. COMA or UNRESPONSIVENESS	**II. FIRST EXAM**	**II. SECOND EXAM**
Absence of any cerebrally-mediated response to auditory and tactile noxious stimulation, peripherally and in the cranium	Yes ☐ No ☐	Yes ☐ No ☐
III. ABSENCE of BRAINSTEM REFLEXES	**III. FIRST EXAM**	**III. SECOND EXAM**
A. Absent pupillary responses		
1. pupillary size midposition or dilated	1. Yes ☐ No ☐ Untestable☐	1. Yes ☐ No ☐ Untestable☐
2. pupils unresponsive to bright light	2. Yes ☐ No ☐ Untestable☐	2. Yes ☐ No ☐ Untestable☐
B. Absent eye movements		
1. absent oculocephalic reflex	1. Yes ☐ No ☐ Untestable☐	1. Yes ☐ No ☐ Untestable☐
2. absent oculovestibular reflex (caloric responses) (N.B. The oculovestibular reflex must always be tested. The oculocephalic test may be contraindicated when C-spine integrity questioned; otherwise it must be tested.)	2. Yes ☐ No ☐ Untestable☐	2. Yes ☐ No ☐ Untestable☐
C. Absent corneal reflexes	C. Yes ☐ No ☐ Untestable☐	C. Yes ☐ No ☐ Untestable☐
D. Absent pharyngeal and tracheal reflexes		
1. absent response to posterior pharyngeal stimulation	1. Yes ☐ No ☐ Untestable☐	1. Yes ☐ No ☐ Untestable☐
2. absent cough to bronchial suctioning	2. Yes ☐ No ☐ Untestable☐	2. Yes ☐ No ☐ Untestable☐
3. absent spontaneous respirations	3. Yes ☐ No ☐	3. Yes ☐ No ☐

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Fig. 18.1 Sample checklist for determination of death in adults by neurological criteria

Pt. Name: Unit No. Visit No.	YNHH Worksheet for the Determination of Death in Adults by Neurological Criteria

IV. APNEA	IV. FIRST EXAM	IV. REPEAT APNEA TESTING IS NOT REQUIRED
A. Prerequisites		
1. core temperature 96.8°F/ 36°C or greater	1. Yes☐ No ☐	
2. systolic BP>100 mmHg (with or without vasopressor agents)	2. Yes☐ No ☐	
3. arterial pCO_2 40 +/-5 mmHg(in known non-CO_2 retainer)	3. Yes☐ No ☐	
4. arterial pO_2 greater than 90 mm Hg	4. Yes☐ No ☐	
B. Apnea testing checklist		
1. preoxygenateto a PaO_2 >200 mm Hg and then administer 100% FIO_2 during the entire test period	1. Yes☐ No ☐	
2. disconnect the ventilator; monitor with pulse oximeter throughout the test period	2. Yes☐ No ☐	
3. deliver 100% FIO_2 into the trachea via a T piece or via a cannula at the level of the carina, maintaining oxygen saturation above 85%	3. Yes☐ No ☐	
4. check arterial blood gases at 8-10 minutes and reconnect the ventilator when either a) pCO_2 is 60 mmHg or greater, or b) pCO_2 is greater than 20 mmHg above the patient's known baseline (in CO_2 retainers)	4. Yes☐ No ☐	
5. abort the apnea test and immediately reconnect the ventilator for any of the following reasons:		
a. systolic BP falls below 90 mm Hg or there is cardiovascular collapse	a. Yes☐ No ☐	
b. significant oxygen desaturation (<85% for >30 seconds)	b. Yes☐ No ☐	
c. significant cardiac arrhythmia	c. Yes☐ No ☐	
d. respiratory movements are noted	d. Yes☐ No ☐	
C. Results of Apnea Testing		
	C. RESULTS of APNEA TESTING 1. APNEA CONFIRMED Yes☐ No☐ OR 2. APNEA TESTING CONTRAINDICATED Yes☐ OR 3. APNEA TEST ABORTED Yes☐	

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Fig. 18.1 (continued)

Pt. Name: Unit No. Visit No.	YNHH Worksheet for the Determination of Death in Adults by Neurological Criteria

I – IV MUST BE MET TO CONFIRM DEATH BY NEUROLOGICAL CRITERIA WITHOUT THE NEED FOR ANCILLARY TESTING

V. ANCILLARY TESTING IS REQUIRED WHEN ITEMS I AND II ARE MET BUT EITHER ITEM III (BRAINSTEM REFLEX TESTING) OR ITEM IV (APNEA TESTING) CANNOT BE COMPLETED OR CONFIDENTLY INTERPRETED

ANCILLARY Study Performed:

☐ **CONVENTIONAL CATHETER-BASED CEREBRAL ANGIOGRAPHY**

☐ **NUCLEAR MEDICINE CEREBRAL BLOOD FLOW STUDY (TECHNETIUM 99^{M} BRAIN SPECT)**

☐ TRANSCRANIAL DOPPLER

☐ ELECTROENCEPHALOGRAPHY

DEMONSTRATED ABSENCE OF CEREBRAL BLOOD FLOW OR CEREBRAL ELECTRICAL ACTIVITY : YES ☐ NO ☐

SUMMARY OF FINDINGS

	YES	NO	OTHER
I. PREREQUISITES	☐	☐	
II. COMA or UNREPSONSIVENESS	☐	☐	
III. ABSENCE of BRAINSTEM REFLEXES	☐	☐	☐ **(Untestable)**
IV. APNEA	☐	☐	☐ **(Apnea test aborted or contraindicated)**
V. BRAIN DEATH ESTABLISHED BY ANCILLARY TESTING	☐	☐	☐ **(Not indicated)**

CONFIRMED DEATH IN ADULTS BY NEUROLOGICAL CRITERIA YES ☐ NO ☐

1st examiner signature: _____ / _____
Printed Name

Date: _____ / _____ / _____ Time: _____

2nd examiner signature: _____ / _____
Printed Name

Date: _____ / _____ / _____ Time: _____

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Fig. 18.1 (continued)

ids and vasopressors. With these supports in place, the patient demonstrates signs that are commonly associated with life such as pink, warm skin, a pulse, and a blood pressure. Family members may have misperceptions about DNC, especially in light of reports in the popular media of recovery after brain death declaration (these reports signify inaccurate determination of brain death). Families may also be concerned about the clinician's motives for DNC declaration, attributing declaration of death to a desire to obtain organs for transplantation. For all critically ill patients, it is important to communicate openly and honestly with family members from the time of initial hospitalization. Precision of language is essential, especially during and after declaration of DNC [12]. Misleading terms such as "life support" are avoided in favor of more accurate descriptors such as "the ventilator is providing oxygen to his body." Supportive professionals such as chaplains and social workers with a clear understanding of DNC can be helpful to the family. Rituals that mark the transition from life to death are encouraged based on family needs and beliefs, and can include prayer or the creation of bereavement keepsakes (e.g., hand tracings or cutting a lock of hair). Family presence at the patient's bedside facilitates understanding, and can include presence during DNC testing if desired by the family [13]. If family members will be present during the DNC examination, a designated staff member with no other responsibilities should be assigned to provide support. In addition, family members should be informed that the patient will be placed back on the ventilator at the conclusion of apnea testing while the results are reviewed and communicated.

If organ donation will not take place either because the individual is medically unsuitable or because the family declines

donation, the team should clearly communicate that respiratory and cardiovascular support will be stopped. A reasonable period of accommodation to allow other family members to arrive is ethically permissible, but prolonged cardiovascular and respiratory support is not required nor recommended with rare exceptions. Those exceptions are based on state law and impact practitioners in New Jersey, New York, Illinois, and California. New Jersey state law recognizes DNC, but provides an exception for situations in which DNC violates the personal religious beliefs of the individual. In the event of religious objection, death can only be declared by cardiorespiratory criteria [14]. New York law requires reasonable accommodation for religious or moral objections to DNC, but empowers hospitals to set their own policies defining reasonable accommodation [15]. In California, a "reasonably brief period of accommodation" is required in the event of any objection to declaration of DNC, during which time only previously initiated supportive measures must continue. The time limit is generally described as sufficient time to gather family unless the objection is based on "religious and cultural practices and concerns," in which case no time limit is specified [16]. In addition, Illinois law includes language pertaining to religious beliefs. Illinois law does not specify a period of accommodation, but requires hospitals to "adopt policies and procedures to allow health care professionals, in documenting a patient's time of death at the hospital, to take into account the patient's religious beliefs concerning the patient's time of death" [17].

18.6 Pediatric Considerations

While this chapter focuses primarily on adults, death can also be declared by neurologic criteria in pediatric patients. Determination of brain death in infants and children is based on guidelines most recently updated in 2011 by the Society of

Critical Care Medicine, the American Academy of Pediatrics, and the Child Neurology Society [18]. The process is similar to that followed for adults, but two exams by two attending physicians are required, and each exam must include an apnea test. The two exams are separated by an observation period that is based on the patient's age. For newborns between 37 weeks gestational age and 30 days old, an interval of 24 h is recommended. For infants and children between 30 days and 18 years old, the minimum recommended interval between exams is 12 h. The observation period can be shorter if ancillary tests are used. There are no standards for brain death declaration in preterm infants less than 37 weeks gestational age. Clinicians who care for pediatric patients are encouraged to review the published guidelines.

18.7 Management of the Patient After Determination of Death

Once the patient has been declared dead, interventions providing support to the body can legally and ethically be stopped, with some exceptions in states where accommodation is required by statute as previously noted. Many patients who are declared dead by neurologic criteria are eligible for organ donation; if authorization for donation is obtained, cardiorespiratory support continues until organ procurement takes place. Best practices for seeking authorization for organ donation have evolved over time, and include routine notification of the local organ procurement agency, the use of trained requestors, and respect for first-person authorization [19]. First-person authorization reflects the patient's personal decision to donate, often expressed through participation in a donor registry or through an advance medical directive [20]. Family consent for donation is not required under first-person authorization.

18.8 Organ Donation

A single individual who becomes an organ donor after declaration of DNC can save multiple lives and improve the quality of many more through tissue donation. Patients who are neurologically devastated but do not meet the criteria for DNC may still be able to donate a limited number of organs and tissue through donation after cardiac death (DCD). The ability to donate organs and tissue was established in 1968 through the Uniform Anatomical Gift Act and supported in subsequent revisions [20]. The Organ Procurement and Transplantation Network was established by the National Organ Transplant Act of 1984 [21]. Since 1986, the United Network for Organ Sharing (UNOS) has been federally designated to coordinate organ donation, which it does through federally regulated organ procurement organizations (OPOs). OPOs work with local hospitals and UNOS to procure and allocate donated organs [22].

The role of the APC focuses on early identification of potential organ donors and management to promote physiologic stability prior to and during evaluation for DNC. The local OPO is contacted for all patients with devastating neurologic insult. It is not the role of the APC or other hospital personnel to screen the patient for donation; the focus of the care team must remain on the patient and their family. Although the exact criteria for a suitable donor vary slightly by OPO, routine referral of all patients meeting triggers is considered best practice and helps avoid perceived or actual conflicts of interest. By contacting the OPO as early as possible, the OPO can determine whether or not the option of donation will be offered even before DNC testing. This facilitates family discussion and helps to avoid the sometimes uncomfortable situation that occurs when the patient has been declared dead but is being main-

tained on corporeal support while the OPO determines whether or not to approach the family regarding donation. Only OPO-designated personnel should discuss donation with families.

In some cases, the APC will also be directly involved in donor management once authorization is obtained, with direction provided by the organ procurement coordinator. Priorities include maintaining euvolemia, providing hemodynamic monitoring and support, hormone replacement therapy, and electrolyte management [19]. Diabetes insipidus occurs in most individuals following DNC and must be aggressively managed to prevent hypovolemia and hemodynamic instability. Hormone replacement therapy may also be utilized [19]. Organ-specific evaluation incudes echocardiography, bronchoscopy, and coronary angiography in select cases [19].

Summary Points

- Declaration of death by neurologic criteria, or brain death, is ethically and legally equivalent to declaration of death by cardiorespiratory criteria. A very limited number of states in the United States require accommodation of religious and/or moral beliefs when declaring death by neurologic criteria.
- The American Academy of Neurology (AAN) has established standards for determination of brain death. These standards include clinical or imaging evidence of an irreversible cause of unresponsiveness, elimination of alternative explanations of the patient's condition, a clinical exam consistent with total absence of brain function including brainstem areflexia, and apnea in response to a CO_2 challenge. Ancillary tests are used if needed.

- The neurocritical care APC has an important role in identifying patients who may progress to brain death, addressing prerequisites prior to testing, management to promote physiologic stability, family support, and communication.
- Prompt referral of patients with devastating neurologic injury to the local organ procurement agency supports the option of donation.
- Because of variations in state law and organizational policy, APCs must be familiar with local guidelines related to both brain death and organ donation.

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Chapter 19
Goals of Care and Difficult Conversations

Christine Hudoba and David Y. Hwang

19.1 Introduction

Goals of care discussions pose unique and sizeable challenges for neuroscience intensive care unit (neuro-ICU) patients, their families and/or surrogate decision-makers, and clinicians. The integration of palliative care principles into the everyday practice of advanced practice clinicians (APCs) in the neuro-ICU is a core skill that includes an appreciation for the nuances of neuroprognostication, shared decision-making with surrogates, best practices for family meetings, and proper management of medical issues for patients whose care is ultimately transitioned to comfort measures only.

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19.2 Definition of Palliative Care

"Palliative care" and "hospice care" share some key and notable features, primarily that they are interdisciplinary, holistic approaches to patient care that stress symptom palliation, mental and spiritual wellness and quality of life, and care coordination and social work involvement for patients and their families [18]. "Palliative care" and "hospice care," however, are not interchangeable terms and are separate entities with important distinctions. Palliative care refers to an interdisciplinary model of care meant to be implemented at any stage after a patient is diagnosed with a serious illness [18]. This model aims to improve quality of life by emphasizing management of physical and mental symptomatology, focusing on early identification of goals of care and alignment of treatment plans with those goals, and integrating care coordination, social work, and spiritual care to support patients and their surrogates [18]. Thus, palliative care should ideally be employed simultaneously with ongoing maximal medical management as a patient's goals of care are being assessed.

In contrast, "hospice care" specifically refers to the care and symptom management of terminally ill patients who have discontinued curative treatments and who have a life expectancy of 6 or fewer months. These criteria are used by Medicare and other insurance entities to determine whether patients are eligible for a specific hospice benefit [18].

19.2.1 "Primary" Palliative Care

Palliative care and neurocritical care are not mutually exclusive, and palliative care is not a service offered exclusively by a specialty team. In the neuro-ICU, the neurocritical care team should integrate primary palliative care early as a fundamental

component of comprehensive patient care. Palliative care specialists can be consulted as well to aid in the management of difficult situations [10, 18]. With the demand for palliative care specialists already exceeding the number of available palliative care experts, it is particularly important that neurocritical care clinicians assume primary responsibility for assimilating principles of palliative care into their patients' care. APCs dedicated to the neuro-ICU are thus uniquely positioned to champion palliative care in this setting [18].

19.3 Prognostication

To address a patient's goals of care properly, accurate prognostic information is an initial fundamental necessity [8]. However, in many cases, prognostication is intrinsically uncertain in neurologic disease and may include consideration of a range of relevant outcomes [11]. Outcomes of particular interest include how long a patient will live, what a patient's cognitive and physical function will be if they survive, and over what timespan a patient might accomplish certain improvements [15]. Prognostication can be complicated by self-fulfilling prophecies in which a high, but not certain, risk of death or disability leads to treatment limitations and subsequent death or disability when implementation of interventions might have precluded a progression to that state [11].

Because early intervention can greatly influence a patient's trajectory and outcome and because of the difficulty, uncertainty, and potential biases and self-fulfilling prophecies associated with prognostication in neurocritical care, providing a minimum of a 24-to-72-h period of maximum intensive care is usually judicious, except in extreme circumstances when a poor outcome is essentially guaranteed and when pursuing aggressive care would definitely be inconsistent with a patient's known

wishes [10, 23]. This 24-to-72-h period allows for serial evaluations that can facilitate greater accuracy and certainty in clinical decision-making [23].

Clinical grading scales in neurocritical care, based off of clinical and radiographic variables on admission, can help provide an initial measure of the severity of a neurocritical illness. The prognostic utility of these scales and their role in clinical decision-making, however, are constrained by multiple factors, including that their calculated values represent only a single point in time on admission and incorporate no subsequent assessments to account for improvement or deterioration. The outcomes literature associated with many scales in common use has not been updated recently [23].

Furthermore, prognostication for any single patient cannot rely solely on a clinical disease scoring scale and must incorporate additional details regarding a patient's characteristics, including comorbidities and baseline functional status [10, 23].

19.4 Shared Decision-Making

For those neuro-ICU patients determined to have a poor or uncertain prognosis, shared decision-making (SDM) – a collaborative process of sharing information and making value-based decisions undertaken by providers and patients (or surrogates) – is broadly regarded as the preferred decision-making model with respect to goals of care planning [19]. In general, treatment preferences for largely value-based decisions are influenced by the burden that a proposed treatment entails, the likely effect of the treatment, and the probability of a given treatment outcome [9]. Treatment burden is a function of its duration and invasiveness [14].

19.4.1 Patient Inability to Participate in Shared Decision-Making

Ideally in SDM, patients can communicate their own wishes; however, especially in neurocritical care, patients are frequently unable to do so. Some patients who cannot verbalize their preferences might nevertheless retain the cognitive ability to make decisions and can be accommodated with other communication tools, including communication boards [6]. However, more often than not, neurocritical illness renders patients without decision-making capacity [6].

Several principles and resources are helpful for guidance in scenarios where patients lack decision-making capacity:

Advance directives

- A living will is an advance directive that outlines a patient's preferences for the future implementation or limitation of treatments in certain prespecified clinical scenarios [6]. It frequently addresses interventions that can only prolong life when a poor outcome is guaranteed: CPR, mechanical ventilation, artificial nutrition, renal replacement therapy, etc. [6].
- Advance directives ideally should convey the cognitive and physical impairments and quality of life acceptable to patients [6]. However, the wide-ranging spectrum of possible scenarios of illness and potential interventions that any individual might encounter cannot be practically anticipated [6].

Surrogate decision-making

- When living wills are not available, a surrogate can assume decision-making responsibility for the patient.
- A surrogate can be formally pre-appointed by the patient, and when one of these official designations has not been made in advance of a patient losing decision-making capacity, there is a widely recognized (though variable by state) hierarchy of

surrogates with decision-making power, often moving from one's spouse to grown children and then to other family members [6].

- When incapacitated patients lack a living will or a surrogate decision-maker, a court-appointed conservator can fill the decision-making role [6], or determinations for these patients can be subject to judicial and/or institutional review [24].
- Decisions to limit life-sustaining interventions in incapacitated patients without a living will, a surrogate, or a next of kin should ideally involve a hospital ethics committee review [24]. In general, independent judgment by a single provider or primary team to limit life-sustaining treatment is cautioned against in these situations because these situations are most susceptible to provider-specific preferences and values [24].

19.4.2 Substituted Judgment

Neuro-ICU clinicians and surrogate decision-makers both serve valuable roles in goals of care conversations and decision-making. Providers contribute medical knowledge and clinical expertise, in addition to addressing surrogates' questions and supporting surrogates throughout the decision-making process. Surrogates' principal roles are to impart the patient's values and preferences [12], to coalesce those with their understanding of the patient's disease and prognosis, and to make decisions for the patient that are congruent with the patient's values and preferences (i.e., substituted judgment) [9, 10].

Although patients might survive the initial impact and subsequent complications in neurocritical illness, they can also face the prospect of a new and unforeseen future with a lifetime of physical and cognitive impairment and managing evolving complications. Participants' conversations and decision-making cannot solely address survival. Discussions must also deal with the realities of the patient's disabilities and possible associated

loss of independence and whether living in such a condition is congruent with the patient's goals, preferences, and values [10]. If a patient's wishes are unclear, clinicians should attempt to guide a surrogate(s) through substituted judgment and inform them that he or she is not choosing what he or she wants for the patient; rather, they should contemplate what the patient would choose for themselves. [6].

19.5 Practical Challenges with Surrogate Decision-Makers

Supporting surrogates throughout the decision-making process is important because it promotes the patient's best interests and because the decision-making process can burden surrogates, who are at risk for developing post-intensive care syndrome-family (PICS-F), a composite of long-term anxiety, complicated grief, depression, and posttraumatic stress disorder [16].

19.5.1 Degree of Involvement in Shared Decision-Making

Different surrogates may wish to be involved with medical decision-making to different degrees. Because surrogates' satisfaction with decision-making is greater when their actual role in decision-making corresponds to their desired role, providers should always attempt to ascertain a surrogate's preferred role in decision-making [12]. This provider-surrogate dynamic can range from a paternalistic model in which the provider exclusively dictates all decisions to an entirely autonomous model in which surrogates make totally unaided decisions. In practice, between those two extremes are shared decision-making paradigms that include providers proactively determining treatment

plans that consider surrogates' sentiments, providers and surrogates sharing "equally" in final decision-making, or surrogates deciding on treatment plans themselves after considering providers' opinions [12].

19.5.2 Surrogate Decision-Makers' Impressions of Prognosis

Understanding the factors that surrogates use to determine their own prognostic impressions empowers providers to more effectively engage them in conversations about goals of care and enables providers to optimize decisions that are most congruent with patient preferences and values.

Few surrogate decision-makers rely exclusively on medical team opinion for outcome prognostication [5]. Surrogates' impressions of patient prognosis usually are a combination of provider-supplied prognostication and other considerations [5]. These considerations include surrogate assessments of the patient's physical appearance, the patient's personality traits and medical and life history, and the patient's "resolve" [5]. Considerations also include surrogates' own intuitions and convictions, including hopefulness [5].

Surrogates' perceptions of patient prognosis have been shown to be optimistically biased oftentimes; this bias may cause them to have favorable interpretations of even poor prognostic estimates, particularly those rendering a high risk of death [25]. Surrogates' optimistic biases in critical care are likely one means by which they attempt to cope with a patient's severe illness and prognosis, although surrogates do not always perceive the presence of this bias and its capacity to distort their decisions [25]. Providers should be particularly cognizant of this bias when it potentially misaligns surrogates' decisions with the patient's preferences and values [25].

19.5.3 Consistency of Communication

Relationships and interactions with providers in the neuro-ICU can be challenging for surrogates, especially at the end of life, because of the number of ICU care providers who often function in their roles in time-limited capacities. The presentation of inconsistent information to surrogates is perceived to be frequent, particularly early in the patient's hospitalization [17]. These inconsistencies in information provided to surrogates negatively influence surrogates' satisfaction and exacerbate the challenges of the already trying decision-making process [17].

In advance of approaching communication with surrogate decision-makers, especially for issues related to prognosis and significant decision-making, neurocritical care team members should confer among themselves to ensure that each team member delivers the same, unified message [10]. APCs dedicated solely to the neuro-ICU and whose involvement in a patient's care extends beyond attending, fellow, and resident coverage can contribute meaningfully to continuity and to fostering more long-standing relationships with patients and their surrogates, which might help facilitate difficult conversations and end-of-life decision-making.

19.6 Family Meetings

Arranging formal meetings with a patient's family and the medical team – the first of which is usually within 48–72 h of admission – is beneficial for establishing rapport and reviewing the patient's diagnosis, the hospital course to date, the anticipated course, and the family's questions and concerns [6]. While early family meetings may be largely informational, these meetings

can lay a foundation of trust between the patient's surrogates and the medical team that may aid decision-making later in the patient's admission [6].

19.6.1 Setup

Productive family meetings necessitate premeeting preparation that should include an evaluation of imaging and other pertinent data. Conferring with other team members is critical to establish the objectives of the meeting, to decide who is leading the meeting, and to ensure a team-wide understanding regarding the diagnosis, prognosis, and the interventions believed to be appropriate and to be offered [6]. At the outset of each meeting, team members should introduce themselves and elicit introductions from all present [6]. Following introductions, it can help to establish a mutually agreeable agenda for the meeting [2].

19.6.2 Approach to Effective Communication

Certain communication styles have been demonstrated to be particularly effective in these settings. The "ask-tell-ask" approach involves providers first asking surrogates to verbalize their understanding of the patient's illness, followed by providers sharing necessary information, with providers returning to the surrogates and gauging their comprehension of what the provider just conveyed and welcoming further questions [2]. This model enables providers to first establish surrogates' baseline knowledge so that they can build on that understanding and right any misunderstandings and facilitates relationship building by demonstrating to the family that providers are invested in listening [2].

Clinicians should provide honest, culturally competent, and spiritually sensitive messages. Often, inquiring whether families are interested in viewing relevant imaging can be well received [10].

Information should be provided in small quantities, and bad news should be preempted by a forewarning [2].

The presentation of quantitative and qualitative information influences surrogates' assessments of risk. When quantitative data is presented, surrogates perceive risk to be greater when the data is reported as a frequency (e.g., "1 in 10"), as opposed to a percentage (e.g., "10%") [7]. When likelihoods of death and survival are presented qualitatively, surrogates perceive more risk when qualitative likelihoods are framed negatively as a high chance of mortality versus framed as a low chance of survival [7]. To address these variabilities, offering multiple portrayals of prognostic information might benefit surrogate decision-makers' risk calculus [7].

19.6.3 Emotional Support

Providers should prompt surrogates to indicate additional information that would assist them and to share their emotions and the effect they foresee the patients' illness having on them [2]. Providers talking less and listening more have been shown to be associated with increased family satisfaction with end-of-life care in ICUs [13].

Empathic statements are associated with increased family satisfaction with end of life in critical care [13]. Even when establishing an appropriate understanding of a serious illness and the prospect of a possible or definite bad outcome, often a clinician's best method of maintaining trust with a patient's family is to express hope as well as an honest expectation for the worst [3]. Anticipating the worst need not preclude concurrent optimism, which can be a valuable coping mechanism [3]. It is also important to emphasize to families that anticipating the worst does not mean the medical team will eventually abandon a patient. Rather, talking about "worst-case" scenarios is important for both providers and surrogates to be honest about likely

outcomes, because such approaches present the opportunity to explore anxieties and concerns associated with end-of-life decision-making [3].

19.6.4 Limitations of Life-Sustaining Therapy

When limitations of life-sustaining therapy are considered at formal family meetings, they can be approached in steps, depending on where any given family is at with respect to their decision-making. These discussions often begin with addressing code status, may involve an agreement to not escalate care and/or to withdraw select therapies, and may end with a formal comfort measure decision.

19.6.4.1 Code Status

When discussing code status, providers should explore surrogates' understanding of cardiopulmonary resuscitation (CPR), including its indications, elements and potential complications, and odds of post-resuscitation survival and discharge home after CPR [22]. To ensure that surrogates make educated decisions about patients' code status and that patients' benefits are maximized and risks minimized, providers must accurately portray CPR, including a delineation of its indications, components and possible adverse effects, as well as realistic expectations for post-CPR survival to discharge home.

19.6.4.2 No Escalation of Care/Withdrawal of Select Therapies

No escalation of care is an approach that is between maximum medical therapy with lifesaving intent and comfort measures, and it entails continuation of existing treatments without the

implementation of new ones [21]. No escalation of care most often precludes commencing of renal replacement therapy, vasopressors, and blood transfusions and often does not exclude introducing or limiting artificial nutrition and intravenous fluids [21]. Withdrawal of life-sustaining interventions can ensue rapidly with a simultaneous removal of all interventions or gradually in stages with therapies routinely considered for withdrawal including mechanical ventilation, vasopressors and inotropes, and renal replacement therapy [8], as well as antibiotics, hydration, and nutrition [21].

19.6.5 Time-Limited Trials

One mechanism that might aid surrogates in the decision-making process is a time-limited trial of interventions. Time-limited trials confer numerous benefits to surrogate decision-makers, including affording added time for letting the patient's condition evolve, enhancing surrogates' understanding of the advantages and disadvantages of interventions, evaluating goals of care, and processing emotions related to the patient's illness and potential fates [14]. Time-limited trials are joint decisions between a patient's surrogate and clinical team; they involve a distinct, limited time for the trial of any specified intervention [14]. Prior to the commencement of the trial, necessary decisions to be made at its conclusion and the outcomes that will guide those decisions are established, and arrangements are made for follow-up [14].

19.7 Conflict Mediation

Despite providers' best efforts to guide reasoned and conflict-free decision-making, occasions may arise when surrogates want therapies that providers oppose, and this may lead to lengthy

processes to try to arrive at an agreeable course of action. These circumstances arise when providers have objections to interventions and "potentially inappropriate" treatments requested by families – therapies capable of producing a desired physiologic effect (e.g., tracheostomy and feeding tube placement for extending life) but which providers question the ethics of implementing [4, 20]. It is important to distinguish between "potentially inappropriate" treatments and truly futile treatments, which should be narrowly defined as therapies incapable of achieving a physiologic outcome (e.g., a request to treat contrast-induced renal failure with antibiotics) and which should not be offered [4]. To reconcile disagreements about "potentially inappropriate" interventions, it is important that providers do not exert unfair control over patients and their surrogates [4, 20]. Patients can continue to receive treatments, while differences are resolved and plans are negotiated. The formal process for conflict resolution involves second prognostic opinions, hospital ethics committee consultations, exploration of transfer to other facilities, and possible external judicial review [4, 20].

19.8 Comfort Care

When a patient's goals of care are modified to comfort measures only, the timing of removal of life-sustaining interventions should be coordinated with the family [10]. High-quality communication with families is imperative before and after the withdrawal of life-sustaining interventions. Providers should explain to families what to expect when life-sustaining therapies are stopped, including the sequence in which interventions will be removed, how patients might appear, and how symptoms will be controlled [1].

Surrogates' perceptions of quality in death and dying in critical care are shaped by optimization of the patient's symptom

management, respect for surrogates' presence during the patient's dying process, efforts on the part of providers to not abandon surrogates and patients, and the overall decision-making and spiritual support provided to surrogates [13]. A well-explained process of the withdrawal of life-sustaining interventions, followed by a fluid withdrawal of life-sustaining therapies without complications and excellent symptom management, all enhance family satisfaction with the withdrawal of life-sustaining interventions [13].

19.8.1 Symptom Management

All interventions not exclusively targeted on symptom relief should typically be stopped, with the exception of antiseizure medications since suffering a seizure would be unpleasant [10]. Pain, agitation, anxiety, dyspnea, secretions, and thirst are the primary physical symptoms that patients experience at the end of life [1, 10]. Providers must be attentive to physiologic manifestations of distress, including tachycardia and tachypnea, because patients are not likely to be able to express what they are experiencing [10]. Opioids can mitigate pain, and anxiolytics can lessen anxiety [10]. Dyspnea can be managed pharmacologically with opioids, which should be immediately available to treat agonal breathing peri- and post-extubation, and secretions can be reduced with anticholinergic medications [10]. Supplemental oxygen should not be delivered, as it is considered a life-sustaining intervention. Good oral care incorporating swabbing the mouth with a moist sponge swab and/or offering ice chips can diminish the sensation of thirst [1]. To ensure adequate symptom palliation in this setting, it may be advantageous to implement distinct, physiologic-based titration parameters that target pharmacologic administration to goal heart rates and respiratory rates [10].

19.8.2 Care Transitions

Social work, spiritual care, and care coordination should be integrated in end-of-life decision-making [23], particularly when families desire hospice care. Depending on the time estimated for the patient to pass away once comfort measures are initiated, a transition to hospice may or may not be practical, and when providers expect that dying patients might be moved from the neuro-ICU to another, lower-acuity unit within the hospital, they should give families advance notice of that possibility [1].

Summary Points

- Neurocritical illness can be difficult for surrogate decision-makers to navigate.
- APCs play a key role in integrating principles of palliative care into primary ICU care.
- APCs should understand communication skills that have been demonstrated to be particularly effective in difficult situations, recognize and acknowledge surrogates' emotions, and demonstrate understanding, support, and empathy.

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Chapter 20
Multimodality Monitoring

Richard Cassa and Nils Petersen

20.1 Introduction

Brain multimodality monitoring (BMM) encompasses a variety of technologies that can provide real time information about the relative health or distress of the brain after various forms of acute injury. Multiple pathologic processes such as inflammation, brain edema and ischemia can lead to evolving brain damage. This so-called secondary brain injury significantly contributes to disability and long-term outcome. By optimizing cerebral hemodynamics, oxygenation and metabolism, BMM can help to create and maintain an optimal physiologic environment for the injured brain.

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20.2 Case Presentation

A 44-year-old man fell and hit his head on a rock while skiing on an unmarked slope. The patient was not wearing a helmet at the time of his injury. At the scene, he intermittently opened his eyes, moaned and had flexion withdrawal of his arms (Glasgow Coma Sore 6). There was a contusion on his forehead but no other signs of injury. The patient was transported to the nearest emergency room where he no longer opened his eyes, had extensor posturing of his arms and made no verbal responses.

A non-contrast head CT revealed bilateral frontal contusions with evidence of transtentorial herniation (Fig. 20.1).

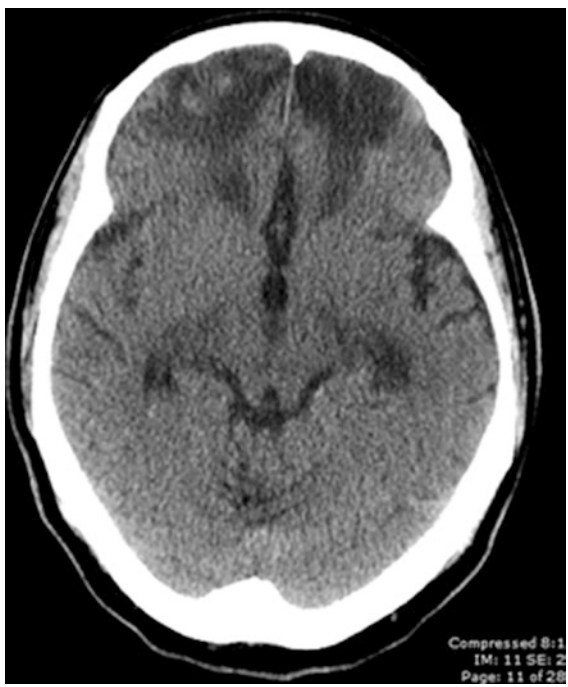

Fig. 20.1 Case presentation head CT showing bilateral frontal contusions

An external ventricular device (EVD) was emergently placed and revealed an elevated opening pressure of 34 mmHg. At the same time a multi-lumen bolt was placed for monitoring of brain tissue oxygen and cellular metabolism. The patient was started on hyperosmolar therapy to counter the effects of the present ICP crisis. Once the patient arrived to the Neuro ICU, he was connected to continuous EEG monitoring, which revealed evidence of subclinical seizures. Data from microdialysis showed evidence of cerebrometabolic crisis. The patient was loaded with an antiepileptic agent to control the seizures. Once the subclinical seizures were controlled, the lactate/pyruvate ratio decreased and the patient's ICP normalized. PbO2 levels in in the brain also stabilized.

An MRI of the brain revealed evolution of the bifrontal contusions, but no strokes were seen. After many days the patient was successfully extubated and was able to eat on his own. Clinically his exam was consistent with a bifrontal injury. He was discharged approximately 2 weeks after admission to an acute rehabilitation facility that specializes in acute brain injury.

20.3 Intracranial Pressure (ICP)

ICP reflects the global pressure in the intracranial vault. Measurement of ICP remains the most commonly performed type of monitoring in patients with acute brain injury and is routinely used to guide medical care. Elevated intracranial pressure can compromise cerebral blood flow and lead to brain herniation. The most common devices for ICP measurement are intraventricular catheters and fiberoptic intraparenchymal monitors. Intraventricular catheters are surgically placed into the frontal horn of the lateral ventricle and connected to an external pressure transducer. They are highly accurate and allow for therapeutic drainage of CSF. The primary disadvantage is a high rate of infection (5–10%) and difficult placement in case of

small or compressed ventricles. Intraparenchymal monitors consist of a small catheter with a fiberoptic microtransducer at the tip. They have a lower complication rate and are not at risk for catheter occlusion or leakage. Their main drawbacks include the inability to drain CSF for diagnostic or therapeutic purposes and the potential to lose accuracy over several days, as catheters cannot be recalibrated after initial placement [1]. The decision to place an ICP monitor is generally made when a patient is suspected to have elevated ICP (imaging and exam findings) and coma (GCS of 8 or less). Normal values range between 7 and 15 mmHg. The threshold that defines intracranial hypertension is uncertain but generally values above 20–25 mmHg are considered pathological [2]. It is important to consider that when little or no CSF volume is left due to brain swelling, compartmentalized intracranial hypertension may exist. Uniformly distributed ICP requires that CSF can circulate freely between all its natural pools, thus equilibrating pressure everywhere. In circumstances where CSF becomes trapped in isolated areas, ventricular catheters may not reflect ICP in all intracranial compartments.

Continuous measurement of ICP can be use to calculate cerebral perfusion pressure (CPP). Under normal circumstances, the cerebral vasculature has the intrinsic ability to maintain a stable blood flow despite changes in cerebral perfusion pressure, a mechanism known as cerebral autoregulation [3, 4]. This mechanism ensures that the cerebral blood flow matches the brain's metabolic demands and protects it from hypo- or hyperperfusion. After acute brain injury, this precise control of cerebral blood flow is frequently impaired, and as a result, acute changes in systemic pressure are passively transmitted to the cerebral circulation. This may lead to insufficiently low cerebral blood flow causing ischemia, or conversely, too high flow causing intracranial hypertension and cerebral edema. Although the optimal CPP for a given patient may vary, it is generally kept between 60 and 110 mmHg.

In addition to absolute pressure measurements, analysis of the ICP waveform can provide clues about reduced brain compliance (Δ volume/Δ pressure), which often precedes frank ICP elevations [5]. As compliance falls, the second peak of the ICP waveform (P2 or tidal wave) becomes elevated relative to the first peak (P1 or percussion wave) giving the wave a more rounded appearance (Fig. 20.2).

Elevated ICP is consistently associated with poor outcome and increased mortality [6]. Refractory ICP is associated with a drastic increase in risk of death [7]. However, a recent randomized controlled trial failed to demonstrate a benefit from ICP monitoring after traumatic brain injury [8]. This trial compared two management strategies, in which treatment was triggered by either ICP monitoring or by a combination of physical exam

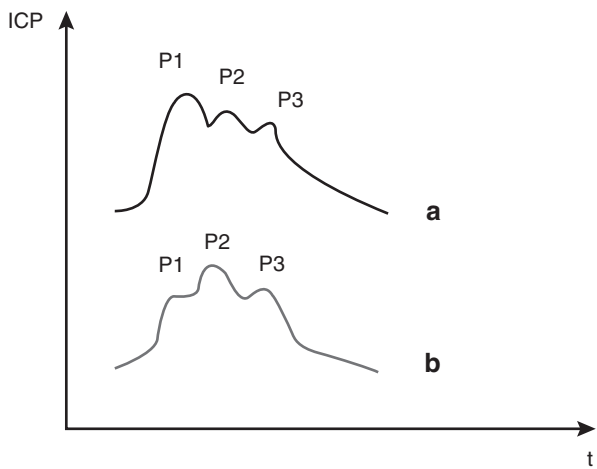

Fig. 20.2 ICP waveform in conditions of normal (**a**) and abnormal (**b**) intracranial compliance. *P1*: Percussion wave; *P2*: Dicrotic wave; *P3*: Tidal wave (Image used with permissions from Welbourne J, Matta B Intracranial Pressure Measurement. In: Bedside Procedures in the ICU. Springer, pp. 191–199)

findings and neuroimaging. It must be emphasized that evaluation and treatment of elevated ICP was fundamental to both groups in this trial, and although there was a trend towards lower mortality and more efficient care, ICP monitoring alone may not be enough to enhance TBI outcome. Care of severe TBI is complex with several mechanisms contributing to secondary brain injury. Consequently, it may require additional monitors (i.e. brain multimodality monitoring) to gain better insight into patient specific pathophysiology and provide more targeted care in order to improve outcome.

20.4 Cerebral Blood Flow

Recent advancements in technology allow direct measurement of regional blood flow via thermal diffusion (TD-rCBF). The probe consists of small catheter that contains two metal plates at its distal tip (about 5 mm apart). The distal plate is minimally heated thereby generating a constant spherical temperature field. Temperature variations at the proximal sensor are a measure of the tissue's ability to transport heat and correlate with cerebral blood flow. The probe is usually inserted into the brain parenchyma through a multi-lumen bolt next to ICP and PbtO2 probes. It provides a continuous and quantitative measure of blood flow in a small volume surrounding the catheter tip. Regional CBF values have shown good agreement with xenon enhanced CT [9]. The technique has been used in combination with PbtO2 to optimize CPP after TBI and guide blood pressure management in SAH patients with vasospasm [10, 11]. While the technology is promising, the available data is limited without clearly defined ischemia thresholds. Although the risks of probe placement are small (1–2% risk of bleeding, infection) and comparable to the complication rate of other intraparenchymal catheters, the utility of rCBF monitoring is limited due to its

invasive nature as well as its small sample volume with uncertainty about where to place the probes. Furthermore, the accuracy of TD-rCBF probes may be influenced by elevations in temperature.

20.5 Jugular Venous Oxygen Saturation (SjvO2)

Venous blood from the brain drains via the cerebral sinuses and jugular veins to the right atrium. Measurement of the oxygen saturation in the draining blood provides information about the balance between oxygen delivery and the cerebral metabolic demand. Simplistically, when metabolic demand exceeds supply the brain extracts more oxygen resulting in a decreased SjvO2.

For the measurement of SjvO2, a catheter is placed retrograde via the internal jugular vein into the jugular bulb (dilated portion of the jugular vein just below the base of the skull). It is important that the catheter tip is positioned beyond the inlet of the facial vein and inferior petrosal sinus to avoid contamination with oxygen-rich, extracerebral blood. Placement of the catheter tip in the jugular bulb should be confirmed with a lateral skull radiograph. The tip of the catheter should be at the level of the mastoid air cells [12].

O2 saturation can be measured continuously using a fiberoptic catheter or intermittently by drawing and analyzing a blood sample.

Under physiologic conditions, cerebral blood flow matches metabolic rate of oxygen (CMRO2) and the difference in oxygen content between arterial and jugular venous blood (AVDO2) remains constant. If arterial oxyhemoglobin saturation and hemoglobin concentration remain stable, the SjvO2 is a good approximation of the AVDO2. A low SjvO2 (i.e. jugular desatu-

Table 20.1 SjvO2 reference values [2, 13]

SjvO2 Value	Interpretation
<55%	Indicates jugular desaturation and suggests inadequate CBF in relation to CMRO2
55–75%	Normal
>75%	Indicates that oxygenation exceeds metabolic demand

ration) indicates increased oxygen extraction from the blood, suggesting inadequate cerebral blood flow in relation to CMRO2. A high SjVO2 indicates that oxygen supply is greater than demand (Table 20.1).

Monitoring of jugular venous oximetry can be considered in comatose patients (GCS ≤8) at risk for cerebral ischemia such as severe traumatic brain injury or high-grade subarachnoid hemorrhage [2]. In these patients monitoring of SjvO2 allows early detection of ischemia and can be used to guide hyperventilation therapy [13–16]. Robertson et al. reported that jugular venous desaturation (SjvO2 <50%) were a frequent occurrence in patients with severe traumatic brain injury and in the majority of cases could be attributed to elevated intracranial pressure, hypocarbia and hypotension. Furthermore, the number of desaturations was associated with an increased risk of death and poor neurologic outcome [14, 16]. Hyperventilation therapy is frequently used in the management of intracranial pressure. Reductions in $PaCO_2$ lead to cerebral vasoconstriction resulting decreased intracranial volume and pressure. However, the reduction in blood flow can also cause cerebral hypoperfusion and thus precipitate or worsen ischemia. SvjO2 has been shown to correlate well with brain tissue oxygen (PbtO2) and SvjO2 monitoring can be useful to optimize hyperventilation therapy [15]. However, small regions of critically hypoperfused brain have been demonstrated even while SvjO2 remained above 50% [17].

It is important to emphasize that SjvO2 is a global measure of cerebral oxygenation and not very sensitive for detecting regional ischemia. For jugular venous desaturations <50% to occur, at least 13% (170 ml) of the brain has to become ischemic [18]. Further limitations include considerable variability in saturations measured from both sides of the brain [19]. The sensitivity to detect jugular venous desaturation can be increased by cannulating the side of the predominant lesion or for diffuse injury the side with the larger jugular foramen on CT imaging [20]. Alternatively, the dominant internal jugular vein can be determined by unilateral compression of the vessel and selection of the side that produces the greater rise in ICP as it likely represents the side of predominant venous drainage [21]. Contamination with extracranial blood can occur if the catheter is placed too proximally or in cases of intermittent sampling if blood is aspirated rapidly (>2 ml/min). Inaccuracies may also occur if catheter tip is thrombosed or impacted against the vessel wall. While the rate of infection and complications related to catheter insertion are rare, the incidence of subclinical thrombosis is reported in up to 40% of cases [22].

20.6 Continuous Electroencephalography

Continuous electroencephalopathy monitoring (cEEG) in the neurocritical intensive care unit is primarily used for the detection of non-convulsive seizures (NCSz) or status epilepticus (NCSE) in patients with unexplained changes in level of consciousness. EEG is also helpful for the characterization of sudden spells such as tremors, twitching, posturing, eye deviation or agitation. Other indications in include detection of cerebral ischemia, monitoring the level of sedation and titration of medication during anaesthetic coma as well as prognostication.

Seizures are seen in 10–30% of patients with acute brain injury [23, 24]. While the majority of them are not exhibiting motor features, subclinical seizures have been associated with increased intracranial pressure and disturbed brain metabolism possibly leading to secondary brain injury [25, 26]. Furthermore, patients with seizures have increased mortality and among patients with SAH seizure burden has been associated with poor functional and cognitive [27, 28].

There is limited data to support the use of cEEG compared to spot EEGs (approximately 30 min); however, spot EEG will not detect nonconvulsive seizures in about half of those having seizures compared to longer monitoring [23].

Another important application of EEG in neurocritical care is the detection of brain ischemia. Brain function is represented on EEG as an oscillating wave of various frequencies. EEG activity is conventionally divided into the following frequencies (number of waveforms per second):

- Delta (0.5–3 Hz)
- Theta (4–7 Hz)
- Alpha (8–12 Hz)
- Beta (>13 Hz).

Most of the waveforms are generated by pyramidal neurons within the cortex. These cells are very sensitive to hypoxia and ischemia and EEG abnormalities can be seen within seconds to minutes. With decreasing cerebral blood flow, the EEG progresses through predictable changes: (1) loss of faster beta frequencies, (2) slowing of background to theta and later delta range, and (3) background attenuation and finally suppression of all frequencies [29]. Therefore, EEG allows providers the opportunity to detect ischemia and to alter treatment before hypoperfusion leads to cell death and permanent injury. However, some of the early changes can be subtle and may not be appreciated on raw EEG. Mathematical processing of the raw data, also known as quantitative EEG (qEEG) analysis,

can help to better visualize these changes. Using frequency analysis, the original EEG can be quantified in terms of frequency, amplitude and rhythmicity, which allows the calculation of numerical values or percentages. Furthermore, this digital form can compress long periods of EEG data into readable graphs allowing for prolonged monitoring of patients and aid detection of ischemia. The ideal qEEG measure to identify ischemia is still being debated and may depend of the clinical situation. A variety of parameters to measure slowing or attenuation have been suggested; they commonly include some ratio between fast and slow frequencies or a measure of the relative power (i.e. amount) of a specific frequency within the entire EEG spectrum.

Ischemia monitoring can be particularly useful in comatose or sedated patients when the clinical exam is limited. A reduction in alpha/delta ratio (8–13 Hz/1–4 Hz) and a decrease in the variability in relative alpha frequency have been shown to correlate with angiographic vasospasm or delayed cerebral ischemia (DCI) in patients with poor-grade SAH [30, 31]. For detection of focal ischemia, the relative delta percentage appears to provide the most robust correlation with CBF [32]. Clinically, qEEG has been correlated with stroke severity as measured by the National Institutes of Health Stroke Scale, infarct volume on MRI, and functional outcome [33–36]. Furthermore, qEEG can be used to assess treatment response, and given the correlation to cerebral perfusion pressure may be helpful to guide blood pressure management in individual patients after large-vessel acute ischemic stroke [37].

Despite the many advantages of cEEG, it does have its drawbacks. The monitoring systems, technician training, and the costs of disposable equipment can be expensive. Frequent review of many hours of data is necessary and can be time consuming. Quantitative EEG has the promise to reduce some of this time; however, having clinicians specially trained to interpret qEEG results is essential.

20.7 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive technique to measure the oxygen saturation of hemoglobin in the brain tissue. Delivered via optodes placed on the skin, near-infrared light has the ability to penetrate through scalp, bone and brain tissue up to a depth of about 3 cm. NIRS operates on the principle that the majority of near-infrared light is absorbed intracranially by oxygenated hemoglobin (HbO2) and de-oxygenated hemoglobin (Hb). Assuming constant scattering and applying knowledge of the absorption spectra for HbO2 and Hb, light attenuation can be converted into concentrations of HbO2 and Hb using the modified Lambert–Beer Law [38]. Their sum provides the total hemoglobin concentration (HbT) and the ratio HbO2/HbT equals the oxygen saturation of hemoglobin in brain tissue (StO2 or ScO2). In the setting of stable arterial oxygenation and cerebral metabolic rate, StO2 has been used as a surrogate for cerebral blood flow [39].

NIRS has many clinical applications. For example, NIRS can be used to monitor for changes in cerebral blood flow and oxygenation without the need for invasive probes and has been used to provide information regarding cerebral autoregulation after TBI, stroke and subarachnoid hemorrhage [40–42].

Despite the increased utilization of NIRS, there are some important limitations. First and foremost, there is concern for extracerebral contamination of the NIRS signal. In order to measure brain tissue oxygen saturation photons must travel through scalp, skull and dura, which contain various concentrations of blood and other tissue-derived chromophores (light absorbing molecules), which potentially confound the signal derived from the cerebral cortex [43]. In addition, NIRS light attenuation is not just the result of absorbtion by target chromophores (Hg and HgO2), but also light scattering. Bone, hair, subgaleal collections, subdural hematomas, and differences in areas of subarachnoid spaces can result in in nonlinear relationships between absorption and attenuation changes [44].

20.8 Cerebral Microdialysis

Cerebral microdialysis is used to measure brain tissue chemistry thus providing important information about brain metabolism and more specifically the adequacy of energy supply and cellular function. A thin catheter is placed through a cranial bolt into an area of interest in the brain parenchyma. The catheter is lined with a semi-permeable dialysis membrane and constantly perfused at a very low rate with an isotonic solution (e.g. artificial cerebrospinal fluid). Molecules below a certain size (usually 20 kDa) diffuse from the extracellular space through the membrane into the perfusion fluid, which is collected at regular intervals (e.g. every 60 min) and analyzed at the bedside using the manufacturer's equipment [45]. The analysis usually includes concentrations of glucose, pyruvate, lactate, glutamate, and glycerol. Many other metabolites as well as exogenous substances such as administered drugs can be studied, however, their clinical utility remains to be determined.

Glucose, pyruvate, and lactate provide information about the available fuel source of the brain as well as the brain's ability to go through aerobic metabolism. When energy is needed, glucose undergoes a series of enzymatic conversions known as glycolysis. Under aerobic conditions, the resulting pyruvate enters the citric acid cycle and gets metabolized to ATP. During hypoxia and ischemia, the end product of pyruvate is lactate resulting in an increased lactate to pyruvate ratio (LPR). Ischemia also results in the release of glutamate, a marker of metabolic distress. High glycerol levels originating from glycero–phospholipid containing cell membranes indicate cellular breakdown. Normal values for the metabolites have been established to help guide clinicians in interpreting this data (Table 20.2), however, variations over time and changes in response to therapeutic interventions may be more useful [46]. Furthermore, analyzing trends for multiple microdialysis markers rather than looking at individual metab-

Table 20.2 Microdialyis reference values

Physiologic parameter	Normal value(s)	Pathologic range	Interpretation
Glucose	1.7 ± 0.9–2.1 ± 0.2 mmol/L	<1.1 or 50% below baseline in 2 h	Decreased delivery (e.g. vasospasm, edema, ICP crisis, hyperventilation)
			Increased glucose consumption (e.g. fever, seizure, shivering)
			Decreased systemic supply (e.g. hypoglycemia)
Lactate	2.9 ± 0.9–3.1 ± 0.2 mmol/L	6.7 ± 1.1	Elevated lactate indicates anaerobic metabolism
Pyruvate	151 ± 12–166 ± 47 μmol/L	84.3 ± 35.8	
Glutamate	14 ± 3–16 ± 16 μmol/L	Not defined	High amounts are a marker for ischemia
Glycerol	82 ± 44–88 ± 14 μmol/L	Not defined	High levels indicate cell membrane destruction caused by energy failure
Lactate/Pyruvate Ratio (LPR)	19 ± 2–23 ± 4	>40 or >50% above baseline	Increased LPR and decreased pyruvate indicate decreased O_2 delivery
			Increased LPR and normal or high pyruvate indicate increased O_2 consumption or mitochondrial dysfunction

From Hillered et al. [45]

olites may allow for a more meaningful interpretation. For example, a typical pattern of cerebral ischemia includes a marked decrease in brain glucose, elevated lactate, increase in LPR and lactate to glucose ratio (LGR) and a moderate decrease in pyruvate [45].

Cerebral microdialysis has been used in various clinical situations and is indicated in patients at risk for cerebral ischemia, hypoxia, energy failure, and glucose deficiency [2]. In patients with severe traumatic brain injury, it may contribute to prognostication. A high lactate to pyruvate ratio has been shown to predict mortality and poor functional outcome [47]. For prognostication cerebral microdialysis should only be used in association with clinical indicators and other brain monitoring techniques [2]. After subarachnoid hemorrhage, cerebral microdialysis may identify ischemic tissue before it progresses to irreversible cell damage, thus providing an opportunity for therapeutic intervention. Cerebral microdialysis can assist titration of medical therapies such as blood pressure management or systemic glucose control. Whether treatments directed towards improving neurochemistry lead to improved outcomes remains to be determined.

Cerebral microdialysis has an excellent safety record and many of the same risks apply as with placing any type of catheter into the brain. However, just like brain tissue oxygen monitoring, cerebral microdialysis is a focal measurement and should be interpreted based on that capital location seen on postinsertion CT scan. Other limitations include the lack of real-time data given the time it takes for metabolite collection and sample analysis. Cerebral microdialysis is labor-intensive and unit staff need to be trained in catheter maintenance, sample collection, and analysis using the manufacturer's equipment. Also, it may be necessary to involve hospital IT personnel in order to integrate this data into the electronic medical record.

20.9 Brain Parenchymal Oxygen Tension

Adequate oxygen delivery to the brain is important to prevent secondary brain injury. Oxygen content in a discrete area of brain tissue can be measured with a small catheter placed through a cranial bolt into the white matter about 2–3 cm below the dura. The catheter provides continuous measurements of the brain parenchymal oxygen tension (PbtO2), thus providing vital information about oxygen delivery and consumption. Some uncertainty exists regarding the ideal placement of the monitor. Because probes provide only regional information (~17 mm^3), they are typically placed in the area of the brain at greatest risk for ischemia and secondary injury. In patients with focal injury such as ICH, well-demarcated cerebral contusions or infarction, a peri-lesional placement is preferred. For detection of ischemia related to vasospasm and DCI after subarachnoid hemorrhage (SAH), the probe is typically placed in the vascular territory supplied by the ruptured artery or hemisphere with the greatest clot burden. In patients with diffuse injury, probes are most commonly placed in the non-dominant frontal lobe.

- A normal PbtO2 value is between 23 and 35 mmHg [48].
- PbtO2 value of less than 20 indicates possible lack of brain oxygen and is considered a warning to clinicians that intervention may be necessary [2].

Most data regarding PbtO2 comes from patients with traumatic brain injury and SAH. Several observational studies have demonstrated an association between brain tissue hypoxia and unfavorable outcome [49]. PbtO2 can be influenced by a variety of local and systemic factors including arterial blood pressure (MAP), ICP, fraction of inspired oxygen (FiO2), arterial partial pressure of oxygen (PaO2), temperature, and blood hemoglobin concentration. Among them

mean arterial pressure and FiO_2 are most strongly correlated with PbtO2 [50]. However, a low PbtO2 can be seen despite maintenance of normal ICP and CPP [51]. Thus, strategies to improve PbtO2 should be tailored to the individual patient and additional monitoring devices (EEG, CBF monitor, brain temperature probe) may help to narrow the differential diagnosis of a low PbtO2. While one patient may respond to hemodynamic augmentation, another patient may require blood transfusion and an increase in oxygen transport capacity. Most common interventions include CPP optimization (treatment of intravascular volume depletion, augmentation of blood pressure and cardiac output), treatment of elevated ICP (CSF diversion, osmotherapy or surgical decompression), ventilator management (adjustment of FiO2 or other ventilator settings), or decreasing metabolic demand (sedation, treatment of fever and seizures, hypothermia) [52]. It is unknown at this time if PbtO2- directed therapy alters prognosis; however current data is promising and a phase II study to test this hypothesis is currently under way.

Probe placement is generally safe with a low complication rate and data is accurate for up to 10 days [49, 53]. There are some limitations and challenges in obtaining PbtO2 data. Because of substantial differences in PbtO2 values between manufacturing companies, the device should not be used interchangeably. Also, the currently used bedside technique does not allow for accurate placement of catheters in the peri-lesional tissue.

20.10 Bioinformatics

To capture the complex pathophysiology underlying acute brain injury, it is important to record and integrate multiple parameters of brain function. However, the systems currently in place

lack data integration, as most devices capture only the data that they acquire. In 2009, the American Society for Testing and Materials envisioned an 'integrated clinical environment' that will help to better assimilate medical devices and understand the complex interaction of various parameters.

Another important aspect of capturing this data is to ensure that the data is captured in a synchronous fashion. All data should be timestamped to coincide with each other. This will help give the clinician insight into physiological changes and how they relate to each other. Finally, a system needs to be designed that can filter data that may contain artifacts. Oftentimes, systems may need to be zeroed or are frequently disconnected in order to provide routine clinical care. A system must be able to recognize gaps and resulting artifact, and separate these periods of data as they may mask underlying trends. By focusing on these key elements to data integration, providers will be able to better understand trends and begin to develop theories.

Currently, a small number of hospitals and institutions have designed the limited number of integrated systems that exist. The disadvantage of these systems is that data can only be collected on one patient at a time. However, these systems are less expensive than distributed systems. Distributed systems are more difficult to set-up because they must be placed in multiple patient rooms. Information must be transferred to a computer server that can handle sensitive patient information.

Despite the advances in monitoring the neurocritical care patient in the ICU, the ability to import multiple data points into a coordinated system has been challenging. As the barriers that limit the design of integrated system lessen, there is an opportunity for health care providers to interpret and understand data that was previously unknown. Hypothesizing about this physiological information may lead to a better understanding of the human brain and how it affects patient outcomes in the future.

Summary Points

- Acute brain injury is a dynamic process that frequently includes hemodynamic, electrical, and metabolic changes.
- A variety of developing modalities are available for evaluating the physiologic parameters of brain activity and metabolism.
- Continued research and development of technology is needed to better integrate multimodality measurements and optimize impact on patient outcomes.

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Chapter 21
Airway and Ventilation Management

Matthew Band and Evie Marcolini

21.1 Introduction

Excellent airway management skills are essential for critical care practitioners. Knowledge of airway adjuncts and ventilators can help prevent the need for intubation and allow for quicker discontinuation of mechanical ventilation. Prolonged intubation leads to higher mortality, longer length of stay, and higher hospital costs. In neurocritical care units, patients are often intubated for neurologic reasons; these are generally categorized as follows:

1. A primary central nervous system process, with no acute underlying pulmonary process, where the patient is intubated for airway protection due to decreased level of arousal
2. Cessation of central respiratory drive due to severe neurologic injury involving the brainstem

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3. Neurologic injury triggering lung injury that in turns causes mechanical failure (neurogenic pulmonary edema)
4. Ventilatory (hypercarbic) failure caused by peripheral nervous disorders (high spinal cord injuries, myasthenia gravis, or Guillain-Barre (sp) syndrome)

21.2 Assessment of Airway and Breathing and Airway Adjuncts

Goals of oxygenation should be targeted to >93% SaO_2; however, this goal may be lower if the patient has a history of COPD or obstructive airway disease. The patient who is breathing spontaneously can achieve adequate SaO_2 with simple oxygenation adjuncts (Table 21.1).

It is suggested that this adjunct can provide positive end expiratory pressure (PEEP) of up to 7.4 cm H_2O, but this is dependent on a closed system; an open mouth diminishes effective PEEP is diminished.

If all adjuncts have been exhausted, noninvasive positive pressure ventilation (NIPPV) can be the last attempt to adequately ventilate a patient prior to making the decision to intubate. This modality maintains positive pressure by using a tight-fitting mask over the nose and mouth, creating a closed

Table 21.1 Oxygenation adjuncts

Adjunct	Liters per minute (LPM)	FiO_2 provided
Nasal cannula	Up to 6	Up to 50%
Simple face mask	Up to 10	Up to 60%
Venturi mask	Up to 12	Up to 60%
Non-rebreather mask	Up to 15	Up to 95%
High-flow nasal cannula	Up to 60	Up to 100%

circuit with effective PEEP. The continuous positive airway pressure (CPAP) mode of provides positive pressure throughout the respiratory cycle, while bilevel positive airway pressure (BiPAP) provides two levels of positive pressure, the higher giving assistance in inspirations and the lower preventing airway closure. Pressures run from 5 to 20 cm H_2O. An important caveat to this adjunct is that the patient must have an adequate mental status as well as a gag reflex in order to avoid aspiration or mechanically pushing air into the stomach. The presence of copious secretions should be an exclusion to the use of NIPPV. BiPAP is preferred over CPAP in patients who develop pulmonary edema or hypercapnic respiratory failure (especially in patients with underlying COPD). NIPPV can also be used to treat nocturnal hypoventilation in patients with neuromuscular disorders.

End-tidal CO_2 is a very useful adjunct in all phases of airway management. A simple probe inserted into the airway circuit in an intubated or non-intubated patients will provide a real-time CO_2 level along with a waveform that provides useful information. Interpretation of CO_2 level interpretation and waveform analysis provide important information such as ventilator status, cardiac output, apnea, and airway obstruction. This adjunct provides important information for the neurocritically ill patient, in light of the acute sensitivity of the brain to CO_2 levels.

21.3 Decision to Intubate

Is the patient oxygenating adequately? If, after all adjuncts are employed, oxygenation is still not adequate, intubation may be indicated. Is the patient ventilating adequately? If pCO_2 is elevated, this may be due to a central or metabolic cause and intubation with closed circuit mechanical ventilation may be required. In the neurologic patient, CO_2 parameters are

important, as they can affect cerebrovascular tone and ICP. If pCO_2 is low, this may be due to hyperventilation from pain, toxins, or a central neurogenic cause. If it is not possible to mitigate the cause of hyperventilation with analgesia or sedation without compromising respiratory drive, endotracheal intubation with the assistance of medications (analgesic, sedating, or paralytic) may be needed in order to maintain adequate pCO_2.

Is the patient able to protect his/her airway? Many critically ill neurologic patients can maintain airway patency and protection from aspiration in spite of neurologic deficits. This is a judgment call; if the patient has a diminished gag reflex, or otherwise is unable to protect his/her airway due to a diminished GCS or global neurologic obtundation, it may be appropriate to endotracheally intubate and mechanically ventilate. If this is a temporary situation that is likely to resolve as the patient recovers, extubation may be anticipated. However, if this is a permanent condition, early tracheostomy should be considered.

Does the patient have adequate inspiratory effort? Some neurologic illnesses, such as Guillain-Barre syndrome or Myasthenia Gravis, are associated with diminished inspiratory effort, resulting in inadequate tidal volumes and/or negative inspiratory flow. This patient will require endotracheal intubation if parameters of inspiratory effort and tidal volume are not met, and depending on the severity of the disease, may require prolonged mechanical ventilation and tracheostomy.

In general, prolonged endotracheal intubation increases the risk of subglottic stenosis and oropharyngeal erosion. Tracheostomy, which is typically more comfortable for the patient, should be considered after roughly 2 weeks of orotracheal intubation. This provides easier access to suctioning and the ability to easily remove and replace mechanical ventilation

by simply removing or replacing the ventilator tubing without needing to intubate with laryngoscopy.

21.4 Intubation

The intubation procedure consists of preparation, execution, and post-intubation assessment and care. Preparation is quite possibly the most important part of the procedure, as excellent preparation will provide ample reserve and easily accessible backup, while poor preparation may lead to an emergency situation with poor decision-making.

21.4.1 Preoxygenation

Every intubation should be preceded by at least 3 min of oxygenation by nasal cannula at 15 lpm (higher than used in maintenance) and face mask. If the patient is obese, has OSA history or habitus, or poor reserve, NIPPV may be considered if no contraindications exist. When the patient is induced, the face mask can be removed for bag valve mask access, but the nasal cannula should be maintained to continue oxygenation.

21.4.2 Positioning

The patient should be positioned with the ear at the same horizontal level as the sternal notch. If the patient is obese, the head of the bed should be elevated to 30–45 degrees to facilitate this positioning, and in obese patients, may also help by taking the pressure from abdominal and thoracic girth off of the diaphragm

and upper airway. This will help immensely during the mechanical component of intubation.

21.4.3 Equipment Preparation

- Suction device
- Oxygenation device
- Airway tree for each oxygenation device
- Bag-valve-mask device
- Oropharyngeal airway
- Laryngoscope (direct or video)
- Endotracheal tube with smaller size backup, both cuff tested and prepared with 10 cc syringe attached and stylet inserted and shaped to preferred form
- Bougie
- Monitoring equipment ($EtCO_2$, SpO_2, ECG, NIBP or arterial line, clamped ventriculostomy)
- Medications

21.4.4 Medications

Having the appropriate medications available is key for intubation success. The following medications should be immediately available in push dose format:

- Fentanyl for pretreatment (50–100 mcg)
- Sedation (etomidate, ketamine, propofol, depending on critical illness and blood pressure requirements)
- Paralysis (rocuronium, vecuronium, succinylcholine)
- Ongoing sedation (propofol, midazolam, dexmedetomidine)
- Intravenous fluids, with pressure bag ready
- Vasoactive agents (phenylephrine, norepinephrine, propofol, nicardipine, labetalol, esmolol), Blood pressure-lowering agents (propofol, nicardipine, labetalol)

21.4.5 Personnel

Adequate personnel should be at the bedside, and each should have one should have a specific role. The procedural plan should be reviewed with the entire group prior to implementation. Duties assigned to personnel may include medication administration, monitoring and alerting the room to blood pressure and SaO_2 levels, backup medication administration or runner, intubation and post-intubation assessment, assistant to intubation, ventilation, and endotracheal tube fixation.

21.4.6 Direct Laryngoscopy (DL) Versus Videolaryngoscopy (VL)

Since the advent of videolaryngoscopy, there has been much discussion over which method should be utilized for intubation. There are many considerations to this decision, but patient safety is the most important factor.

DL provides visualization of the cords via manipulation of the mandible, which in some cases may be challenging due to an extreme anterior cord anatomy, small mouth opening, or excessive posterior pharyngeal tissue. In the case of vomiting or blood in the airway, the DL view can be enhanced with suctioning. With DL, a curved blade is typically used, but the challenge of excessive posterior pharyngeal tissue can be overcome by employing a straight blade method of lifting the epiglottis manually to reveal a view of the vocal cords.

VL provides indirect visualization of the cords, especially helpful with anterior cord anatomy, via a hyperacute angled blade. This approach makes placement of the endotracheal tube challenging, as it must navigate around the sharply angled blade. This is facilitated by the rigid stylet, and as the most difficult component of VL intubation, should be practiced in order to

overcome mechanical pitfalls. If the patient has excessive vomiting or blood in the airway, the camera view of the VL may be obliterated and thereby not useful in real time. VL by definition includes the use of electronic equipment, which may be subject to failure, including battery power. In this way, it requires a dependable backup.

There are many new laryngoscopic tools available, some of which combine videolaryngoscopy with straight and curved as well as hyperacute curved blades, which resolves the issue of obtaining a view in different challenging situations. These are expensive, and it is the opinion of the authors that the medical professional doing the procedure should be familiar with both DL and VL.

The details of the intubation procedure are outside of the scope of this chapter, but this procedure can be lifesaving or life-threatening and should be practiced under the supervision of an experienced professional before practicing without backup. It is always optimal to have anesthesia personnel available as backup in case of need.

21.5 Post-intubation Assessment and Care

Successful intubation should be assessed by multiple methods: visualization of the tube going through the cords, auscultation of breath sounds over both lung fields and none over the gastrum, end-tidal capnography confirming CO_2 levels and appropriate waveform, end-tidal capnometry with confirmed color change, pulse oximetry, fog on the endotracheal tube fogging, and chest x-ray. The patient's hemodynamic and oxygenation status should be monitored closely, including pre, peri and post-intubation to assess for any needed medications to maintain adequate blood pressure and CO_2 levels. If long-acting paralytics are used, it is vitally important to start an infusion for sedation, as the paralytic effect will likely outlast the effect of

sedation used for intubation. Chest x-ray should be viewed to confirm endotracheal tube placement as well as to assess for other complications such as pneumothorax.

21.6 Modes of Ventilation [6, 10]:

There are many different modes of mechanical ventilation. Each institutional preference may vary, depending on the type of ventilator and previous experience of respiratory therapists and clinical staff. There are four conventional modes of ventilation, volume assist-control mode (VAC), synchronized intermittent mechanical ventilation (SIMV), pressure control ventilation (PCV), and pressure support ventilation (PSV).

21.6.1 Volume Assist-Control Mode

Volume assist-control (VAC) mode is most often used at the start of mechanical ventilation (Hasan). In VAC the clinician sets a respiratory rate (RR) and tidal volume (TV). In general the RR is set for normal breathing (12–16 breaths per minute), and the TV is set anywhere between 6 and 10 ml/kg of ideal body weight. Lower tidal volumes reduce the risk of barotrauma on the lungs. The clinician should set the RR and TV to generate a normal minute ventilation (6–8 L/min). If the ventilator is set with an RR of 12 and a TV of 500 ml, the patient will receive 12 breaths with associated TV of 500 ml every minute. If able, the patient can breathe at an RR greater than 12, and in this ventilation mode, every breath will still be delivered at a TV of 500 ml. Most patients who have intact brainstem function will be able to independently regulate minute ventilation. With VAC ventilation, the clinician can guarantee the minute ventilation by setting the RR and TV, and limit the work of breathing, which

is ideal for chemically paralyzed or high spinal cord injury patients with limited or no diaphragm function. There are some disadvantages associated with VAC, including the possibility of barotrauma in patients with decreased compliance, and muscle atrophy due to minimal respiratory effort in patients with prolonged course of mechanical ventilation.

21.6.2 Synchronized Intermittent Mechanical Ventilation

SIMV is similar to VAC in which the clinician sets the RR and the TV. The difference is that the TV for every patient triggered breath is generated by patient effort. Pressure can be added to the patient's spontaneous breaths to help generate a preset spontaneous tidal volume (SIMV + PSV). This mode tends to be more comfortable for patients as they are able to independently generate TV rather than a set forced volume. SIMV can be utilized in patients who will require long-term ventilation to help prevent muscle atrophy by allowing the respiratory muscles to remain active.

21.6.3 Pressure Control Ventilation

PCV allows the clinician to set RR, inspiratory pressure, and inspiratory time (I-time). The set pressure then generates a tidal volume depending on the lung compliance. The inspiratory pressure is set to achieve TV of 6–8 ml/kg of ideal body weight. The I-time can be adjusted to allow for a longer expiratory phase and therefore a decrease in CO_2 levels. The advantage of PCV over VAC is that the risk of barotrauma is reduced, as the provider sets the inspiratory pressure. The disadvantage, however, is that a change in lung compliance can drastically alter the TV generated by a given pressure, leading to changes in CO_2 and pH disturbances.

21.6.4 Pressure Support Ventilation

PSV is a common mode of ventilation for determining if a patient is ready for extubation. The patient's respiratory effort is supplemented with a set level of pressure to achieve adequate tidal volumes. PSV is comfortable for patients as they control the RR and TV with minimal support from ventilator. Unlike pressure control ventilation, the patient determines when the breath is terminated. PSV best mimics normal breathing. In neuro ICU patients, who typically have adequate respiratory function, but are intubated for airway protection, this should be the default mode whenever possible.

21.6.5 Positive End Expiratory Pressure and Fraction of Inspired Oxygen

In all the above modes of ventilation, the clinician also sets the PEEP and the FiO_2. PEEP is used to help prevent airway collapse and closure in a patient without a functioning glottis due to the presence of an endotracheal tube. It helps with oxygenation by recruiting and keeping alveoli open at the end of expiration preventing ongoing atelectrauma. Typical PEEP setting is 5 cm H_2O. The FiO_2 of room air is 0.21, and typical ventilator settings are anywhere from 0.21 to 1.

21.6.6 Arterial Blood Gas and Ventilator Adjustments [10]

An arterial blood gas should be obtained to ensure ventilator settings are appropriate for the patient. Normal values for pH range from 7.35–7.45, and for CO_2 35–45 (Table 21.2). In VAC and SIMV, the two settings on the ventilator that adjust CO_2 are

Table 21.2 Arterial blood gas values

Henderson equation: $[H^+] = 24 \times (PCO_2/HCO_3)$		
Acidosis	Normal	Alkalosis
pH <7.40	pH 7.40	pH >7.40
CO_2 >40 mm Hg	CO_2 40 mm Hg	CO_2 <40 mmHg
HCO_3 <24 mEq/L	HCO_3 24 mEq/L	HCO_3 >24 mEq/L

the RR and the TV; the oxygenation is adjusted with PEEP and FiO_2. Increases in RR and TV will cause a decrease in CO_2, as the patient will be breathing faster and deeper. In PCV the inspiratory pressure and the I-time can affect CO_2 clearance. Increases in the inspiratory pressure will cause a decrease in CO_2 levels from an increase in TV.

21.7 Specific Considerations in Neurocritical Care Patients and Mechanical Ventilation

21.7.1 Sedation/Pain Control with Mechanical Ventilation [9]

Sedation and pain control are the keystone to the important balance of keeping a patient comfortable without losing the neurologic exam. Ideally, one would utilize no sedating medication and only intermittent dosing of short-acting drugs to help maintain a neurologic exam. If continuous sedation and pain medicine are needed, aim for medications with short half-lives to prevent a suboptimal neurologic exam attributed to over-sedation (Table 21.3). See Chap. 22 for further information on commonly utilized sedatives and analgesics in the neuro ICU.

Table 21.3 Commonly used sedatives and analgesics in mechanical ventilation

Drug	Half-life (IV dose)
Propofol	4–10 min
Fentanyl	30–60 min
Remifentanil	3–10 min
Morphine	1.5–4.5 h
Hydromorphone	2.3 h

21.7.2 Hyperventilation and Elevated ICP [3]

Hypocapnia reduces intracranial pressure by inducing an alkalotic pH which causes cerebral vasoconstriction and decreased cerebral blood flow. The decrease in cerebral blood flow leads to a decrease in ICP. However, this is only a short-term fix as the body can adapt to lower CO_2 levels with increased bicarbonate production. The use of hyperventilation should be utilized only as a bridging measure until osmotic or surgical management of elevated ICP. Long-term hypocapnia should be avoided as it can lead to hypoxia and cerebral ischemia.

21.7.3 Neurogenic Pulmonary Edema (NPE) [2]

Neurogenic pulmonary edema (NPE) is pulmonary compromise related to acute neurologic illness. Anywhere from 2% to 20% patients with subarachnoid hemorrhage and 13–18% of brain dead patients develop NPE. The exact mechanism is unknown, but the major initial factor is a large increase in alpha-adrenergic discharge, which leads to systemic and pulmonary vasoconstriction followed by increase in catecholamines. Associated hypertension and increase in pulmonary blood flow cause pulmonary capillary damage leading to capillary leak and edema. The release of cytokines also causes pulmonary capillary permeabil-

ity. An increase in intracranial pressure (ICP) leads to a decrease in cerebral blood flow to certain areas of the brain (hypothalamus and medulla oblongata) resulting in over activation of sympathetic system.

Patients with NPE present with hypoxia, a PaO_2/FiO_2 ratio below 200, and chest x-ray and physical exam findings consistent with pulmonary edema. There is an acute form (30–60 min after neurologic injury) and late form (12–24 h after injury) and usually resolves in 48–72 h. In order to treat NPE, the clinical should focus on treating the underlying neurologic condition and reducing ICP. Most of the treatment is supportive with supplemental O_2 and diuretics with/without vasoactive drugs to maintain cerebral perfusion. Also, the goal is to maintain normal CO_2 and PaO_2 >60 mm Hg.

21.8 Weaning Parameters

Providers should routinely consider patients for extubation. Unfortunately, there is no gold standard test or diagnostic modality to tell a clinician when a patient is appropriate for extubation. There are, however, a number of weaning parameters that help guide the process. Most of the weaning parameters measure lung function. However, as previously mentioned, most neurocritical care patients are intubated for neurologic reasons rather than pulmonary disease.

21.8.1 Rapid Shallow Breathing Index (RSBI) [8, 15]

The RSBI is a measure of the respiratory rate/tidal volume in liters. Over the years it has evolved into a 30–120-min pressure support trial or T-piece trial. The T-piece method consists of dis-

connecting the patient from the ventilator and providing oxygen via a T-shaped tube attached to the endotracheal tube. The pressure support method consists of pressure support of 1–5 cm H_2O with 0–5 cm H_2O positive end expiratory pressure (PEEP). The added pressure support helps overcome the difficulty of breathing through a small endotracheal tube. Yang and Tobin described sensitivity of 97% and specificity of 64% if the RSBI was <105. A patient with a RSBI >105 is likely to fail extubation. While the trial is ongoing, the clinician should observe for signs of distress that may prevent extubation such as hemodynamic instability or a decrease in SpO_2. The downside of RSBI is anxiety of breathing through an ETT which may cause RSBI >105 despite normal lung function and no underlying lung pathology. Also, sedating medications given prior to trial may alter results.

21.8.2 Maximum Inspiratory Pressure or Negative Inspiratory Force (PImax or NIF) [10]:

The maximum inspiratory effort against an occluded airway after complete exhalation is considered the negative inspiratory force. An NIF of <−15 to −30 cm H_2O is considered adequate for extubation. The NIF assesses the strength of inspiratory muscles. The downsides of NIF are the number is heavily influenced by patient participation and it does not measure stamina.

21.8.3 Forced Vital Capacity (Forced VC) [10]

The forced vital capacity is a measure of respiratory strength. The patient takes a large deep breath while on the ventilator. Again this number is heavily influenced by patient participation. The number considered appropriate for extubation is around >10–15 mL/kg.

21.8.4 Other Criteria [1, 4, 5, 11]

Some other questions that a clinician should ask prior to extubation should be related to mental status.

Does the patient have the ability to maintain and protect his/her airway? Is he able to follow commands? The ability to maintain and protect an airway is paramount for extubation success. Not everyone who follows commands needs to remain intubated, but he must be able to protect his airway.

GCS scores and extubation success differ in neurocritical care literature. The lack of consensus data associated with GCS scores may be related to attending bias of extubation only when GCS >8; however some data in neurologic patients has shown patients with GCS<8 who meet all other criteria may be appropriate for extubation.

Is the patient able to manage his own secretions or is he developing pneumonia? Does he have increased secretions requiring frequent suctioning by nursing and respiratory therapy? How thick are the secretions? Thicker secretions have been associated with extubation failure in neurocritical care population.

Another parameter to consider is whether or not the patient has a cuff leak on his endotracheal tube. Endotracheal tube cuffs help prevent aspiration of oral secretions into the airway. Deflating this cuff should allow audible air to pass around the tube and out the oral cavity or have a decrease in TV return on the ventilator. A cuff leak is present if the patient has an audible leak or a 15.5% difference between the volumes returned to the ventilator with the cuff inflated and deflated. The lack of a cuff leak suggests edema, especially in traumatic brain injury patients, but may also be present if the endotracheal tube is too large for the patient's trachea.

Other things to consider are if the patient is requiring frequent return trips to the operating room, if he needs imaging that may require sedation, how difficult of an intubation was it initially, and if there is a cervical collar in place or unstable cervi-

cal spine injury. Also, trauma to the airway or oral cavity may prevent direct visualization of intubation, and extra caution should be warranted when extubating these patients.

The majority of neuro ICU patients are intubated for a neurologic reason; therefore successful weaning parameters that assess lung function may not be helpful. The inability to follow commands, thick secretions, lower GCS, and longer mechanical ventilation may predict extubation failure. In general, it is prudent to gather as much information as possible prior to extubation and make an appropriate educated clinical decision [7, 14].

21.9 Extubation [6]

When extubating a patient, every team member needs to be aware of the decision to remove the breathing tube, and every effort should be made to optimize the patient's clinical status. Sit the patient upright in bed as able, make sure there is proper supplemental oxygen in the room, and ensure that a bag valve mask is easily available. If difficult reintubation is anticipated, make sure proper personnel and equipment are available. In patients with a difficult airway, the clinician may opt to utilize a tube exchange catheter that is placed through ETT into the airway prior to extubation. It allows an easy reintubation, if the need arises, by placing the ETT over the catheter back into patient's trachea. However, it may cause increased irritation of an already edematous airway. Prior to extubation, pre-oxygenate with 100% O_2 while suctioning the mouth, throat, and trachea. Unsecure ETT from anchoring system, deflate the ETT cuff, and withdraw the ETT in one motion while the patient coughs. Continue close monitoring after extubation for upper airway stridor, increased work of breathing, and hemodynamic instability. Extubation failure rate in neurocritical care patients is around 17% which is on par with the general population of about 15% [1, 3, 4, 7, 11].

21.10 Goals of Care and Extubating for End of Life

Extubation is required when transitioning patient care to hospice or comfort measures. In this setting noisy audible secretions and airway obstruction at end of life can be distressing to families [12]. Several pharmacologic therapies are helpful in alleviating these symptoms (Table 21.4).

Table 21.4 Medications used for secretion management and respiratory distress in end of life care [14]

Drug	Class	Advantages	Disadvantages
Atropine eye drops	Anticholinergic	Delivered sublingual	Tachycardia
		No need for IV access	Restless/ delirium at high doses
		Less expensive	
		Minimal volume	
Glycopyrrolate	Anticholinergic	Does not penetrate CNS	Severe xerostomia
		Less sedation/ delirium	
Scopolamine patch	Anticholinergic	Ease of use	Several hours to work
			Penetrates CNS
			Expensive
Opioids – morphine most recommended	Opiate	Beneficial in dyspneic patients	Constipation
		Low cost	Delirium
		Euphoric effects	
		Intermittent vs infusion	
Benzodiazepines	Benzodiazepines	Sedative	Can worsen delirium
		Hypnotic	
		Anxiolytic	
		Amnestic	

Summary Points

- Several airway adjuncts can help keep your patient from being intubated and should be utilized when appropriate.
- When considering intubation, make sure the team is prepared and everyone is on the same page to decrease chances of potential complications.
- The clinician should tailor the ventilator mode and settings to individual patient needs.
- Extubate as soon as possible to avoid further complications. When extubating, gather as much data as possible – there is no gold standard parameter for successful extubation.

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Chapter 22
Pharmacology

Kent A. Owusu and Leslie Hamilton

22.1 Pharmacokinetics in Neurocritical Care

Pharmacokinetics, 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. The distribution of medications into the cerebrospinal fluid (CSF) and extracellular brain space is determined by the molecular size, lipophilicity, plasma protein binding, and active transport mechanisms [1]. Smaller molecular weight compounds are likely to have better CNS penetration via lipid-mediated transport [1].

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The blood-brain barrier typically excludes most hydrophilic substances. Although no antimicrobial agent has been approved by the United States Food and Drug Administration (FDA) for intraventricular or intrathecal use, both routes of administration of antimicrobials can be considered in select cases to overcome limited CNS penetration (See Table 22.1) [2]. Following intraventricular administration of antimicrobials, medications move through the CSF flow tracks and are absorbed into the peripheral bloodstream across the arachnoid villi to enter the general circulation [3]. CSF drug

Table 22.1 Commonly used intraventricular/intrathecal antibiotics [2, 5, 6]

General spectrum of activity	Antimicrobial	Typical daily dosing range (admixture in preservative-free solutions)	Common adverse effects
Gram positive	Vancomycin	10–20 mg /1 mL NS	Headache, mental status changes, possible hyponatremia
	Daptomycin	5–10 mg/1 mL NS	None reported
Gram negative	Gentamicin	4–8 mg/1 mL NS	Seizures
	Tobramycin	4–8 mg/1 mL NS	Seizures
	Amikacin	30 mg/1 mL NS	Seizures
	Polymyxin B	5 mg/1 mL NS	Hypotonia, seizures, meningeal inflammation
	Colistimethate	10 mg/3 mL NS	Meningeal inflammation
Fungal	Amphotericin B deoxycholate	0.5 mg/3 mL SWI	Nausea, vomiting

clearance may also be affected by physiologic alterations secondary to insertion of external ventricular drain devices and reservoir systems [4]. Intrathecal administration consists of direct delivery into the lumbar cistern by means of a lumber puncture or temporary placement of a lumbar catheter. It is important to utilize appropriate administration technique during both intraventricular and intrathecal antimicrobial administration.

Procedure for intraventricular/intrathecal antimicrobial administration: [2, 5]

- Withdraw CSF volume equivalent to volume of drug to be administered.
- Inject drug solution into the proximal port of the ventriculostomy or lumbar device.
- Slowly flush solution into drain with a small amount of normal saline. Instillation of small volumes (<3 ml) over 1–2 min appears to be safe. Rapid administration of solution may cause brain tissue damage.
- Clamp ventriculostomy tubing or lumbar drain for at least 15 min to allow injected solution to equilibrate in the CSF. Closely monitor patients with persistent elevated intracranial pressure who may not tolerate interruptions in CSF drainage during clamping.

Drug metabolism, the process of parent-drug breakdown into smaller active or non-active compounds, may be affected by neurologic injury. Different doses of medications may be necessary in the setting of decreased or increased drug metabolism. For example, traumatic brain injury increases hepatic metabolic capacity and may increase dosing requirements for medications frequently used in neurocritically ill patients such as phenytoin. Major enzyme-inducing antiepileptic drugs (AEDs) such as phenytoin stimulate the rate of metabolism of most coadminis-

tered AEDs, including valproic acid, lamotrigine, and topiramate, among others, and the affected agents may require subsequent dose increases. Valproic acid, a broad enzyme inhibitor, inhibits the metabolism of phenytoin leading to increased serum concentrations and consequently increased risk of phenytoin toxicity.

22.2 Hyponatremia [9]

Hyponatremia (serum sodium <135 mEq/L) and hypernatremia (serum sodium >150 mEq/L) are common findings in neurocritically ill patients. Both hyponatremia and hypernatremia are associated with potentially significant complications in neurocritically ill patients including cerebral edema (hyponatremia), elevated ICP (hyponatremia), agitation, delirium, seizures, tremors, or coma.

22.2.1 Cerebral Salt Wasting (CSW) vs SIADH

CSW is defined as renal loss of salt with concomitant extracellular fluid loss. CSW has been commonly described in patients with subarachnoid hemorrhage. A major difference between CSW and SIADH is that in CSW there is a decrease in extracellular fluid volume (ECFV) leading to hypovolemia. Fluid restriction should be avoided in most neurocritically ill patients. Table 22.2 describes a variety of medications and medical conditions that can cause SIADH.

Table 22.2 General causes of SIADH [9]

Drug induced		Other
Desmopressin	Carbamazepine, oxcarbazepine, eslicarbazepine	Malignancy
Vasopressin	Methylenedioxy-methamphetamine (MDMA or "ecstasy")	CNS disorders (stroke, demyelinating disorders, TBI)
Oxytocin	Cyclophosphamide, ifosfamide	Pulmonary conditions (infections, respiratory failure)
Phenothiazine antipsychotic agents (chlorpromazine, prochlorperazine, thioridazine)	Serotonin-reuptake inhibitors	Surgical procedures
	Tricyclic antidepressants (such as amitriptyline, nortriptyline, etc.)	

22.3 Hypernatremia

Hypernatremia is a common medical condition in neurocritically ill patients. It is most caused by an increase in salt-free water or loss of serum sodium or most commonly iatrogenic in nature due to use of hypertonic solutions in this patient population.

Conditions including diabetes insipidus are among other common causes of hypernatremia. Table 22.3 describes the strategies employed in the treatment of both hyponatremia and hypernatremia.

Table 22.3 Treatments for hyponatremia and hypernatremia [9, 10]

Hyponatremia	Hypernatremia
Correct underlying cause	Hypotonic solutions
Demeclocycline	
Modest/non-statistically significant slow increase in plasma sodium at 3 weeks	Generally avoid dextrose 5% water in neurocritically ill patients due to risk of cerebral edema
Increased incidence of nephrotoxicity	May consider 0.45% sodium chloride
	Rapid overcorrection may result in cerebral edema as water uptake by brain cells increases the dissipation of accumulated electrolytes and organic osmolytes
Diuresis with loop diuretics (euvolemic and hypervolemic)	
Fludrocortisone: 0.1–0.4 mg/day	Vasopressin analogs
May require potassium supplementation	Titrated to normalized urine output in diabetes insipidus, serum sodium correction, and urine-specific gravity
	Desmopressin (IV/SQ): 0.5–4 mcg every 8–12 h
	Vasopressin IV infusion: 1–15 units per h (titrated to normalized urine output)

Table 22.3 (continued)

Hyponatremia	Hypernatremia
Hypertonic saline	
In patients with severe symptoms, may correct up to 5 meq/L within first hour or until resolution of symptoms	
Maximum recommended increase: 8–12 mEq/L per 24 h, 18 meq/L per 48 h	
Rapid overcorrection may lead to central pontine myelinolysis	
Correct more slowly in patients with chronic hyponatremia	
Oral sodium supplementation	
Vasopressin antagonists (oral tolvaptan, injectable conivaptan) in euvolemic and hypervolemic hyponatremia	
Hepatotoxic	
CYP 3A4 substrates/inhibitors	
Increased cost	
Phlebitis (conivaptan)	

22.4 Hemodynamic Management

Patients in the Neuro ICU commonly require treatment for hemodynamic instability. See Table 22.4 for outline of common etiologies and management points.

Table 22.4 Common etiologies and management for hemodynamic instability

Hypotension	Hypertension
Euvolemia is usually the clinical goal for fluid status in neurocritically ill patients, especially in patients with aneurysmal SAH (aSAH)	Nicardipine and clevidipine are drugs of choice in patients who require immediate control of blood pressure
Nimodipine can cause hypotension in aSAH. Standard dose is 60 PO q4h for 21 days. May be adjusted to 30 mg PO q2h in patients with hypotension. A recent publication of nimodipine use in aSAH patients concluded that nimodipine dose reductions due to changes in mean arterial pressure may be associated with unfavorable clinical outcome [7]	Nicardipine: Dose: 5 mg/h up to 15 mg/h; Half-life: 3 min (longer with prolonged infusions) Clevidipine: Dose: 1–2 mg/h up to 21 mg/h. Infusion rates up to 32 mg/h have been studied for short periods of time; Shorter half-life: 1 min
Patients with spinal cord injury often experience neurogenic shock and require adjunctive medications to manage hypotension and bradycardia. Pseudoephedrine and theophylline have both been used in patients with spinal cord injury as an adjunct to facilitate the discontinuation of intravenous vasopressors	
Midodrine is also useful in neurocritically ill patients with hypotension requiring adjunctive therapy to facilitate the discontinuation of continuous intravenous infusion vasopressors	
Droxidopa, a novel oral synthetic precursor to norepinephrine, may be useful in neurocritically ill patients with neurogenic orthostatic hypotension. As more clinical trials become available, the role of Droxidopa may be expanded for other uses in neurocritically ill patients	
Adrenergic agents should be avoided in patients with Guillain-Barré syndrome, as these patients have increased sensitivity to these agents and use can worsen weakness	
Resuscitation with albumin is associated with worse outcomes in traumatic brain injury and is therefore not recommended in this setting	

22.5 Analgesia and Sedation

Current guidelines support the use of non-benzodiazepine sedatives, dexmedetomidine and propofol, as first-line pharmacologic treatment when continuous intravenous sedation is necessary, with the majority of recommendations based on evidence from studies including only general ICU patients. Propofol is preferred over benzodiazepines in patients requiring frequent neurologic assessments (e.g., hourly) due to its relatively shorter half-life and decreased risk of delirium. Propofol is limited by potentially severe adverse effects including hypotension and accumulation usually with prolonged use (>48 h) leading to propofol-related infusion syndrome (PRIS) with characteristics including acute refractory bradycardia, hypertriglyceridemia, cardiovascular failure, metabolic acidosis, rhabdomyolysis, and renal failure. Analgesia should be optimized first to address underlying pain followed by a focus on anxiolysis as pain often manifests as agitation. Various pain scales including the critical care pain observation tool (CPOT) may be utilized to adequately assess pain in order administer appropriate pharmacologic interventions. See Tables 22.5 and 22.6.

Table 22.5 Commonly used intravenous analgesics in neurocritical care [12]

	Comparative dose (IV)	Usual infusion dose	Time to onset (min)	Half-life (h)	Clinical pearls
Fentanyl	100–200 mcg	0.7–10 mcg/kg/h	<1	2–4	High lipophilicity can lead to prolonged duration of action especially after repeated dosing or infusion
Hydromorphone	1.5 mg	7–15 mcg/kg/h	5–10	2–3	
Morphine	10 mg	0.07–0.5 mg/kg/h	5–10	3–4	Active metabolites (M6-G active) M3G inactive metabolite potentially neurotoxic
Methadone	2.5 mg	Not recommended	Oral: 30 IV: 10–20	9–59	Weak NMDA receptor antagonist Potential to prolong QT interval Potential to increase intracranial pressure

Table 22.6 Commonly used intravenous sedative agents in neurocritical care [13, 14]

	Dosing	Onset of action (min)	Time to arousal	Clinical pearls
Dexmedetomidine	LD: Not generally recommended MD: 0.2–1.4 mcg/kg/h	1–3	Up to 10 min Note: terminal $t_{1/2}$ of 2 h	No active metabolites; does not cause respiratory depression May cause hypotension and bradycardia May have clinical utility in patients with persistent dysautonomia of central origin refractory to opiates, adrenergic blockade, and bromocriptine May have clinical utility in patients with traumatic brain injury who are not mechanically ventilated and require a continuous infusion of a sedative to facilitate care Added benefit in control of shivering
Lorazepam	LD: 0.02–0.06 mg/kg MD: 0.01–0.1 mg/kg/h	5–20	Up to 6 h	May cause respiratory depression and hypotension No active metabolites IV formulation contains propylene glycol (risk of anion gap metabolic acidosis)

(continued)

Table 22.6 (continued)

	Dosing	Onset of action (min)	Time to arousal	Clinical pearls
Midazolam	LD: 0.02–0.2 mg/kg MD: 0.04–0.2 mg/kg/h	1–5	Up to 2 h	May cause respiratory depression and hypotension Has active metabolites IV formulation does not contain propylene glycol
Propofol	LD: 2.5–1 mg/kg	Immediate (<1)	Up to 15 min	May cause respiratory depression, hypotension, hypertriglyceridemia, pancreatitis, propofol infusion syndrome (metabolic acidosis, bradycardia, cardiac arrest, rhabdomyolysis, renal failure) Contraindicated in patients with hypersensitivity to egg or soy products
	MD: 25–75 mcg/kg/min			Monitor pH, bicarbonate, triglycerides, lipase with prolonged therapy (>48 h) or high doses (>80 mcg/kg/min)

LD loading dose, *MD* maintenance dose

22.6 Antiepileptic Drugs

Many antiepileptic drugs (AEDs) are available for use in status epilepticus, and their use varies amongst institutions (see Table 22.7). See Chap. 12 for a more comprehensive clinical overview.

A drug-drug interaction is an interaction that will likely occur in the majority of patients and will require a dose adjustment or a change in agent so as to avoid an adverse outcome (seizure breakthrough or exacerbation of side effect) taking into account patient-specific factors.

Table 22.7 Medications commonly used in status epilepticus [8]

AED	Dosing	Clinically relevant pharmacokinetic interactions with other AEDs	Recommended target drug levels	Comments
Clobazam	LD: 10–20 mg MD: up to 60 mg/day (divided twice daily)	Minimal clinically significant drug-drug interactions	Dose guided by clinical response	May be an effective add-on therapy in RSE Improved safety and tolerability compared to other benzodiazepines. Decreased sedation compared to other benzodiazepines
Diazepam	LD: 0.25 mg/kg IVP over 1–2 min(up to 10 mg per dose); may repeat in 5 min	Longer half-life compared to other benzodiazepines	Dose guided by clinical response	Rapid redistribution Has active metabolites IV formulation contains propylene glycol IV solution may be administered rectally if no IV access

Fosphenytoin	LD: 20 mg PE/kg IVP (up to 150 mg/min); may repeat 5 mg PE/kg	See phenytoin	See phenytoin	Rapid and complete conversion to phenytoin within 30 min to 1 h of IV administration May be administered IM if no IV access (up to 99% absorption after IM administration) Compatible in saline, dextrose, and lactated ringers solution May cause hypotension, arrhythmias
	MD: (use phenytoin)			Nontoxic diluent; ↓cutaneous reactions with extravasation

(continued)

Table 22.7 (continued)

AED	Dosing	Clinically relevant pharmacokinetic interactions with other AEDs	Recommended target drug levels	Comments
Ketamine	LD: 1.5 mg/kg every 5 min up to 4.5 mg/kg. MD: 0.3–7.5 mg/kg/h	Minimal clinically significant drug-drug interactions	Dose guided by clinical response (continuous infusion titrated to EEG)	Non-GABA-mediated activity (NMDA receptor antagonism) provides a different mechanism of action Sympathomimetic properties = vasopressor sparing effects May cause emergent delirium May ↑ICP (conflicting evidence)
Lacosamide	LD: 200–400 mg IVP MD: Up to 600 mg/day in divided doses	Minimal clinically significant drug-drug interactions	Dose guided by clinical response	May prolong PR interval
Levetiracetam	LD: 20–60 mg/kg (generally 1,000–4,000 mg) MD: Up to 4,000 mg/day in two divided doses	Minimal clinically significant drug-drug interactions	Dose guided by clinical response	May cause behavioral disturbances

Lorazepam	LD: 0.1 mg/kg IVP up to 4 mg per dose (may repeat in 5 min)	Minimal clinically significant drug-drug interactions	Dose guided by clinical response	Rapid redistribution IV formulation contains ~80% propylene glycol IV Push preferred initial treatment of active convulsive seizures
Midazolam	LD: 0.2 mg/kg IV (over 5 min);may repeat every 5 min until seizure cessation (up to total of 2 mg/kg) MD: 0.05–2.9 mg/kg/h		Dose guided by clinical response (continuous infusion titrated to EEG)	Rapid redistribution Has active metabolites May be administered via alternate routes: 0.2 mg/kg (up to 10 mg) IM, intranasal, or buccal Preferred benzodiazepine to treat active seizures when no IV access/in the field

(continued)

Table 22.7 (continued)

AED	Dosing	Clinically relevant pharmacokinetic interactions with other AEDs	Recommended target drug levels	Comments
Pentobarbital	LD: 5 mg/kg IVP (administered at a rate not to exceed 50 mg/min); repeat with 5 mg/kg boluses until seizure cessation MD: 0.5–10 mg/kg/h (titrated to burst suppression)	Minimal clinically significant drug-drug interactions	Dose guided by clinical response (continuous infusion titrated to EEG)	Prolonged half-life (up to 50 h) May cause hypotension, gastric stasis, myocardial suppression, thrombocytopenia, metabolic acidosis (diluted in ~40% propylene glycol)
Phenobarbital	LD: 20 mg/kg IV (up to 60 mg/min) MD: 1–3 mg/kg/day in 2–3 divided doses	Strong inducer of UGT, CYP 3A4, 2B6, 2C9, 2A6, 1A2. Dose adjustments of AEDs including phenytoin and valproate might be necessary	20–50 mcg/ml	Prolonged half-life (53–140 h) May cause hypotension, metabolic acidosis (diluted in 70% propylene glycol)

Phenytoin	LD: 20 mg/kg IVP (up to 50 mg/min; 25 mg/min in elderly, patients with preexisting cardiovascular conditions) MD: 300–600 mg per day (individualize doses)	Induces CYP 1A2, 2B6, 2C, 3A3/4 Generally avoid use with most CYP3A4 substrates Coadministration with valproate displaces phenytoin from protein binding sites. Also induces metabolism of valproate	Total: 10–20 mcg/ml Free: 1–2 mcg/ml Monitor free level when on highly protein-bound medications or if low albumin	May cause rash, fever May cause hypotension, arrhythmias, metabolic acidosis (diluted in 40% propylene glycol) Only compatible in saline (unlike fosphenytoin); precipitation may occur drug diluents due to incompatibilities (D5W, potassium, insulin, heparin, norepinephrine, cephalosporin, dobutamine) Purple glove syndrome [*Low albumin states*] Adjusted = Total level/(Alb × 0.2) + 0.1 [*Renal failure*] Adjusted = Total level/(Alb × 0.1) + 0.1

(continued)

Table 22.7 (continued)

AED	Dosing	Clinically relevant pharmacokinetic interactions with other AEDs	Recommended target drug levels	Comments
Propofol	LD:1–2 mg/kg IV over 5 min(repeat boluses until seizure cessation up to a total LD max of 10 mg/kg) MD: 30–100 mcg/kg/min	Minimal clinically significant drug-drug interactions	Dose guided by clinical response (continuous infusion titrated to EEG)	May cause respiratory depression, hypotension, hypertriglyceridemia, pancreatitis, propofol infusion syndrome (metabolic acidosis, bradycardia, cardiac arrest, rhabdomyolysis, renal failure) Contraindicated in patients with hypersensitivity to egg or soy products Monitor pH, bicarbonate, triglycerides, lipase with prolonged therapy (>48 h) or high doses (>80 mcg/kg/min)

Valproate	LD: 40 mg/kg/dose over 10 min. May repeat with 20 mg/kg over 5 min (max rate 6 mg/kg/min) Maintenance: 1 g IV every 6 h	Phenytoin: displacement of phenytoin from protein binding sites may occur Lamotrigine: synergistic pharmacological effect improving seizure control. Inhibition of lamotrigine metabolism and ↑concentrations → ↑ neurotoxic effects or risk of lamotrigine-induced rash	50–100 mcg/ml	Highly plasma protein bound (up to 90%) May cause hyperammonemic encephalopathy (treated with l-carnitine supplementation), hepatotoxicity, platelet dysfunction

Recommended first-line agents include benzodiazepines, phenytoin/fosphenytoin, and valproic acid. Levetiracetam, lacosamide, and phenobarbital may be considered. Simultaneous continuous anesthetic agents (midazolam, propofol) may be considered in patients who continue to seize despite benzodiazepine therapy

RSE refractory status epilepticus, *IM* intramuscularly, *IVP* intravenous push, *LD* loading dose, *SC* subcutaneously, *MD* maintenance dose, *PR* per rectum

22.7 Anticoagulants and Antiplatelets (Tables 22.8, 22.9, 22.10, and 22.11)

Table 22.8 Anticoagulants

Agent	Dosing	Mechanism	Clinical pearls
Argatroban (IV)	Titrated to aPTT	Direct thrombin inhibitor	Falsely elevates INR Reduce doses in moderate to severe liver impairment Monitored by aPTT
Bivalirudin (IV)	Titrated to aPTT	Direct thrombin inhibitor	Falsely elevates INR Reduce doses in renal impairment Monitored by aPTT
Enoxaparin (SQ)	1 mg/kg (treatment doses)	Inhibits Xa	Renally adjusted Monitored by anti-Xa levels
Fondaparinux (SQ)	5–10 mg daily (dependent on weight)	Inhibits Xa	Monitored by anti-Xa levels
Heparin (IV/SQ)	Titrated to aPTT	Inactivates thrombin	Monitored by aPTT
Apixaban (PO)	10 mg Q12h × 7 days and then 5 mg BID (DVT/PE) 5 mg BID (non-valvular atrial fibrillation)	Inhibits Xa	Can be administered via feeding tube Dose adjusted if two of following: age ≥80, weight ≤60 mL/min, or SCr ≥1.5 mg/dL
Dabigatran (PO)	150 mg BID	Direct thrombin inhibitor	Capsules cannot be opened Renally adjusted

Table 22.8 (continued)

Agent	Dosing	Mechanism	Clinical pearls
Edoxaban (PO)	60 mg daily	Inhibits Xa	Cannot be administered if CrCl >95 mL/min Renally adjusted
Rivaroxaban (PO)	15 mg BID × 21 days and then 20 mg daily (DVT/PE) 20 mg daily (non-valvular atrial fibrillation)	Inhibits Xa	Can be administered via feeding tube Renally adjusted
Warfarin (PO)	5 mg daily and follow patient-specific dosing	Inhibits VKOR complex	Multiple drug interactions Genetic testing available Monitored by PT/INR

Table 22.9 Antiplatelet agents

Agent	Dosing	Mechanism	Clinical pearls
Aspirin (PO/PR)	81–325 mg daily	Inhibition of cyclo-oxygenase	
Aspirin/dipyridamole (PO)	25/200 mg Q12h	Inhibition of cyclo-oxygenase and adenosine uptake	High incidence of headaches often precludes use. May consider initiating with once daily dosing and up-titrating to twice daily dosing to decrease incidence of headache
Clopidogrel (PO)	75 mg daily	Inhibition of P2Y12 component on ADP	P2Y12 genetic testing Potential risk with concomitant PPI therapy

Table 22.10 Time to hold anticoagulants and antiplatelets prior to surgery [15]

Agent	Time to hold prior to surgery in most patients
Argatroban (IV)	Stop 4 h prior to surgery
Enoxaparin (SQ)	Stop 24 h prior to surgery for treatment doses
Fondaparinux (SQ)	Stop 2–4 days prior to surgery
Heparin (IV)	Stop 4–6 h prior to surgery
Apixaban (PO)	Stop 24 (mild risk of bleeding) – 48 h (moderate to severe risk of bleeding) prior to surgery or longer in renal dysfunction
Dabigatran (PO)	Stop 24–48 h (CrCl ≥50 mL/min) or 3–5 days (CrCl <50 mL/min)
Edoxaban (PO)	Stop at least 24 h prior to surgery or longer in renal dysfunction
Rivaroxaban (PO)	Stop at least 24 h prior to surgery or longer in renal dysfunction
Warfarin (PO)	Stop 5 days prior to surgery
Aspirin (PO/PR)	Continue if high cardiac risk, stop 7–10 days prior to surgery if low cardiac risk
Aspirin/dipyridamole (PO)	Stop 7–10 days prior to surgery
Clopidogrel (PO)	Stop 5 days prior to surgery

Table 22.11 Reversal agents for anticoagulants and antiplatelets in intracranial hemorrhage [16, 17]

Agent	Reversal agent
Argatroban (IV)	FEIBA or four-factor IV PCC 50 units/kg
Enoxaparin (SQ)	Protamine 1 mg IV for every 1 mg enoxaparin dosed within previous 8 h, 0.5 mg IV if dosed within 8–12 h (max 50 mg)
Fondaparinux (SQ)	FEIBA 20 units/kg or rFVIIa 90 mcg/kg IV (rFVIIa is not as effective as FEIBA)
Heparin (IV)	Protamine 1 mg IV for every 100 units of heparin administered in previous 2–3 h (max 50 mg)
Apixaban (PO)	[a]Activated charcoal if with 2 h of ingestion FEIBA or four-factor IV PCC 50 units/kg
Dabigatran (PO)	[a]Activated charcoal if with 2 h of ingestion Idarucizumab IV 5 g (2.5 g×2 doses) FEIBA or four-factor IV PCC 50 units/kg

Table 22.11 (continued)

Agent	Reversal agent
Edoxaban (PO)	[a]Activated charcoal if with 2 h of ingestion FEIBA or four-factor IV PCC 50 units/kg
Rivaroxaban (PO)	[a]Activated charcoal if with 2 h of ingestion FEIBA or four-factor IV PCC 50 units/kg
Warfarin (PO)	Vitamin K three- or four-factor IV PCC FFP
Aspirin (PO/PR)	DDAVP 0.4 mcg/kg IV × 1 Platelet transfusion
Aspirin/dipyridamole (PO)	DDAVP 0.4 mcg/kg IV × 1 Platelet transfusion
Clopidogrel (PO)	DDAVP 0.4 mcg/kg IV × 1 Platelet transfusion
Alteplase (IV)	Cryoprecipitate, antifibrinolytics (tranexamic acid or aminocaproic acid)

[a]Two new antidotes for the novel oral anticoagulants are currently in development

All anticoagulants and antiplatelet agents are contraindicated with spinal/epidural analgesia except for prophylactic doses of unfractionated heparin and aspirin. Prasugrel is contraindicated in patients with ischemic stroke due to increased risk of hemorrhage.

22.8 Hyperosmolar Therapy

Hyperosmolar agents are utilized for a variety of purposes in the neurointensive care unit, the chief reason being the treatment of cerebral edema and increased intracranial pressure. See Chap. 11 for approach to clinical management. Information are summarized in Table 22.12 and Fig. 22.1.

Table 22.12 Hyperosmolar agents [11]

Agent	Dosing	Mechanism	Clinical pearls
Hypertonic saline (common doses 3%, 7.5%, and 23.4% NaCl) (IV)	23.4% NaCl: 30–60 mL × 1 dose 7.5% NaCl: 2 mL/kg × 1 dose 3% NaCl: 250 mL × 1 dose or titrated via continuous infusion	Osmotic diuretic	Central line administration Na goals dependent on patient 3% NaCl contains 513 mEq/L of Na, 23.4% NaCl contains 4 mEq/mL of Na or 4,000 mEq/L Hyperchloremic acidosis (certain concentrations may contain sodium acetate in a 1:1 ratio to mitigate risk) Osmotic demyelination may occur from large/acute increases in serum sodium (≥8–12 mEq/24 h)
Mannitol (IV)	0.25 g–1 g/kg/dose	Osmotic diuretic	Requires serum osmolarity monitoring and osmolar gap monitoring Can be administered via peripheral IV catheter Filter for administration Rebound ICP elevation

Serum osmolality can be calculated with the following equation:
SOsm (mOsm/kg) = [Na (mEq/L) x 2] + [(Glucose (mg/dL)/18)] + [(BUN (mg/dL)/2.8)]

Osmolar gap can be calculated with the following equation:
Osmol gap (mOsm/kg) = SOsm (mOsm/kg) – Cosm (mOsm/kg)

Fig. 22.1 Osmolality calculations

22.9 Neuromuscular Blocking Agents

Neuromuscular blocking agents (Table 22.13) are most commonly administered in the Neuro ICU for intubation and airway management; however, many patients receive these agents

Table 22.13 Neuromuscular blocking agents [18]

Agent	Dosing	Duration	Clinical pearls
Depolarizing agents			
Succinylcholine	0.2–0.6 mg/kg IV	2–3 min	Caution in hyperkalemia and rhabdomyolysis
Non-depolarizing agents			
Aminosteroidal agents			
Rocuronium	0.6–1 mg/kg IV loading dose, 8–12 mcg/kg/min	30 min	Some renal excretion
Vecuronium	0.08–0.1 mg/kg IV loading dose, 0.8–1.7 mcg/kg/min	35–45 min	Renally excreted, active metabolite, cannot be administered IM
Benzylisoquinolinium agents			
Atracurium	0.4–0.5 mg IV loading dose, 4–20 mcg/kg/min	25–35 min	Hofmann elimination, no active metabolites
Cisatracurium	0.1–0.2 mg/kg IV loading dose, 3 mcg/kg/min continuous infusion	45–60 min	Hofmann elimination, no active metabolites, literature for use in early ARDS patients

during operative intervention, and they are sometimes used during therapeutic hypothermia to prevent shivering. Historically, paralytic agents have also been used in the treatment of refractory intracranial pressure.

22.10 Myasthenia Crisis

Myasthenia crisis is a life-threatening neurological emergency with a prevalence of up to 20% in the first year upon diagnosis of myasthenia gravis and a reported morality rate of up to 4.47% [19, 20]. About 30–40% of patients who present with myasthenia crisis have no reported precipitating factors. However, common precipitating factors include infections, stress, electrolyte imbalances, and changes in medication regimen (discontinuation or new medication initiation), summarized in Table 22.14. Please refer to Chap. 16 for further clinical information about the management of myasthenia gravis.

Management of myasthenia crisis

- Respiratory management: consider elective intubation based on clinical picture.
- Targeting precipitation factors.
  - Consider initiating antimicrobial therapy for treatment of underlying infection (avoid agents likely to worsen MG). Discontinue or modify triggering pharmacotherapy.
  - Consider holding acetylcholinesterase inhibitors such as pyridostigmine in order to reduce airway secretions.
  - Electrolyte repletion.

Table 22.14 Medications associated with myasthenia gravis [21]

	Medication	Comments
Likely to worsen MG or induce a myasthenic crisis	Aminoglycosides Bacitracin or polymyxin Botulinum toxin Colistin Clindamycin Class 1 antiarrhythmic agents Inhalational anesthetics Neuromuscular blocking agents Quinidine	Should be used only in a setting where ventilatory support in a hospital is available
May worsen MG	Beta-blockers (including topical) Calcium channel blockers Chlorpromazine Hydroxychloroquine Lithium Quinolone antibiotics Macrolide antibiotics Phenytoin Statins Tetracyclines	Usually tolerated. Use with caution

- Consider immediate initiation of immune globulin or plasmapheresis.
- Consider immunomodulating therapy with high-dose glucocorticoids (may temporarily worsen symptoms).
- Consider immunologic therapy with azathioprine, cyclosporine, or mycophenolate although delayed onset of action (3–6 months).
- Rituximab therapy may be considered in patients with refractory disease.

22.11 Pregnancy Considerations in Neurocritical Care (Table 22.15)

Table 22.15 Medication therapies for pregnancy-related neurological emergencies [22]

Condition	Medication therapy
Cerebral venous thrombosis	Enoxaparin 1 mg/kg q12h (treatment doses)
HELLP syndrome	Platelets
Hemorrhagic stroke	Rapid correction of blood pressure, reversal of coagulopathy
Hypertensive conditions, preeclampsia, eclampsia	Antihypertensives: labetalol, hydralazine, nicardipine
	Seizures: magnesium
	Long-term antihypertensives in pregnancy: labetalol, methyldopa, nifedipine, hydralazine
Ischemic stroke	Risk vs. benefit of r-tPA, intra-arterial r-tPA, aspirin
Seizures (non-eclamptic)	Lorazepam, fosphenytoin, levetiracetam
TTP-HUS	Plasma exchange

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Chapter 23
Common Complications in the Neuro ICU

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23.1 Introduction

In many ways the neurocritical care unit can be thought of as simply an ICU for patients with primary neurological and neurosurgical diagnoses. Although neurocritical care patients have many unique characteristics, they are also prone to common complications that occur in general medical-surgical ICUs such as hospital-acquired infections, fever, electrolyte disturbances, and bleeding and thrombosis. The physiologic responses, preventive strategies, and treatment of these complications, on the other hand, are complicated by underlying neurological conditions commonly treated in the neurocritical care unit. This chapter focuses on the nuances of managing the most common ICU complications in patients who are critically ill from neurological conditions, focusing on fever, disorders of sodium balance, prevention and treatment of venous thromboembolism, hospital-acquired infections, and glycemic control.

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23.2 Hospital-Acquired Infections

Hospital-acquired infections (HAI) are associated with increased hospital length of stay, which significantly increases healthcare costs and worse outcomes. Optimal patient management and focus on the prevention of HAIs have recently come to the forefront as financial incentives to reduce HAI rates have surfaced [21].

23.3 Catheter-Associated Urinary Tract Infection (CAUTI)

Catheter-associated urinary tract infection (CAUTI) is the presence of a UTI when an indwelling urinary catheter is present for greater than 48 h (cdc.gov). While the majority of neurocritical care patients require urinary catheters at some point, many can be quickly removed or alternatives can be used. The longer a urinary catheter is in place, the greater the risk of infection. This principle has prompted development of protocols to evaluate the need for the urinary catheters on daily rounds. The focus of the advanced practice clinician in decreasing the incidence of CAUTI in the neurocritical care unit should be on appropriate ordering and timely discontinuation of indwelling urinary catheters. Examples of patients with appropriate indications for urinary catheters include those with need for strict assessment of volume status who have polyuria or oliguria, hemodynamically unstable patients, and those with dysnatremia. Patients who have pressure ulcers or urinary retention, as seen in spinal cord injuries, may require intermittent straight catheterization or indwelling catheters [23].

It is important to quickly recognize CAUTI and treat appropriately to prevent urosepsis from systemic dissemination of infection. *Escherichia coli* is the organism most frequently associated with CAUTI. Other common organisms include

Klebsiella, *Pseudomonas*, *Enterococcus*, *Proteus*, and *Enterobacter* [23]. Treatment should be initiated with broad-spectrum IV antibiotics until a specific organism is isolated. After an organism is identified, antibiotic coverage can be narrowed and may be converted to oral dosing for completion of the course of treatment.

By definition, patients without indwelling urinary catheters cannot develop a CAUTI. Methods of decreasing catheter days include an electronic medical record best practice alert that notifies the provider daily to evaluate the need for continuation of the catheter and questioning of catheter necessity during daily rounds with the multidisciplinary team. "Bladder bundles" that prompt nurses to focus on aseptic catheter insertion, sterile catheter maintenance with a closed system, and proper placement of the drainage bag below the level of the bladder to ensure unobstructed urine outflow are also useful [16]. Alternatives to indwelling catheters include intermittent straight catheterization with the use of bladder scanning, condom catheters, and daily weights.

23.4 Central Line-Associated Bloodstream Infection (CLABSI)

CLABSI is the presence of a bloodstream infection in a patient who currently has a central venous catheter (CVC) or has had a CVC during the prior 48 h. Non-tunneled CVCs, which are commonly used in the neurocritical care unit, have the highest risk of developing CLABSI (Fig. 23.1). There are two methods of introducing organisms into the bloodstream in CLABSI. Extraluminal contamination occurs if the skin is not adequately cleaned with chlorhexidine prior to line insertion, the sterile field is contaminated during line insertion, or proper care is not taken during dressing changes. Intraluminal contamination occurs if medications or intravenous fluids are administered without scrubbing the hub of the CVC with an alcohol swab appropriately [21].

If symptoms of infection are noted, all CVC sites should be closely examined for erythema or signs of infection. If present, the CVC should be removed and the tip sent for culture. Blood cultures (optimally two sets) should be obtained peripherally. Obtaining a blood culture from the CVC if left in place is also an option. With the usage of antibiotic-impregnated catheters, it is unlikely that the CVC tip will grow an organism. The prevalence of organisms varies by institution. Knowing what organisms are common in your institution will help guide the choice of antibiotic treatment while awaiting culture results.

CLABSI bundles and line placement checklists have been instituted to help standardize the placement and care of CVCs (Figs. 23.1 and 23.2). Additionally, assessing the need for continuing the CVC daily on multidisciplinary rounds will reduce CVC duration.

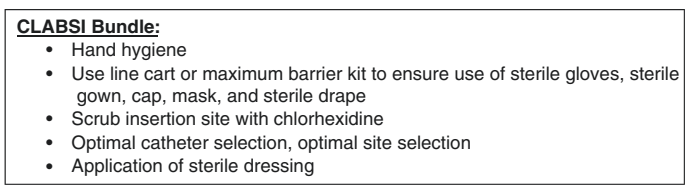

Fig. 23.1 Example of a CLABSI bundle

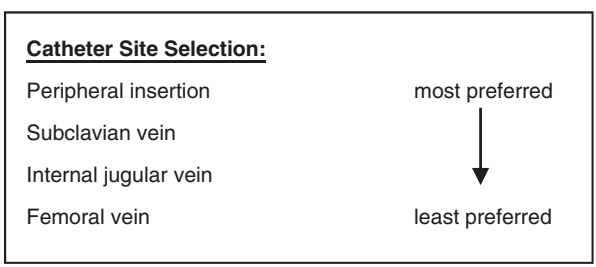

Fig. 23.2 Preferred sites for venous access

23.5 Ventilator-Associated Pneumonia

Ventilated-associated pneumonia (VAP) is one of the most common complications in mechanically ventilated critically ill patients. VAP was previously defined by signs of systemic infection developing within 48 h after intubation and a new infiltrate on chest x-ray. In 2015, the Centers for Disease Control introduced new definitions for ventilator-associated condition (VAC) and VAP. The new definitions require a sustained increase in oxygenation requirements after a period of stability coupled with signs of inflammation or infection. Prolonged intubation, which is the greatest risk factor for VAP, is frequently required for the neurocritically ill patient due to conditions such as severe TBI or status epilepticus requiring pharmacological coma. Decreased level of consciousness, loss of airway protective reflexes, and positive pressure provided by mechanical ventilation are factors that contribute to the risk of developing VAP [10].

In neurocritical care, an accurate diagnosis of VAP can be challenging. The patient may be febrile due to noninfectious causes, and bronchoalveolar lavage (BAL) is less commonly performed in patients at risk for elevated intracranial pressure [4]. For diagnosis and treatment purposes, it is important to obtain a sputum sample, either by endotracheal suctioning, BAL, or mini-BAL. The mini-BAL is often preferred due to the lower risk of increasing intracranial pressure. Calculating the clinical pulmonary infection score (CPIS) is useful in diagnosing VAP. A CPIS of greater than 6 has a strong correlation with VAP. Variables used to calculate the CPIS include:

- Temperature
- Leukocyte count
- Presence of purulent tracheal secretions
- P/F ratio
- Appearance of infiltrate on chest x-ray
- Culture results of tracheal aspirate

Common organisms that cause VAP are listed below (Table 23.1). Antibiotic sensitivity of individual organisms varies by institution. Broad-spectrum initial antibiotic therapy with narrowing of coverage after isolation of the organism helps to reduce development of multidrug-resistant organisms. Organisms that tend to be drug resistant are typically seen in late-onset VAP, which is defined as VAP occurring after more than 4 days of intubation [10].

Bundles are widely used to standardize practices and help decrease the incidence of hospital-acquired infections. Elements in the Institute of Healthcare Improvement's VAP bundle are listed in Fig. 23.3 [8].

Historically, the endotracheal tube has been maintained at 2–4 cm above the carina on chest x-ray and adjusted daily after

Table 23.1 Common VAP pathogens

Common organisms in early VAP	Common organisms in late VAP
Streptococcus pneumoniae	Methicillin-resistant *Staphylococcus aureus* (MRSA)
Haemophilus influenzae	*Acinetobacter* species
Escherichia coli	*Pseudomonas* species
Enterobacter species	Extended-spectrum beta-lactamase-producing bacteria (ESBL)
Proteus species	
Serratia marcescens	

VAP Bundle

- Head of bed elevation to 30°
- DVT prevention through use of compression devices or chemoprophylaxis
- Stress ulcer prophylaxis
- Daily sedation interruptions
- Daily oral decontamination with chlorhexidine

Fig. 23.3 Institute of Healthcare Improvement VAP bundle

reviewing the radiograph. In recent studies, endotracheal tube repositioning has been associated with approximately a threefold increased risk in VAP [17]. A wider margin for endotracheal tube depth can be tolerated to reduce the occurrence of tube repositioning, which decreases the chance of VAP from oral secretions draining into the airway. Other factors that have been identified to decrease the incidence of VAP include [10]:

- Alcohol-based handwashing
- Subglottic suctioning endotracheal tubes
- Avoiding unnecessary repositioning of the endotracheal tube
- Small bowel feeding versus gastric feeding
- Use of oral gastric tubes versus nasogastric feeding tubes
- Early tracheostomy
- Prophylactic probiotics

23.6 Ventriculostomy-Related Infection

External ventricular drains (EVDs) are frequently used in neurocritical care to treat a variety of conditions. While the drainage of CSF from an EVD can be lifesaving and necessary, the presence of an EVD increases a patient's risk of developing a HAI. The CDC definition of ventriculostomy-related infection (VRI) states that the patient must have clinical symptoms of infection, abnormal laboratory findings indicative of infection, and positive CSF cultures, whereas some studies define VRI as the presence of positive CSF cultures alone [7]. Due to the urgent nature of EVD placement and previous absence of formalized guidelines, insertion technique and care of EVDs tend to vary widely and have not been evaluated in large studies. In 2016, the Neurocritical Care Society published an evidence-based consensus statement on the insertion and management of EVDs.

Increased risk of infection has been associated with longer duration of EVD; thus it is recommended that the EVD be removed as soon at the clinical situation allows [5]. Despite striving to remove EVDs as soon as possible, many neurocritically ill patients do require EVDs for an extended period. Therefore, to mitigate the risk of infection, the use of antimicrobial-impregnated EVDs, in addition to the administration of a single dose of a prophylactic antibiotic prior to the EVD insertion, is recommended. Historically, ongoing prophylactic antibiotics were prescribed throughout the duration of the EVD. This is not currently recommended due to the associated increased risk of the development of *Clostridium difficile* colitis and infections from drug-resistant organisms [5]. The use of a care bundle for EVDs has been shown to reduce rates of VRI (Fig. 23.4).

If a VRI is detected in the neurocritical care patient, antibiotics that cross the blood-brain barrier must be chosen. At times, it may be necessary to treat VRI with intraventricular antibiotics

EVD Care Bundle:

- Attention to sterile technique
  - Use an insertion checklist
  - Have a monitor to observe the procedure
- Antibiotic use
  - Single dose of peri-procedure prophylactic antibiotic
  - Do not continue prophylactic antibiotics while EVD in situ
- Catheter placement
  - Tunnel the EVD away from the insertion site
  - Do not change the EVD site after placement
- EVD dressing
  - Cleanse the site with antimicrobial at time of EVD insertion
  - Reapply sterile dressing when soiled
- EVD tubing and collection bags
  - Routine changes not recommended
  - Avoid breaching closed system
- CSF sampling - avoid routine sampling of CSF

Fig. 23.4 Example of EVD care bundle

to achieve high CSF concentrations in multidrug-resistant infections or in patients who do not have an adequate response to intravenous antibiotics [5].

23.7 Treatment of Fever and Shivering

Fever is defined as elevation of core body temperature above 38.0–38.5 °C. Fever is a very common systemic complication encountered in neurocritical care patients and has a higher incidence in the neurocritical care unit compared to other ICUs [15]. For patients with intracranial temperature probes, brain temperature should be monitored and recorded. For patients without intracranial temperature probes, the core temperature should be monitored from esophageal or bladder temperature probes. Independent of the underlying cause, fever is associated with both acute and chronic neurological problems. For patients with brain injury and encephalopathy, elevated brain temperature is associated with worsening encephalopathy and lower seizure threshold [3]. In addition, fever increases cerebral metabolic demands which can worsen ischemic in the setting of brain hypoperfusion due to cerebral vasospasm and stroke. In observational studies, fever has been independently associated with increased chance of death and worse neurological outcomes in ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, traumatic brain injury, and hypoxic-ischemic encephalopathy from cardiac arrest. The area under the fever curve – referring to both the degree and duration of fever – is strongly associated with poor outcomes in patients with severe brain injuries. Aside from cardiac arrest survivors, there are currently limited data to prove that fever control results in improved outcomes so few guidelines exist. The topic of targeted temperature management can be referenced in Chap. 17 “Hypoxic Ischemic Injury After Cardiac Arrest.”

Table 23.2 Common causes of fever in the neurocritical care unit

Meningitis/encephalitis/ventriculitis	Malignant neoplasm
Sinusitis	Drug fever
Pneumonia	Pancreatitis
Urinary tract infection	Autonomic instability
Bloodstream infection	Paroxysmal sympathetic hyperactivity
Clostridium difficile colitis	Deep venous thrombosis
Central fever	Seizures
Atelectasis	Soft tissue infection/ cellulitis
Blood transfusion reaction	Alcohol withdrawal
Adrenal insufficiency	Hyperthyroidism

Fever can be produced by a variety of systemic and neurological causes in patients with injuries to the brain and spinal cord. These can include both infectious and noninfectious etiologies. See the Table 23.2 for the differential diagnosis of fever in the neurocritical care unit. Patients with acute brain injury can be particularly susceptible to noninfectious causes of fever, in particular patients with subarachnoid and intraventricular hemorrhage. The term "central fever" is used to describe fever caused by dysregulation of temperature homeostasis caused by injury to the hypothalamus either due to direct involvement or inflammatory hemolysis in cerebrospinal fluid bathing the hypothalamus located in the walls of the third ventricle. It can be challenging to differentiate patients with infectious and noninfectious causes of fever, which contributes to overuse of empiric antibiotics in neurocritical care patients. One group found that nearly half of neurocritical care patients with fever had noninfectious etiologies [6]. They found that independent predictors of central fever – as opposed to infectious fever – were:

- Onset within 72 h of admission to the neurocritical care unit
- Absence of an infiltrate on chest x-ray

- Recent blood transfusion
- Diagnosis of subarachnoid hemorrhage, intraventricular hemorrhage, or brain tumor

Based on these findings, the combination of negative cultures, absence of infiltrate on chest x-ray, diagnosis or subarachnoid/intraventricular hemorrhage or brain tumor, and fever onset within 72 h was strongly predictive of central fever (positive predictive value 90%) [6]. In the absence of guidelines, these criteria provide a practical approach to discontinuation of empiric antibiotics. Other groups have explored using serum procalcitonin levels as a biomarker for infectious causes of fever, but this approach remains investigational.

Suppression and treatment of fever can be challenging in neurocritical care patients and often require multiple pharmacological and non-pharmacological strategies deployed in concert. Shivering represents the greatest impediment to fever control. Shivering results from involuntary systemic muscle contraction which dramatically raises resting energy expenditure and the systemic rate of oxygen consumption which produces heat as a byproduct of metabolism [1]. Using indirect calorimetry, the resting energy expenditure can increase by as much as 2.5-fold during severe shivering [1]. The increase in metabolic demand and associated temperature increase may negate the potential salutary effects of temperature modulation in patients with acute brain injuries. The recognition and treatment of shivering should be an integral part of any neurocritical care unit's targeted temperature management protocol. Hospitals that are most successful at fever and shivering control utilize a standard nurse-driven assessment and treatment algorithm and physician order set. The most commonly applied recognition tool for shivering is the Bedside Shivering Assessment Scale (BSAS), outlined in Table 23.3 [1]. The BSAS requires regular nursing assessments to evaluate for the presence and severity of shivering. Shivering can be insidious and surprisingly difficult to detect, especially in

Table 23.3 The bedside shivering assessment scale

Score	Definition
0	*None:* no shivering noted on palpation of the masseter, neck, or chest wall
1	*Mild:* shivering localized to the neck and/or thorax only
2	*Moderate:* shivering involves gross movement of the upper extremities (in addition to the neck and thorax)
3	*Severe:* shivering involves gross movements of the trunk and upper and lower extremities

Adapted from Badjatia et al. [1]

patients who are clothed or covered by bed linens or surface temperature management devices. In addition to physical examination, display of the EKG and bispectral index (BIS) EEG waveforms on the bedside monitor can assist in recognition of shivering.

Institutions should adopt a standard treatment protocol for targeted temperature management and shivering control. As an example of a fever control algorithm, see below. Note, this protocol is intended for intubated and mechanically ventilated patients with severe brain injury and persistent temperature >38.0 °C.

23.7.1 Normothermia/Fever Control Protocol

1. Remove all clothing and blankets to expose the patient.
2. Place ice packs on the axilla, groin, and trunk.
3. Administer Tylenol 650–1,000 mg oral, intravenously, or rectally,
4. Record Bedside Shivering Assessment Scale (BSAS) score Q1 hour.
5. Goal BSAS score 0.
6. Consider infusing two 1 L bags of 0.9% NaCl chilled to 4 °C over 30 min.

7. For persistent fever, consider inserting an intravascular cooling device or attaching thermal exchange adhesive pads with closed-loop feedback automated cooling system.

8. Institute the anti-shivering protocol:

   Step 1

   - Magnesium sulfate bolus 4 g IV followed by continuous infusion of 0.5–2 g/h IV (hold for Mg level >4.0 mEq/L)
   - Buspirone 30 mg oral bolus followed by 20 mg oral Q8 hours
   - Tylenol 650 mg oral Q4 hours
   - Dexmedetomidine 0.2–1.4 mcg/kg/h IV (hold for HR <50)
   - Meperidine 25–50 mg IV Q1 hour PRN for breakthrough shivering (up to max dose of 600 mg/24 h)
   - BAIR hugger surface counter-warming set at 43 °C

   Step 2

   - Propofol infusion 10 mcg/kg/min and titrate by 5–10 mcg/kg/min q10 min to maintain RASS score to −4 to −5 and BSAS score of 0
     or fentanyl infusion 50–100 mcg/h and midazolam infusion 1–4 mg/h, titrated to maintain RASS score of −4 to −5 and BSAS score of 0
   - If shivering occurs despite sedation and patient above target temperature, give vecuronium 0.1 mg/kg IV.
   - Consider vecuronium 0.1 mg/kg IV Q30–60 min PRN to maintain BSAS score 0,
     or vecuronium infusion 1 mcg/kg/min, titrated to maintain one to two twitches on TOF nerve stimulator and BSAS score 0,
     or cisatracurium 0.2 mg/kg IV once STAT followed by 2 mcg/kg/min infusion, titrated to maintain one to two twitches on TOF nerve stimulator and BSAS score 0.

23.8 Disorders of Sodium

Sodium is closely monitored and corrected in the neurocritical care unit due to the potential for hyponatremia to worsen cerebral edema. In addition, hypovolemic hypernatremia – as occurs in diabetes insipidus – can be detrimental to the neurocritical care patient by lowering blood pressure and cerebral perfusion pressure [25]. Characteristics of commonly encountered causes of hyponatremia are outlined in Table 23.4.

23.8.1 Diabetes Insipidus (DI)

Neurogenic DI is caused by the lack of production of antidiuretic hormone (ADH) by the hypothalamus or damage to the posterior pituitary where ADH is stored [25]. Decreased ADH results in the inability to concentrate urine, thus producing large volumes of dilute urine. In the critically ill patient, this can result in rapid intravascular volume depletion. Diagnosing DI requires measurement of serum sodium and urine specific gravity

Table 23.4 Characteristics of conditions causing hyponatremia

Condition	Serum Na	UO	Risk associated	Common in	Treatment
DI	High >145	High	Low BP	Pituitary surgery	Fluid replacement, DDAVP
			Low CPP	Brain death	
SIADH	Low <135	Low	Cerebral edema	TBI	Free water restriction
				Meningitis	Salt tabs
CSW	Low <135	High	Low BP Low CPP Cerebral edema	SAH	Fluid replacement

and an assessment of overall volume status. The serum sodium will be elevated (>145 mmol/L) and the urine specific gravity will be low (<1.005). Accurate volume status can be difficult to discern in the neurocritical care patient due to confounders such as mannitol use. It is recommended that multiple methods of volume assessment be used including fluid balance, central venous or cardiac filling pressure, clinical assessment, and weight. High urine output typically occurs in DI, although low urine output may occur in patients with inadequate resuscitation.

DI in the neurocritical care patient may be transient, permanent, or triphasic (see below). Patients undergoing neurosurgical procedures, particularly with resection or manipulation of the pituitary, may develop DI postoperatively even if it was not present prior to surgery. In some studies, up to 90% of adult patients undergoing craniopharyngioma resection developed DI postoperatively [20]. DI is also commonly seen in patients with severe TBI or in patients who progress to brain death.

The mainstay for treatment of DI is repletion of the free water deficit. In the ICU setting, this is accomplished through IV or enteral rehydration. Desmopressin (DDAVP), a synthetic form of ADH, is given IV or subcutaneously to help slow the fluid loss from extreme diuresis. One common mistake is over-reliance on DDAVP administration to slow the urine output without replacing the free water deficit. This mistake can lead to circulatory collapse since neurocritical care patients who develop DI tend to rapidly develop hypovolemia from diuresis. Subcutaneous DDAVP can be erratically absorbed, so dosing must be tailored to the individual patient. In most cases, dosing is needed two to three times per day. Polyuria is an indicator that the patient's sodium is rising, and DDAVP may be required in addition to fluid replacement. Patients who are in DI or who have a high risk of developing DI should have serial serum sodium levels checked, strict monitoring of fluid intake and

output, and urine specific gravity checked in the presence of polyuria. In the outpatient setting, intranasal DDAVP is used mainly for symptomatic control of polyuria since an individual's intact thirst mechanism will allow their body to compensate and keep up with the volume loss. In a critical care setting where the urine output is monitored closely, the goal is to mimic an intact thirst mechanism that would be prompting the patient to drink.

Complications that are seen in DI include wide variations in serum sodium that result from the treatment of DI. It is important to frequently check the sodium level to make certain that the patient is not overcorrected, typically aiming for normonatremia of 135–145 mmol/L. If the neurocritically ill patient becomes volume depleted and hypotension ensues, low cerebral perfusion can induce cerebral ischemia and worse outcomes [25].

23.8.2 Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

SIADH is the most common cause of hyponatremia in the neurocritical care unit. It occurs when too much ADH is released from the posterior pituitary, resulting in a euvolemic to slightly hypervolemic state with excess extracellular water. It is important to recognize that SIADH is not due to a sodium deficit, but to excess water retention. A serum sodium value and an assessment of volume status are essential for diagnosing SIADH. SIADH is common in TBI and bacterial meningitis; a multitude of conditions in neurocritical care can also contribute to SIADH.

The basis of treatment for SIADH is free water restriction. In the setting where more rapid correction of sodium is needed, treatment includes IV administration of a vasopressin-2 receptor antagonist (V2RA), which promotes free water excretion without

electrolyte loss and raises serum sodium [18]. Direct salt augmentation can be provided with oral salt tablets although they may cause nausea and only modestly increase serum sodium concentration. If hypertonic saline is necessary due to the critical nature of the patient's presentation, then serial sodium values should be closely monitored so as to avoid overly rapid correction. Typically, a slow IV infusion of 3% saline through a central line is used [25].

Seizures and exacerbation of cerebral edema are two main complications of hyponatremia in SIADH. Pontine and extrapontine osmotic demyelination can occur due to osmotic shifts if the serum sodium is corrected too abruptly, particularly in patients with chronic hyponatremia. If the serum sodium concentration falls precipitously or if the benefits outweigh the potential risks (e.g., status epilepticus or cerebral edema), rapid correction may be necessary. Otherwise, the rate of correction should be 10–12 mmol/L over 24 h.

23.8.3 Cerebral Salt Wasting (CSW)

Cerebral salt wasting (CSW) is characterized by hypovolemic hyponatremia. The assessment of volume status is of utmost importance in determining the difference between SIADH and CSW [12]. CSW is most frequently encountered in the neurocritical care unit in patients with aneurysmal subarachnoid hemorrhage, but CSW occurs less commonly in TBI, bacterial meningitis, and other conditions.

The treatment focus of CSW is the repletion of volume loss with isotonic or hypertonic saline solutions. With aggressive volume replacement, the serum sodium should normalize. It is important to continue to monitor the serum sodium frequently. At times, the fluid loss can be extreme, and patients may require cc-for-cc fluid replacement protocols, where the exact volume

of urine output is measured each hour and then replaced with saline during the following hour. This process can be labor intensive and requires strict monitoring of the intake and output, especially in subarachnoid hemorrhage patients who may be awake and able to swallow oral fluids. In addition to fluid balance, obtaining daily weights and trending the central venous pressure are useful to determine when a patient needs more volume replacement.

Volume contraction from CSW may lead to strokes due to cerebral hypoperfusion in the setting of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. With CSW, the subarachnoid hemorrhage patient can quickly become volume depleted, greatly increasing the risk for development of symptomatic vasospasm and cerebral ischemia [25].

23.8.4 Special Case: Triphasic Sodium Response

Patients who undergo neurosurgical procedures for pituitary tumors may develop postoperative DI that quickly progresses to SIADH and then returns to a state of DI. Wide variations in sodium and osmotic shifts put the patient at risk for osmotic demyelination, seizures, and cerebral edema. Close postoperative monitoring with serial sodium checks and strict fluid balance monitoring are needed. This triphasic response occurs when there is transient dysfunction of the pituitary stalk or hypothalamus during the immediate postoperative period, followed by recovery. Phase one is a polyuric phase due to injury of the pituitary stalk or hypothalamus during which DI is caused by a decline in ADH secretion. In the second phase, excess ADH is released from the damaged hypothalamic-pituitary axis until the stores of ADH are depleted. This is followed by return of polyuria due to DI, which occurs after the reserves of ADH are depleted [20].

23.9 Prevention and Treatment of Venous Thromboembolism

Complications related to venous thromboembolism (VTE) – deep venous thrombosis (DVT) and pulmonary embolus (PE) – are the third leading cause of death in the USA, and VTE is especially common in ICU patients. Patients in the neurocritical care unit have significant risk of VTE related to immobilization from paralysis and sedation, delayed initiation of chemoprophylactic agents in patients with brain and spinal cord hemorrhages, delayed mobilization of patients with paralysis or intracranial hypertension, and underlying neurological conditions that lead to systemic prothrombotic states. Depending on the underlying neurological condition, the incidence of VTE has been reported as high as 40–80% in patients in the neurocritical care unit with the highest incidence reported in patients with quadriplegia due to spinal cord injury and in patients with high-grade malignant brain tumors with paralysis [19]. VTE has been shown to increase mortality, morbidity, and length of stay in the neurocritical care unit.

The most common signs of DVT include unilateral limb edema, fever, and limb pain, but these signs are frequently overlooked or obscured in neurologically ill patients. For high-risk conditions like spinal cord injury, some institutions perform routine duplex ultrasonography to screen for DVT, but the cost-effectiveness of this approach has not been studied. Common strategies for the prevention of VTE include early mobilization of patients, passive range of motion and massage, intermittent pneumatic compression (IPC), compression stockings (CS), and chemoprophylaxis with anticoagulant medications. CS are not currently recommended for DVT prevention due to poor reported efficacy and high incidence of skin injury in recent clinical trials. Chemoprophylactic agents include subcutaneous

unfractionated heparin (UH), low molecular weight heparin (LMWH), and the factor Xa inhibitor fondaparinux. UH can be administered every 8 or 12 h, and LMWH can be administered daily or twice daily with dose adjustments based on renal clearance, weight, and VTE risk. Patients with impaired renal function who are receiving LMWH should undergo periodic testing with anti-factor Xa assays to monitor systemic anticoagulation. Inferior vena cava (IVC) filters are not currently recommended for prevention of PE in patients without known DVT, even among patients who are quadriplegic due to spinal cord injury.

Because many neurocritical care conditions increase the risk of brain and spinal cord hemorrhage, the timing of initiation of anticoagulant chemoprophylactic medications has been controversial, and practices vary among institutions and providers. A recent meta-analysis of TBI patients found that early (<72 h) initiation of chemoprophylaxis was associated with a 0.52 relative risk of VTE compared to later initiation with no increased risk of hematoma enlargement [9]. For patients with aneurysmal SAH and indwelling ventriculostomy catheters, a recent retrospective case-control study found that patients treated with chemoprophylaxis had half the incidence of VTE and no significant hemorrhagic complications compared to patients without chemoprophylaxis [26].

The Neurocritical Care Society (NCS) recently published evidence-based guidelines for prophylaxis against VTE in neurocritical care patients that included recommendations for the prophylactic agent and timing of initiation in the most common conditions treated in the neurocritical care unit. The NCS guidelines are summarized in Table 23.5. These are general guidelines that must be tailored to individual patients, and clinical judgment must be applied. The guidelines do not directly address the timing of initiation of chemoprophylaxis in patients with acute subdural or epidural hematomas, thrombocytopenia, or coagulopathy.

Table 23.5 NCS guidelines for timing of chemical VTE prophylaxis initiation

Condition	Risk of VTE	Prophylaxis	Timing of initiation
Ischemic stroke	2.5%	LMWH + IPC	Within 24 h
Intracerebral hemorrhage[a]	5–40%	LMH or UFH + IPC	Within 48 h
Aneurysmal SAH	1.5–24%	UFH + IPC	24 h after secured
Traumatic brain injury[a]	13–17%	LMH or UFH + IPC	Within 24–48 h
Malignant brain tumor	20–30%	LMH or UFH + IPC	Immediate
Spinal cord injury	12–80%	LMH or UFH + IPC	As soon as bleeding is controlled
Neuromuscular diseases	4–7%	LMH or UFH or fondaparinux +IPC	Immediate
Postspinal surgery	0–15.5%	LMH or UFH + IPC	24 h post-op
Post craniotomy	3–28%	LMH or UFH + IPC	24 h post-op
Post endovascular procedure	Unreported	LMH or UFH + IPC	Immediate

[a]With stable hematoma volume [19]

Central venous catheter (CVC)- and peripherally inserted central catheter (PICC)-associated DVTs also commonly occur in the neurocritical care unit. The risk of PE and appropriate management of these DVTs have been controversial. PICC line placement has increased in frequency in the neurocritical care time due to the increasing prevalence of nurse-driven PICC teams, ease of insertion, and lower bloodstream infection and mechanical complication rates. However, the incidence of catheter-associated DVT is higher in PICC lines compared to CVC. In a recent study, the incidence of symptomatic PICC-associated DVT was 8.4% [24]. Independent risk factors for

PICC-associated DVT included insertion in a paretic arm (odds ratio (OR) 9.9), surgery longer than 1 h with PICC line in place (OR 3.3), history of prior VTE (OR 7.7), and mannitol use (OR 3.3). For these reasons, PICC lines should be preferentially placed in the non-paretic arm and should be delayed until the postoperative period in cases where lengthy surgery is planned. Mannitol and volume contraction should be avoided in patients with PICC lines, if possible, and the PICC line should be removed when central access is no longer needed.

There are no current guidelines for appropriate management of patients with neurocritical care conditions who develop VTE, so general guidelines must be cautiously applied to this population. The 2016 CHEST guidelines continue to recommend systemic anticoagulation for proximal DVT in the arms and legs with duration of therapy and anticoagulant choice determined by clinical factors [11]. Removable IVC filter placement should be reserved for patients with VTE who cannot be anticoagulated or developed PE despite adequate anticoagulation. In patients with distal (calf vein) DVT, CHEST guidelines recommend surveillance with repeat duplex ultrasonography in 2 weeks rather than anticoagulation in patients without severe symptoms. If severe symptoms develop or the DVT extends on repeat imaging, systemic anticoagulation is recommended [11]. The CHEST guidelines do not specifically address the management of catheter-associated DVT of the arms, and randomized trials are lacking. For patients with catheter-associated DVT who can be safely anticoagulated, most groups recommend systemic anticoagulation similar to leg DVT with or without removal of the catheter. The catheter should be removed if central access is no longer needed, bloodstream infection is present, or the patient develops severe symptoms despite anticoagulation. For patients who cannot be safely anticoagulated, it is reasonable to remove the catheter and repeat duplex ultrasonography to evaluate for DVT propagation.

23.10 Glycemic Control in the Neurocritical Care Unit

Acute hyperglycemia is very common as a systemic stress response in the setting of acute brain injuries and has been well documented to be associated with in ischemic stroke, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and anoxic-ischemic encephalopathy. Acute neurological injuries result in a combination of sympathetic activation, systemic inflammatory response, and increased hepatic synthesis of glucose which combine to produce hyperglycemia. Impaired glucose metabolism also occurs to a lesser extent even in nondiabetic patients with acute neurological injuries. In ischemic stroke, hyperglycemia is associated with larger infarct volume and increased risk of malignant cerebral edema. The recent GAMES clinical trial suggested that treatment with the oral hypoglycemic agent glyburide reduced the incidence of malignant cerebral edema in patients with large hemispheric strokes [22]. Severe hyperglycemia has also been associated with increased risk of hemorrhagic transformation and poor outcomes in stroke patients treated with thrombolytic therapies.

Although hyperglycemia is associated with increased mortality, worse outcomes, and impaired wound healing, ideal glucose targets in neurocritical care patients are still being elucidated. It is also unclear whether hyperglycemia is a marker of injury or independently contributes to neurological injury. A recent meta-analysis of 16 clinical trials of glycemic control strategies in neurocritical care patients compared tight glycemic control (target glucose <140 mg/dl) and conventional glycemic control (target glucose <144–300 mg/dl depending on the study) [13]. Intensive insulin therapy was associated with a threefold incidence in the number of hypoglycemic events with no difference

in mortality. There was a reduction in the incidence of poor neurological outcomes in patients with tight glycemic control when compared to very loose glycemic control (glucose >200 mg/dl) but not moderate glycemic control (glucose 110–180 mg/dl) [13].

Since glucose is the primary metabolite and energy source for the central nervous system (CNS), hypoglycemia can also be deleterious to neurocritical care patients. Marked hypoglycemia can result in cerebral energy failure, coma, seizures, and irreversible neuronal injury if it is unrecognized and untreated. Patients with acute brain injuries may have impaired glucose transport into the CNS resulting in a relative dissociation of serum and cerebral glucose concentrations whereby patients can develop severe depletion of brain glucose and cerebral metabolic failure in the face of relatively normal serum glucose concentration. In cerebral microdialysis studies that include simultaneous measurement of serum glucose levels and brain interstitial glucose, lactate, and pyruvate levels, low normal serum glucose values have been associated with low cerebral glucose and markers of metabolic failure in neurocritical care patients [14]. Accordingly, tight glycemic control protocols in the neurocritical care unit have been reported to be associated with elevated cerebral lactate-pyruvate ratios consistent with energy metabolic failure and conversion to anaerobic metabolism. An elevated lactate-pyruvate ratio >40 has been associated with poor neurological outcomes and increased risk of death in patients with acute brain injuries. In one study, the median brain-serum glucose ratio was only 0.12 in neurocritical care patients compared to the expected norm of 0.4 [14], indicating impaired glucose transport into the CNS. Brain-serum glucose ratios below 0.12 were associated with increased lactate-pyruvate ratios – indicating brain energy metabolic distress – and in-hospital mortality [14].

Although guidelines for glycemic control have not yet been developed that are specific to neurocritical care patients, the Neurocritical Care Society published the results of an international multidisciplinary consensus conference of multimodality

monitoring in 2014 [2]. The consensus document addressed methods of monitoring glucose in neurocritical care patients by recommending frequent blood glucose monitoring during the critical care phase of the patient's illness but did not recommend specific glucose targets. Given the absence of definitive evidence, a practical strategy would be to calibrate insulin sliding scale protocols to maintain the serum glucose <180 mg/dl while avoiding hypoglycemia. In specialized neurocritical care units that utilize cerebral microdialysis monitors, the target serum glucose can be further individualized to maintain an adequate cerebral glucose concentration, lactate-pyruvate ration, and brain-serum glucose ratio.

Until guidelines for glycemic control are developed for neurocritical care patients, the following is a practical guidance for management of patients in the neurocritical care units:

- All patients should have standardized blood glucose measurement every 4–6 h for the first 24–48 h or until they are able to meet caloric goals by eating or enteral feeding.
- For patients with any hyper- or hypoglycemic events during the first 24–48 h, standardized blood glucose measurement should continue during the critical care period.
- Protocols should target a glucose <180 mg/dl using protocols for subcutaneous (SQ) or intravenous infusion of insulin (Fig. 23.5).
- Sliding scale SQ insulin or insulin infusion should be based on initial glucose measurements according to the algorithm presented in Fig. 23.5.
- After glucose measurements stabilize, patients should be converted to a combination of scheduled long-acting and immediate-release insulin formulations along with a supplemental sliding scale insulin.
  - For example, if a patient is receiving four units of insulin per hour, the total insulin requirement is 96 units per day. ~75% of the total dose (70 units) should be given as scheduled insulin.

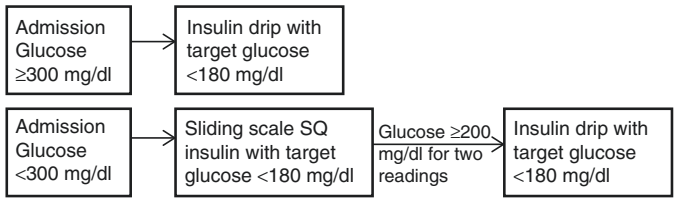

Fig. 23.5 Algorithm for glucose management

~70% of the scheduled dose (50 units) should be given as long-acting insulin, e.g., insulin glargine 25 units Q12 hours or 50 units daily.

~30% of the scheduled dose (20 units) should be given as immediate-release insulin, e.g., insulin lispro seven units TID with meals.

A sliding scale insulin protocol should be ordered with glucose monitoring prior to meals and at nighttime or scheduled every 4–6 h.

- When converting from an insulin infusion to subcutaneous insulin, caution must be applied to appropriately time the first dose of long-acting insulin, discontinuation of the insulin infusion, first measurement of serum glucose, and first application of the SQ insulin sliding scale.

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Chapter 24
Helpful Links and Resources

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24.1 Organizations

American Heart Association (AHA)/American Stroke Association
Neurocritical Care Society (NCS)
American Academy of Neurology (AAN)
Brain Trauma Foundation
American Association of Neurological Surgeons (AANS)
Society for Critical Care Medicine (SCCM)

24.2 Guidelines

24.2.1 Subarachnoid Hemorrhage

- AHA Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage (2012)
  http://stroke.ahajournals.org/content/43/6/1711

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- NCS Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage (2011)
  http://www.neurocriticalcare.org/Portals/61/Docs/Guidelines/Critical%20Care%20Management%20of%20Patients%20Following%20Aneurysmal.pdf

24.2.2 Intracerebral Hemorrhage

- AHA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage (2010)
  http://stroke.ahajournals.org/content/strokeaha/41/9/2108.full.pdf

24.2.3 Acute Ischemic Stroke

- AHA Recommendations for Cerebral and Cerebellar Infarction with Swelling (2014)
  http://stroke.ahajournals.org/content/strokeaha/41/9/2108.full.pdf
- AHA Update on Endovascular Treatment (2015)
  http://stroke.ahajournals.org/content/46/10/3020
- AHA Statement on Palliative Care and End of Life Care in Stroke (2014)
  http://stroke.ahajournals.org/content/45/6/1887
- NCS Guidelines for Management of Large Hemispheric Infarction (2015)
  http://www.neurocriticalcare.org/Portals/61/Docs/Guidelines/LHI%20Final%20GL-Published.pdf
- Alberta Stroke Program Early CT Score (ASPECTS)
  http://www.ajnr.org/content/22/8/1534

24.2.4 Cerebral Venous Thrombosis

- AHA Statement on Diagnosis and Management of Cerebral Venous Thrombosis (2011)
  http://stroke.ahajournals.org/content/strokeaha/42/4/1158.full.pdf

24.2.5 Traumatic Brain Injury

- Brain Trauma Foundation Guidelines for Management of Severe Traumatic Brain Injury (2016)
  https://braintrauma.org/uploads/07/04/Guidelines_for_the_Management_of_Severe_Traumatic.97250__2_.pdf

24.2.6 Seizures and Status Epilepticus

- NCS Guidelines for Evaluation and Management of Status Epilepticus (2012)
  http://www.neurocriticalcare.org/Portals/61/Docs/Guidelines/SE%20Guidelines%20NCS%200412.pdf

24.2.7 Spinal Cord Injury

- Congress of Neurological Surgeons Guidelines for the Management of Acute Cervical SpIne and Spinal Cord Injuries
  https://www.cns.org/guidelines/guidelines-management-acute-cervical-spine-and-spinal-cord-injuries

24.2.8 Neuromuscular Disease

- AAN International Consensus Guidance for Management for Myasthenia Gravis (2016)
  http://www.neurology.org/content/87/4/419.full.pdf+html
- AAN Guideline for Intravenous Immunoglobulin in the Treatment of Neuromuscular Disorders (2012)
  http://www.neurology.org/content/78/13/1009.full.pdf+html
- AAN Immunotherapy for Guillain-Barre Syndrome (2003)
  http://www.neurology.org/content/61/6/736.full.pdf+html

24.2.9 Brain Death

- AAN Guidelines for Determining Brain Death (2010)
  http://www.neurology.org/content/74/23/1911.full.html
- NCS Recommendations for Critical Care Management of Devastating Brain Injury (2015)
  http://www.neurocriticalcare.org/Portals/61/Docs/Guidelines/Online%20First%20Version-%20Critical%20Care%20Management%20of%20Devastating%20Brain%20Injury.pdf

24.3 Neuroradiology Tutorials

www.Headneckbrainspine.com
www.radiologyassistant.nl